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The great tragedy of science:
The slaying of a beautiful hypothesis by an ugly fact
Thomas Huxley (1825-1895)
The Third International Consultation on Sexual Medicine (ICSM), which took place on July 10 to July 13, 2009 at the Palais de Congres in Paris, France was organized under the auspices of the International Consultation on Urological Diseases and the International Society for Sexual Medicine (ISSM). This year’s ICSM was a truly memorable scientific event full of impressive discoveries, never before seen studies backed by robust data and an overwhelming interest from the audience. After having watched and listened to each and every one of the presentations given during the four day meeting, we are pleased to affirm that the field of Sexual Medicine for both Men and Women is making enormous progress. This well deserved success is due to the dedication, perseverance and hard work done by the renowned experts in the field who selflessly devote their time, intellect and energy to promoting the results and findings obtained by their studies.

To successfully carry out a meeting and publication as important as this, careful preparation was necessary. In early 2008, Chairman Francesco Montorsi, Secretary Saad Khoury, Honorary President Tom Lue and Vice Chairs; Ganesan Adaikan, Rosemary Basson, Edgardo Becher, Anita Clayton, François Giuliano, Ira Sharlip all met together in person or by phone conference in Paris with the ISSM office representatives to brainstorm on how a reference such as the Recommendations for Sexual Medicine should be developed. Much thought and consideration went into deciding what topics should be considered as chapters and how the meeting and eventual publication would be organized.

Choosing the Chairpersons, Members and Consultants was not an easy task as the experts in these fields are many and each very distinguished. The identification of the members of all the committees started from a very rigorous assessment of the chairpersons and members of the 2003 Consultation as we clearly wanted to have on board again all those who had given a substantial contribution to that meeting and were still available to actively participate this further endeavour.

In addition, a very extensive PubMed search and a thorough evaluation of the scientific programmes of the most important international scientific meetings devoted to sexual medicine served to identify the names of the top experts from the five continents.

The topics that were discussed in the 2003 Consultation served as the basis to build the programme of the 2009 meeting. We considered the advances done in the field during the last six years and we identified all the areas which deserved to be specifically investigated by the experts of the new Consultation. In the end, we were able to produce a table of contents composed of 25 Chapters covering a vast spectrum of the critical topics concerning aspects of sexual medicine for both men and women.

The lists of topics and experts were then matched and the committees were formed. Although a few of those on each of our “wish lists” could not be included due to economic restraints, we were able to guarantee the participation of 186 experts to the final program.

The preparatory meetings held at the various major national meetings, the ISSM in Brussels and the American Urological Association 2009 annual meeting in Chicago, were essential to understand how each chapter was progressing and what the next steps should be. These meetings allowed everyone to finally meet face-to-face under the same roof to streamline ideas and final recommendations of their respective chapters. We were impressed to see the close collaboration the committees had with one another to make sure that ideas were shared without overlap.

The work of the various committees was indeed very hard and was witnessed by the exchange of a huge number of emails aimed at discussing the contents of the various chapters. We are very pleased to inform you that we were always able to touch with our hands the enthusiasm and passion for science shown by the chairs and members of the committees. Sometimes there were strong views which would be contrasting but at the end it was always possible to find a general consensus and the final editing of the chapters text was overall very smooth.

In Paris, the presentations of the committees were really top quality and it was clear to the audience that a huge amount of work was behind the slides that were shown. The discussion sessions were always very lively and many ideas that came out of these were used to improve the final text of the chapters.

In the end, we believe that our objective to create and update a set of standards from evidence based studies and years of research has been reached. This gratifying accomplishment could not have been made without the support from the previously mentioned organizations, the various sponsors and the ambitious staff of the Consultation.

We are grateful to everyone involved and especially to Ira Sharlip who was instrumental in maintaining the necessary geographical balance when identifying the top experts and also in obtaining funding for the meeting; to Tom Lue and all the Vice Chairs who were extremely active during all the preparatory phases and to David Casalod and his team who were the responsible persons for the very efficient logistics.

We are convinced that these contributions will be key in advancing our knowledge in the field of sexual medicine and ultimately in improving the care of our patients.

FRANCESCO MONTORSI  
Chairman, ICSM

CATHERINE J. PIERCE  
Assistant to the Chairman, ICSM

SAAD KHOURY  
Secretary, ICSM
Some of the members of the International
Committees Paris, France
## MEMBERS OF THE COMMITTEES

*(Alphabetical order - Chair persons in bold)*

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# Members of the Committees (by Committee)

## 1. Historical Highlights of Sexual Dysfunctions in Men and Women
- **Dirk Schultheiss**, Germany
- **Gorm Wagner**, Denmark
- **Sidney Glina**, Brazil

## 2. Definitions, Classification and Epidemiology of Sexual Dysfunction
- **Alessandra Rellini**, Italy
- **Dale Glasser**, USA
- **Edward Moreira**, Brazil
- **Giovanni Corona**, Italy
- **Kerstin Fugl Meyer**, Sweden
- **Taylor Segraves**, USA
- **William Fisher**, Canada

## 3. Psychological and Interpersonal Dimensions of Sexual Function and Dysfunction
- **Chiara Simonelli**, Italy
- **Kevan Wylie**, UK
- **Marie Chevret-Measson**, France
- **Marita McCabe**, Australia
- **Pierre Assalian**, Canada
- **Sandra Leiblum**, USA
- **Stanley Althof**, USA

## 4. Ethical, Socio-Cultural and Educational Aspects of Sexual Medicine
- **Eusebio Rubio-Aurioles**, Mexico
- **Fernando Velez y Roman**, Mexico
- **John Dean**, UK
- **Khaled Debes**, Egypt
- **Leonore Tief**, USA
- **Sharon Parish**, USA

## 5. Economic Aspects of Sexual Dysfunction
- **Carolyne Earle**, Australia
- **Geoff Hackett**, UK
- **Luis Otavio Torres**, Brazil
- **Nicola Ramchalan**, USA
- **Ridwan Shabsigh**, USA
- **Siegfried Meryn**, Austria
- **YasuSuke Kimoto**, Japan

## 6. Clinical Evaluation and Symptom Scales: Sexual Dysfunction Assessment
- **Dimitrios Hatzichristou**, Greece
- **Eric Meuleman**, USA
- **Leonard Derogatis**, USA
- **Marina Pfaus**, USA
- **Michael Rosen**, USA
- **Raymond Symonds**, Australia
- **Yoram Vardi**, Israel

## 7. Experimental Models for the Study of Female and Male Sexual Function
- **Balasubramanian Srilatha**, Singapore
- **François Giuliano**, France
- **Kim Wallen**, USA
- **Jim Marson**, Canada
- **Petter Hisaue**, Japan

## 8. Cardiovascular Aspects of Sexual Medicine
- **Ahmed El Sakka**, Saudi Arabia
- **Charalambos Vlachopoulos**, Greece
- **Edward Kim**, USA
- **Graham Jackson**, UK
- **Edward Montorsi**, Italy
- **Edward Anis**, Canada
- **Siegfried Meryn**, Austria
- **Shin-Ichi Hisaue**, Japan

## 9. Sexual Function in Chronic Illness and Cancer
- **Angel Luis Montejo**, Spain
- **Antonio Martin Morales**, Spain
- **Leslie Schover**, USA
- **Luca Incrocci**, Netherlands
- **Peter Rees**, Canada
- **Rosemary Basson**, Canada

## 10. Sexually Transmitted Diseases and Sexual Function
- **David Goldmeier**, UK
- **Hossein Sadeghi Nejad**, USA
- **Lucia O'Sullivan**, Canada
- **Marlene Weidner**, Germany
- **Zhangcheng Xin**, China

## 11. Future Treatment Targets for Sexual Dysfunctions
- **Antonio Argiolas**, Italy
- **Arthus Burnett**, USA
- **George Christ**, USA
- **Irwin Goldstein**, USA
- **Karl-Eric Andersson**, Sweden
- **Karel-Vardi**, Israel

## 12. Standards for Clinical Trials in Male Sexual Dysfunctions
- **Allen Seftel**, USA
- **Arnold Melman**, USA
- **Claudio Akkus**, Turkey
- **Emre Porst**, Germany
- **Hartmut Barada**, USA
- **Jamie Wyllie**, UK
- **Karolien Vandi**, Canada

## 13. Physiology and Pathophysiology of Men's Sexual Arousal and Penile Erection
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- **Eric Wespies**, Belgium
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INTRODUCTION

The International Consultation on Urological Diseases (ICUD) is a non-governmental organization registered with the World Health Organisation (WHO). In the last ten years Consultations have been organised on BPH, Prostate Cancer, Urinary Stone Disease, Nosocomial Infections, Erectile Dysfunction and Urinary Incontinence. These consultations have looked at published evidence and produced recommendations at four levels; highly recommended, recommended, optional and not recommended. This method has been useful but the ICUD believes that there should be more explicit statements of the levels of evidence that generate the subsequent grades of recommendations.

The Agency for Health Care Policy and Research (AHCPR) have used specified evidence levels to justify recommendations for the investigation and treatment of a variety of conditions. The Oxford Centre for Evidence Based Medicine have produced a widely accepted adaptation of the work of AHCPR. (June 5th 2001 http://minerva.minervation.com/cebm/docs/levels.html). The ICUD has examined the Oxford guidelines and discussed with the Oxford group their applicability to the Consultations organised by ICUD. It is highly desirable that the recommendations made by the Consultations follow an accepted grading system supported by explicit levels of evidence.

The ICUD proposes that future consultations should use a modified version of the Oxford system which can be directly ‘mapped’ onto the Oxford system.

1. 1st Step: Define the specific questions or statements that the recommendations are supposed to address.

2. 2nd Step: Analyse and rate (level of evidence) the relevant papers published in the literature.

   The analysis of the literature is an important step in preparing recommendations and their guarantee of quality.

2.1 What papers should be included in the analysis?

• Papers published, or accepted for publication in the peer reviewed issues of journals.

• The committee should do its best to search for papers accepted for publication by the peer reviewed journals in the relevant field but not yet published.

• Abstracts published in peer review journals should be identified. If of sufficient interest the author(s) should be asked for full details of methodology and results. The relevant committee members can then ‘peer review’ the data, and if the data confirms the details in the abstract, then that abstract may be included, with an explanatory footnote. This is a complex issue – it may actually increase publication bias as “uninteresting” abstracts commonly do not progress to full publication.

• Papers published in non peer reviewed supplements will not be included.

An exhaustive list should be obtained through:

I. the major databases covering the last ten years (e.g. Medline, Embase, Cochrane Library, Biosis, Science Citation Index)

II. the table of contents of the major journals of urology and other relevant journals, for the last three months, to take into account the possible delay in the indexation of the published papers in the databases.

It is expected that the highly experienced and expert committee members provide additional assurance that no important study would be missed using this review process.

2.2 How papers are analysed?

Papers published in peer reviewed journals have differing quality and level of evidence.

Each committee will rate the included papers according to levels of evidence (see below)

The level (strength) of evidence provided by an individual study depends on the ability of the study design to minimise the possibility of bias and to maximise attribution.

is influenced by:

• the type of study

The hierarchy of study types are:

- Systematic reviews and meta-analysis of randomised controlled trials
- Randomised controlled trials
- Non-randomised cohort studies
- Case control studies
- Case series
- Expert opinion

• how well the study was designed and carried out

Failure to give due attention to key aspects of study methodology increase the risk of bias or confounding factors, and thus reduces the study’s reliability.

The use of standard check lists is recommended to insure that all relevant aspects are considered and that a consistent approach is used in the methodological assessment of the evidence.

The objective of the check list is to give a quality rating for individual studies.

• how well the study was reported

The ICUD has adopted the CONSORT statement and its widely accepted check list. The CONSORT statement and the checklist are available at http://www.consort-statement.org

2.3 How papers are rated?

Papers are rated following a «Level of Evidence scale».

ICUD has modified the Oxford Center for Evidence-Based Medicine levels of evidence.

The levels of evidence scales vary between types of studies (e therapy, diagnosis, differential diagnosis/symptom prevalence study).

the Oxford Center for Evidence-Based Medicine Website: http://minerva.minervation.com/cebm/docs/levels.html

3. 3rd Step: Synthesis of the evidence

After the selection of the papers and the rating of the level of evidence of each study, the next step is to compile a summary of the individual studies and the overall direction of the evidence in an Evidence Table.

4. 4th Step: Considered judgment (integration of individual clinical expertise)

Having completed a rigorous and objective synthesis of the evidence base, the committee must then make a judgement as to the grade of the recommendation on the basis of this evidence. This requires the exercise of judgement based on clinical experience as well as knowledge of the evidence and the methods used to generate it. Evidence based medicine requires the integration
of individual clinical expertise with best available external clinical evidence from systematic research. Without the former, practice quickly becomes tyrannised by evidence, for even excellent external evidence may be inapplicable to, or inappropriate for, an individual patient: without current best evidence, practice quickly becomes out of date. Although it is not practical to lay our "rules" for exercising judgement, guideline development groups are asked to consider the evidence in terms of quantity, quality, and consistency; applicability; generalisability; and clinical impact.

5. 5th Step: Final Grading

The grading of the recommendation is intended to strike an appropriate balance between incorporating the complexity of type and quality of the evidence and maintaining clarity for guideline users.

The recommendations for grading follow the Oxford Centre for Evidence-Based Medicine.

The levels of evidence shown below have again been modified in the light of previous consultations. There are now 4 levels of evidence instead of 5.

The grades of recommendation have not been reduced and a "no recommendation possible" grade has been added.

6. Levels of Evidence and Grades of Recommendation

Therapeutic Interventions

All interventions should be judged by the body of evidence for their efficacy, tolerability, safety, clinical effectiveness and cost effectiveness. It is accepted that at present little data exists on cost effectiveness for most interventions.

6.1 Levels of Evidence

Firstly, it should be stated that any level of evidence may be positive (the therapy works) or negative (the therapy doesn't work). A level of evidence is given to each individual study.

• Level 1 evidence (incorporates Oxford 1a, 1b) usually involves meta-analysis of trials (RCTs) or a good quality randomised controlled trial, or 'all or none' studies in which no treatment is not an option, for example in vesicovaginal fistula.

• Level 2 evidence (incorporates Oxford 2a, 2b and 2c) includes "low" quality RCT (e.g. < 80% follow up) or meta-analysis (with homogeneity) of good quality prospective 'cohort studies'. These may include a single group when individuals who develop the condition are compared with others from within the original cohort group. There can be parallel cohorts, where those with the condition in the first group are compared with those in the second group.

• Level 3 evidence (incorporates Oxford 3a, 3b and 4) includes:
  - good quality retrospective 'case-control' studies where a group of patients who have a condition are matched appropriately (e.g. for age, sex etc) with control individuals who do not have the condition.
  - good quality 'case series' where a complete group of patients all, with the same condition/disease/therapeutic intervention, are described, without a comparison control group.

• Level 4 evidence (incorporates Oxford 4) includes expert opinion where the pinion is based not on evidence but on 'first principles' (e.g. physiological or anatomical) or bench research. The Delphi process can be used to give 'expert opinion' greater authority. In the Delphi process a series of questions are posed to a panel; the answers are collected into a series of 'options'; the options are serially ranked; if a 75% agreement is reached then a Delphi consensus statement can be made.

6.2 Grades of Recommendation

The ICUD will use the four grades from the Oxford system. As with levels of evidence the grades of evidence may apply either positively (do the procedure) or negatively (don't do the procedure). Where there is disparity of evidence, for example if there were three well conducted RCT's indicating that Drug A was superior to placebo, but one RCT whose results show no difference, then there has to be an individual judgement as to the grade of recommendation given and the rationale explained.

• Grade A recommendation usually depends on consistent level 1 evidence and often means that the recommendation is effectively mandatory and placed within a clinical care pathway. However, there will be occasions where excellent evidence (level 1) does not lead to a Grade A recommendation, for example, if the therapy is prohibitively expensive, dangerous or unethical. Grade A recommendation can follow from Level 2 evidence. However, a Grade A recommendation needs a greater body of evidence if based on anything except Level 1 evidence

• Grade B recommendation usually depends on consistent level 2 and or 3 studies, or 'majority evidence' from RCT's.

• Grade C recommendation usually depends on level 4 studies or 'majority evidence' from level 2/3 studies or Dephi processed expert opinion.

• Grade D "No recommendation possible" would be used where the evidence is inadequate or conflicting and when expert opinion is delivered without a formal analytical process, such as by Delphi.

7. Levels of Evidence and Grades of Recommendation for Methods of Assessment and Investigation

From initial discussions with the Oxford group it is clear that application of levels of evidence/grades of recommendation for diagnostic techniques is much more complex than for interventions.

The ICUD recommend, that, as a minimum, any test should be subjected to three questions:

1. does the test have good technical performance, for example, do three aliquots of the same urine sample give the same result when subjected to 'stix' testing?

2. Does the test have good diagnostic performance, ideally against a "gold standard" measure?

3. Does the test have good therapeutic performance, that is, does the use of the test alter clinical management, does the use of the test improve outcome?

For the third component (therapeutic performance) the same approach can be used as for section 6.

8. Levels of Evidence and Grades of Recommendation for Basic Science and Epidemiology Studies

The proposed ICUD system does not easily fit into these areas of science. Further research needs to be carried out, in order to develop explicit levels of evidence that can lead to recommendations as to the soundness of data in these important aspects of medicine.

CONCLUSION

The ICUD believes that its consultations should follow the ICUD system of levels of evidence and grades of recommendation, where possible. This system can be mapped to the Oxford system.

There are aspects to the ICUD system that require further research and development, particularly diagnostic performance and cost effectiveness, and also factors such as patient preference.

P. Abrams, S Khoury, A. Grant 19/1/04
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SEXUAL DYSFUNCTIONS
IN MEN AND WOMEN

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History of Sexual Medicine

DIRK SCHULTHEISS
SIDNEY GLINA
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Today we have a clear concept of sexual medicine and how to define this medical discipline. But historically the unification of sexuality and medicine was not a given condition. Medicine was mainly focused on human reproduction and how to prevent and treat sexually transmitted diseases (STD). Hardly any other aspect would have met the interest of medical doctors for centuries. Perhaps the first true medicalization of sexuality, i.e. the fusion of medicine and sexuality, was the dreadful anti-masturbation campaign led by doctors, beginning with Tissot, since the middle of the 18th century. Therefore, we have chosen this period as the starting point for this article and only included the respective development before that time in some aspects.

We would like to point out that this article can only highlight developments and milestones of sexual medicine and is not intended to be encyclopaedic. The historical primary literature has not been referenced extensively, but the reader is referred to selected secondary literature sources that will provide detailed information on each respective topic. Moreover, the focus is on the medical perspective rather than on the interdisciplinary aspect that defines the discipline of sexology.

II. TERMINOLOGY

Sexuality: Before the 18th century only the adjective sexual (Latin: sexualis) was used in the sense of “belonging to the sex or gender”. To our knowledge the noun sexuality appeared after 1800 in the field of botanics and was first adopted in the title of a German monography by August Henschel “Von der Sexualität der Pflanzen (On the sexuality of plants)” in 1820 [1]. After its transfer to human sexuality the term was primarily reserved for the aspect of reproduction and not for sexual desire and emotionality. Even Paolo Mantegazza was still talking of love (amore) when he was referring to the sexual relation of two individuals. He never used the terms sexual or sexuality. However this changed in the late 19th century and culminated in the 2nd half of the 20th century by even reducing the term to the abridged version sex.

Sexology (“Sexualwissenschaft”): According to Sigusch [1] the term sexology appeared first in a book entitled “Sexology as the philosophy of life: implying social organization and government” written by Elizabeth Osgood Goodrich Willard and published in Chicago, Illinois, in 1867. It is a parafeministic monography with religious fundamentalistic tendency reflecting the human female and male interaction. In a lecture on “The woman’s question” from 1885 and published in 1888 the English mathematician, statistician and eugenicist Karl Pearson asked for a “real science of sexology”.

In the German literature the equivalent term Sexualwissenschaft was popularized by the dermatologist Iwan Bloch from Berlin in his famous book “Das Sexualleben unserer Zeit (The sexual life in our time)” officially published in 1907, but actually already on the market in fall 1906 [2]. A clear definition of the interdisciplinary approach of sexology is stated in this work. However, Sigmund Freud had used the same term earlier in 1898 in an essay dealing with the importance of sexual events for the development of neurosis, but without earning the same or even any public recognition. So did the writer Karl Vanselow in 1904...
and the sexologist Magnus Hirschfeld in 1906 [1]. “Sexualwissenschaft” was initially translated literally as “Sexual Science” but was rapidly transformed more adequately in “Sexology”. The subsequent development of sexology after 1907 and reference of later authors to the text of Bloch underline the importance of his book. Another founding milestone not only in terms of terminology is the journal “Zeitschrift für Sexualwissenschaft (Journal for Sexual Science)” founded in January 1908. Neither the introducing article “Über Sexualwissenschaft (On Sexual Science)” written by the journal’s editor Magnus Hirschfeld [3], nor another contribution in the journal’s first issue “Bemerkungen zur Nomenklatur der Sexualwissenschaft (Remarks on the Nomenclature of Sexual Science)” mentioned the term sexual medicine [4].

Sexual Medicine: However, the above mentioned first issue of the journal “Zeitschrift für Sexualwissenschaft” does contain an article entitled “Forensische Sexualmedizin (Forensic Sexual Medicine)” written by the lawyer Joh. Werthauer from Berlin [5]. The article is only reviewing legal cases that include some kind of sexual act or misconduct. Therefore, the modern definition of sexual medicine is in no way indicated in this publication. Although aspects of sexuality in medicine were addressed by many physicians and sexologists in the following decades the term sexual medicine was not established before the 1970’s. It is quite difficult to identify the exact time or even person who deserves the credit for introducing the term in its modern definition. One interesting question in this context might be the shift from the understanding of “Clinical Sexology” towards “Sexual Medicine”. In 1972 Volkmar Sigusch from Germany published a book “Ergebnisse zur Sexualmedizin (Results for Sexual Medicine)” in which he defines this new academic speciality but also complains about the fact that medical faculties and the majority of the medical community are still unwilling to accept the developing discipline of sexual medicine [6]. Since April 1972 the German journal “Sexualmedizin” and one year later the “British Journal of Sexual Medicine” were the first periodicals literally dedicated to the new discipline and several monographies and textbooks including the term sexual medicine in their title were published in the 2nd half of the 1970’s [7].

III. “THE TREATMENT OF ONANISM” - THE FIRST SYSTEMATIC MEDICALIZATION OF SEXUALITY

Around 1712 an anonymous author, most likely the quack doctor and medical pornographer John Marten [8], published the pamphlet “Onania; or, the Heinous Sin of Self Pollution, and all its Frightful Consequences, in both SEXES Considered, with Spiritual and Physical Advice to those who have already injured themselves by this abominable practice.” that experienced several re-editions and translations and resulted in a first public awareness for a new medical entity, i.e. masturbation which also included involuntary seminal loss often referred to as spermatorrhoea. This publication was indeed the beginning of an anti-masturbation campaign that lasted until the mid-20th Century. It was not only a socio-cultural and religious issue but increasingly gained interest of medical doctors.

In 1758 the Swiss physician Simon Auguste David Tissot (1728-1797) published a book entitled “L’Onanisme, Dissertation sur les Maladies produites par la Masturbation” (“Onanism, Treatise on the Diseases produced by Masturbation”) (Fig. 1).

(Fig.1) Simon Auguste David Tissot (portrait and frontispiece of his publication from 1758.

With this writing the young medical doctor from Lausanne became the most influential medical propagandist of the alleged dangers of masturbation. For more than 150 years, the fear of «masturbatory insanity» remained a dominant theme of disease prevention and adolescent sexual education. As outlined above Tissot was not the first to imagine that nocturnal emissions and masturbation were a medical problem, but he definitely anthropologized and summarized earlier thoughts on this subject. Tissot’s work helped reshape medicine’s attitude towards sexuality and provided an additional scientific basis upon which the process of pathologization of sexual anatomy and sexual functions could proceed. Tissot’s primary contribution was not as an innovator but as a skilful collator and editor of independently expressed, roughly contemporary medical views on masturbation. His highly original argument was carefully constructed and supported by references to earlier authorities, such as Galen, Aretaeus, Celsus, Boerhaave, Gaubius, Koempf, Sennert, Regis, Craanem, Zimmermann, G.M. Wepfer, and Veslin. Going through many editions, each of which
allowed Tissot to make additions, emendations, and annotations, his erudite book created the partly inaccurate impression that there existed a powerful consensus among the respectable and leading European doctors, in harmony with the views of classical authors, that masturbation was a dangerous disease and gathering threat to human welfare.

Tissot had a major impact on the development of the professional anti-masturbation movement from the second half of the eighteenth century onwards. Physicians adopted his theories and invented a wide array of severe surgical, medical, dietary, and behavioral therapies for the prevention of masturbation over the next 150 years.

Especially in the United States, where an unregulated organization of the medical profession pushed doctors towards radicalism and extremism in theory and practice, circumcision — in some cases executed without anaesthesia in order to combine “treatment” with punishment — became the most common surgical intervention against masturbation in boys during the 19th and 20th centuries. Some authors conclude that “extremist religion, and extreme anti-sexualism and anti-phallicism provided a fertile ground for the acceptance of an obviously anti-phallic, intentionally destructive surgery” [9].

Preputial infibulation, i.e. avoiding retraction of the foreskin by generally piercing the distal part with a metal clasp or ring, was also employed as a means of controlling male sexuality since antiquity. It experienced a revival during the Victorian Era as another clinical weapon in the medical war on masturbation. Although circumcision was the most commonly employed means of preventing masturbation in the United States and Britain, infibulation was frequently employed as an alternative procedure, being used in mental institutions and orphan asylums and receiving endorsement from leading medical authorities [10].

Even vasectomy was used to treat excessive masturbation. The first use of vasectomy by the physician Harry Sharp, later a well-known protagonist of eugenic sterilization in the US, in 1899 was on a 19 year male who had complained of excessive masturbation. Following the surgery, the patient is reported to have acquired a higher intellectual level in addition to reduced masturbation [11].

All these medical theories and resulting treatments were not only focused on male children, adolescents and adults but were also adapted to female sexuality, especially masturbation and nymphomania. The most extreme example probably occurred in Victorian England when the renowned gynaecological surgeon Isaac Baker Brown (1811-1873) suggested and performed clitoridectomy for the treatment of various nervous disorders. The public dispute on his respective book “On the curability of certain forms of insanity, epilepsy, catalepsy, and hysteria in females” from 1866 finally resulted in the downfall of Baker Brown [12] (Fig. 2).

Closure of the introitus vaginae as part of “female circumcision” procedures is also called infibulation and done with the intention to alter women’s sexual activity. This procedure is still practiced in some African and Muslim cultures today.

In conclusion the widespread medicalization and pathologization of masturbation following Tissot’s publication “l’Onanisme, Dissertation sur les Maladies Produites par la Masturbation” resulted in the fact that medical doctors for the first time became increasingly engaged in issues of human sexuality. Although inglorious in many aspects this part of history must be considered as one origin of sexual medicine.

IV. SELECTED EARLY PIONEERS OF SEXOLOGY

In Europe of 19th century sexual subjects were considered taboo and repression was the main position towards them. However many scientists and thinkers brought up new ideas about sexuality during this period and in the first part of 20th century.

It is generally assumed that modern sexual medicine was founded by German psychiatrists and dermatologists. However Paolo Mantegazza (1831-1910) (Fig. 3), an Italian professor of pathology and anthropology, was probably the founder of the modern sexual medicine. Decades before the studies of e.g. Albert Moll and Havelock Ellis, he had developed experimental work and had formulated new sexual theories, founding a new science, which Mantegazza called “science of embrace”; curiously he referred to love (amore) when he was talking of sexual relation. He never used the term sexual. Besides his interest
on physiology of «nervous» states (the beginning of neurophysiology) and the action of drugs (e.g. cocaine), Mantegazza wrote about female sexuality, sexuality in children, masturbation, erectile dysfunction, vaginism, and male and female infertility. He had tried gonad transplantations in frogs and he had measured the blood flow and temperature increase during penile erection [13].

Even before Mantegazza, scientists in Europe studied sexual function without considering this as a new field of its own in science or medicine. One outstanding representative is Conrad Eckhard (1822-1905), a German physiologist from Giessen, who followed the transformation that scientific medicine underwent in the 19th century. He conducted basic anatomical and physiological research on the erection process in animals and showed that it was possible to produce an erection through electrical stimulation of the nervous structures of the brain and spinal cord. He described the “nervi erigentes” and claimed that erection did not depend only on venous congestion, the general belief at his time [14] (Fig.4).

Richard Freiherr von Krafft-Ebing (1840-1902) (Fig.5) was an Austrian-German psychiatrist. His main work was “Psychopathia Sexualis” (1886), one of the first monographies to study sexual topics as clitoral orgasm and female sexual pleasure, consideration of the mental states of sexual offenders, and homosexuality. In contrast to the popular and scientific belief at that time, Krafft-Ebing was one of the first authors to point out that homosexuals did not suffer from mental illness or perversion [15].

Through the discovery and development of psychoanalysis as an important psychotherapeutic school Sigmund Freud (1856-1939) (Fig.6) from Vienna had also great influence on sexology, and his famous “Three Essays on the Theory of Sexuality” from 1905 is considered as his boldest and most impressing contribution. According to Hartmann: “It was Freud’s intention to establish psychoanalysis not only as a part of the medical science but as a comprehensive heuristic method that should make a new and unique contribution to the understanding of the conditio humana. By its transversal approach the psychoanalysis could contribute new concepts to many fields of knowledge and performed a profound influence on literature, philosophy and forming art” [16].

The most eminent person of a group of sexologists working in Berlin before 1933 was Magnus Hirschfeld (1868-1935) (Fig.7). He founded the the
first "gay rights organization" "Wissenschaftlich-humanitäre Komitee" (Scientific Humanitarian Committee) in 1897 dedicated to the scientific study of homosexuality. In 1908 he edited the first journal for sexology "Zeitschrift für Sexualwissenschaft" in Berlin. Although this monthly journal was only published for one year, sexology was formally launched and quickly developed into an academic specialty. In 1914 Iwan Bloch and Albert Eulenburg re-started the "Zeitschrift für Sexualwissenschaft" as the official organ of the newly founded «Ärztliche Gesellschaft für Sexualwissenschaft und Eugenik" (Medical Society for Sexology and Eugenics). As they state in their preface to the journal, it intended to serve «the study of medical, natural, and cultural problems of sexology». By organizing the first "International Congress of Sexology" in Berlin in 1921, Magnus Hirschfeld initiated an international cooperation of sexologists. In 1928, he co-founded the "World League for Sexual Reform" together with Havelock Ellis and Auguste Forel. Among his many publications was one of the first comprehensive textbooks of sexology entitled «Geschlechtskunde» (Sexual Knowledge) in 5 volumes published between 1926 and 1930. Hirschfeld was also the pioneer of educational sexual movies. His most important project was the establishment of the "Institut für Sexualwissenschaften" (Institute of Sexology) in 1919. It was a place for public information and education, treatment of patients and scientific research located in the centre of Berlin. Many scientist worked at the institute, most of them like Hirschfeld himself were Jewish, e.g. Felix Abraham and Ludwig Levy-Lenz (transsexual surgery), Arthur Kronfeld (psychiatrist), and Bernhard Schapiro (first hormonal treatment of cryptorchidism). Due to the political circumstances in Germany the institute and its co-workers increasingly came under pressure. Hirschfeld left Germany in 1930 for a world tour giving lectures and studying sexology in foreign countries. He never returned to his home country. In 1933 the institute in Berlin was plundered and its library destroyed by the national socialists. Hirschfeld, according to an American newspaper "The Einstein of Sex", died in 1935 in Nice, France [http://www2.hu-berlin.de/sexology/Entrance_Page/History_of_Sexology/history_of_sexology.html][14].

Henry Havelock Ellis (1859-1939) (Fig.8), an English physician who had never practiced medicine, devoted his life to scientific studies of sexual subjects. He was a supporter of sexual liberation and was one of the first modern thinkers to challenge Victorian taboos against the open and objective discussion of sex. His interest in human biology ended on the six volume "Studies in the Psychology of Sex", published between 1897 and 1910. Those books caused a huge controversy and were banned for many years. However, it is considered a comprehensive masterpiece of human sexual biology, behaviour, and attitudes. Ellis viewed sexual activity as the healthy and natural expression of love, and he became known as a champion of women’s rights and of sex education [http://adbonline.anu.edu.au/biogs/A040139b.htm][17].

Harry Benjamin (1885-1986) (Fig.9) was born in Berlin but developed his clinical and scientific research in the USA where he moved to in 1914. His special interest was hormonal research but his main work was devoted to what he himself later described as «transsexualism». He was a pioneer in the research and in the understanding of the transsexual phenomena, treated many patients, and opened a new area of research, at a time when even wearing clothes associated with the opposite sex in public was often illegal [1].
Ernst Gräfenberg (1881–1957) (Fig. 10) was another German-born physician who emigrated to the USA during World War II. He is known for developing the intrauterine device (IUD), and for his studies on the role of the woman’s urethra in orgasm, describing the controversial female ejaculation and an erogenous zone where the urethra is nearest to the vaginal wall, which was later named the Grafenberg spot or G-spot by John D. Perry and Beverly Whipple in his honour [18].

Benjamin and Gräfenberg are prominent representatives of what could be called the American link to Europe. Having left Germany at different times and for different reasons, they both built up a career in the U.S. and were part of the medical community restarting the discipline of sexology after it’s complete destruction in Europe between 1933 and 1945.

Historically, sexually transmitted diseases (STD) are the major link between sexuality and the medical profession since antiquity and until the 20th century and were commonly addressed as venereal diseases until the 1990s. Veneris is the Latin genitive form of the name Venus, the Roman goddess of love. Social disease was another euphemism [19]. Gonorrhoea was described by the ancient Egyptians, and was recognized by Greek and Roman medical writers [19]. Syphilis was apparently brought to Europe by Christopher Columbus’ sailors on their return from America; others argue that it originated in the Old World. An archeological find of the bones of an Essex woman suggested that she had advanced syphilis, between 1300 and 1450. This would predate Columbus’ voyage of 1492 [20, 21].

In October 1495 French soldiers of King Charles VIII coming back from Naples arrived in Lyons and the soldiers suffering from syphilis were treated in the Hospitalhôtel-Dieu, which became the first French Hospital to treat syphilitic patients. This hospital had been founded in 542 and at the beginning it was a place to receive and assist the poor and pilgrims and in the middle of the 15th century it received infectious patients during some epidemic periods. For three centuries the Hospitalhôtel-Dieu tried to move away syphilitic patients and it succeeded in 1802 as the Hospital L’Antiquaille was built [22].

The prevalence and spread of these diseases was exacerbated by war and growing of the cities. By the Middle Ages both gonorrhoea and syphilis were widespread. The term syphilis was not part of the English language until 1717, following the translation of an Italian work, it was called the pox. The clap referred to gonorrhoea, from the old French word clapier, meaning a brothel. The etymology of gonorrhoea is probably from the Greek for seed low that it was assumed that the urethral discharge was semen [21].

During years both diseases were considered just one, many authors believed that the symptoms of gonorrhoea were the early stages of syphilis. This view was substantiated by the British surgeon John Hunter, who self-injected his own penis with material taken from a patient with gonorrhoea in 1767. On developing the signs of syphilis he concluded the two infections were the same, although he did not realize that the patient actually suffered from both infections at the same time [19, 21].

In 1793, Benjamin Bell, an Edinburgh surgeon confirmed that the diseases were distinct as a result of experimentation on medical students. The eminent Guy’s surgeon Sir Astley Cooper recognized
the two diseases as distinct and in 1824 he wrote in The Lancet «a man who gives mercury (a drug used to treat syphilis) in gonorrhoea deserves to be flogged out of the profession because he must be quite ignorant of the principle in which the disease is cured» [21].

In the middle of the 19th century a French physician, Philippe Ricord determined the three stages — primary, secondary, and tertiary — of syphilis. Shortly afterwards Rudolph Virchow established that syphilis was spread through the body by the blood, explaining the known cardiovascular, muscular, and psychiatric complications. At the turn of the 20th century up to a third of inmates in mental asylums were reckoned to be suffering from tertiary syphilis [19].

The main orthodox treatment for syphilis from the Middle Ages until the early years of the 20th century consisted of the application of a mercury ointment. However, during the 17th through to the 20th centuries many useless "miraculous" treatments to cure the disease had appeared to exploit the sufferers [19].

Curiously, the legendary Giacomo Casanova was said to have invented the condom, fashioned from a sheep's intestine, not as a contraceptive but as protection against syphilis. However he might have used it with this intention but condoms appear in some of the pictures of "A Harlot's Progress" by William Hogarth (1697-1764). This series of paintings was completed in 1731, when Casanova would have been 6 years old [21].

During the nineteenth century an increasing number of public health measures, usually aimed at prostitutes, were taken to prevent or control the spread of STDs. The publication in 1847 of Regulations for the repression of the excesses of prostitution in Madrid inaugurated an era of regulated prostitution in Spain. In view of the spread of prostitution and venereal diseases, police measures, and especially medical measures were both considered in the development of these regulations, which had first been proposed by the Count of Cabarrús in 1792. Although completely confidential, the new system of regulations, drawn up in 1847, set the stage for the wide-reaching regulation of prostitution that came into effect in several cities in Spain during and after the mid-19th century, and which included city residence and periodic health surveillance for prostitutes [23].

In 1861 in Italy a repressive law was passed against prostitution to reduce syphilis transmission. After the constitution of the Kingdom of Italy there began a debate on this law which was harsh on prostitutes and failed to resolve the health problem in question. In 1880, in Italy, studies were promoted under the aegis of a royal commission to understand the social situation of prostitution and the epidemic spread of syphilis. In 1888 Crispi issued new regulations concerning prostitution, prevention and therapy of infectious diseases: three years later a new regulation was established which partly restored the 1861 law [24].

In 1864 the English Parliament passed the "Contagious Diseases Act". This legislation allowed policeman to arrest prostitutes in ports and army towns and bring them in to have compulsory checks for venereal disease. If the women were suffering from sexually transmitted diseases they were placed in a locked hospital until cured. It was claimed that this was the best way to protect men from infected women. Many of the women arrested were not prostitutes but they still were forced to go to the police station to undergo a humiliating medical examination. A vociferous campaign was mounted by women's groups, civil rights activists, and members of the medical profession, and the Acts were repealed in 1886 [19, 21].

During the First World War, with a great movement of the troops, STDs became very common. USA Army lost nearly 7 million person-days and discharged more than 10,000 men because of STDs. Only the great influenza pandemic of 1918–1919 accounted for more loss of duty during that war. The STDs remained a significant threat in the early years of World War II, prompting the American War Department to embark on a massive educational and prophylactic campaign. Numerous posters were produced, warning soldiers and sailors of the dangers of excessively sexual behavior [25].

Advances against the diseases were notably improved by the discovery of their causative microorganisms. That of gonorrhoea was found in 1879 and that of syphilis in 1905. Shortly after this the German bacteriologist Paul Ehrlich announced the efficacy of Salvarsan, an arsenic-based treatment for syphilis. The development of the sulpha drugs and more potent antibiotics provided a wider range of effective drugs against these diseases [19]. The discovery that penicillin can treat syphilis has revolutionized its management [21]. With the discovery of antibiotics, a large number of sexually transmitted diseases became easily curable, and this, combined with effective public health campaigns against STDs, and the recognition of the importance of contact tracing in treating STDs a great advance was made in the control of those diseases. By tracing the sexual partners of infected individuals, testing them for infection, treating the infected and tracing their contacts in turn, STD clinics could be very effective at supressing infections in the general population [http://family.jrank].

Herpes (from the Greek, to creep) is another STD with a long history. Herodotus, a Roman physician, described cold sores in the second century, and genital herpes was first described by John Astruc, a French physician in the 18th century, Shortly
thereafter, other physicians noted that genital herpes often afflicted a patient shortly after the onset of syphilis or gonorrhea [http://family.jrank].

In the 1980s, AIDS (Acquired Immunodeficiency Syndrome) emerged into the public consciousness showing that the battle against STDs were not completely won. AIDS was first reported June 5, 1981, when the U.S. Centers for Disease Control (CDC) recorded a cluster of *Pneumocystis carinii* pneumonia in five homosexual men in Los Angeles [26]. In the beginning, the disease was called GRID Gay-related immune deficiency by the public. The CDC called it the “the 4H disease,” because the disease was prevalent in four communities Haitians, homosexuals, hemophiliacs, and heroin users. In 1982 AIDS was introduced for the first time. In this year epidemiologic data defined that contamination occurred by sexual, blood and mother-to-child transmission. In 1983 Human Immunodeficiency Virus, HIV, was aisled in Pasteur Institute in Paris [27].

**VI. ENDOCRINOLOGY: THE ROLE OF THE TESTICLES AND THE DISCOVERY OF ANDROGENS**

Ancient knowledges on testicle function: Tales and myths about aphrodisiacs and especially extracts from testicular tissue or blood were reported from ancient times up to the present. As early as 140 BC Sushruta of India advocated the ingestion of testis tissue for the cure of impotence. A vague foreshadow of the endocrine function of the testis was speculated by Aretaeus of Cappadocia (2nd till 3rd century A.D.) and more vigorously in 1775 by de Bordeu. They proposed that each organ of the body produced a substance, which was secreted into the blood to regulate bodily function [28]. On the other hand the appearance of castrates with their typical body composition and characteristics can be looked at as an interesting in vivo model of androgen depletion at all periods of history. Some of them, especially some castrati singers of the baroque period, are reported of having been actively involved in love affairs and sexual activities.

Study of sexual differentiation: It was not until the 1930s, however, that testosterone, the primary androgen responsible for male physiology and behaviour, was biochemically identified. Prior to that, many attempts were made to study the sexual differentiation of male and female individuals and to slow or reverse the effects of aging in men and to rejuvenate them. As early as 1767, John Hunter (1728-1793) (Fig.11) performed first documented testicular transplantation experiments in animals and hereby opened the door to transplantation of far more interested in the technique of grafting and tissue acceptance than the secondary effects on sex characteristics. In 1849, Arnold Berthold (1801–1863) again made the connection between male sexual and behavioural characteristics and a substance secreted by the testes and concluded that transplanted testes affect behavioural and sexual characteristics by secreting a substance into the blood stream (Fig 12). In Vienna the physiologist Eugen Steinach (1861-1944) started experiments with testicular transplantation in animals at the turn of the century in order to study the sexual differentiation and the hormonal function of the gonads [28, 29].

Rejuvenation and early “modern” organotherapy: In 1889 Charles Edouard Brown-Séquard (1817-1894) reported the rejuvenating effects of self-administered subcutaneous injections of a mixture of extracts from sperm, testicular tissue and venous blood of young and vigorous dogs and guinea pigs (Fig.13). Although based on a placebo effect, this can be considered the birth of modern clinical androgen therapy. In his theory of «autoplastic» treatment of aging Eugen Steinach (Fig.14) postulated an increased incretory hormonal production following the cessation of the secretory output of the gonads after surgical ligation of the seminal ducts. With help from the urologist Robert Lichtenstern he successfully performed this surgical procedure in a human patient for the first time in 1918, resulting in a vasectomy boom over the next two decades.
especially to counter the effects of aging in «middle-aged, listless individuals». Steinach nicely summarized the results of his scientific life in his late biography: “It has frequently been said that a man is as old as his blood vessels. One may have greater justification for saying that a man is as old as his endocrine glands.”

In the 1920’s one of the main protagonists of testicular transplantation in Europe was Serge Voronoff (1866-1951) who grafted slices of primate testis to the capsule of human recipient’s testes. He claimed to have treated 300 patients and that hormonal secretion lasted for about 1-2 years, then decreased due to fibrosis of the graft. Testicular homotransplantation had been reported earlier in very few hypogonadal patients in America by Frank Lydston in 1914 and V. D. Lespinasse in 1915. None of these was performed with vascular anastomoses.

The methods proposed by Brown-Séquard, Steinach, and Voronoff were widely popular in their time throughout Europe and North America, despite never undergoing rigorous validation. Voronoff’s grafting technique, which was enthusiastically adopted in many countries for agricultural and medical purposes, was later proved to be scientifically unfounded. Steinach’s theories were also widely popular in their time and scores of men underwent Steinach operations, including Sigmund Freud and the Irish poet William Butler Yeats. Brown-Séquard’s miraculous results were not reproducible and most likely the result of a placebo effect. Nevertheless, his report gave rise to the lucrative industry known as «organotherapy», in which extracts from a variety of animal tissues were used to treat diseases and counter the effects of aging. Organotherapy remained popular until the early 20th century, when modern endocrinology emerged as a scientific discipline [30].

**Discovery of androgens in the 1930’s:** Ernest Starling and William Hardy first coined the term «hormone» in 1905. Pezard in 1912 reported that aqueous extract of pig testes maintained the comb and wattles of the capon. 18 years later, Gallagher and Koch developed the response in the capon into a quantitative assay procedure, which was adopted with minor modifications by most laboratories as the standard assay procedure for male hormone activity. As early as 1927, Lemuel Clyde McGee demonstrated the isolation of a biologically active extract of the lipid fraction of bull testicles. In 1933 McCullagh and co-workers reported in a very elegant paper that extracts from blood, urine or spinal fluid of men by using the chick comb assay for measuring androgenic activities are useful for treatment of the male hypogonadism. The authors called the substance which is produced in the testes “Androtiln”. The magnitude of the problem faced by steroid chemists has been illustrated by the fact that labor-intensive extracts from up to 100g of testes were required for a positive result in the so-called chick comb bioassay. It is not surprising, therefore, that 15 mg of the first known androgen – androsterone – was isolated under the leadership of Adolf Butenandt (Fig.15) in his age of 28 years - from 15000-25000 liters of policemen’s urine in 1931. The name of this relatively weak urinary 5α-reduced androgen comes from “andro” = male, “ster” = sterol, and “one” = ketone. The chemical synthesis of androsterone was performed by Leopold Ruzicka (Fig.16) and coworkers 3 years later. The Japanese Ogata and Hirano – not enough acknowledged by the Europeans and Americans – found in 1934 that the androgen from the urine (Butenandt’s androsterone) is not identical with the androgen extracted from boar testes. The androgenic properties of this crystal hormone were more active than any of the testicular preparations that have been reported heretofore.
One year later, Karoly David, Elizabeth Dingemanse, Janos Freud, and Ernst Laqueur reported the isolation of the main secretion product from the testes and the main androgen in the blood, testosterone, from several tons of bull testes. The term “testosterone”, coined by this Dutch group, combines “testo” = testes, “ster” = sterol, and “one” = ketone. In the same year, the chemical synthesis of testosterone was published by altogether three groups from Germany, Netherland, and Switzerland led by Adolf Butenandt, Ernst Laqueur, and Leopold Ruzicka. Ruzicka and Butenandt were offered the 1939 Nobel Prize for chemistry for their work, but Butenandt was forced by the Nazi government to decline the honour [28, 31, 32].

Substitution therapy with testosterone:
The biochemical identification and synthesis of testosterone and other steroid hormones was a “conditio sine qua non” for the further development of modern endocrinology and the basis for a rational therapy with sexual hormones. The first years obviously implied a too generous application of this new therapeutic option especially in regard to the problem of the “Climacteric in aging male” as was hinted at by an editorial in the “Journal of the American Medical Association (JAMA)” in 1942 [33]: “Recently many reports have appeared in medical journals claiming that a climacteric occurs in middle aged men. Brochures circulated by pharmaceutical manufacturers depict the woeful course of aging man. None too subtly these brochures recommend that male hormonal substance, like a veritable elixir of youth, may prevent or compensate for the otherwise inevitable decline. What of the postulated occurrence of a climacteric in men?” In the following years systematic studies like “The male climacteric, its symptomatology, diagnosis and treatment: use of urinary gonadotropins, therapeutic test with testosterone propionate and testicular biopsies in delineating the male climacteric from psychoneurosis and psychogenic impotence” from 1944 (Fig.17) finally opened the door for modern research projects in the field of “androgen deficiency in the aging male” [34].

Societal attitudes towards same-sex relationships have varied over time and place, from strong repression until acceptance. Many times the fight for liberation of homosexuality crossed with research and studies on sexual function. The increasing scientific interest in homosexuality in the 19th century can be interpreted as one promoter for scientists, including medical doctors, to investigate medical issues and questions related to sexuality in general and by doing so creating the new field of sexology and later sexual medicine.

In many cultures sodomy has been considered as a transgression against divine law or a crime against nature. However sexual relationships among same sex have been known for thousands of years and in every continent. It was an accepted practice in Africa and Americas before the European conquerors arrived and repressed those activities. Homosexuality in China, has been recorded since approximately 600 BC. In Japan it has been documented for over one thousand years and was an integral part of Buddhist monastic life and the samurai tradition. Similarly, in Thailand, has been a feature of Thai society for many centuries, and Thai kings had male as well as female lovers.

Throughout most of the history of ancient Israel, intercourse between males was condemned outright as an «abomination» and Mosaic Law demanded the death penalty for those men who «lie with a man as with a woman». In Greece male homosexuality was part of a normal man’s love life, besides the heterosexual relationships. Plato praised its benefits in his early writings but in his late works proposed its prohibition [35]. In Crete homosexuality was, according to Aristotle, officially supported as a “population control tactic” [36].

(Fig.17) Elevated gonadotropins in “Male Climacteric” reported in JAMA 1944.
In Ancient Rome there were common relationships between older free men and slaves or freed youths. Many Roman emperors had male lovers. Christianity followed the Hebrew tradition of condemnation of male sexual intercourse and certain forms of sexual relations between men and women, labeling both as sodomy [37]. In the year 528, the emperor Justinian I, responding to an outbreak of pederasty among the Christian clergy, issued a law which made castration the punishment for sodomy.

During the Renaissance, Florence and Venice were famous for their widespread practice of homosexual love. However, at that time, the authorities, under the aegis of the Officers of the Night court, were prosecuting, fining, and imprisoning a good portion of the homosexual practitioners. In the Europe of the 17th and 18th century repression had gained strength and executions for sodomy continued in the Netherlands until 1803, and in England until 1835.

Between 1864 and 1880 Karl Heinrich Ulrichs published a series of twelve books, entitled “Research on the Riddle of Man-Manly Love”. In 1867 he became the first self-proclaimed homosexual person to speak out publicly in defense of homosexuality when he pleaded at the Congress of German Jurists in Munich for a resolution urging the repeal of anti-homosexual laws. “Sexual Inversion” by Havelock Ellis, published in 1896, challenged theories that homosexuality was abnormal, as well as stereotypes, and insisted on the ubiquity of homosexuality and its association with intellectual and artistic achievement [38]. Magnus Hirschfeld created the Scientific Humanitarian Committee, which campaigned from 1897 to 1933 against anti-sodomy laws in Germany. Richard Freiherr von Krafft-Ebing probably was one of the first heterosexual professionals to see homosexuals as normal people with a different sexuality [39].

In the 1950s in the United States, homosexuality was taboo and many politicians treated the homosexual as a symbol of antinationalism. Senator Joseph McCarthy used accusations of homosexuality to stigmatize his opponents. Although there is societal tolerance to homosexuality, in 2001, 51% of the general public declared that «homosexual behavior» was morally wrong.

Homosexual relationships were decriminalized in many European countries such as Poland in 1932, Denmark in 1933, Sweden in 1944, and the United Kingdom in 1967, but a turning point was reached in 1973 when the American Psychiatric Association removed homosexuality from the Diagnostic and Statistical Manual of Mental Disorders, thus negating its previous definition of homosexuality as a clinical mental disorder [40]. In 1977, discrimination based on sexual orientation was prohibited for the first time in Canada, extended to many other countries during the 1980s. However, many countries today in the Middle East, Africa, Asia, the Caribbean and the South Pacific, outlaw homosexuality. In six countries, homosexual behavior is still punishable with life imprisonment and in ten with death penalty [http://www.ilga.org/statehomophobia/World_legal_wrap_up_survey_November2006].

VIII. CONTRACEPTION

Contraceptive methods have a long history and different levels of societal acceptance, depending upon cultural, religious, and political background.

Prehistoric societies had a slow population growing although they had total fertility rates of 4 to 6 [41]. Approximately half the children who were born died before they could reproduce. Furthermore puberty was in the upper teens, babies were breastfed for 3–4 years, which spaced pregnancies. With the first urban civilizations and settled agriculture, puberty began at an earlier age and breastfeeding was often shortened or supplementary food introduced earlier than in primitive societies. This increased the rate of fertility. Nowadays if a couple initiates sexual intercourse when the woman is 20 years old or younger and continues at least until her menopause, without artificially limiting fertility, she can expect to conceive and carry to term an average of 10 live-born children [42, 43]. Sooner or later, all human societies have to adopt restraints on family size [43].

There are references of contraceptive methods in many historical records [43]. Written records survive from the Egyptian Ebers Papyrus (1550 BC), the Latin works of Pliny the Elder (23–79 AD) and Dioscorides (De materia medica, c. 58–64 AD), and the Greek writings of Soranus (Gynecology, c. 100 AD). During the flowering of Arabic medicine in the 10th century, a variety of contraceptive recommendations were detailed, particularly in the works of Al-Razi (Razes, d. 923 or 924 AD, Quintessence of Experience), All ibn Abbas (d. 994 AD, The Royal Book), and Avicenna (Ibn Sina, d. 1037 AD) [43].

The evidence of ancient contraceptive knowledge, methods of birth control which are used before conception, is very large. A list of contraceptive methods include: withdrawal by the male (coitus interruptus); melting suppositories designed to form a barrier over the cervix; diaphragms, caps, or other devices which are inserted into the vagina over the cervix and withdrawn after intercourse; intrauterine devices; douching after intercourse designed to kill or drive out the sperm; condoms; and varieties of the rhythm methods. The main new acquisition was the birth control pill introduced in 1960 [43].

It were the ancient Greeks who first realized that male and female union caused pregnancy and since then many contraceptive methods have been used
with varying degrees of success. Probably the oldest methods of contraception (aside from abstinence of vaginal intercourse) are coitus interruptus, lactational, certain barrier methods, and herbal remedies [44].

There are historic records of Egyptian women using a pessary (a vaginal suppository) made of various acidic substances and lubricated with honey, oil or beeswax, which may have been somewhat effective at killing sperm or blocking its passage through the female genital tract [http://www.mnsu.edu/emuseum/prehistory/egypt/dailylife/midwifery.htm]. However, it is important to note that the sperm cell was not discovered until the late 17th century, so those methods were completely empiric at that time.

Another kind of pessary was a solid object to block the cervix. This method was popular in pre-industrial societies, especially Africa; here women used plugs of chopped grass or cloth. Balls of bamboo tissue paper were used by Japanese prostitutes, wool by Islamic and Greek women, linen rags by Slavic women. The sponge used by Ancient Jews was considered the most effective contraceptive in use until the development of the diaphragm. The sea sponge was wrapped in silk with a string attached [45].

During the 2nd century A.D., Greek gynecologists advised women to spread substances such as ginger or olive oil around the vagina to prevent pregnancy [45].

Coitus interruptus, where man withdraws his penis before the ejaculation, was practiced in Africa, Australasia, the Middle East, and in Europe. Though condemned by Judaism and Roman Catholicism, its practice was common enough in Medieval Europe and later [42].

Coitus obstructus was a method recommended in several Sanskrit texts which required pressing on the urethra on its scrotal part; the pressure could prevent semen flow through the urethra forcing it into the bladder. Coitus reservatus is a method whereby the male avoids ejaculation entirely. This method was used by the Hindus [43].

The rhythm methods (based on calculating the woman’s fertile period and abstaining from intercourse during it) have been used since the 19th century. However the female fertility cycle was completely understood in 1920. Before that time it was common believe that ovulation occurred either during menstruation or just before it, which made this a very ineffective contraceptive method earlier on [43].

Condoms had been known since the 17th century and were made from animal intestines. Initially it was fully advocated in campaigns against sexual transmitted diseases, but in the 1920’s and 1930’s it was the second contraceptive method used in USA, after coitus interruptus [43]. Leather and linen versions were used early on. By the start of the 19th century, condoms were openly sold in drugstores, pubs and other businesses throughout the world. In 1844, rubber was invented, and condoms were able to be mass-produced for the first time, making them accessible to a wider population [43].

At the beginning of 19th century female barrier methods were well established. In 1838, in Europe, Wilde proposed the cervical cap and later Mensinger advised a diaphragm without spermicide. By 1915, Rutgers proposed the use of diaphragms with spermicides and individual fitting by a physician [43].

At that time, attempts were made to block the cervix with metal pessaries. The devices required an intra-uterine portion to hold them in place, and sometimes they broke, when it was noted that they still acted as successful contraceptives. In 1909, Richter, in a German medical journal, described a flexible ring made of silk that he placed in the uterus of women seeking contraceptive help. By 1923, Proust claimed to have distributed 23,000 intrauterine devices (IUDs). At about the same time, Grafenberg presented IUDs of silk and later of silver wire [46].

The biologic possibility of imitating early pregnancy to inhibit ovulation was well understood by the Austrian physiologist Haberlandt when he published a series of papers, beginning in 1921, on what he called “hormonal sterilization.” Ovaries from pregnant does were transplanted into nonpregnant rabbits, rendering them infertile for several months. By 1927, Haberlandt was exploring the possibility of oral contraception, and he collaborated with a pharmaceutical firm in Budapest to produce a preparation called “Infecundin” [43].

In 1959, the first hormonal birth control pill, “Enviod”, was approved by the FDA for contraception. Though very effective, this early birth control pill produced major side effects, such as blood clots and high blood pressure. By the 1980s, low dose pills were widely available with fewer side effects and high efficacy. In the 1990s, the “Depo-Provera” hormone injection was created, and was able to prevent pregnancy for several months at a time. In 1999, the FDA approved “Plan B” (the morning after pill) for sale by prescription only. This emergency contraceptive gives women the chance to prevent pregnancy after having unprotected sex, and can be used as a backup if contraception methods fail. By 2003, “Plan B” was available over-the-counter throughout the U.S.A [47].

Sir Astley Cooper experimented with vasectomy in dogs in 1830. Harrison recommended the operation as a cure for enlarged prostate in 1889. Male medical sterilization was first carried out in Indiana in 1899 and spread in the USA until 22 states had sterilization laws in 1929 based on genetic and eugenic indications. In the same year, Switzerland was the first country in Europe with a sterilization
law; Denmark introduced a test law which became final in 1935. Between 1933 and 1945 the totalitarian regimes used forced sterilization for genetic diseases and on undesired races. Only in the 1950’s family planning was introduced as a basis for male sterilization, initially in Asian countries [11].

Tubal ligation for female sterilization was first proposed by Blundell in 1823 in London. Lungren was the first to ligate a woman’s tube in 1880 in Toledo, Ohio, USA. In 1936 in Switzerland, Bosch performed the first laparoscopic tubal occlusion as a method for sterilization. Prior to the 1960s, female sterilization in the United States was generally performed only for medical indications (when additional pregnancies would be hazardous to the mother). Many centers used a formula (endorsed by the American College of Obstetricians and Gynecologists until 1969) in which age multiplied by parity had to be greater than or equal to 120 before elective sterilization could be considered [48, 49].

Infanticide, the killing of newborn babies, was the most universal solution to periodic overpopulation in pre-industrial societies. It was used to control population and, at times, the sex ratio where the sexual division of labor dictated. Some groups practiced infanticide because, in the absence of medical techniques, it was less risky and painful than abortion. Among some Australian tribes and among the Cheyenne and other Northern Plain Indians, infanticide was practiced so the tribe could maintain its mobility. The Pima of Arizona practiced infanticide when a child was born after the death of its father—thereby relieving the mother of the added economic burden [45]. It is significant to note that infanticide was not just a ‘primitive’ practice; Aristotle and Plato recommended it for eugenic reasons. And if infanticide is not acceptable today, it may be because we have better birth control methods [45]. Infanticide and abortion were considered criminal practices during the 18th and 19th centuries and their practice is documented in the transcripts of trials and in newspapers. This evidence suggests that both practices were widespread. Three cases of infanticide have been found reported in the Maryland Gazette on one day in 1761 [45].

Women have wanted to abort undesired pregnancies since ancient times. A standard method of inducing abortion (ancient and modern) is the abortifacient or potion. Abortifacients are part of a folk culture of herbal medicine handed down among women for thousands of years. In German folk medicine mar-joram, thyme, parasely and lavender in tea form were used. The root of worm fern was used by German and French women and was also prescribed by a Greek physician in the time of Nero; in French it was called the “prostitute root”. Other ancient recipes called for a paste of mashed ants, foam from camels’ mouths, tail hairs of blacktail deer dissolved in bear fat. In modern times, women have been reported to use turpentine, castor oil, tansy tea, quinine water in which a rusty nail has been soaked, horseradish, ginger, epsom salts, ammonia, mustard, gin with iron filings, rosemary, lavender, and opium [45, 50].

Aside from internal abortifacients, women have attempted external methods such as severe exercise, heavy lifting, climbing trees, hot baths, jumping and shaking. As late as the 20th century, Jewish women of the Manhattan Lower East Side attempted to abort by sitting over a pot of steam (or hot stewed onions), a technique described in an 8th century Sanskrit source [50].

The majority of women before the 19th century and many in the 19th century did not consider abortion a sin. Until the early part of the century, there were no laws against abortions done in the first few months of pregnancy. Prior to the 19th century, Protestants and Catholics held abortion permissible until ‘quickening”—the moment the fetus was believed to gain life [45].

Massage abortion is a technology that has been described in Burma, Thailand, Malaysia, the Philippines, and Indonesia. The procedure is usually attempted when the woman is 12–20 weeks pregnant. She lies on her back with her knees drawn up and the traditional birth attendant attempts to fix the uterus and then presses as hard as possible with her fingers, the heel of her bare foot, or even the wood pestle used to grind rice. This practice still occurs tens of thousands of times a year in this part of Asia [51].

A number of methods were available for performing abortion in the 19th century. The operation of dilation and curettage was established and, as early as 1863, Simpson described a procedure for “dry cupping” the uterus. Today it would be called vacuum aspiration. Vacuum aspiration using a hand-held syringe and a flexible plastic cannula was first described by Karman and Potts in 1972 [52].

The acceptance of a contraceptive behavior (which included contraceptive methods, abortion techniques and sometimes infanticide) over time depended upon cultural, economical and religious background. Abortion has not always been seen as a sin or a crime. It presented an easier moral problem for the ancients than today, because they assumed that life started after birth. In the Roman Empire there was an incentive to have small families. The custom that required the equal division of the estate among one’s children was the main reason usually advanced to explain why Roman families were so small. Even the intermittent attempts of the state to encourage population growth proved futile [36].

Christianity propagated the idea that the child was sent by God and, unlike other religions, made few
concessions to the social realities that justified the avoidance of pregnancy. If one had too many children it had to be viewed as a cross to bear [36].

Some idea of Medieval attitudes towards contraception can be obtained from the Penitentials—the religious compilations used by many priests as a framework for their work in the confessional. Sexual sin exceeded all others in the Penitentials. Noonan has categorized the sexual content of Penitentials from the 6th to 11th century. A nocturnal ejaculation warranted 7 days’ fasting, while contraception, fellatio, and anal intercourse attracted penances from 3–15 years. Religious records are supplemented by civil cases from 14th and 15th century Venice. Men guilty of homosexual anal intercourse were being burned alive between the Columns of Justice in St. Mark’s Square. But anal intercourse in marriage was also sometimes prosecuted with exile for a few years. Ruggiero concluded anal intercourse was a form of birth control that was practiced by some people at every social level, from nobility to humble fishermen. In the Penitentials, the punishment for abortion was sometimes less than that for contraception and was similar to that for coitus interruptus, although St. Jerome was particularly uncharitable in describing women who died from attempting an abortion as a “threefold murderess: as suicides, as adulteress to their heavenly bridegroom Christ and as murderess of their still unborn child” [53, 54]. In 1557, Henri II declared that any concealed pregnancy that ended with the death of the child would be presumed to be murder. A similar statute was passed in England in 1624 [36].

By 1860, the U.S. had banned all abortions except those deemed necessary to save a woman’s life. In 1873, Congress passed the Comstock Act, which made any and all forms of contraception illegal. The ban also prohibited anyone from providing information about birth control or abortion. In 1918, a woman named Margaret Sanger was charged under this Act with providing information on contraceptive devices. She appealed and won, with the courts finding that contraception was necessary to protect a woman’s health. Sanger would go on to found Planned Parenthood in the 1930’s [36, 43].

Based on Sanger’s victory and other challenges, the Comstock laws were repealed at both the state and federal levels during the 1930’s. It took another 40 years before women won the right to choose abortion as a method of contraception. From 1860 to 1973, abortion was illegal in the U.S., with few exceptions. The landmark Supreme Court case of Roe v. Wade in 1973 found that laws prohibiting abortion were unconstitutional. This ruling gave women the right to choose abortion in the U.S. freely within the first trimester [36].

By the 1980s, something like 90 per cent of married couples in most western countries were employing contraceptives. An international survey of contraceptive users found that 33 per cent had been sterilized, 20 per cent employed the oral contraceptive, 15 per cent the IUD and 10 per cent the condom [36].

IX. MALE SEXUAL DYSFUNCTION

The crucial function in male sexuality is penile erection. Besides different forms of ejaculatory disorders, penile deformities and other hypoactive and hyperactive sexual dysfunctions, the male erection has always been of main interest in medicine and therefore the below overview will concentrate on this aspect [14, 55, 56].

Early physiology and pathophysiology of male erection:

In “De aëre aquis et locis” Hippocrates (5th-4th century BC) described the high incidence of impotence and infertility in the people of the Scythians and explained it by continuous perineal trauma due to excessive horse riding. Aristotle (384 till 322 BC) - like the other Greek authors - outlined the physiological concept of “pneuma” (= wind, air) as the initiator of erection.

In respect to Arabian medicine the famous Avicenna (980-1037 AD) - also known as Abu Ali al-Hussein Ibn Abdallah Ibn Sina or “Medicorum princeps (Prince of Physicians)” – was perhaps rather a philosopher than a physician. Although his notes on anatomy and physiology of the genital tract are full of errors he was a very subtle observer of human sexual behaviour, especially when writing about the difference between male and female orgasm.

Leonardo da Vinci (1452-1519) – the great artist and genius of the Renaissance - can not only be considered as the founder of modern medical illustration but was also the first author to describe the increased blood inflow to the penis as the cause of erection. He drew this conclusion from his own observations and dissections in human corpses.

Although the “Musculi erectores penis” (i.e. Mm. bulbospongiosi and ischiocavernosi) had already been described by Galen in the 2nd century AD, this knowledge was lost at the time of Costanzo Varolio (1543-1575), who re-discovered them and gave an astonishingly correct description of the mechanisms of erection.

The book “De la generation de l’homme” (On the generation of man), written by the master of French Renaissance surgery Ambroise Paré (1510-1590) in 1573, constitutes a real guide to good sexual practices. In this book Paré described in very vivid language and with many details how to perform sexual intercourse to ensure the greatest chances of fertilization and moreover how to diagnose
pregnancy, how to follow pregnancy and finally how to conduct delivery.

In his “Tractus de virorum organis generationi inservientibus, de cysteribus et de usu siphonis in anatonia” (1668) the Dutch physician Regnier de Graaf (1641-1673) (Fig.18) succeeded in causing an erection in a corpse by injecting water into the hypogastric artery. At that time a very meaningful example of experimental science.

Although the “Nodus penis” had been described centuries before, Francois de LaPeyronie (1678-1747) gave the first extended clinical report on the disease named after him in his article “Sur quelques obstacles qui s’opposent à l’éjaculation naturelle de la semence” (On some obstacles to the natural ejaculation of the semen) from 1743. In his opinion the plaque was predominantly caused by venereal diseases.

The famous surgeon and anatomist John Hunter (1728-1793) (Fig.19) from London is well-known for his contributions on venereal diseases, the prostate and urethral strictures. He also dedicated an interesting chapter on impotence in his book “A Treatise on the Venereal Disease” (1786) in which he clearly defined an impotence depending on the mind and an organic impotence as “from want of proper correspondence between the actions of the different organs”.

In 1863 the German physiologist Conrad Eckhard (1822-1905) (Fig.20) from Giessen published his results on animal experiments inducing penile erections by applying electrical stimulation at different levels of the nervous system (also see above). More detailed contributions on the neurophysiology of erection were made by J.N. Langley and H.K. Anderson from England in the mid 1890’s.

**Conservative treatment:**

Aphrodisiacs have been adopted for the treatment of all kinds of sexual dysfunction since ancient times and are still in use in our days.

In 1896 the chemist Leopold Spiegel (1865-1927) from Berlin performed chemical characterization of yohimbine from the bark of the African yohimbe tree. He was well aware of the aphrodisiac effect that the bark was said to have in its country of origin and clinical application followed immediately in Europe.
Spiegel patented his chemical discovery in the UK in 1900 and this resulted in a more than 100 years story of oral drug treatment of erectile dysfunction especially in psychogenic and mild organic disorders.

The essay with the remarkable title “Über die allgemeinste Erniedrigung des Liebeslebens (The most prevalent form of degradation in erotic life)” was published in 1912 and is one of the few publications in which Sigmund Freud (1856-1939) (Fig.21) deals directly with male erection disorders. Here he introduced the term “psychical impotence” into his writings and stressed the high prevalence of this condition which is manifested by “a refusal of the sexual organs” to execute the sexual act [16]. Historically, there was a certain negative impact of Freudism through the resulting focus on a psychogenic understanding of sexual dysfunction. Especially in erectile dysfunction organic concepts of pathophysiology as well as new approaches of somatic therapy were inhibited for many decades.

The first milestone in effective medical treatment of severe organic erectile dysfunction was the intracavernous injection of vasoactive drugs. By accident the French vascular surgeon Ronald Virag from Paris discovered the proerectile effect of papaverine during a revascularization surgery of the penis and suggested therapeutic injection into the corpus cavernosum in 1982.

One year later Giles S. Brindley reported a list of experiments where he described the possibility of getting an efficient erection through what he called “cavernosal alpha-blockade”. He reported that large doses of oral phenoxybenzamine caused penile tumescence that lasted for 24 to 48 hours. He also produced erections with parenteral and penile injection of phentolamine and phenoxybenzamine. He proposed the therapeutical use of intracavernous injection for patients with erectile dysfunction and he stated that intracavernous injection could be a diagnostic tool; he believed that a good response could rule-out a vascular cause, but not a neurogenic one. Brindley also made history with his dramatic presentation of the effect of intracavernous injection of the alpha-receptor antagonist phenoxybenzamine into his own penis at the 1983 meeting of the American Urological Association (AUA) [57].

Finally, Adrian W. Zorgniotti from New York introduced drug combination of papaverine and phentolamine in 1985 [58].

With his biochemical research, as outlined in the paper “Fractionation and characterization of a cyclic adenine ribonucleotide formed by tissue” from 1958, the American Earl W. Sutherland (1915-1974) discovered the physiological significance of cyclic nucleotides in the regulation of cell and tissue function. This basic knowledge – for which he was awarded the Nobel Prize in Medicine and Physiology in 1971 – was fundamental for the understanding of the first effective oral treatment of erectile dysfunction with PDE-5-inhibitors at the end of the 20th century.

Vacuum constriction devices:
The curative application of negative pressure to different parts of the body was well established in 19th century medicine. The American physician John King was the first to suggest a continuous and repeated application of a vacuum device to the penis for the cure of impotence in 1874. Finally, the Viennese physician Otto Lederer (1872-1944/45) made the significant improvement of adding a compression ring to the use of the vacuum device to facilitate an on-demand erection in 1913 (Fig.22); long before Geddings D. Osbon constructed his modern device in 1960.

Surgical treatment:
Ambroise Paré (1510-1590) suggested an “artificial penis” made of a wooden pipe or tube for patients after traumatic penile amputation in order to facilitate a proper micturition in the standing position. Although not intended for sexual activities one might call this device a 16th century “penile prosthesis” as per definition a prosthesis – in contrast to an implant - replaces the whole organ or part of the body.

In 1873 the Italian physician Francesco Parona (1842-1907) injected the varicous dorsal penile vein of an impotent young patient with hypertonic saline in order to cause sclerosis and by this reduce the excessive venous outflow. More then two decades after this first case report several American doctors started performing surgical dorsal vein ligation or resection as e.g. Frank Lydston in 1908.

Since the early 1930’s Oswald S. Lowsley (1884-1955) (Fig.23) from New York was the main protagonist of surgical treatment for corporovenoocclusive dysfunction. He combined simple dorsal vein plication with a surgically more advanced perineal crural technique in which he plicated the...
bulbocavernous and ischiocavernous muscles with several mattress sutures.

The first penile implant to facilitate an erection was used in a phalloplasty procedure performed by the Russian surgeon Nikolaj A. Bogaraz (1874-1952) (Fig.24) in 1936. He used the patient's rip cartilage and in later years he even performed this operation in patients with morphologic intact penis but suffering from erectile dysfunction [59].

In 1948 the French surgeon René Leriche (1879-1955) (Fig.25) firstly mentioned arterial vascular impotence in thrombotic obliteration of the aortic bifurcation, a syndrome he had already described in detail in the 1920's and which today is named after him. During the following time several strategies were outlined to save or reconstruct the internal iliac artery during abdomino-pelvic vascular surgery to maintain or restore erectile function.

In 1973 Václav Michal from Prague reported the first microsurgical treatment of vascular erectile dysfunction by performing a revascularization with direct anastomosis of the inferior epigastric artery to the corpus cavernosum. He was one of the first researchers to observe that failure of the hemodynamics of erection played an important role in the pathogenesis of impotence in many patients. He also discussed the use of phallo-arteriography with saline-filled erection to visualize the proximal arterial disease. In the 1980's further techniques were introduced later by Michal himself, as well as by Ronald Virag from Paris and Dieter Hauri from Zurich.

The very breakthrough of penile implant surgery was initiated by F. Brantley Scott (Fig.26) from Houston, Texas, together with his colleagues William E. Bradley and Gerald W. Timm when they implanted the first silicone inflatable device on February 2nd, 1973.
This was one of the first effective treatments of erectile dysfunction. The authors were very imaginative for that time, describing a completely new concept, instead of rods, using inflatable cylinders which could be filled – on the man’s demand – through pressing a pump positioned subcutaneously in the scrotum, transferring the fluid from a reservoir implanted in the Retzius space to the cylinders promoting penile rigidity. This device – the basis of the modern ones - had had an extraordinary evolution since this publication in 1973. Scott is also recognized for the creation the urinary artificial sphincter which revolutionized the treatment of urinary incontinence [60].

Alfred Kinsey:

Alfred Charles Kinsey (1894–1956) can be considered the pioneer in the quantitative and epidemiologic study of human sexuality collecting sexual histories from a large number of men and women, resulting in a final sample of around 18,000. His interest in human sexuality fortuitously began when in 1938 he was responsible for a course on marriage at the University of Indiana and found that little survey research was available on human sexuality. In 1941, Kinsey obtained a grant from the “National Council’s Committee for Research in the Problems of Sex”, which was at the time funded by the Rockefeller Foundation. He assembled a multidisciplinary research team that included Clyde E. Martin, a student assistant who became a research associate; Wardell B. Pomeroy, a clinical psychologist; and Paul H. Gebhard, an anthropologist. Kinsey and his colleagues established the “Institute for Sex Research” in 1947 as a separate, nonprofit organization.

Kinsey published «Sexual Behavior In The Human Male» in 1948, which came to be known as the «Kinsey Report». It sold more than 250,000 copies and was translated into a dozen languages. In 1953 the Institute published "Sexual Behavior In The Human Female", which also sold more than 250,000 copies and was translated into several languages. These two reports sharply challenged many myths about sexual behavior in American society and revealed findings on various previously taboo topics, such as extramarital sexuality, homosexuality, bisexuality, oral sex, masturbation, and prostitution. Only relatively few male individuals with erectile dysfunction were analyzed. Although those studies were devoted only to white, young Americans they contributed strongly for the change of sexual behaviour in the USA in the second part of the 20th century. Despite the wide-spread acceptance of the scientific study of sexuality in U.S. society, conservative forces continued to attack the work pioneered by Kinsey as well as on-going studies by the Institute for Sexual Research, which resulted in the suspension of the research grants and ended up the work [http://www.pbs.org/wgbh/amex/kinsey/peopleevents/p_kinsey.html] [1].

X. SEXUAL MEDICINE AS A TRUE SPECIALITY AFTER WORLD WAR II

After World War II and mainly after Kinsey’s reports the field of Sexual Medicine experienced a fast development. It is impossible to cover all the individuals who contributed to that research, but four of the early pioneers from the 1950’s and 1960’s should be cited in detail.

F. Brantley Scott (portrait and illustration of first inflatable penile implant from 1973)
Giuseppe Conti:
The Italian anatomist Giuseppe Conti from Padua was a pioneer in scholarly research into erectile function. His seminal report “L’erection du penis humain et ses bases morphologico-vasculaires” (The erection of the human penis and its morphologic-vascular basis) was published in 1952 and represents one of the earliest attempts to scientifically and precisely characterize penile hemodynamics and structure as they relate to the phenomenon of erection.

Conti found that the penile arteries contained areas of subintimal longitudinal smooth muscle that protruded into the lumen. Busche referred to these structures as “Polsterkissen”; i.e. cushions or polsters near branch points of the deep penile artery. Based on composition and location Conti postulated that these structures permitted selective shunting of arterial blood to either “nutritive” arteries or anastomotic arteries that communicated with the cavernous spaces. Depending on their opening or closing an erection or detumescence would result. This theory persisted until 1980. Counter to his contemporaries, Conti proposed that rather than a single mechanism, a number of events are responsible for penile erections. Specifically, he hypothesized that the interplay of arterial inflow with the shunting of blood into the corpora cavernosal spaces and the obstruction of venous outflow resulted in the engorgement of the penis [61].

James Semans:
James H. Semans (1910-2005), a Duke University surgeon and urologist combined a career as a leading medical scientist and physician with a passion for the arts and charitable causes. He was a pioneer in rehabilitative and urinary surgery.

The cultural climate of the southern United States in the immediate period after World War II was quite reserved and conservative, not in a political sense, but in a social sense. Deeply religious and very homogeneous the south was not progressive in any sense, particularly when it comes to sexual matters. In this environment Semans published in 1956 a classical article on the treatment of premature ejaculation. He was the first to describe a direct, behavioral treatment for premature ejaculation, the stop-start technique.

This article is one of the first major open discussion of the behavioral issues surrounding sexual dysfunction to appear in the literature. For the first he pointed out that premature ejaculation could lead to erectile dysfunction. The paper consists of an observational series of cases, each discussed individually which together form the basis for a recommend technique to decrease the stimulation leading to a retarded ejaculation [62].

William Masters and Virginia Johnson:
William Howell Masters (1915-2001) was one the first to study the anatomy and physiology of human sexuality in the laboratory, and the publication of the reports on his findings created much interest and criticism. Since then, he and his colleague and wife, Virginia Eshelman Johnson (born 1925), have become well-known as researchers and therapists in the field of human sexuality, and together they have established the Reproduction Biology Center and later the Masters and Johnson Institute in St. Louis, Missouri.

In 1954 Masters started his research on human sexual response. He was concerned that the medical profession had too little information on sexuality to understand clients’ problems. As Kinsey had based his research on case histories, interviews, and secondhand data, Masters decided to study human sexual stimulation using measuring technology in a laboratory situation.

In 1956 he hired Virginia Johnson, a sociology student, to help in the interviewing and screening of volunteers. The study was conducted over an eleven-year period with 382 women and 312 men participating. Masters and Johnson described a four-phased cycle relating to male and female sexual responses. To measure physiological changes, they used electroencephalographs, electrocardiographs, color cinematography, and biochemical studies. They estimated that they had observed «10,000 complete cycles of sexual response». Their findings about female sexual arousal described the mechanisms of vaginal lubrication and orgasm and proved that some women were capable of being multiorgasmic.

In 1966 Masters and Johnson published “Human Sexual Response” and in 1970 “Human Sexual Inadequacy”, where they discussed sexual problems such as impotence [14].

Epilogue
Around 1970 many physicians were dealing with issues of sexual medicine and the term itself and it’s modern definition became established in the medical community, as has been outlined in the introducing chapter on terminology of this article (see above). Several societies had already been or were about to be founded in the field of sexology at that time [7]. A key event for the formation of another important society was the “First International Conference on Corpus Cavernosum Revascularization” in New York in October 1978. Adrian W. Zorgniotti, a visionary urologist from the Cabrini Medical Center in New York, identified and invited experts on vasculogenic impotence from all over the world for this meeting. From the subsequent activities and meetings of this group arose the “International Society of Impotence Research” (ISIR), that later opened it’s arms to other
specialities as e.g. psychiatrists, psychologists, gynecologists, general practitioners to be renamed as the "International Society for Sexual Medicine" (ISSM). This evolution has been outlined in detail in a recent article by Lewis and Wagner [63].

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Committee 2

Definitions, Classification, and Epidemiology of Sexual Dysfunction

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Definitions, Classification, and Epidemiology of Sexual Dysfunction

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I. GENERAL INTRODUCTION

Epidemiological data are the basis for assessing the impact of a condition on a given society. The two components of epidemiology, descriptive epidemiology (incidence and prevalence by persons, place and time) and analytical epidemiology (the search for disease or condition risk that may serve to increase prospects for prevention) are the main components for this chapter, in addition to defining the sexual disorders in women and men. Incidence is defined as the number of new cases with a certain condition during a specific time period in relation to the size of the population studied. Prevalence characterizes the proportion of a given population that at a given time has the condition. Therefore, it is important that epidemiological studies are reasonably valid, and particularly that they cover representative samples. In case of sexual dysfunctions, incidence and prevalence are usually measured using self-reports. Lack of consensus in definition of the condition and in scaling does, however, lead to considerable problems for comparing incidence and prevalence of sexual conditions described in different investigations. Different methodological rationales, such as the time period studied (1 month, 3 months, 6 months, 1 year, life-time), different age strata included and (self-) selection biases are other problems in comparative analysis. Some reports included only one particular sexual dysfunction, most prominently for studies of erectile dysfunction, while some include different conditions in both genders, making it possible to perform cross-gender epidemiological calculations. This heterogeneity in the literature means that we are often unable to disentangle true population effects from differences in reported prevalence that are simply due to inconsistent use of definitions. For example, where researchers follow DSM-IV definitions [1] then only persons who experience both sexual dysfunction per se and sexual distress are classed as having a sexual dysfunction. [2-4] Studies that only measure sexual function per se are likely to report higher prevalence estimates compared to studies based strictly on DSM-IV definitions. Those reading the literature might erroneously conclude that the higher prevalence is due to population differences when in fact a large part of the difference in prevalence may simply be due to the inconsistent use of definitions.

Thus, a uniform nomenclature including categorizations as well as quantifications is necessary in order to pave the road for valid and reliable: 1) comparative studies between nations and regions 2) identification of risk factors/co-morbidities 3) primary and secondary preventions and 4) evidence based interventions.

A major thrust of this and the last [5] consultation was to use evidence based medicine standards for inclusion of material analysed and cited. [6] For the summary of descriptive epidemiology, this committee has adhered to the classification of epidemiological validity described by Prins et al [7], who identified 15 dichotomizable (yes/no) points for being recognized as valid from the prevalence or incidence point of view (see Table 1). In this chapter only nationally or regionally representative studies published in peer-reviewed journal or in books, and judged to be at least reasonably valid, i.e. reaching at least 10 of 15 possible yes-answers on the Prins et al assessment, are included. Articles cited in the analytical section are mainly scored 10 or higher using the evidence based criteria. [6]
**Recommendation 1:**

In rating level of evidence for epidemiological studies, there is probably a need to expand the point allowed for percentage of responders. The current score of 1 for percentage of 70% or greater is probably too narrow for modern epidemiological studies. We may wish to have more flexibility for this point such as maximum points for 70% and greater, mid-range for 40-70%, low-range for 20-40%, and subtraction point for those with response rate of less than 20%. **Grade C.**

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**II. INTRODUCTION TO DEFINITIONS OF SEXUAL DYSFUNCTIONS**

At present, the two most widely used sets of definitions of sexual dysfunctions are those given by the World Health Organization (WHO), 1980 [8] in the ICD-10, and by the American Psychiatric Association, (DSM-IV) in 1994. [1] In sexual medicine, the ICD-10 has mainly been used within somatic care and the DSM-IV psychological/model. Both sets of definitions are mainly built upon the physiological model of genital...
responses and symptoms disturbing coital intercourse first described by Masters and Johnson [9]; later modified by Kaplan. [10] Both sets add to the sexual response “cycle” in which, for women, vaginismus is included. Both sets regard sexual dysfunctions (ICD-10)/disorders (DSM-IV) as involving combinations of physical and psychological constituents but believe it possible to separate these.

A basic feature of the ICD-10 definitions is that sexual function per se is defined as the various ways in which an individual is able to participate in a sexual relationship as he or she wishes. The ICD-10 uses definatory categories, which are sub-categorized into organic (N-series) and non-organic (F-series) dysfunctions; but several inconsistencies are built into the system. For example, female arousal disorder is included in the ED-definition. The ICD-10 does not include delayed ejaculation as a category by itself, presumably regarding retarded ejaculation as equivalent to lack of orgasm.

The DSM-IV has two defined (A and B) categories describing psychogenically based disorders: The A category focuses on defining sexual disorders per se. The common denominator of all being: “persistent or recurrent”. It is explicitly pointed out that each disorder must be separated from a dysfunction exclusively due to a general medical condition or a substance-induced sexual dysfunction. Here, a set of subtypes is introduced. The latter set of definitions is valid only if the dysfunction is fully explained by the medical condition or the physical effects of a substance/drug, respectively. When combinations of psychological and organic conditions are judged to be causal for a certain dysfunction, the DSM-IV advocates the subtype: “due to combined factors”. The B category of the DSM-IV definitions add to all dysfunctions, a distress dimension: “The disturbance causes marked distress or interpersonal difficulty”. These A and B sets of definitions enable distinguishing a dysfunction per se from its emotional impact (but only if marked) – intra- as well as interpersonally. The B category does not leave a possibility for inclusion of mild or sporadically occurring distress. The DSM-IV has been criticized for its lack of operational criteria for the diagnosis of sexual dysfunction. [11] It has been suggested that criteria specifying severity and duration be added in order to distinguish sexual disorders requiring medical intervention from transient alterations in sexual function related to life stress or relationship difficulties. [12] These alterations should lead to more homogenous groups for clinical research and to revised estimates of the prevalence of sexual dysfunction in the general population. At this time, the criteria for the sexual dysfunctions are being evaluated for DSM-V and ICD-11.

Some years ago a consensus panel [13] recommended a new diagnostic and classification system for women’s sexual dysfunctions incorporating both physiological and psychological pathophysiology and personal distress. An important feature of the DSM-IV and the Basson et al sets of definitions is a classification into lifelong vs. acquired (after a period of “normal” functioning). Moreover, the DSM-IV calls attention to another dimension, namely whether the dysfunction is generalized (occurring in different situations) vs. situational (occurring only in certain situations). It is underlined that the clinical evaluation should include etiological factors. There is a discussion on the adequacy of the ICD-10 and DSM-IV definatory systems which to many experts, and perhaps particularly pertaining to women’s sexuality, appear too “medicalized” [14] ironically labeled biological innocence. Leiblum [15] and Basson [16] from the perspective of women’s sexuality criticize the concept of a linearly progressing sequential Desire → Arousal → Orgasm model which does not regard women’s sexuality. They suggest that many cases of impaired sexual response or interest are not dysfunctions per se, but are adaptive reactions to problems in sexual relationships. [17] It has also been suggested [18] that women’s sexual dysfunctions may be best conceptualized as a global inhibition of sexual response due to intrapersonal factors, an inhibition which may also be true for male sexual disorders. In epidemiological research it has been found that, for women and men alike, all sexual dysfunctions are generally significantly associated. [19–21] Hence, whereas definitions from a classificatory and differential diagnostic point of view are necessary, it appears unsound to assume that one sexual disorder per se can, a priori, be expected to be a solitary phenomenon for any given individual.

A number of serious problems can arise for research when presumed etiology is incorporated into definitions. While it is important to recognize that sexual problems can stem from a wide range of causes, this approach of including – or excluding – possible etiology in the definition of sexual dysfunction may undermine research aimed at improving our understanding of women’s and men’s sexuality. Problems arise because including etiology in the definition means that the case definition is inextricably entangled with the potential risk factors of interest. This makes it difficult to undertake a valid analysis of risk factors or demonstrate causal relationships between these risk factors and sexual responses. For example there is evidence that relationship factors play a very important role in female sexual responses. [2] We therefore might be tempted to exclude low sexual function that is a product of a poor relationship from our definition of FSD. If we did, we would not be able to assess the impact of poor relationships on FSD because couples with poor relationships who experienced sexual difficulties would no longer be classified as having FSD. If we include various relationship factors as
part of sexual dysfunction definitions in this way then it will not be possible to assess the impact of these relationship factors in future epidemiological studies. Furthermore, while certain factors may appear particularly important today this may change in the future or between populations. Currently much of the literature relating to FSD, and to some extent to MSD, is based on western populations. The etiological factors that are important in western societies may be very different to those in other cultures. In some instances it is not clear whether factors associated with FSD are the cause or the consequence of the sexual difficulties. Consequently we could run the risk of including in the definitions of sexual dysfunctions factors that are actually a consequence of FSD rather then part of the etiology or factors that are simply markers for the true underlying causes that we have not yet fully investigated.

Recommendation 2.:

There is a need to recognize that definitions for sexual dysfunction may be different for epidemiological studies versus those needed for clinical applications. Epidemiology studies may ask the incidence or prevalence of a disorder in a community but for clinical definitions further expansion such as duration and severity may need to be part of the defined disease evaluated and treated. The latter in epidemiological studies go beyond the per se definition of the disorder itself. There is a need to keep these parallel as possible. Grade C.

III. DEFINITIONS OF SEXUAL DYSFUNCTION FROM THIS CONSULTATION

On the basis of these deliberations, this committee has selected the following definitions. These do not generally separate organic from psychological caused dysfunctions which should (if adequate) be clarified through the etiology and they are not mutually exclusive.

1. DEFINITIONS OF SEXUAL DYSFUNCTIONS IN WOMEN

The definitions of sexual dysfunction in women came primarily from deliberations by the work by Basson et al [22] and the members of chapter 16 of this consultation.

a) Sexual interest/desire dysfunctions are diminished or absent feeling of sexual interest or desire, absent sexual thoughts or fantasies and a lack of responsive desire. Motivation (here defined as reasons/incentives), for attempting to become sexually aroused are scarce or absent. Sexual aversion disorder is anxiety and/or disgust at the anticipation of/or attempt to have any sexual activity.

b) The area of sexual arousal disorder is divided into three subtypes. Genital sexual arousal dysfunction are absent or impaired genital sexual arousal; self-report may include minimal vulval swelling or vaginal lubrication from any type of sexual stimulation and reduced sexual sensation from caressing genitals. Subjective sexual excitement still occurs from non-genital sexual stimuli. Subjective sexual arousal dysfunction is the absence of or markedly diminished feelings of sexual arousal, (sexual excitement and sexual pleasure), from any type of sexual stimulation. Vaginal lubrication or other signs of physical response still occur. Combined genital and subjective arousal dysfunction is absence of or markedly diminished feelings of sexual arousal (sexual excitement and sexual pleasure) from any type of sexual stimulation as well as complaints of absent or impaired genital sexual arousal (vulval swelling, lubrication).

c) Persistent genital arousal dysfunction is spontaneous, intrusive and unwanted genital arousal (i.e. tingling, throbbing, pulsating) in the absence of sexual interest and desire. Any awareness of subjective arousal is typically but not invariably unpleasant. The arousal is unrelieved by one or more orgasms and the feeling or arousal persists for hours or days.

d) Orgasmic dysfunction in women is lack of orgasm, markedly diminished intensity of orgasmic sensations or marked delay of orgasm from any kind of stimulation. There is a self-report of (high) sexual arousal/excitement in this disorder.

e) Dyspareunia is persistent or recurrent pain with attempted or complete vaginal entry and/or penile vaginal intercourse. Vaginismus is the persistent or recurrent difficulties of the woman to allow vaginal entry of a penis, a finger and/or any object, despite the women’s expressed wish to do so. There is often (phobic) avoidance and anticipation/fear of pain. Structural or other physical abnormalities must be ruled out/addressed.

For clinical studies and relevance to clinical situations, various descriptors are recommended for the various sexual dysfunctions in women and men. They include degree of distress scales, life-long or acquired status, situational or generalized occurrence, and other relevant conditional states.

2. DEFINITION OF SEXUAL DYSFUNCTIONS IN MEN

a) Sexual interest/desire dysfunction has to some extent been neglected in epidemiological research but is quite commonly seen in clinical practice. This committee suggests a definition identical to the one for women (see above).

b) Erectile dysfunction (ED) is defined as the consistent or recurrent inability of a man to attain
and/or maintain penile erection sufficient for sexual activity. A 3-months minimum duration is accepted for establishment of the diagnosis. In some instances of trauma or surgically induced ED (e.g. post radical prostatectomy), the diagnosis may be given prior to or 3 months. Objective testing (or partner reports) may be used to support the diagnosis of ED, but these measures cannot substitute for the patient’s self-report in classifying the dysfunction or establishing the diagnosis.

c) In August, 2007, the International Society for Sexual Medicine (ISSM) convened a panel of experts to review criteria for premature ejaculation. This panel proposed the following evidence-based definition of lifelong premature ejaculation: “ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences such as distress, bother, frustration and/or the avoidance of sexual intimacy.” The panel concluded that there was insufficient evidence to propose definitions for acquired premature ejaculation [23].

**Recommendation 3.** 

This committee recommends using the ISSM derived definition (from the convened panel of experts) for lifelong premature ejaculation as the new epidemiological definition. **Grade B.**

d) **Anejaculation** is the absence of ejaculation during orgasm.

e) **Orgasmic dysfunction** is inability to achieve an orgasm, markedly diminished intensity of orgasmic sensations or marked delay of orgasm during any kind of sexual stimulation. There is a self-report of (high) sexual arousal/excitement in this disorder and orgasmic dysfunction can occur together with ejaculatory function.

f) **Dyspareunia** is persistent or recurrent genital pain during sexual activities.

### 3. CLASSIFICATION OF SEVERITY

To make studies comparable, it seems to be of importance not only to have uniform definitions but also to use uniform scales. The two grade scales (yes/no), for example used by Laumann et al [20], Kadri et al [24], and Smith et al [25], may be too rigorously undifferentiated and may lead to exaggeration of the severity of any given dysfunction. In the USA, a four-graded (No/Mild/Moderate/Complete) scale has been used [26], while in Sweden [27] in another large prevalence study a 6-graded scale (Never/Hardly ever/Rather rarely/Rather/often Never/hardly ever/Rather rarely/rather often/Often/Always, Nearly always) has been used applying single questions both for characterization of dysfunction per se and for dysfunction-caused distress. This scale has been trichotomized: No dysfunction (never), Mild dysfunction (hardly ever, rather rarely) and Manifest dysfunction (rather often, often, always, nearly always).

The common mode used in population-based epidemiological research is single variables, each intended to cover one particular sexual dysfunction. The possible adequacy of using single question self-assessment was looked upon by Derby et al [28], who found close correlations between the prevalence of erectile dysfunction, tapped simultaneously by the IIEF erection domain, three erectile domain items of the BSMFI [29] and the one four grade (No, Mild, Moderate, Complete) item used by Feldman et al [26] in their now classical treatise of the prevalence of ED.

During recent decades different clinically well validated questionnaires, some examples being for men the IIEF [30] and for women FSFI [31], have been introduced. Furthermore, aggregated scores have been questioned [32-33] as a summed score may obscure a sexual aspirations-achievement gap within pertinent sub-domains. Furthermore, newer scales for measuring FSD have some advantages over single item questions. Recently, the Standardization Committee of International Society for sexual Medicine has completed a thorough review of the questionnaires constructed to assess female and male sexual function. (in preparation)

Of the questionnaires taken into consideration, for women the FSDS [34] and the SFQ [35-36] were recommended for both clinical and research use. Problems can arise when single questions are used in epidemiological studies. For example in a number of studies respondents are simply asked to report problems (or difficulties) with sexual desire that occurred for one month or more in previous 12 months. [20,37-38]. Both distress (i.e. problem or difficulty) and sexual function (desire) components are therefore combined into the one question. This makes it difficult to separate out the relative contribution of distress versus low function or recognize which factors are associated with the each of these two components. Moreover, we cannot be sure to what extent distress has been taken into account in participant responses or whether some participants have incorporated distress in their answers and others have not.

Overall, it appears that the field lacks questionnaires able to measure sexual function for women not in a relationship and no questionnaire has been further validated on non-heterosexual women, although some preliminary data exists on the FSFI in lesbian women. Although several epidemiological studies have used single items to assess sexual function in different domains, currently there is a lack of empirical evidence for the discriminant validity of single-item measures of sexual dysfunction in women.
We now have good evidence that a single item question can produce very different prevalence estimates than a validated multi-item scale when measuring FSD. In recent study prevalence estimates produced by simple non-validated questions were compared against those obtained using validated multi-item scales in the one sample of women. [39] When instruments with the same recall (the previous month) were examined side by side, simple questions produced significantly different prevalence estimates for desire, arousal, orgasm and pain disorders compared to the validated multi-item scales that incorporated sexual distress. [39] Furthermore, that investigation provided evidence that compared to validated multi-item scales, simple questions identify different sub-groups of women as experiencing FSD. [39] Compared to a single question, validated, multi-item scales such as the FSFI, [31] and PFSF [40-41] that simply examine sexual function have the advantage of being able to examine both frequency and intensity of sexual experiences with out asking women to self diagnose or guess what is normal sexual function. Some multi-item scales [36] have the added advantage of providing cut off scores for a number of different sub-categories (or sub-domains) of sexual function. These instruments have been translated into a variety of different languages [42-43] and are beginning to be more widely used in epidemiological, observational studies. [44] Although self-reported questionnaires such as IIEF, FSFI and BSMFI have demonstrated their utility for the evaluation of male and female sexual dysfunctions, they do not provide any pathogenetic information. SIEDY (Structured Interview on Erectile Dysfunction) is the only case history tool sufficiently validated for this purpose. [45] This is a 13-item structured interview composed of three scales, which identify and quantify three domains simultaneously present in ED patients (organic: Scale 1, relational: Scale 2 and intrapsychic: Scale 3). Organic, relational, and intrapsychic factors are often to be found together and mutually interacting in ED patients. Hence, an anamnestic instrument which simultaneously and quantitatively evaluates them can provide an interesting option to overview them. In addition, SIEDY can predict with 70% sensitivity and specificity the presence of an organic component of ED. SIEDY is therefore a unique, validated anamnestic and diagnostic instrument available to physician confronting ED. [46]

IV. DESCRIPTIVE EPIDEMIOLOGY

1. INCIDENCE OF SEXUAL DYSFUNCTIONS IN MEN

There are few epidemiological surveys addressing the incidence of sexual disorders. For erectile dysfunction there are five population-based studies that describe the incidence of erectile dysfunction, two from the USA [47-48], one from Brazil [49]; one from the Netherlands [50], and one from Finland [51, 52] (See Tables 2 and 3.) Two other papers have been identified that report on incidence in a preventive medical care clinic in the USA [53] or in a group of general practices in the UK [54]. The most important conclusion that can be drawn from these studies is that incidence is strongly associated with age. In the study from the UK the incidence of ED varied between 8-10 cases per 1000 man years in the period 1999-2000 (in men aged 40-79). This incidence had more than doubled from about 4 cases per 1000 man years in the period 1996-1997, that is, before the introduction of Sildenafil.

The first published, population-based study on incidence came from the MMAS (Massachusetts Male Aging Study) [47]; the participants were predominantly white. Analyses were performed on 847 ED-free men at baseline (with a baseline age between 40 and 69 years; average 52.2 years). After an average follow-up of 8.8 years a crude incidence rate of 26 cases per 1000 man-years was found (95% CI: 22.9-29.9). The annual incidence rate increased with each decade of age (table 2). The age-adjusted risk for ED was higher for men with lower education, diabetes, treated heart disease, and treated hypertension.

The Brazilian study was conducted in the city of Salvador, the third largest city of the country, with a racially diverse population. [49] Analyses were performed on 428 ED-free men at baseline (with a baseline age between 40 and 69 years; 53% of the men were below the age of 50 at baseline). After an average follow-up of 2 years (range 1.7-2.3) a crude incidence rate of 65.6 cases per 1000 man years was found (95% CI: 49.6-85.2). The annual incidence rate increased with each decade of age (table 2). The age-adjusted risk for ED was higher for men with lower education, diabetes, treated heart disease, treated hypertension, depression and benign prostatic hyperplasia. Based on an analysis of baseline characteristics of men in the study, the authors conclude that the analysis sample was similar to the sample of men lost to follow-up.

In Europe, the Krimpen study was conducted in the town of Krimpen aan den IJssel (The Netherlands), this is a commuter town near Rotterdam with a predominantly Caucasian population. [50] Analyses were performed on 1487 “clinically-relevant-ED”-free men and 1432 ED-free men (see table 2, for definitions of ED) at baseline (with a baseline age between 50 and 78 years; therefore, in comparison with the other two studies, all men were above the age of 50 at baseline). Inasmuch as this study consisted of a baseline measurement and 2 follow-up measurements after an average of 2.1 and 4.2 years, respectively, it was possible to determine
Table 2. Incidence rates of erectile dysfunction in population based cohort studies.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Geographic location</th>
<th>Population type</th>
<th>Age range of participants</th>
<th>Eligibility criteria</th>
<th>Method of assessment</th>
<th>Response rate</th>
<th>Differences Non-responders</th>
<th>Study design</th>
<th>Instrument</th>
<th>Definition of ED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johannes et al (MMAStudy)</td>
<td>Massachusetts (USA)</td>
<td>Random population sample</td>
<td>40-69</td>
<td>Men with sexual partner</td>
<td>At home interview</td>
<td>52% (77% (8.8 y))</td>
<td>Participants more heart disease and cancer</td>
<td>Cohort study</td>
<td>Validated single assessment question (scale: 4 grades)</td>
<td>Sometimes or never able to get and keep an erection adequate for satisfactory sexual intercourse</td>
</tr>
<tr>
<td>Moreira et al</td>
<td>Salvador (Brazil)</td>
<td>Random population sample</td>
<td>40-70</td>
<td>No cancer of prostate or bladder, radical prostatectomy, neurogenic bladder disease or negative advice by GP</td>
<td>At home interview</td>
<td>92% (83% (2 y))</td>
<td>Men in analysis sample similar to loss to follow-up</td>
<td>Cohort study</td>
<td>Validated single assessment question (scale: 4 grades)</td>
<td>Sometimes or never able to get and keep an erection adequate for satisfactory sexual intercourse</td>
</tr>
<tr>
<td>Schouten et al</td>
<td>Krimpen aan den Ijssel (The Netherlands)</td>
<td>All men registered in all general practices in Krimpen</td>
<td>50-78</td>
<td>No cancer of prostate or bladder, radical prostatectomy, neurogenic bladder disease or negative advice by GP</td>
<td>Self-administered questionnaire handed in at visit to health center / Clinic</td>
<td>50%</td>
<td>Participants more LUTS and better health status compared to 261 non-responders questioned</td>
<td>Cohort study</td>
<td>Cohort Study Two question assessment for obtaining and maintaining erection (scaled: 4 grades)</td>
<td>Erections with severely reduced rigidity or erection not possible</td>
</tr>
<tr>
<td>Shiri et al</td>
<td>Finland</td>
<td>Men living in Tampere or surrounding municipalities from national population register</td>
<td>50-75</td>
<td>No institutionalized patients</td>
<td>Mailed Self-administered questionnaire</td>
<td>62% (46% (5 y))</td>
<td>Men without follow-up were older and more frequently had a history of chronic disease</td>
<td>Cohort Study</td>
<td>Cohort Study Two question assessment for obtaining and maintaining erection (scaled: 4 grades)</td>
<td>NIH definition: inability to achieve or maintain erection sufficient for satisfactory sexual function.</td>
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<td></td>
<td>Scale 3 grades: Minimal: some difficulties Moderate: fairly/frequent Complete: intercourse does not succeed at all</td>
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</tr>
<tr>
<td>Authors</td>
<td>Johannes et al. (^{47}). (MMA Study)</td>
<td>Moreira et al. (^{49}).</td>
<td>Schouten et al. (^{50}). (Krimpen study)</td>
<td>Shiri et al. (^{51,52}).</td>
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<tr>
<td><strong>Alternative definition of ED</strong></td>
<td>NA</td>
<td>NA</td>
<td>Clinically relevant ED (including concern): Erections with reduced rigidity, severely reduced rigidity or erection not possible and quite a problem or a serious problem for the man</td>
<td>NA</td>
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<tr>
<td><strong>Mean follow-up (range) yrs.</strong></td>
<td>8.8 (?-?)</td>
<td>2 (1.7-2.3)</td>
<td>2.1 (1.8-3.3)</td>
<td>4.2 (3.6-5.8)</td>
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<tr>
<td><strong>Person years of follow-up</strong></td>
<td>7475</td>
<td>853</td>
<td>2135</td>
<td>2174</td>
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<tr>
<td><strong>Crude Incidence: Cases / 1000 person years (95% CI)</strong></td>
<td>25.9 (22.5-29.9)</td>
<td>65.6 (49.6-85.2)</td>
<td>32.8 (28.0-38.4)</td>
<td>28.1 (23.9-32.9)</td>
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<tr>
<td><strong>Age specific incidence rates Cases/1000 person years</strong></td>
<td>40-49 y 12.4</td>
<td>50-59 y 29.8</td>
<td>50-59 y 21.2</td>
<td>50-59 y 25.3</td>
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<tr>
<td></td>
<td>50-59 y 33.3</td>
<td>50-59 y 30.9</td>
<td>50-59 y 28.9</td>
<td>50-59 y 10.1</td>
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<tr>
<td></td>
<td>60-69 y 46.4</td>
<td>60-69 y 34.0</td>
<td>60-69 y 23.9</td>
<td>50-59 y 11.4</td>
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<tr>
<td></td>
<td>60-69 y 189.5</td>
<td>70-78 y 96.6</td>
<td>70-78 y 39.1</td>
<td>60-69 y 14.7</td>
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<tr>
<td></td>
<td>50-59 y 70-78 y 64.4</td>
<td>70-78 y 26.8</td>
<td>60-69 y 120</td>
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<td>60-65y 187 (129-271)</td>
<td>60-65y ALL 22 (17-29)</td>
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<td>Min 96 (77-120)</td>
<td>Min 49 (40-60)</td>
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<td>Mod 23 (18-29)</td>
<td>Min 166 (131-209)</td>
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<td>Comp 5 (3-8)</td>
<td>Mod 51 (41-62)</td>
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<td>Comp 23 (17-30)</td>
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<td></td>
<td>70-75y All 84 (64-110)</td>
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<td>Mod 92 (70-120)</td>
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<td></td>
<td>Comp 52 (39-69)</td>
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</tbody>
</table>
### Table 3. Sexual function incidence (1996–2004) without prevalent cases for men in the Olmsted County Study of Urinary Symptoms and Health Status among Men [48]

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Incident cases</th>
<th>Person-years</th>
<th>Incidence/1,000 man-years</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erectile dysfunction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>8</td>
<td>1,328</td>
<td>6</td>
<td>3, 12</td>
</tr>
<tr>
<td>50-59</td>
<td>54</td>
<td>4,406</td>
<td>12</td>
<td>9, 16</td>
</tr>
<tr>
<td>60-69</td>
<td>88</td>
<td>2,346</td>
<td>38</td>
<td>30, 46</td>
</tr>
<tr>
<td>70+</td>
<td>102</td>
<td>866</td>
<td>118</td>
<td>96, 143</td>
</tr>
<tr>
<td>40+</td>
<td>252</td>
<td>8,946</td>
<td>28</td>
<td>25, 32</td>
</tr>
<tr>
<td><strong>Low libido</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>13</td>
<td>1,333</td>
<td>10</td>
<td>5, 17</td>
</tr>
<tr>
<td>50-59</td>
<td>94</td>
<td>4,211</td>
<td>22</td>
<td>18, 27</td>
</tr>
<tr>
<td>60-69</td>
<td>98</td>
<td>2,269</td>
<td>43</td>
<td>35, 33</td>
</tr>
<tr>
<td>70+</td>
<td>96</td>
<td>813</td>
<td>118</td>
<td>96, 144</td>
</tr>
<tr>
<td>40+</td>
<td>301</td>
<td>8,626</td>
<td>35</td>
<td>31, 39</td>
</tr>
<tr>
<td><strong>Ejaculatory dysfunction</strong></td>
<td></td>
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<td></td>
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<tr>
<td>40-49</td>
<td>5</td>
<td>1,354</td>
<td>4</td>
<td>1, 9</td>
</tr>
<tr>
<td>50-59</td>
<td>41</td>
<td>4,481</td>
<td>9</td>
<td>7, 12</td>
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<tr>
<td>60-69</td>
<td>75</td>
<td>2,552</td>
<td>29</td>
<td>23, 37</td>
</tr>
<tr>
<td>70+</td>
<td>110</td>
<td>1,065</td>
<td>103</td>
<td>85, 124</td>
</tr>
<tr>
<td>40+</td>
<td>231</td>
<td>9,452</td>
<td>24</td>
<td>21, 28</td>
</tr>
<tr>
<td><strong>Perceived sexual problems</strong></td>
<td></td>
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<tr>
<td>40-49</td>
<td>9</td>
<td>1,362</td>
<td>7</td>
<td>3, 13</td>
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<td>50-59</td>
<td>37</td>
<td>4,495</td>
<td>8</td>
<td>6, 11</td>
</tr>
<tr>
<td>60-69</td>
<td>88</td>
<td>2,145</td>
<td>41</td>
<td>33, 51</td>
</tr>
<tr>
<td>70+</td>
<td>75</td>
<td>1,174</td>
<td>64</td>
<td>50, 80</td>
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<tr>
<td>40+</td>
<td>155</td>
<td>9,815</td>
<td>16</td>
<td>13, 18</td>
</tr>
<tr>
<td><strong>Low sexual satisfaction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>28</td>
<td>1,242</td>
<td>23</td>
<td>15, 33</td>
</tr>
<tr>
<td>50-59</td>
<td>119</td>
<td>3,796</td>
<td>31</td>
<td>26, 38</td>
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<tr>
<td>60-69</td>
<td>88</td>
<td>2,145</td>
<td>41</td>
<td>33, 51</td>
</tr>
<tr>
<td>70+</td>
<td>75</td>
<td>1,174</td>
<td>64</td>
<td>50, 80</td>
</tr>
<tr>
<td>40+</td>
<td>310</td>
<td>8,357</td>
<td>37</td>
<td>33, 41</td>
</tr>
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</table>
incidence rates based on two different follow-up periods. After an average follow-up of 2.1 years (range 1.8-3.3), a crude incidence rate of 32.8 cases per 1000 man-years was found (95% CI: 28.0-38.4). Furthermore, after an average follow-up of 4.2 years (range 3.6-5.8) a crude incidence rate of 19.2 cases per 1000 man-years was found (95% CI: 16.1-22.9). The annual incidence rate increased with each decade of age (Table 2).

In this study, an attempt was made to determine the incidence rate of “clinically relevant”- ED which means that “concern” of the man was considered in the definition. This analysis showed that the age-specific incidence rates as compared to the rates based on the usual definition of ED, were higher in the men aged 50-59, slightly lower in men between 60 and 69, but considerably lower in men above 70 years of age (Table 2). Based on an analysis of lost to follow-up cases, the authors conclude that the influence of this problem on age-specific incidence rates is negligible.

In another European study a target population of 3152 men born in 1924, 1934, or 1944 residing in Tampere, Finland, or 11 surrounding municipalities received by mail a questionnaire during the first quarter of 1994 with two questions regarding erectile dysfunction, trouble getting an erection or maintaining the erection once intercourse had begun.[51, 52] A similar questionnaire was sent in May, 1999. Analyses were performed on 1442 (46%) men responding at both time periods and answering the erectile questions. The erectile dysfunction was stratified into minimum (some difficulty in obtaining and/or maintaining erection), moderate (fairly frequently) or complete (intercourse does not succeed at all). Incidence rates varied for age groups and types of ED as shown in Table 2. The effect of age showed increasing incidence of ED and in this study diabetes was a major predictor of ED.

The most recent study was a longitudinal study of a group of men in the Olmsted County Study from Mayo clinic. [48] Men who had a history of prostate or bladder surgery, urethral surgery or stricture, or medical or other neurological conditions that could affect normal urinary function were excluded. These men were studied biennially from 1996 (when the brief male sexual function inventory (BSMSF) was first used in this population study) to 2004. Incidence rates for sexual dysfunctions were expressed as incidence per 1000 person years. Of the 2,213 men (mean age at baseline 58.39 years) who participated in the Olmsted county study, 1,827 men (83%) had complete data on sexual function. The person-years of follow-up ranged from 8,357 years for the sexual satisfaction domain to 9,815 years for the sexual problem assessment domain. Incidence data were stratified for decades of age from 40 years to 70 plus years. Results are shown in Table 3. Men who had ED at baseline experienced smaller declines in all sexual function domains compared to men who did not have ED at baseline. Other baseline characteristics, including education level; smoking status; and presence of diabetes, hypertension, or coronary heart disease, were not significantly associated with the rate of decline in sexual function. Change in erectile function was significantly correlated with change in all other sexual function domains. Correlations among changes in erectile function, sexual drive, and ejaculatory function were consistent across age groups. However, significantly smaller correlations between these measures, and sexual satisfaction and problem assessment were observed among older men, suggesting that while sexual function may worsen among these men, older men may be less likely to perceive this as a problem and be dissatisfied compared to younger men.

It is clear that there are large differences in incidence rates between these studies. Some of the differences can be explained by the design of the different studies. A younger baseline age (such as in the MMAS and Brazil study compared to the Krimpen study) would result in a population that is on average healthier. Surveys conducted as at home interviews might result in a baseline population that is less healthy than in a study where the men have to make an effort to visit a health center or clinic. An eligibility criterion such as in involvements with a sexual partner (MMAS) also theoretically results in a potentially healthier baseline population. Differences in socio-economic status (SES) between studies have probably played an important contribution to the variance in incident rates. In Brazil, more than one third of the men had less than 4 years of education. It is well known that level of education is a good proxy for SES.

The comparison of the different follow-up periods in the Krimpen study highlights that a longer follow-up leads to decrease of the crude incidence rate. There are several reasons why this is the case. ED may be a self-limiting problem in some men. After a longer follow-up, more men may have died or have become so ill that they cannot participate any further, leaving a healthier population for the follow-up measurements.

The above-mentioned factors and biases may work in one direction or the other, making it very difficult to compare studies in which one or more of the factors or biases may be at work. It is clear that it is impossible to identify “THE” incidence of ED. The most important common theme of the studies is the fact that incidence increases with age but also that concern in men above 60 and certainly above 70 is generally less, explaining the decreasing incidence of “Clinically-relevant”- ED. But there is also a censoring problem- differential mortality of the sick and less-well purges the older population of the potentially interested.

Table 2

Table 3
In the Krimpen study the crude incidence of 14.1 cases per 1000 person years for “Clinically relevant”-ED after a follow-up of 4.2 years is strikingly similar to the incidence of ED (8-10 cases per 1000 man years) that was recorded in general practices in the UK in men aged 40-79 years, which is somewhat younger than the Krimpen population. [54] The crude incidence rates for ED were very similar between the two studies from the United States but both included men who were mostly Caucasian. [47, 48] However the two year incidence rate for clinically relevant ED from the Netherlands was also very similar to these latter studies. [50]

2. INCIDENCE OF SEXUAL DYSFUNCTIONS IN WOMEN

In the early 1990’s, about 45% of Finnish women and 40% of men aged 18-74 reported decreased sexual desires during the past 5 years. [55] This incidence was closely age-related as less than 20% of women and men among those younger than 25 but 70-80% of those aged 55-74 reported decreased desire. Similar 5-year incidence (40% of women and 36% of men) was found in the mid 1990’s in Sweden. [56] In the latter investigation, 11% of women and 5% of men reported markedly decreased desire. One explanation for this decrease may be that with longer duration of partnership, desire tends to decrease [57] and, as discussed in Chapter 24, sexual desire, to a greater degree than sexual interest, may be seen as a partner-related aspect of sexuality, not really separable from arousal.

Recommendation 4. : 

There is a need for more incidence studies, from all regions of the world, for sexual dysfunction in men and women, even more so for all types of dysfunctions in women and other that ED in men. Grade C.

3. PREVALENCE OF SEXUAL DYSFUNCTIONS IN WOMEN AND MEN

As mentioned above, prevalence tables for sexual dysfunctions for women and men, Tables 4-6, were constructed from reports in peer review journal articles or books which met strict inclusion criteria of at least 10 of 15 possible assessment points from the Prins et al article. [7] One of the chairmen of this committee and at least one other of the members of the committee have screened all to meet the criteria. The literature was located through data-bases, the two previous chapters on epidemiology of Sexual Dysfunction from the past consensus consultations [5, 58], and surveys from Spector and Carey (1990) [59], Simons and Carey (2001) [60], Lewis [61], Kubin et al. [62] and Melman and Gingell. [63] A few of the references were found by crosschecking the bibliographies from the articles sourced by the methods stated above. All of the articles included in the tables furnish evidence at the lb hierarchical level. [6] There is, by and large, (in spite of different numbers of dysfunctions registered, different classifications of severity and different age strata studied) reasonably valid descriptive epidemiological data indicating that about 40-45% of adult women and 20-30% of adult men have at least one manifest (as opposed to mild – i.e. sporadically occurring – or none) sexual dysfunction defined according to the DSM-IV A- category. Assuming an approximately even distribution in societies worldwide, this means that about one third of all adults, at least in the western hemisphere where these investigations were conducted, have a manifest sexual dysfunction per se.

4. PREVALENCE OF WOMEN’S SEXUAL DYSFUNCTIONS

An overview of the reasonably valid studies on prevalence of women’s sexual dysfunctions, when feasible, dichotomized into mild/sporadic (MiD) and manifest (MaD) is given in table 4 which includes investigations with a reported response rate ≥ 40%. Among these eighteen descriptive epidemiological studies seven were from Europe, four from the USA, three from Australia, and one each from Canada, Iran, Morocco, and Puerto Rico. There were pronounced methodological differences between these studies. Thus, ten used face-to-face interviews. Five of the studies used mail questionnaires. Telephone interviews of varying length were utilized in three studies. While interviews, whether face-to-face or by telephone for pragmatic reasons, can be regarded reliable [25], there is in the literature some doubt about the reliability of mailed questionnaires. A main reason for this is that a mailed questionnaire may be answered in consensus between partners. Such a questionnaire may also yield a relatively low response rate. However, it is also possible that interviewees may be particularly prone to social desirability bias, where the presence of an interviewer results in respondents being more likely to give answers that they think will be socially acceptable.

Another difficulty is the difference in the age strata studied. As can be seen in table 4, the Icelandic investigation covered a very narrow age span – but included half the population at this age. Some focused only on elderly women while others cover an age span from the teens and up to old age. Two studies, the Finnish and the Swedish, from the sample selection and definatory points of view, can be regarded as twins. However, these two countries are neighbors with rather small total populations.

Even the time frame of having had sexual functions/ dysfunctions differs considerably. Thus, while some studies describe life long prevalence, others address the past year or even briefer periods (as three months or last month).
Table 4. Reasonably Valid epidemiological investigations of prevalence of women’s sexual dysfunctions. Prins score at least 10, response-rate at least 40%.

<table>
<thead>
<tr>
<th>Authors, Performed/published</th>
<th>Country/Regional National</th>
<th>Method Scale steps</th>
<th>Age years</th>
<th>n (% respons. Approx.)</th>
<th>Validity score (Prins)</th>
<th>Desire (D)</th>
<th>Interest (I)</th>
<th>Arousal (A) Lubrication (L)</th>
<th>Orgasm MiD/MaD</th>
<th>Dyspareunia MiD/MaD</th>
<th>Vaginismus MiD/MaD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osborn et al NG/1988</td>
<td>GB/R Interview 5</td>
<td>35-59</td>
<td>436</td>
<td>12</td>
<td>I-/17%</td>
<td>L-/17%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lindal, Stefansson 1987-88/1993</td>
<td>ICL/N Interview 2</td>
<td>55-57</td>
<td>417</td>
<td>14</td>
<td>D16%</td>
<td>6%*</td>
<td>4%**</td>
<td>3%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kontula, Haavio-Manilla 1992/1995</td>
<td>FI/N Interview 6</td>
<td>18-74</td>
<td>1146</td>
<td>13-14</td>
<td>D-/35%</td>
<td>L-/15%</td>
<td>63%/30%</td>
<td>30%/7%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Barlow et al 1993/1997</td>
<td>GB/R Interview 2</td>
<td>&gt;55</td>
<td>2011</td>
<td>10</td>
<td>-</td>
<td>L-/8%</td>
<td>-</td>
<td>2%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Johannes, Avis 1988-89/1997</td>
<td>USA/R Telephone 3</td>
<td>51-62</td>
<td>349</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-1/41%</td>
<td>-/13%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Group ACSF Bajos et al 1991-92/1998</td>
<td>FR/N Telephone 4</td>
<td>18-69</td>
<td>1137 (&gt;70%)</td>
<td>11</td>
<td>D55%/8%</td>
<td>-</td>
<td>44%/11%</td>
<td>43%/5%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Laumann et al 1992/1994,1999</td>
<td>USA/N Interview 2</td>
<td>18-59</td>
<td>1486 (79%)</td>
<td>13</td>
<td>I-/32%</td>
<td>L-/21%</td>
<td>-/26%</td>
<td>-/16%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fugl-Meyer group 1996-1999-2006</td>
<td>SE/N Interview 6</td>
<td>18-74</td>
<td>1475 (59%)</td>
<td>13-14</td>
<td>I 54%/33%</td>
<td>L 49%/13%</td>
<td>60%/22%</td>
<td>33%/6%</td>
<td>5%/1%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kadri et al NG/2002</td>
<td>MO/R Interview 5</td>
<td>&gt;20</td>
<td>465 (94%)</td>
<td>10</td>
<td>D-/18%</td>
<td>-/8%</td>
<td>-/12%</td>
<td>-/8%</td>
<td>-/6%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Richters et al 2000-01/2003</td>
<td>AU/N Telephone 2</td>
<td>16-59</td>
<td>8280 (65%)</td>
<td>13</td>
<td>I-/55%</td>
<td>L-/24%</td>
<td>-/29%</td>
<td>-/20%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Johnson et al 2004</td>
<td>USA Interview 18-96</td>
<td>1802 (87%)</td>
<td>13</td>
<td>D-/11%</td>
<td>A-/4%</td>
<td>-/16%</td>
<td>-/19%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 4. Reasonably Valid epidemiological investigations of prevalence of women’s sexual dysfunctions. Prins score at least 10, response-rate at least 40%. (Continued)

<table>
<thead>
<tr>
<th>Authors, Performed/published</th>
<th>Country/Regional National</th>
<th>Method Scale</th>
<th>Age years</th>
<th>n (% respons. Approx.)</th>
<th>Validity score (Prins)</th>
<th>Desire (D) MiD/MaD</th>
<th>Interest (I) MiD/MaD</th>
<th>Arousal (A) Lubrication (L) MiD/MaD</th>
<th>Orgasm MiD/MaD</th>
<th>Dyspareunia MiD/MaD</th>
<th>Vaginismus MiD/MaD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gruszecki et al 76. 2005</td>
<td>Canada Mailquest</td>
<td>15-44</td>
<td>1575 (50%)</td>
<td>12</td>
<td>D 41%/ -</td>
<td>-</td>
<td>-23%</td>
<td>-14%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dennerstein et al 73. 2006</td>
<td>AU Mailquest 2</td>
<td>18-74</td>
<td>1356 (70%)</td>
<td>13</td>
<td>D-9%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Safarinejad 75. NG/2006</td>
<td>Iran/N Interview 5</td>
<td>20-60</td>
<td>2424 (92%)</td>
<td>13</td>
<td>D/I 35%*</td>
<td>A 30%*</td>
<td>-37%</td>
<td>27%*</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eplov et al 74. 2007</td>
<td>DK/N Interview 3</td>
<td>16-67</td>
<td>4917 (86%)</td>
<td>13</td>
<td>D 53%/19%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hayes et al 39. 2008</td>
<td>AU/N Interview 3</td>
<td>20-70</td>
<td>12 D-/16%</td>
<td>12</td>
<td>A-/7%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Shifren et al 70. 2008</td>
<td>USA Mailquest 2</td>
<td>18-102</td>
<td>31581 (63%)</td>
<td>14</td>
<td>D-/39%</td>
<td>A-/26%</td>
<td>-21%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Avellanet et al 72. 2008</td>
<td>Puerto Rico Mailquest 1</td>
<td>40-59</td>
<td>919 (55%)</td>
<td>12</td>
<td>D* 41%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

MiD = mild, sporadically occurring dysfunction. MaD = manifest dysfunction occurring at least quite often. NG = Not given. *excitement **anorgasmia
Also definitions and classification of severity vary considerably ranging from DSM-III or DSM-IV based face-to-face interviews which post hoc are transformed into a yes/no dichotomy and up to strictly structured questions applying 4, 5, or 6 graded scales. Regardless of the method used, there appears to be reasonable consensus at the turn of the century [20, 65, 70] that the prevalence of women who report at least one manifest sexual dysfunction is in the order of about 40-50%.

a) Interest/Desire

As pointed out in chapter 24, the defined category “desire” is probably not separable from the psychological aspects of arousal – yet another argument for universal consensus. Furthermore, interest and desire seems to be equivalent for several authors.

Using different methods and scaling, descriptive epidemiological investigations have found that the prevalence of manifest low level of sexual interest varies between 17% (GB) in 35-59 year old women [64] through 33-35% (USA 18-59 years old, Sweden 18-74 years old, Iran 20-60 years old) [20, 65, 75] and up to 55% in Australia [37,]. Neither in the USA [20] nor in Sweden [56] is there an age dependency up to the age of about 60-65. In Australia 16-19 year old teenagers had significantly lower level of sexual interest dysfunction than older cohorts. A major difference between the USA and Sweden in this respect was that the oldest Swedish women had considerably higher prevalence than the 18-59 year old USA women but clearly lower prevalence among the youngest women. In Sweden, 54% of the 18-74 year old women reported mild (sporadically occurring) dysfunction during the preceding year. This is very close to the French 55% prevalence [69] of mild desire dysfunction. Both those with manifest and those with mild dysfunctions had significantly lower level of overall sexual satisfaction than had those with none of these dysfunctions [27].

Low level of sexual desire was reported in Puerto Rico in as much as 41% of 40-59 year old women [72]; however, the definition utilized by the authors does not provide enough information to determine whether symptoms were mild or manifest. This “loss of libido” was associated with greater symptoms of depression. Manifest low desire dysfunction was reported in as much as 39% in the large scale investigation of American women 18-102 years old [70] and in 35% of Finnish women aged 18-74 [55]. Shifren et al. [70] found desire dysfunction to be more prevalent in the 45-64 age-cohorts. In this study 15-25% of women younger than 55 had this dysfunction; but the prevalence increased to about 50% in women aged 55-74. Lower levels of manifest desire dysfunction – about 10% - were reported from Sweden, France, USA, and Australia (of 18-74 year olds [27, 68, 71, 73] Hayes et al [2] found 16% of Australian women with manifest desire dysfunction and a Danish study by Epol et al [74], found that 19% of women 16-67 year old have a manifest desire dysfunction. Greater desire levels were found in younger women, physically active, unmarried, with no children under 15 years, in good physical and mental health and without medication. Concerning age related desire dysfunction the Swedish prevalence (11%) doubled to 22% in those 50-65 years of age and again doubled to 47% in the 66-74 year olds. These numbers appear to agree rather well with those reported in Iceland [66] and in Morocco [24], while in France [69] clearly fewer have manifest, but 55% have mild desire dysfunction.

b) Arousal and Lubrication

As previously mentioned, the traditional biologic definition of arousal nearly exclusively covers genital events, foremost lubrication. However, these genital events may not at all be accompanied by psychosexual pleasure (i.e. “arousal”). The obvious need of redefining arousal in relation to desire is discussed in chapter 24.

Using the DSM-IV definition, 16% of 55-57 year old Icelandic women were found to have low levels of excitement [66]. Furthermore, arousal disorder was found to have occurred in 26% of American (aged 18-102) and in 30% of Iranian (aged 20-60) women. However, most valid epidemiological research has focused on genital response in terms of vaginal dryness/insufficient lubrication. Even in this aspect, there are considerable differences between epidemiological data (table 4). Generally, manifest lubrication dysfunction is prevalent in 8-15%, while Laumann et al [20] and Richters et al [37] reported this to be the case in 21-28% of sexually active women. These investigations used a dichotomous yes/no scale. Safarinejad [75] found 34% of lubrication dysfunction in Iranian women. Öberg et al [27] found that 49% of Swedish women aged 18-65 years had mild (sporadically occurring) lubrication insufficiency. Some studies have evidenced that with increasing age, in particular age >50 years, lubrication insufficiency becomes more prevalent [64, 68], while others have not found age dependency in this respect [20].

c) Orgasm

The prevalence of manifest orgasmic dysfunction varies considerable in the available epidemiological reports. Again, this may to a great extent be due to de facto incompatibilities of reports. Nevertheless, it appears that in Australia [37,], Sweden [65], the USA [20, 70, 71] and Canada [76] the prevalence of manifest orgasmic dysfunction is about 16-25% and in Iran as high as 37% [75]. In most of these countries, age dependency has not been traced; while in Australia for about the same overall
prevalence, 50-59 year old women were more likely to report orgasmic dysfunction than were those aged between 16 and 49 years. An age-dependency was also found in the Iranian sample. Also, in the USA orgasmic dysfunction was more prevalent among women 45 or older. A somewhat higher prevalence of orgasmic dysfunction (30%) has been reported from Finland [55]. A significant higher prevalence (41%) of manifest orgasmic dysfunction among 51-62 year old women has been reported from Massachusetts [68]. In other studies [24, 39, 64, 68, 71], the prevalence of manifest orgasmic dysfunction is much lower (11-16%), while that of mild orgasmic dysfunction is remarkably high (about 60%) in the two Nordic countries, where identical methodology were used. Thus, in these two countries, more than 80% of all sexually active women aged 18-74, age independently; report some degree of orgasmic dysfunction.

In Swedish women it was found that women reached orgasm more easily through stimulation of both clitoris and vagina, and furthermore, experienced women reported more pleasurable orgasms during intercourse when the penis was in the vagina. During masturbation a small minority stimulated only the vagina. For American women use of marijuana and alcohol was associated with greater orgasmic dysfunction.

Dyspareunia and Vaginismus

These conditions are discussed in Chapter 25. The syndromes are clearly less prevalent in the general population. Thus, 6% of the Moroccan [24] and Swedish [64] women reported some degree of vaginismus, which does not appear to be related to age. The prevalence of manifest dyspareunia has been reported as low as 1% in Australian women [72] and 2% in elderly British women [66] while another studies [20, 37, 68, 71, 75, 76] found that dyspareunia prevailed in as many as 14-27%. Mild (sporadically occurring) dyspareunia is 4-8 fold more common than is manifest. Several investigations have described increasing dyspareunia with increasing age [21, 65, 78] while in Australia the opposite has been found with a systematic decrease of reported physical pain during intercourse from the age of 30 years and onwards [37].

5. PREVALENCE OF MEN’S SEXUAL DYSFUNCTIONS

a) Desire/Interest

Altogether we have identified 24 epidemiologically valid reports (table 5) that include men’s interest and/or desire. Whereas in Sweden [65] and the USA [20] the prevalence of low or decreased level of sexual interest during the last 12 months by and large are remarkably similar and age independent up to the age of about 60 years, a sharp increase appears to emerge at older age. It is, therefore not surprising that the elderly population of men, with greater prevalence of, for instance, ED (see below) is not more sexually distressed than their younger peers. In Australia [37], Argentina [82], Southeast Asia [85], Korea [94], and Italy [92], a clearly higher prevalence of desire/interest dysfunction, without any pronounced age effect, of about 25% was reported by 16-59 and 40-80 year old men. In the study from the Netherlands [100], a very high incidence of desire problems were reported, 41-58% from ages 58-78 years. Generally dysfunction of sexual desire/drive is much less prevalent than dysfunction of interest, whether life-long (France [69] and Iceland [66]) or during the past year (Sweden [65]) or so. However, at higher ages (50-65 and >70) both Panser et al [77], the Swedes [65] have demonstrated sharp increase also in this prevalence. A national random sampled population of men in China reported a prevalence rate of 53% at anytime within the previous year and 11% for persistent lack of interest for the most part increasing with age. [84] In summary the populations’ level of sexual interest appears quite stable from the late teens and up to about 60, where after it decreases markedly. The same may be true for sexual desire/drive which may in many men, however, start to decline already around the starts of their 6th decade of life. In general studies reported in this chapter since the last consultation for prevalence of desire/interest have been reported for 40-80 year olds without age adjustment to range from 8 to 18% around the world except for the citations presented above. (See Table 5)

b) Ejaculation Dysfunctions

Ejaculation is distinct from orgasm, which is a purely cerebral cortical event. If current understanding of ejaculation is limited, the knowledge regarding orgasm remains even more obscure. It is not until very recent time that is was accepted that ejaculatory disorders may have a neurobiological origin rather than being a pure psychological issue. [102]

We have been able to locate [22] descriptive epidemiological investigations of ejaculatory disturbances fulfilling our validity criteria. These are given in table 5. The prevalence varies from 8% and up to 30% for all age groups covered by the tabulated data for early or premature ejaculation. Two exceptions to this were a prevalence of 55% in 50 to 59 year old men in one US study [20] and a very low prevalence in 18-75 year olds surveyed in London where the rate of 3.7% was seen [81]. The 15% life-time prevalence found in France [69] covers 5% who often had experienced ejaculation prior to penetration and 10% who often had ejaculated too rapidly after vaginal intromission. The 2-3 fold higher prevalence expressed as “climax too early” and still higher for 50-59 year old men reported from the USA may be a result of the dichotomous scale (yes/no)
Table 5. Valid epidemiological investigations (arranged according to publication year) of prevalence of men’s sexual dysfunctions. Erectile dysfunction not included.
<table>
<thead>
<tr>
<th>Authors (s) Performed/ Published</th>
<th>Country Regional National</th>
<th>n</th>
<th>Method</th>
<th>Age</th>
<th>Desire (D) Interest (I)</th>
<th>Early Ejaculation</th>
<th>Delayed Ejaculation</th>
<th>Orgasm</th>
<th>Dyspareunia</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fugl-Meyer</td>
<td>Sweden/N</td>
<td>1475</td>
<td>Interview</td>
<td>18-74</td>
<td>3%/16%</td>
<td>9%</td>
<td>2%</td>
<td>-</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Fugl-Meyer&lt;sup&gt;65&lt;/sup&gt; 1996/1999</td>
<td></td>
<td></td>
<td></td>
<td>18-24</td>
<td>1%/6%</td>
<td>4%</td>
<td>4%</td>
<td>-</td>
<td>&lt;1%</td>
<td></td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>25-34</td>
<td>2%/16%</td>
<td>7%</td>
<td>0</td>
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<td>&lt;1%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>35-49</td>
<td>1%/15%</td>
<td>8%</td>
<td>2%</td>
<td>-</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-65</td>
<td>22%/18%</td>
<td>8%</td>
<td>3%</td>
<td>-</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>66-74</td>
<td>4%/41%</td>
<td>14%</td>
<td>10%</td>
<td>-</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td>Blanker et al&lt;sup&gt;9&lt;/sup&gt; 1995-98/2001</td>
<td>Nether-lands/R</td>
<td>1605</td>
<td>Questionnaire</td>
<td>50-78</td>
<td>13%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Richters et al&lt;sup&gt;7&lt;/sup&gt; 2000-01/2003</td>
<td>Australia/N</td>
<td>8517</td>
<td>Telephone</td>
<td>16-59</td>
<td>(I) 25%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16-19</td>
<td>25%</td>
<td>-</td>
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<td></td>
<td>20-29</td>
<td>20%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>30-39</td>
<td>22%</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40-49</td>
<td>29%</td>
<td>-</td>
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<td></td>
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<td></td>
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<td>50-59</td>
<td>32%</td>
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<tr>
<td>Rosen et al&lt;sup&gt;60&lt;/sup&gt; 2001/2003</td>
<td>US/Europe: UK, Italy, France, Germany, Nether-lands, Spain</td>
<td>All 12,815, Eur 10,900</td>
<td>CS/SAQ</td>
<td>50-59</td>
<td>28.7%</td>
<td>55.4%</td>
<td>73.8%</td>
<td>46.2%</td>
<td>45.3%</td>
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<td></td>
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<td>60-69</td>
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<td></td>
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<td></td>
<td></td>
<td>70-80</td>
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<td></td>
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<td></td>
<td>All  Europe</td>
<td>45.3%</td>
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<tr>
<td>Nazareth et al&lt;sup&gt;81&lt;/sup&gt; not reported/2003</td>
<td>London (UK)</td>
<td>447</td>
<td>CS/SAQ</td>
<td>18-75</td>
<td>6.7 (4.6 – 9.4)%</td>
<td>3.7 (2.1 – 5.7)%</td>
<td>2.4 (1.2 – 4.4)%</td>
<td>1.1 (0.4 – 2.6)%</td>
<td></td>
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</table>
Table 5. Valid epidemiological investigations (arranged according to publication year) of prevalence of men’s sexual dysfunctions. Erectile dysfunction not included. (continued)

<table>
<thead>
<tr>
<th>Authors (s)</th>
<th>Country</th>
<th>n</th>
<th>Method</th>
<th>Age</th>
<th>Desire (D)</th>
<th>Early Ejaculation</th>
<th>Delayed Ejaculation</th>
<th>Orgasm</th>
<th>Dyspareunia</th>
<th>Other</th>
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<td>Regional</td>
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<td></td>
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<tr>
<td></td>
<td>National</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Nolazco et al&lt;sup&gt;82&lt;/sup&gt; 2001/2004</td>
<td>Argentina/R</td>
<td>2715</td>
<td>Interview by questionnaire</td>
<td>34.97</td>
<td>23.8%</td>
<td>28.3%</td>
<td>14.1%</td>
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<tr>
<td>Enzlin et al&lt;sup&gt;83&lt;/sup&gt; 1999 /2004</td>
<td>Belgium</td>
<td>799</td>
<td>CS/SAQ</td>
<td>40-49</td>
<td>2.7%</td>
<td>-</td>
<td>-</td>
<td>1.8%</td>
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<table>
<thead>
<tr>
<th>Age</th>
<th>Desire (D)</th>
<th>Early Ejaculation</th>
<th>Delayed Ejaculation</th>
<th>Orgasm</th>
<th>Dyspareunia</th>
<th>Other</th>
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<tr>
<td></td>
<td>40-49</td>
<td>4.7%</td>
<td>-</td>
<td>-</td>
<td>1.8%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>50-59</td>
<td>9.9%</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td></td>
<td>60-69</td>
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<td>-</td>
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</table>
Table 5. Valid epidemiological investigations (arranged according to publication year) of prevalence of men's sexual dysfunctions. Erectile dysfunction not included. (continued)

<table>
<thead>
<tr>
<th>Authors (s) Performed/ Published</th>
<th>Country Regional National</th>
<th>n</th>
<th>Method</th>
<th>Age</th>
<th>Desire (D) Interest (I)</th>
<th>Early Ejaculation</th>
<th>Delayed Ejaculation</th>
<th>Orgasm</th>
<th>Dyspareunia</th>
<th>Other</th>
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<tbody>
<tr>
<td>Nicolosi et al. \textsuperscript{a} 1997-1998/2004</td>
<td>Northern Europe Austria/Belgium Germany/Sweden UK</td>
<td>13618 (19%)</td>
<td>CS/SAQ</td>
<td>All</td>
<td>40-49</td>
<td>7%</td>
<td>13%</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>9%</td>
<td>14%</td>
<td>6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60-69</td>
<td>12%</td>
<td>17%</td>
<td>11%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70-80</td>
<td>16%</td>
<td>18%</td>
<td>17%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>40-80</td>
<td>9(9-10)%</td>
<td>14(14-15)%</td>
<td>7(7-8)%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Southern Europe Italy/France/ Israel/Spain</td>
<td></td>
<td></td>
<td>North. Europe</td>
<td>7(6-8)%</td>
<td>10(9-11)%</td>
<td>5(4-6)%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-European West Australia/Canada New Zealand South Africa/US</td>
<td></td>
<td></td>
<td>South. Europe</td>
<td>6(5-7)%</td>
<td>13(12-15)%</td>
<td>7(6-8)%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Central/South America Brazil/Mexico</td>
<td></td>
<td></td>
<td>Non- Europe West</td>
<td>9(8-11)%</td>
<td>16(14-17)%</td>
<td>8(7-9)%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Middle East Algeria/Egypt/ Morocco/Turkey</td>
<td></td>
<td></td>
<td>Central South. Amer.</td>
<td>9(7-11)%</td>
<td>22(19-25)%</td>
<td>8(6-11)%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>East Asia China/Hong Kong/Japan/ Korea/Taiwan</td>
<td></td>
<td></td>
<td>Middle East</td>
<td>13(11-15)%</td>
<td>8 (7-10)%</td>
<td>7(6-9)%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Southeast Asia Malaysia/ Philippines/ Singapore/ Thailand</td>
<td></td>
<td></td>
<td>East Asia</td>
<td>12(11-14)%</td>
<td>19 (17-21)%</td>
<td>10(9-12)%</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SE Asia</td>
<td>20(17-23)%</td>
<td>25 (22-29)%</td>
<td>15(13-18)%</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Table 5. Valid epidemiological investigations (arranged according to publication year) of prevalence of men’s sexual dysfunctions. Erectile dysfunction not included. (continued)

<table>
<thead>
<tr>
<th>Authors(s)</th>
<th>Country</th>
<th>Regional National</th>
<th>n</th>
<th>Method</th>
<th>Age</th>
<th>Desire (D) Interest (I)</th>
<th>Early Ejaculation</th>
<th>Delayed Ejaculation</th>
<th>Orgasm</th>
<th>Dyspareunia</th>
<th>Other</th>
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<tr>
<td>Moreira et al&lt;sup&gt;86&lt;/sup&gt; 2001-2002/2005</td>
<td>Brazil/N</td>
<td></td>
<td>471</td>
<td>Computer-assisted telephone interview survey</td>
<td>40-80</td>
<td>11.2%</td>
<td>30.3%</td>
<td>-</td>
<td>14.0%</td>
<td>4.6%</td>
<td>-</td>
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<tr>
<td>Moreira et al&lt;sup&gt;87&lt;/sup&gt; 2001-2002/2005</td>
<td>Germany/N</td>
<td></td>
<td>750</td>
<td>Computer-assisted telephone interview survey</td>
<td>40-80</td>
<td>8.1</td>
<td>15.4</td>
<td>-</td>
<td>5.6</td>
<td>1.8</td>
<td>-</td>
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<tr>
<td>Moreira et al&lt;sup&gt;88&lt;/sup&gt; 2001-2002/2005</td>
<td>Spain/N</td>
<td></td>
<td>750</td>
<td>Computer-assisted telephone interview survey</td>
<td>40-80</td>
<td>16.9</td>
<td>31.2</td>
<td>-</td>
<td>15.3</td>
<td>3.6</td>
<td>-</td>
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<td>Nickel et al&lt;sup&gt;89&lt;/sup&gt; 2003/2005</td>
<td>Europe, Latin America, Middle East, Asia, Canada</td>
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<td>5096</td>
<td>Questionnaire</td>
<td>Mean 65.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Painful ejaculation 16.8%</td>
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<td>Oksuz et al&lt;sup&gt;90&lt;/sup&gt; 2004/2005</td>
<td>Turkey</td>
<td></td>
<td>2288</td>
<td>Survey/SAQ</td>
<td>15-60</td>
<td>7.3%</td>
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</table>
Table 5. Valid epidemiological investigations (arranged according to publication year) of prevalence of men’s sexual dysfunctions. Erectile dysfunction not included. (continued)

<table>
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<tr>
<th>Authors (s) Performed/ Published</th>
<th>Country Regional National</th>
<th>n</th>
<th>Method</th>
<th>Age</th>
<th>Desire (D) Interest (I)</th>
<th>Early Ejaculation</th>
<th>Delayed Ejaculation</th>
<th>Orgasm</th>
<th>Dyspareunia</th>
<th>Other</th>
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<tr>
<td>Stulhofer et al&lt;sup&gt;PR&lt;/sup&gt; 2004/2005</td>
<td>Croatia</td>
<td>888</td>
<td>RPS</td>
<td>≤39</td>
<td>-</td>
<td>15.7%</td>
<td>10.9%</td>
<td>-</td>
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<tr>
<td>Corona et al&lt;sup&gt;PR&lt;/sup&gt; 2001-2004/2005</td>
<td>Italy</td>
<td>1563</td>
<td>Interview/SAQ</td>
<td>18-88</td>
<td>35.9%</td>
<td>-</td>
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<tr>
<td>Basile-Fasolo et al&lt;sup&gt;PR&lt;/sup&gt; 2001/2005</td>
<td>Italy</td>
<td>12558</td>
<td>Survey/SAQ</td>
<td>&lt;40</td>
<td>-</td>
<td>31.8%</td>
<td>17.6%</td>
<td>-</td>
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<td>Moreira et al&lt;sup&gt;PR&lt;/sup&gt; 2001-2002/2006</td>
<td>Korean/N</td>
<td>600</td>
<td>Intercept Protocols</td>
<td>40-80</td>
<td>28.3</td>
<td>32.7</td>
<td>-</td>
<td>19.3</td>
<td>6.1</td>
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<tr>
<td>Brock et al&lt;sup&gt;PR&lt;/sup&gt; 2001-2002/2006</td>
<td>Canada/N</td>
<td>500</td>
<td>Computer-assisted telephone interview survey</td>
<td>40-80</td>
<td>15.2</td>
<td>22.5</td>
<td>-</td>
<td>11.8</td>
<td>4.4</td>
<td>-</td>
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<tr>
<td>Parish et al&lt;sup&gt;PR&lt;/sup&gt; 2001-2002/2008</td>
<td>China/N</td>
<td>1,261</td>
<td>Computer-assisted interview</td>
<td>20-64</td>
<td>53 anytime last year 11% ≥ 2 months</td>
<td>69% anytime last year 8% ≥ 2 mths.</td>
<td>-</td>
<td>52% last year 5% ≥ 2 months</td>
<td>25% anytime last year 2% ≥ 2 months</td>
<td>Performance Anxiety 49% last year 4% ≥ 2 months</td>
</tr>
<tr>
<td>Moreira et al&lt;sup&gt;PR&lt;/sup&gt; 2001-2002/2008</td>
<td>UK and Europe/N</td>
<td>4500</td>
<td>Comp.assttele interview</td>
<td>40-80</td>
<td>15.1</td>
<td>19.8</td>
<td>-</td>
<td>13.7</td>
<td>2.9</td>
<td>-</td>
</tr>
<tr>
<td>Authors (s)</td>
<td>Country Regional National</td>
<td>n</td>
<td>Method</td>
<td>Age</td>
<td>Desire (D) Interest (I)</td>
<td>Early Ejaculation</td>
<td>Delayed Ejaculation</td>
<td>Orgasm</td>
<td>Dyspareunia</td>
<td>Other</td>
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<tr>
<td>Moreira et al¹⁷ 2001-2002/2008</td>
<td>Australia/N</td>
<td>750</td>
<td>Computer-assisted telephone interview survey</td>
<td>40-80</td>
<td>17.5</td>
<td>23.3</td>
<td>-</td>
<td>13.9</td>
<td>2.7</td>
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<td>Laumann et al⁸ 2001-2002/2009</td>
<td>USA/N</td>
<td>742</td>
<td>Computer-assisted telephone interview survey</td>
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<td>18.0</td>
<td>26.2</td>
<td>-</td>
<td>12.4</td>
<td>3.1</td>
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<td>Andersen et al⁹ 2004/2008</td>
<td>Denmark</td>
<td>863</td>
<td>RPS</td>
<td>20-45</td>
<td>3%</td>
<td>24%</td>
<td>-</td>
<td>2%</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Korfage et al¹⁰¹ 1993-1999/2008</td>
<td>Netherlands</td>
<td>3893</td>
<td>CS/SAQ</td>
<td>58-61</td>
<td>40.8%</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td></td>
<td></td>
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<td>62-64</td>
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<td>41.4%</td>
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<td></td>
<td></td>
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<td>65-67</td>
<td></td>
<td>46.1%</td>
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<td></td>
<td></td>
<td></td>
<td>68-70</td>
<td></td>
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<td></td>
<td></td>
<td>71-78</td>
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<td>57.7%</td>
<td>-</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>Corona et al¹⁰⁷ 2001-2007/2008</td>
<td>Italy</td>
<td>2437</td>
<td>Interview/SAQ</td>
<td>51.9 ± 13.0</td>
<td>25.9%</td>
<td>4.4%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Valid epidemiological investigations (arranged according to publication year) of prevalence of men’s sexual dysfunctions. Erectile dysfunction not included. (continued)
used by Laumann et al [20] while the European investigations used pluri-step scales. However, more recent surveys reported in Table 5 from the last consultation have shown higher prevalence rates for early or premature ejaculation from around the world and particularly from Asia and Latin America. An exception was the study from China in which a rate of persistent premature ejaculation was 8% (≥ 2 months), a rate of 69% of any occurrence of the complaint within the previous year. In a recent study not shown on the Table 5 Ahn et al reported from Korea in 1,570 men aged 40-79 years of age. A prevalence rate of 24.9% for not being able to control their ejaculation time, further broken down based on self-reported intravaginal ejaculation latency time a rate of 11% for a 2 minute cutoff time and 33.1% for a 5 minute cutoff time increasing significantly with aging. [103] Still fewer investigators have reported on the prevalence of delayed ejaculation. [64, 68, 80, 82, 84, 101] (See Table 5) Rates for this disorder vary from 1 to 10%.

It is, in fact, probable that many men who have difficulties in maintaining an erection during vaginal intercourse also report delayed ejaculation. Hence the already relatively low reported prevalence may be exaggerated. These prevalence studies applied various frequently non-validated definitions of and methodologies for evaluation of early ejaculation. However, it should be emphasized that normative data on ejaculation latency time obtained by the stopwatch method in the general male population are mandatory to really establish the prevalence of early ejaculation. Obviously, an accurate definition of early ejaculation is necessary, not only for clinical diagnosis and treatment, but also for comparing data from different studies and performing epidemiological studies. [102] Unfortunately, there is a real paucity of studies dealing with either clinical or non-clinical samples from which we can really draw valid figures in keeping with the Prins’ criteria listed elsewhere. Since definitions regarding ejaculatory, orgasmic and desire disorders in males, broadly known and accepted, were lacking, this “scenario” was in some way expected.

One of the problems of surveys regarding early ejaculation is the inconsistency of how the condition is defined. Some investigators have defined PE as ejaculation which occurs within one minute of vaginal penetration whereas others have defined PE as ejaculation which occurs within seven minutes of penetration. [23] Other investigators have defined premature ejaculation based on the number of thrusts between vaginal penetration and ejaculation. [104] or sense of control over ejaculation. [105] Giuliano et al [106] proposed that PE be defined by a combination of direct measures of ejaculatory latency and patient reported outcomes. In 2007, the International Society for Sexual Medicine convened an international panel to review current evidence and to recommend an evidence-based definition. This committee proposed that lifelong PE in heterosexual men be defined as ejaculation which always or nearly always occurs prior to or approximately one minute after vaginal penetration on all or nearly all vaginal penetrations with negative personal consequences. [23] It is recommended that future research adopt this definition. There is insufficient data at this time to precisely define acquired PE or PE in other sexual activities.

c) Orgasm

It is, at least in men, quite difficult to assess the prevalence of orgasmic dysfunction. The simple reason being that, in contrast to many men with complete spinal cord injury, some men may be unable to distinguish between ejaculation and orgasm. In the USA 8% age independently reported that they had been unable to achieve orgasm (cf Table 5) during the last year. [20] A much lower prevalence (<1%) was reported in 55-57 year old Icelandic men [66]; while in France [69] the (life-time) prevalence of men’s organic dysfunction was (7%). Since the last consultation 13 of the 23 published prevalence data for male dysfunctions other than ED have reported orgasm problem analysis in their surveys. Most of the studies report a prevalence rates in the range of 11.8-19.4%. (See Table 5) Nicolosi’s world-wide report showed 5-8% for all areas of the world except for East and Southeast Asia where the prevalence was 10-15%. [85] Five of the surveys reported lower rates, Nazareth from London reported a prevalence rate of 2.4% [81], Enzlin from Belgium, a rate of 1.8% [83], Moreira from Germany, a rate of 5.6% [87], Corona from Italy, a rate of 4.4% [101], and Parish from China a rate of 5% [84]. This last study reported a rate of 52% for occurring anytime in the previous years versus the 5% rate for persistent greater than 2 month’s occurrence.

d) Dyspareunia

The prevalence of genital pain in men during sexual intercourse has only been fragmentarily studied (Table 5). In France [69] 5% of the adult male population (of 18 to about 70 years) report that they at least quite often suffer such pain. This rate from 3-6% was reported in seven studies (see Table 5) Clearly lower prevalence of 1% -2% have been found in Finland [55], Sweden [65], China [84], the Netherlands [79], London [81], and Germany [87]. The China study reported a rate of 25% when occurring anytime within the previous year but only 2% for persistent greater than 2 month’s occurrence [84]. With this low prevalence it is hardly surprising that no age-dependency of men’s dyspareunia has been found. Nickel and al reported a prevalence rate of painful ejaculation on a world survey of 16.8%. [89]
e) Erectile Dysfunction

Tables 6A-F are compilations of the data from 59 studies around the world regarding prevalence of ED (male sexual arousal dysfunction) from 1993 to 2009. At the time of the first consultation on ED there were very few studies that would meet this more stringent evidence-based criteria. In fact, 24 studies in this table were presented in the last chapter, only six were included in the first consultation chapter. [5, 58] There continues to be a better global representation. Again it should be stressed that in order to adhere to the most scientifically valid studies to be included only those studies that obtained a Prins score of 10 or above are included in these tables. There have been several other epidemiologic studies that have been published regarding prevalence of ED but they do not meet this standard for scientific validity. The Prins scores are included in Table 6 in the first columns so that the readers can be aware of those with higher scientific validity. There are 5 studies from Asia and 4 from Australia (Table 6A and B). There are 30 studies from Europe (6C), 7 papers from South and Central America, 7 from North America, and 6 studies classified as worldwide representing data collected in different regions of the world and published as a single paper. For the European studies; 4 each were from the Netherlands and the United Kingdom, 3 each from Finland, France and Germany, 2 each from Denmark, Sweden, Spain and one each from Italy, Belgium, Turkey, Croatia, and Portugal. Two of the studies were European multinational. Most of the Latin American studies were from Brazil except one study from Columbia, Venezuela, and Ecuador. The North American studies were all from the US except one Canadian report.

Design of the studies included survey questionnaire only (survey) or cross-sectional study with additional measurements (CS) and the table shows 30 of the former and 28 of the latter. Richter’s data from Australia was conducted by telephone and was a single question only. [37] Self-administered questionnaires was the instrument used in 40 of the survey designed studies and interviews in the remaining 19 of these. In the cross-sectional studies all studies used the instrument of self-administered questionnaires except one study from Wales [127] which used an interview. A unique feature of a study from Denmark was that 100 of the men who had not reported ED on the self-administered questionnaire were subsequently interviewed in an office setting and seven of these reported at the interview ED of a significant nature, thus increasing the original 4% percentage of ED in this group of 51 year old Danish males by 7% in these 100 men. [112, 113]

However, as in the case for women’s dysfunctions, there is great variety in methodologies of the studies. The authors of this chapter have eliminated many reported categories of mild ED reported in some of the studies, since that particular description is so varied. The definition of ED used for the particular study and reported on the table is included in table 6 A-F. The reader can see that the definition of ED varied among the studies and thus comparison between studies is from the beginning hampered. Time period covered by the questions about ED varied from one month to one year, and 10 of the studies did not specify a time period questioned about ED.

Most were random population studies, some stratified by age or region. The Japanese study from Masumori included all men 40-79 years of age in a fishing village with 42.3% participating the study. [107] In the study from Denmark reported by Solstad and Hertoft [112-113], all men of the age of 51 year from selected communities were sent questionnaires with an 81% response rate. Five of the studies were from general practice (GP) settings; three that included all men registered in the general practice. These three included one from the United Kingdom, 40 years and older, with a 65% response rate [117], one from the Netherlands, 50-75 years of age, with a 47% response [79, 124-125], and one from Wales, UK, 55-75 years of age, with a 50% response rate [127]. Two of the other studies were random population studies of the GP registrations, one from the United Kingdom, 18-75 years of age, with a 39% response [78, 119] and one from Italy, age 18 years and older, with a 82% response rate [120]. The percentage of response was determined from data presented in the paper or chapter regarding the eligible number who were scheduled to be screened and ranged from 17 to 82%. Only eight of the fifty-nine were under 500 participants in number. Eight of the studies reported no differences between responders and non-responders and another 12 did report differences as summarized in the table. Thirty-nine did not address this issue.

All the studies which were stratified by age showed rising prevalence of ED as the population aged. Two of the Asian studies showed doubling of the prevalence rate at age 60-70 with almost another doubling at age 70-79 years. [107-108] The study not stratifying from Korea reported a 31.9% prevalence rate for ages 40-80 which seemed to represent a mean of the stratified studies. [94] The more recent Korean report stratified by age showed a tripling of the prevalence for the 60-69 age group compared to those younger whether self reported or scored by IIEF. [103] In that same study using IIEF-5 diagnosis of \( \frac{17}{17} \) as defining ED tripled the self-reported ED in the younger age groups and the total group and doubled it for the older age groups. [see Table 6A]

One of the Australian reports did not show much of a difference in prevalence over stratification from 16-59 years until age 40 was reached and then the prevalence was low for the 40-49 and 50-59 year decades of 13 and 19%. [37] The other stratifying for
### Table 6A. Asian Prevalence of Erectile Dysfunction.

<table>
<thead>
<tr>
<th>Author(s)/ Year/ Published/ (Prins Score)</th>
<th>Country of study</th>
<th>Population Type</th>
<th>Age of participants</th>
<th>Eligibility Criteria</th>
<th>Number (% respondents)</th>
<th>Differences/ Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masumori, et al. 1999&lt;sup&gt;107&lt;/sup&gt; (10)</td>
<td>Japan</td>
<td>All men in a fishing village</td>
<td>40-79</td>
<td>No prostate or bladder cancer or surgery, anti- androgen, CVA or neurogenic bladder</td>
<td>289 (46.8%)</td>
<td>42.3% analyzed</td>
</tr>
<tr>
<td>Kongkanand 2000&lt;sup&gt;108&lt;/sup&gt; (11)</td>
<td>Thailand</td>
<td>Region stratified RPS</td>
<td>40-70</td>
<td>NS</td>
<td>1250</td>
<td>NS</td>
</tr>
<tr>
<td>Moreira et al. 2001-2002/2006&lt;sup&gt;14&lt;/sup&gt; (14)</td>
<td>Korean</td>
<td>RPS</td>
<td>40-80</td>
<td>40 to 80 years</td>
<td>600 (32.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Parish et al. 1999-2000/2007&lt;sup&gt;14&lt;/sup&gt;</td>
<td>China</td>
<td>Region stratified RPS</td>
<td>20-64</td>
<td>Sexually active within stable relationship</td>
<td>1,261 (76%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ahn et al&lt;sup&gt;102&lt;/sup&gt; 2004/2007 (12)</td>
<td>Korea</td>
<td>Region stratified RPS</td>
<td>40-79</td>
<td>All men</td>
<td>1,570</td>
<td>Similar(stat. sigf.) to population published in Nat Health and Nutrition Survey</td>
</tr>
</tbody>
</table>

<sup>( ) Prins Score</sup>
<table>
<thead>
<tr>
<th>Authors/Date Published</th>
<th>Design/Instrument</th>
<th>Definition of ED</th>
<th>Time Period</th>
<th>Prevalence Rate Age (years)</th>
<th>Prevalence Rate Percentage (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masumori, et al. 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10) CS/SAQ Ability</td>
<td>to have an</td>
<td>One month</td>
<td>40-49</td>
<td>15 (6-28)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>erection when</td>
<td></td>
<td>50-59</td>
<td>23 (14-35)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>stimulated none</td>
<td></td>
<td>60-69</td>
<td>39 (30-49)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or little of the time</td>
<td></td>
<td>70-79</td>
<td>71 (59082)</td>
<td></td>
</tr>
<tr>
<td>Kongkanand 2000</td>
<td>Survey/Interview</td>
<td>Sometimes or never</td>
<td>Six months</td>
<td>7 (5-9)</td>
<td></td>
</tr>
<tr>
<td>(11)</td>
<td>able to achieve or keep erections good enough for intercourse</td>
<td></td>
<td>40-49</td>
<td>22 (18-26)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>49 (42-56)</td>
<td></td>
</tr>
<tr>
<td>Moreira et al. 2001-2002/2006</td>
<td>Survey/SAQ Had trouble achieving or maintaining an erection</td>
<td>One year</td>
<td>31.9 (27.9; 36.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parish et al. 1999-2000/2007</td>
<td>Survey/ Interview Difficulty achieving and trouble maintaining an erection</td>
<td>One year and persistent (≥ 2 months)</td>
<td>Age stratification by bar graph only therefore raw percentages by age not available</td>
<td>52-58% last year</td>
<td>5-8% persistent</td>
</tr>
<tr>
<td>Ahn et al. 2004/2007</td>
<td>Survey/Interview by questionnaire</td>
<td>Self reported (SR) and IIEF-5 ≤ 17 defined ED</td>
<td>40-79</td>
<td>13.4 SR / 32.4 IIEF</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>40-49</td>
<td>4.2 SR / 17 IIEF</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>13 SR / 29.5 IIEF</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60-60</td>
<td>30.1 SR / 62 IIEF</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>70-79</td>
<td>41.1 SR / 84.4 IIEF</td>
<td></td>
</tr>
</tbody>
</table>
### Table 6B. Australian Prevalence of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Author(s)/ Year/ Published/ (Prins Score)</th>
<th>Country of study</th>
<th>Population Type</th>
<th>Age of participants</th>
<th>Eligibility Criteria</th>
<th>Number (% respondents)</th>
<th>Differences/ Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinnock 1999109, 110 (13)</td>
<td>South Australia</td>
<td>Probability population sample</td>
<td>40+</td>
<td>NS</td>
<td>371 (49.8%)</td>
<td>Compared to 374 nonresponders – Similar</td>
</tr>
<tr>
<td>Richters et al. 2000-01/2003 37 (13)</td>
<td>Australia</td>
<td>Weighted RPS Nationally representative</td>
<td>&gt;40</td>
<td>NS</td>
<td>8367 (57)</td>
<td>No difference from general population</td>
</tr>
<tr>
<td>Moreira et al. 2001-2002/200887 (14)</td>
<td>Australia</td>
<td>RPS</td>
<td>40-80</td>
<td>40 to 80 years</td>
<td>750 (16.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Chew et al. 2001-2002/2008111</td>
<td>Western Australia</td>
<td>RPS</td>
<td>20-99</td>
<td>Voter enrollment</td>
<td>1,580 (37)</td>
<td>No difference from general population</td>
</tr>
</tbody>
</table>
Table 6B. Australian Prevalence of Erectile Dysfunction (continued)

<table>
<thead>
<tr>
<th>Authors/Date Published</th>
<th>Design/Instrument</th>
<th>Definition of ED</th>
<th>Time Period</th>
<th>Prevalence Rate Age (years)</th>
<th>Prevalence Rate Percentage (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinnock 1999</td>
<td>Survey/SAQ</td>
<td>Erections inadequate for intercourse</td>
<td>Three months</td>
<td>40-49</td>
<td>6 (3-11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>12 (6-19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60-69</td>
<td>41 (29-53)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70-79</td>
<td>63 (49-76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80+</td>
<td>81 (54-96)</td>
</tr>
<tr>
<td>Richters et al 2000-01/2000</td>
<td>Telephone Individual question</td>
<td>Last 3 months</td>
<td>16-59</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16-19</td>
<td>4%</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>20-29</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30-39</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40-49</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>19%</td>
</tr>
<tr>
<td>Moreira et al. 2001-2002/2008</td>
<td>Survey/Interview</td>
<td>Had trouble achieving or maintaining an erection</td>
<td>One year</td>
<td>20-29</td>
<td>40.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30-39</td>
<td>15.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40-49</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60-69</td>
<td>31.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70-79</td>
<td>52.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;80</td>
<td>69.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>68.2</td>
</tr>
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</table>
Table 6C. European Prevalence of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Author(s)/ Year/ Published/ (Prins Score)</th>
<th>Country of study</th>
<th>Population Type</th>
<th>Age of participants</th>
<th>Eligibility Criteria</th>
<th>Number (% respondents)</th>
<th>Differences/ Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sölstad, Hertoft 1993 (12)</td>
<td>Denmark</td>
<td>All men in selected communes</td>
<td>51</td>
<td>NS</td>
<td>439 (81)</td>
<td>Comparison with other Danish samples/ different employment status</td>
</tr>
<tr>
<td>Helgason, et al. 1996 (13)</td>
<td>Sweden</td>
<td>Stratified by age RPS</td>
<td>50-80</td>
<td>Born in Sweden, no prostate cancer</td>
<td>315 (72)</td>
<td>Participants more hypertension; prostate cancer, diabetes mellitus and myocardial infarction similar</td>
</tr>
<tr>
<td>McFarlane, et al. 1996 (12)</td>
<td>France</td>
<td>Stratified by region RPS</td>
<td>50-80</td>
<td>No previous urethral or bladder disease, prostate cancer, radiotherapy to prostate or pelvis area</td>
<td>1734 (53)</td>
<td>NS</td>
</tr>
<tr>
<td>Frankel, et al. 1998 (10)</td>
<td>United Kingdom</td>
<td>All men registered in general practice</td>
<td>40+</td>
<td>Ambulant, no prostate cancer or surgery, urinary problems secondary to surgery, neurologic damage</td>
<td>423 (65)</td>
<td>NS</td>
</tr>
<tr>
<td>Koskimaki et al 1998 (10)</td>
<td>Finland</td>
<td>Stratified birth cohort RPS</td>
<td>50, 60, 70</td>
<td>Not in an institution</td>
<td>1983 (63)</td>
<td>NS</td>
</tr>
<tr>
<td>Author(s)/ Year/ Published/ (Prins Score)</td>
<td>Country of study</td>
<td>Population Type</td>
<td>Age of participants</td>
<td>Eligibility Criteria</td>
<td>Number (% respondents)</td>
<td>Differences/ Nonresponders</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>------------------</td>
<td>-----------------</td>
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</tr>
<tr>
<td>Dunn, et al. 1998[18, 119] (11)</td>
<td>United Kingdom</td>
<td>Stratified by age and gender, random sample from general practice registers</td>
<td>18-75</td>
<td>NS</td>
<td>780 (39)</td>
<td>NS</td>
</tr>
<tr>
<td>Fugl-Meyer 1999[65] (13)</td>
<td>Sweden</td>
<td>18-74</td>
<td>RPS</td>
<td>Living in Sweden, fit mentally and physically</td>
<td>1288 (52%)</td>
<td>Compared to all nonresponders: participants younger</td>
</tr>
<tr>
<td>Parazzini 2000[20] (10)</td>
<td>Italy</td>
<td>Random sample of general practice</td>
<td>18+</td>
<td>NS</td>
<td>2010 (82)</td>
<td>NS</td>
</tr>
<tr>
<td>Meuleman 2001[122] Boyle, et al. 123 (15)</td>
<td>Netherlands</td>
<td>Age stratified RPS</td>
<td>40-79</td>
<td>Dutch-speaking</td>
<td>1233 (70)</td>
<td>Participants more symptoms and more married compared to 45 NR interview</td>
</tr>
<tr>
<td>Blanker, et al. 2001[79, 124, 125] (13)</td>
<td>Netherlands</td>
<td>All men registered in general practice</td>
<td>50-75</td>
<td>No cancer of prostate or bladder, radical prostatectomy, neurogenic bladder disease or negative advice by GP</td>
<td>1605 (47)</td>
<td>Participants more LUTS and better health status compared to 261 nonresponders questioned</td>
</tr>
<tr>
<td>Martin-Morales, et al. 2001[126] (15)</td>
<td>Spain</td>
<td>Age, community, population density stratified RPS</td>
<td>25-70</td>
<td>Non-institutionalized</td>
<td>2467 (75)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table 6C. European Prevalence of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Author(s)/ Year/ Published/ (Prins Score)</th>
<th>Country of study</th>
<th>Population Type</th>
<th>Age of participants</th>
<th>Eligibility Criteria</th>
<th>Number (% respondents)</th>
<th>Differences/ Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green, et al. 2001 127 (10)</td>
<td>Wales, UK</td>
<td>All men registered in 11 general practices</td>
<td>55-70</td>
<td>NS</td>
<td>2027 (50)</td>
<td>Compared to census data, more married</td>
</tr>
<tr>
<td>Mak et al. 2002 128 (10)</td>
<td>Belgium</td>
<td>Random population sample (RPS)</td>
<td>40-69</td>
<td>Men living in two comparable Belgian urban areas</td>
<td>799 (47.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Shiri et al., 2003 129 Shiri et al. 2004 130 (12)</td>
<td>Finland</td>
<td>Stratified/birth cohort</td>
<td>50-75</td>
<td>Men living in Tampere or surrounding municipalities</td>
<td>2198 (70%)</td>
<td>NS</td>
</tr>
<tr>
<td>Nazareth et al. 2003 81 (10)</td>
<td>London (UK)</td>
<td>Men and women registered in general practice</td>
<td>18-75</td>
<td>People attending general practitioner visit</td>
<td>1512 (71%) 447 men</td>
<td>NS</td>
</tr>
<tr>
<td>De Boer et al. 2004 137 (12)</td>
<td>Netherlands</td>
<td>Men registered in general practice</td>
<td>18-91</td>
<td>Men able to complete questionnaire, not mentally retarded, and Dutch speaking</td>
<td>2117 (38%)</td>
<td>NS</td>
</tr>
<tr>
<td>Author(s)/ Year/ Published/ (Prins Score)</td>
<td>Country of study</td>
<td>Population Type</td>
<td>Age of participants</td>
<td>Eligibility Criteria</td>
<td>Number (% respondents)</td>
<td>Differences/ Nonresponders</td>
</tr>
<tr>
<td>-----------------------------------------</td>
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<td>-----------------</td>
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<td>---------------------</td>
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<td>--------------------------</td>
</tr>
<tr>
<td>Oksuz et al. 2005 (^{90}) (10)</td>
<td>Turkey</td>
<td>Membership list of the Turkish health website</td>
<td>15-60</td>
<td>Men registered on the membership list of the Turkish health website</td>
<td>2288 (72%)</td>
<td>NS</td>
</tr>
<tr>
<td>Stulhofer et al. 2005 (^{91}) (10)</td>
<td>Croatia</td>
<td>RPS</td>
<td>35-84</td>
<td>People living in private households</td>
<td>615 (69%)</td>
<td>NS</td>
</tr>
<tr>
<td>Moreira et al. 2001-2002/2005 (^{88}) (14)</td>
<td>Spain</td>
<td>RPS</td>
<td>40-80</td>
<td>40 to 80 years</td>
<td>750 (23%)</td>
<td>NS</td>
</tr>
<tr>
<td>Moreira et al. 2001-2002/2005 (^{87}) (14)</td>
<td>Germany</td>
<td>RPS</td>
<td>40-80</td>
<td>40 to 80 years</td>
<td>750 (17.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>May et al. 2007 (^{132}) (11)</td>
<td>Germany</td>
<td>RPS</td>
<td>18-79</td>
<td>Men living in a well established relationship</td>
<td>3124 (31.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Teles et al. 2008 (^{133}) (13)</td>
<td>Portugal</td>
<td>RPS</td>
<td>40-69</td>
<td>Men attending a visit or accompanying patients in primary healthcare centres</td>
<td>3,067 (81.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Andersen et al. 2008 (^{99}) (10)</td>
<td>Denmark</td>
<td>RPS</td>
<td>20-45</td>
<td>People born and living in Denmark</td>
<td>863 (26%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table 6C. European Prevalence of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Author(s)/ Year/ Published/ (Prins Score)</th>
<th>Country of study</th>
<th>Population Type</th>
<th>Age of participants</th>
<th>Eligibility Criteria</th>
<th>Number (% respondents)</th>
<th>Differences/ Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korfage et al. 2008. 100 (10)</td>
<td>Netherlands</td>
<td>Men in the Eur. Randomized study on screening for Prostate Cancer</td>
<td>58-78</td>
<td>Men without prostate cancer diagnosis</td>
<td>3893 (81%)</td>
<td>NS</td>
</tr>
<tr>
<td>Moreira et al. 2001-2002/2008 14 (14)</td>
<td>UK and Europe</td>
<td>RPS</td>
<td>40-80</td>
<td>40 to 80 years</td>
<td>750 (17%)</td>
<td>NS</td>
</tr>
<tr>
<td>Buvat et al. 2001-2002/2009 134 (14)</td>
<td>France</td>
<td>RPS</td>
<td>40-80</td>
<td>40 to 80 years</td>
<td>750 (23.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Corona et al. 2009 in preparation 135 (14)</td>
<td>8 centres from the European Union (Italy), Leuven (Belgium), Lodz (Poland), Malmo (Sweden), Manchester (UK), Santiago de Compostela (Spain), Szeged (Hungary), Tartu (Estonia).</td>
<td>RPS</td>
<td>40-80</td>
<td>Randomly recruited from population registers</td>
<td>3,369 (40%)</td>
<td>No difference in reported general health, and number of morbidities between participating or not in the study</td>
</tr>
<tr>
<td>Authors/Date Published</td>
<td>Design/Instrument</td>
<td>Definition of ED</td>
<td>Time Period</td>
<td>Prevalence Rate</td>
<td>Prevalence Rate Percentage (CI 95%)</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
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<td>----------------------------------------------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td><strong>Solstad, Hertoff</strong></td>
<td>CS/SAQ</td>
<td>Impaired erection sexual intercourse impossible – more that few occasions</td>
<td>One year</td>
<td>51</td>
<td>4 (2-6) [In a separate interview of 100 of original group +7%]</td>
<td></td>
</tr>
<tr>
<td>1993(^{12, 113})</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(12)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Kontula, Haavio-Manilla</strong></td>
<td>Survey/ Interview</td>
<td>Penis does not become erect or loses rigidity during intercourse quite often, almost constantly</td>
<td>One year</td>
<td>18-74</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>1992/95(^{13-14})</td>
<td></td>
<td></td>
<td></td>
<td>18-24</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>(13 - 14)</td>
<td></td>
<td></td>
<td></td>
<td>25-34</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35-44</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45-54</td>
<td>7%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>55-64</td>
<td>16%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65-74</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td><strong>Helgason, et al.</strong></td>
<td>Survey/SAQ</td>
<td>Erectile stiffness seldom, hardly ever or never sufficient for intercourse</td>
<td>Few months</td>
<td>50-59</td>
<td>3 (0-11)</td>
<td></td>
</tr>
<tr>
<td>1996(^{114, 115})</td>
<td></td>
<td></td>
<td></td>
<td>60-69</td>
<td>24 (1-33)</td>
<td></td>
</tr>
<tr>
<td>(13)</td>
<td></td>
<td></td>
<td></td>
<td>70-80</td>
<td>49 (41-58)</td>
<td></td>
</tr>
<tr>
<td><strong>McFarlane, et al.</strong></td>
<td>Survey/SAQ</td>
<td>Difficulty in having an erection each time or some time</td>
<td>Month</td>
<td>50-59</td>
<td>20 (17-23)</td>
<td></td>
</tr>
<tr>
<td>1996(^{116})</td>
<td></td>
<td></td>
<td></td>
<td>60-69</td>
<td>33 (29-37)</td>
<td></td>
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<tr>
<td>(12)</td>
<td></td>
<td></td>
<td></td>
<td>70-79</td>
<td>38 (33-43)</td>
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</tr>
</tbody>
</table>
Table 6C. European Prevalence of Erectile Dysfunction (continued)

<table>
<thead>
<tr>
<th>Authors/Date Published</th>
<th>Design/Instrument</th>
<th>Definition of ED</th>
<th>Time Period</th>
<th>Prevalence Rate Age (years)</th>
<th>Prevalence Rate Percentage (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frankel, et al. 1998</td>
<td>CS/SAQ</td>
<td>Erections – rigidity reduced, severely reduced or none</td>
<td>NS</td>
<td>40-49</td>
<td>9 (5-14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>29 (21-38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60-69</td>
<td>57 (46-67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70-79</td>
<td>79 (65-90)</td>
</tr>
<tr>
<td>Koskimaki, et al. 1998</td>
<td>Survey/SAQ</td>
<td>Moderate or complete ED, often difficulties with erection (obtain/maintain) during sexual intercourse or none</td>
<td>NS</td>
<td>50</td>
<td>12 (10-15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td>24 (21-28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70</td>
<td>49 (44-53)</td>
</tr>
<tr>
<td>Dunn, et al. 1998</td>
<td>Survey/SAQ</td>
<td>Difficulty in getting or maintaining an erection</td>
<td>Three months Lifetime</td>
<td>18-75</td>
<td>Ed last 3 months – 26 (23-30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lifetime – 39 (35-42)</td>
</tr>
<tr>
<td>Fugl-Meyer 1998</td>
<td>Survey/Interview</td>
<td>Penis does not become or lose rigidity during intercourse quite often, nearly all the time or all the time</td>
<td>One year</td>
<td>18-24</td>
<td>3 (1-6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25-34</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>35-49</td>
<td>3 (1-4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-65</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>66-74</td>
<td>24 (17-33)</td>
</tr>
<tr>
<td>Parazzini 2000</td>
<td>Survey/Interview</td>
<td>Ability to attain and maintain erection sufficient for satisfactory sexual performance</td>
<td>NS</td>
<td>18-29</td>
<td>2 (1-6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30-39</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40-49</td>
<td>5 (3-8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>16 (12-21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60-69</td>
<td>27 (22-34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70+</td>
<td>48 (39-61)</td>
</tr>
<tr>
<td>Authors/Date Published</td>
<td>Design/Instrument</td>
<td>Definition of ED</td>
<td>Time Period</td>
<td>Prevalence Rate Percentage (CI 95%)</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
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<td>-----------------</td>
<td>-------------</td>
<td>-----------------------------------</td>
<td></td>
</tr>
<tr>
<td>Blanker, et al. 2001</td>
<td>CS-SAQ</td>
<td>No erections or erections of severely reduced rigidity</td>
<td>NS</td>
<td>50-54: 3 (1-5) 55-59: 5 (3-8) 60-64: 11 (8-14) 65-69: 19 (14-23) 70-78: 26 (19-33)</td>
<td></td>
</tr>
<tr>
<td>Mak al. Eur Urol 2002</td>
<td>CS/Saq</td>
<td>Erectile function domain score of IIEF &lt; 26</td>
<td>Eight months</td>
<td>40-49: 19.4% 50-59: 39.8% 60-69: 65.9%</td>
<td></td>
</tr>
</tbody>
</table>
Table 6C. European Prevalence of Erectile Dysfunction (continued)

<table>
<thead>
<tr>
<th>Authors/Date Published</th>
<th>Design/Instrument</th>
<th>Definition of ED</th>
<th>Time Period</th>
<th>Prevalence Rate Age (years)</th>
<th>Prevalence Rate Percentage (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shiri et al. 2003 and Shiri et al. 2004 2004 (12)</td>
<td>Survey/SAQ</td>
<td>NIH definition: inability to achieve or maintain erection sufficient for satisfactory sexual function</td>
<td>Four months</td>
<td>50</td>
<td>67% (CI 95%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>75</td>
<td>89%</td>
</tr>
<tr>
<td>Nazareth et al. 2003  (10)</td>
<td>CS/SAQ</td>
<td>ICD-10 diagnostic classification: No erection or penis too soft for penetration</td>
<td>NS</td>
<td>18-75</td>
<td>8.8 (6.4-11.8)%</td>
</tr>
<tr>
<td>De Boer et al. 2004  (11)</td>
<td>CS/SAQ</td>
<td>NIH definition: inability to achieve or maintain erection sufficient for satisfactory sexual function</td>
<td>NS</td>
<td>18-30</td>
<td>4.0 (1.8-6.3) %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31-40</td>
<td>5.6 (3.5-7.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>41-50</td>
<td>13.7 (10.8-16.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>51-60</td>
<td>23.7 (19.5-27.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>61-70</td>
<td>40.0 (32.9-47.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>71-80</td>
<td>41.9 (33.6-50.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;80</td>
<td>33.3 (17.9-48.7)</td>
</tr>
<tr>
<td>Oksuz et al. 2005  (10)</td>
<td>Survey/SAQ</td>
<td>Florida Sexual History Questionnaire: erectile function score ≤22</td>
<td>Two months</td>
<td>15-60</td>
<td>59.7%</td>
</tr>
<tr>
<td>Stuhofer et al. 2005  (10)</td>
<td>CS/SAQ</td>
<td>Difficulty in obtaining/maintaining erection</td>
<td>Two months</td>
<td>≤39</td>
<td>5.8%</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>30-49</td>
<td>7.0%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>50-59</td>
<td>17.7%</td>
</tr>
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<td></td>
<td></td>
<td>60-69</td>
<td>17.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70-79</td>
<td>30.0%</td>
</tr>
</tbody>
</table>
**Table 6C. European Prevalence of Erectile Dysfunction (continued)**

<table>
<thead>
<tr>
<th>Authors/Date Published</th>
<th>Design/Instrument</th>
<th>Definition of ED</th>
<th>Time Period</th>
<th>Prevalence Rate Age (years)</th>
<th>Prevalence Rate Percentage (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moreira et al. 2001-2002/2005&lt;sup&gt;93&lt;/sup&gt; (14)</td>
<td>Survey/Interview</td>
<td>Had trouble achieving or maintaining an erection</td>
<td>One year</td>
<td></td>
<td>12.7 (9.8; 14.6)</td>
</tr>
<tr>
<td>Moreira et al. 2001-2002/2005&lt;sup&gt;97&lt;/sup&gt; (14)</td>
<td>Survey/Interview</td>
<td>Had trouble achieving or maintaining an erection</td>
<td>One year</td>
<td></td>
<td>7.9 (5.6; 9.9)</td>
</tr>
<tr>
<td>May et al. 2007&lt;sup&gt;132&lt;/sup&gt; (11)</td>
<td>CS/SAQ</td>
<td>Erectile function domain score of IIEF &lt; 26</td>
<td>Three months</td>
<td>18-29</td>
<td>9.4%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>30-39</td>
<td>10.1%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>40-49</td>
<td>15.5%</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>50-59</td>
<td>39.1%</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>60-69</td>
<td>67.4%</td>
</tr>
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<td></td>
<td>70-79</td>
<td>88.7%</td>
</tr>
<tr>
<td>Teles et al. 2008&lt;sup&gt;133&lt;/sup&gt; (11)</td>
<td>CS/SAQ</td>
<td>Erectile function domain score of IIEF &lt; 26</td>
<td>Seven months</td>
<td>40-49</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>50%</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>60-69</td>
<td>70%</td>
</tr>
<tr>
<td>Andersen et al. 2008&lt;sup&gt;99&lt;/sup&gt; (16)</td>
<td>CS/SAQ</td>
<td>Erection inadequate to obtain or maintain sexual intercourse almost all the time or quite often</td>
<td>One year</td>
<td>20-45</td>
<td>6%</td>
</tr>
<tr>
<td>Korfage et al. 2008&lt;sup&gt;100&lt;/sup&gt; (10)</td>
<td>CS/SAQ</td>
<td>Problems with getting or maintaining erection</td>
<td>Five months</td>
<td>58-61</td>
<td>12.0%</td>
</tr>
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<td></td>
<td></td>
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<td>62-64</td>
<td>14.6%</td>
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<td></td>
<td></td>
<td>65-67</td>
<td>18.4%</td>
</tr>
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<td></td>
<td>68-70</td>
<td>21.9%</td>
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<td>71-78</td>
<td>26.3%</td>
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</tbody>
</table>
### Table 6C. European Prevalence of Erectile Dysfunction (continued)

<table>
<thead>
<tr>
<th>Authors/Date Published</th>
<th>Design/Instrument</th>
<th>Definition of ED</th>
<th>Time Period</th>
<th>Prevalence Rate Age (years)</th>
<th>Prevalence Rate Percentage (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moreira et al. 2001-2002/2008(^{14})</td>
<td>Survey/Interview</td>
<td>Had trouble achieving or maintaining an erection</td>
<td>One year</td>
<td></td>
<td>17.8 (14.4; 21.3)</td>
</tr>
<tr>
<td>Buvat et al. 2001-2002/2009(^{134})</td>
<td>Survey/Interview</td>
<td>Had trouble achieving or maintaining an erection</td>
<td>One year</td>
<td></td>
<td>15.0 (12.2; 18.2)</td>
</tr>
<tr>
<td>Corona et al. 2009(^{135}) in preparation(^{(14)})</td>
<td>CS/SAQ</td>
<td>Sometimes or never able to get or keep an erection sufficient for sexual intercourse</td>
<td>Two years</td>
<td>40-49 50-59 60-69 &gt;70</td>
<td>6% 19% 38% 64%</td>
</tr>
</tbody>
</table>
Table 6D. Latin America Prevalence of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Author(s)/ Year/ Published/ (Prins Score)</th>
<th>Country of study</th>
<th>Population Type</th>
<th>Age of participants</th>
<th>Eligibility Criteria</th>
<th>Number (% respondents)</th>
<th>Differences/ Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moreira et al. 1998/ 2002 136 (15)</td>
<td>Brazil/ R</td>
<td>Random population sample (RPS)</td>
<td>40 - 70</td>
<td>40 - 70 years</td>
<td>602 (92)</td>
<td>NS</td>
</tr>
<tr>
<td>Rhoden et al. 1998 / 2002 137 (11)</td>
<td>Brazil/ R</td>
<td>All men participating in a free screening program for prostate cancer</td>
<td>45 - 90</td>
<td>?</td>
<td>965 (90.1)</td>
<td>-</td>
</tr>
<tr>
<td>Moreira et al. 1999 -2000/ 2002 138 (14)</td>
<td>Brazil/ R</td>
<td>RPS</td>
<td>40 - 70</td>
<td>40 - 70 years</td>
<td>342 (91.2)</td>
<td>The participants in the study had higher educational attainment than the average Brazilian men</td>
</tr>
<tr>
<td>Moreira et al. 2000/ 2001 139 (13)</td>
<td>Brazil/ N</td>
<td>Community based sample</td>
<td>≥ 18</td>
<td>≥ 18 years</td>
<td>1170 (91)</td>
<td>The nonresponders were similar to participants in regard to age, education, and prevalence of medical conditions</td>
</tr>
<tr>
<td>Morillo et al. 2002 140 (15)</td>
<td>Colombia, Venezuela, Ecuador/ N</td>
<td>RPS</td>
<td>≥ 40</td>
<td>≥ 40 years</td>
<td>1963 (82)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table 6D. Latin America Prevalence of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Author(s)/ Year/ Published/ (Prins Score)</th>
<th>Country of study</th>
<th>Population Type</th>
<th>Age of participants</th>
<th>Eligibility Criteria</th>
<th>Number (% respondents)</th>
<th>Differences/ Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moreira et al. 2001 - 2002/ 2005 (14)</td>
<td>Brazil/ N</td>
<td>RPS</td>
<td>40 - 80</td>
<td>40 - 80 years</td>
<td>471 (18)</td>
<td>NS</td>
</tr>
<tr>
<td>De Almeida Claro et al. 2006 (13)</td>
<td>Brazil/ R</td>
<td>RPS</td>
<td>≥ 20</td>
<td>≥ 20 years</td>
<td>2000 (?)</td>
<td>Participants had higher educational achievement</td>
</tr>
</tbody>
</table>
Table 6D. Latin America Prevalence of Erectile Dysfunction (continued)

<table>
<thead>
<tr>
<th>Author(s)/ Year/ Published/ (Prins Score)</th>
<th>Design/ Instrument</th>
<th>Definition of ED</th>
<th>Time Period</th>
<th>Prevalence Rate Age (years)</th>
<th>Prevalence Rate Percentage (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moreira et al. 1998/2002 (15)</td>
<td>Survey/Interview</td>
<td>Sometimes or never able to get and keep an erection adequate for satisfactory sexual intercourse</td>
<td>Six months</td>
<td>40-49 50-59 60-70</td>
<td>9.9% 11.8% 31.7%</td>
</tr>
<tr>
<td>Rhoden et al. 1998/2002 (11)</td>
<td>Survey/SAQ</td>
<td>IIEF-5 (scores ≤21)</td>
<td>Four weeks</td>
<td>40-49 50-59 60-69 70-79 &gt;80</td>
<td>36.4% 42.5% 58.1% 79.4% 100%</td>
</tr>
<tr>
<td>Moreira et al. 1999-2000/2002 (14)</td>
<td>Survey/SAQ</td>
<td>Sometimes or never able to get and keep an erection adequate for satisfactory sexual intercourse</td>
<td>Six months</td>
<td>40-49 50-59 60-70</td>
<td>3.5% 16.7% 39.6%</td>
</tr>
<tr>
<td>Moreira et al. 2000/2001 (13)</td>
<td>Survey/SAQ</td>
<td>Sometimes or never able to get and keep an erection adequate for satisfactory sexual intercourse</td>
<td>One month</td>
<td>18-39 40-49 50-59 60-69 ≥70</td>
<td>9.4% 15.5% 22.1% 37.0% 39.6%</td>
</tr>
<tr>
<td>Morillo et al. 2002 (14)</td>
<td>Survey/Interview</td>
<td>Sometimes or never able to get and keep an erection adequate for satisfactory sexual intercourse</td>
<td>Four weeks</td>
<td>40-49 50-59 60-69 70-79 &gt;79</td>
<td>Colombia 36.2% 40.0% 75.2% 78.4% 84.1%</td>
</tr>
<tr>
<td>Moreira et al. 2001-2002/2005 (14)</td>
<td>Survey/Interview</td>
<td>Had trouble achieving or maintaining an erection</td>
<td>One year</td>
<td>40-80</td>
<td>13.1%</td>
</tr>
<tr>
<td>De Almeida Claro et al. 2006 (13)</td>
<td>Survey/Interview</td>
<td>IIEF</td>
<td>Four weeks</td>
<td>20-30 31-40 41-50 51-60 &gt;61</td>
<td>0.2% 0.2% 1.0% 2.8% 7.0%</td>
</tr>
</tbody>
</table>
### Table 6E. North American Prevalence of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Author(s)/ Year/ Published/ (Prins Score)</th>
<th>Country of study</th>
<th>Population Type</th>
<th>Age of participants</th>
<th>Eligibility Criteria</th>
<th>Number (% respondents)</th>
<th>Differences / Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feldman, et al. 199426, 28, 142, 143 (13)</td>
<td>USA</td>
<td>Random population sample (RPS)</td>
<td>40-70</td>
<td>Men with sexual partner</td>
<td>1290 (40?)</td>
<td>Participants more heart disease and cancer</td>
</tr>
<tr>
<td>Panser, et al. 199577 (12)</td>
<td>USA</td>
<td>RPS</td>
<td>40-79</td>
<td>No prostate or bladder cancer, low back surgery, CVA neurogenic bladder or antiandrogen use</td>
<td>2115 (55)</td>
<td>Participants more urological disease, chronic disease similar</td>
</tr>
<tr>
<td>Laumann, et al. 199923 (12)</td>
<td>USA</td>
<td>RPS</td>
<td>18-59</td>
<td>Not from barracks, college dorms or prisons, English speaking, at least one partner in previous year</td>
<td>1244 (70)</td>
<td>NS</td>
</tr>
<tr>
<td>Ansong, et al. 200044 (18)</td>
<td>USA</td>
<td>Age stratified RPS</td>
<td>50-76</td>
<td>NS</td>
<td>1408 (27)</td>
<td>Questionnaire to non-responders – 21/110 prevalence of ED similar</td>
</tr>
<tr>
<td>Bacon, et al. 2003146 (10)</td>
<td>USA</td>
<td>Health professionals</td>
<td>53-90</td>
<td>NS</td>
<td>31742 (25)</td>
<td>NS</td>
</tr>
<tr>
<td>Brock et al. 2001-2002/200695 (14)</td>
<td>Canada</td>
<td>RPS</td>
<td>40-80</td>
<td>40 to 80 years</td>
<td>500 (9.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Laumann et al. 2001-2002/200998 (14)</td>
<td>USA</td>
<td>RPS</td>
<td>40-80</td>
<td>40 to 80 years</td>
<td>742 (9.0%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table 6E. North American Prevalence of Erectile Dysfunction (continued)

<table>
<thead>
<tr>
<th>Authors/Date Published</th>
<th>Design/Instrument</th>
<th>Definition of ED</th>
<th>Time Period</th>
<th>Prevalence Rate Age (years)</th>
<th>Prevalence Rate Percentage (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feldman, et al. 1994+</td>
<td>CS/SAQ</td>
<td>Sometimes able or never able to get and keep an erection for sexual intercourse</td>
<td>Six months</td>
<td>40</td>
<td>23 (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50</td>
<td>32</td>
</tr>
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<td>60</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70</td>
<td>49</td>
</tr>
<tr>
<td>Panser, et al. 19957(12)</td>
<td>Survey/SAQ</td>
<td>Constant inability to have erection when sexually stimulated</td>
<td>Month</td>
<td>40-49</td>
<td>1 (0-1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>6 (4-8)</td>
</tr>
<tr>
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<td>60-69</td>
<td>22 (18-26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70-79</td>
<td>44 (38-51)</td>
</tr>
<tr>
<td>Laumann, et al. 199923(12)</td>
<td>Survey/Interview</td>
<td>Trouble maintaining or achieving an erection</td>
<td>Year</td>
<td>18-29</td>
<td>7 (5-10)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>30-39</td>
<td>9 (6-12)</td>
</tr>
<tr>
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<td></td>
<td>40-49</td>
<td>11 (8-15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>18 (13-26)</td>
</tr>
<tr>
<td>Ansong, et al. 2000144(10)</td>
<td>Survey/SAQ</td>
<td>Recurrent inability to attain or maintain erection for satisfactory intercourse</td>
<td>Six months</td>
<td>50-54</td>
<td>26 (20-32)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>55-59</td>
<td>35 (29-41)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>60-64</td>
<td>47 (40-53)</td>
</tr>
<tr>
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<td>65-69</td>
<td>58 (54-66)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>70-76</td>
<td>69 (62-75)</td>
</tr>
<tr>
<td>Bacon, et al. 1452003(10)</td>
<td>Survey/SAQ</td>
<td>Poor or very poor Ability to have and maintain erection adequate for intercourse</td>
<td>2000</td>
<td>&lt;60</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60-69</td>
<td>26</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>70-79</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;79</td>
<td>60</td>
</tr>
<tr>
<td>Authors/Date Published</td>
<td>Design/Instrument</td>
<td>Definition of ED</td>
<td>Time Period</td>
<td>Prevalence Rate Age (years)</td>
<td>Prevalence Rate Percentage (CI 95%)</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>-------------</td>
<td>-----------------------------</td>
<td>-----------------------------------</td>
</tr>
</tbody>
</table>
(14) | Survey/Interview | Had trouble achieving or maintaining an erection | One year | | 16.0 (12.5; 19.9) |
| Laumann et al. 2001-2002/2009aa  
(14) | Survey/Interview | Had trouble achieving or maintaining an erection | One year | | 22.5 (19.6; 25.7) |
Table 6F. Worldwide Prevalence of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Author(s)/ Year/ Published/ (Prins Score)</th>
<th>Country of study</th>
<th>Population Type</th>
<th>Age of participants</th>
<th>Eligibility Criteria</th>
<th>Number (% respondents)</th>
<th>Differences/ Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosen et al. 2003 (12)</td>
<td>US/ Europe: UK France Germany Netherlands Italy Spain</td>
<td>Random population sample (RPS)</td>
<td>50-80</td>
<td>Householder</td>
<td>All 12.815 (36.8%) Europe 10,900</td>
<td>NS</td>
</tr>
<tr>
<td>Nicolosi et al. 2003 (11)</td>
<td>Brazil Italy Japan Malaysia</td>
<td>Random population sample (RPS)</td>
<td>40-70</td>
<td>Householder</td>
<td>Total number 2513 Brazil (92%) Italy (72%) Japan (51%) Malaysia (16%)</td>
<td>NS</td>
</tr>
<tr>
<td>Rosen et al. 2004 (10)</td>
<td>US, Brazil, Mexico/ Europe: UK Germany France Italy Spain</td>
<td>Random population sample (RPS)</td>
<td>25-75</td>
<td>NS</td>
<td>All 27,839 US 9284 (45%) Mexico 2735 (55%) Brazil 5091 (51%) Europe UK2053 (48%) Germany 3040 (45%) France 2053 (48%) Italy 2130 (53%) Spain 1453 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>Author(s)/ Year/ Published/ (Prins Score)</td>
<td>Country of study</td>
<td>Population Type</td>
<td>Age of participants</td>
<td>Eligibility Criteria</td>
<td>Number (% respondents)</td>
<td>Differences/ Nonresponders</td>
</tr>
<tr>
<td>----------------------------------------</td>
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</tr>
<tr>
<td>Nicolosi et al. 2004 (11)</td>
<td>Northern Europe</td>
<td>Random population sample (RPS)</td>
<td>40-80</td>
<td>Men and women householder</td>
<td>27500 (19%) 13618 men</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Austria/Belgium/Germany/Sweden/UK</td>
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<tr>
<td></td>
<td>Southern Europe</td>
<td></td>
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<tr>
<td></td>
<td>Italy/France/Israel/Spain</td>
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<tr>
<td></td>
<td>Non-European West</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Australia/Canada/ New Zealand/</td>
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<tr>
<td></td>
<td>South Africa/US</td>
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<tr>
<td></td>
<td>Central/South American</td>
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<tr>
<td></td>
<td>Brazil/Mexico</td>
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<td></td>
<td>Middle East</td>
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</tr>
<tr>
<td></td>
<td>Algeria/Egypt/Morocco/Turkey</td>
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</tr>
<tr>
<td></td>
<td>East Asia</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>China/Hong-Kong/Japan/Korea/Taiwan</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Southeast Asia</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malaysia/Philippines/Singapore/Thailand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shabsig et al. 2005 (10)</td>
<td>US/Germany/UK/Italy/Spain</td>
<td>Men registered in general practice</td>
<td>20-75</td>
<td>Men attending general practice, family practice or general internal medicine visit</td>
<td>28691</td>
<td>NS</td>
</tr>
<tr>
<td>Laumann et al. 2001-2002/ 2005 (14)</td>
<td>World*</td>
<td>Random population sample (RPS)</td>
<td>40-80</td>
<td>40 to 80 years</td>
<td>13750 (19%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table 6F. Worldwide Prevalence of Erectile Dysfunction (continued)

<table>
<thead>
<tr>
<th>Authors/Date Published</th>
<th>Design/Instrument</th>
<th>Definition of ED</th>
<th>Time Period</th>
<th>Prevalence Rate Age (years)</th>
<th>Prevalence Rate Percentage (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosen et al. 2003 40</td>
<td>CS/SAQ</td>
<td>Reduced or no erection according to Danish Prostatic Symptom Score questionnaire</td>
<td>Four months</td>
<td>50-59 60-69 70-80</td>
<td>30.8% 55.1% 76.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All countries Europe</td>
<td>48.9% 45.3%</td>
</tr>
<tr>
<td>Nicolosi et al. 2003 146</td>
<td>Survey/ SAQ</td>
<td>Sometimes or never able to maintain erection to complete sexual intercourse</td>
<td>Nine months</td>
<td>40-70</td>
<td>Brazil (15.5%) Italy (17.2%) Japan (34.5%) Malaysia (22.4%)</td>
</tr>
<tr>
<td>Rosen et al. 2004 147</td>
<td>Survey/Interview</td>
<td>Erection difficulties</td>
<td>Three months</td>
<td>20-29 30-39 40-49 50-59 60-69 70-75</td>
<td>8% 11% 15% 22% 30% 37% 16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All US Brazil Mexico Europe: UK Germany France Italy Spain</td>
<td>22% 14% 14% 13% 13% 11% 13% 10%</td>
</tr>
</tbody>
</table>
Table 6F. Worldwide Prevalence of Erectile Dysfunction (continued)

<table>
<thead>
<tr>
<th>Authors/Date Published</th>
<th>Design/Instrument</th>
<th>Definition of ED</th>
<th>Time Period</th>
<th>Prevalence Rate</th>
<th>Prevalence Rate Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Age (years)</td>
<td>(CI 95%)</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Nicolosi et al. 2004</td>
<td>CS/SAQ</td>
<td>Trouble in achieving or maintaining erection</td>
<td>Two months or more in previous years</td>
<td>All countries</td>
<td>40-49 5.0% 9.0% 15.2% 22.0% 10 (9-10)%</td>
</tr>
<tr>
<td>(12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shabsig et al. 2005</td>
<td>Survey/SAQ</td>
<td>Difficulty in getting or keeping erection</td>
<td>Seven months</td>
<td>30-75</td>
<td>US (25%)  France (13%)  Germany (22%)  Italy (12%)  Spain (12%)  UK (19%)</td>
</tr>
<tr>
<td>(10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laumann et al. /2001-2002/2005</td>
<td>Survey/Interview or SAQ</td>
<td>Had trouble achieving or maintaining an erection</td>
<td>One year</td>
<td>13 (12; 15) in Northern Europe 13 (11; 14) in Southern Europe 21 (19; 22) in Non-European West 14 (11; 16) in Central/South America 14 (12; 16) in Middle East 27 (25; 29) in East Asia 28 (25; 32) in South East Asia</td>
<td></td>
</tr>
</tbody>
</table>
older ages showed marked increasing rates with each of the three decades beginning with age 60. [109-110] The study that did not stratify for age reported a 21.1% prevalence rate for ages 40-80 years again reflecting a blend of the stratified studies. [97] The most recent report from western Australia [111] had a older age range in their study and reported an overall prevalence rate of 40.3%, almost 4 times the prevalence from the other age stratified study with an overall rate of 10% [37]. In the younger age groups the former study reported higher rates for ED until the decade of 40-49 where the rates were almost the same but in the next decade again the former study reported higher rates. (See Table 6B)

Prevalence studies from Europe were difficult to compare. (See Table 6C) In the Scandinavian studies, the prevalence seemed to rise sharply after the age of 65 years, with rates of 20% or greater after this age and this rate doubling when reaching the age of 70 years or older. The only exception to this trend was the study from Finland where much higher prevalence rates were reported beginning with age 50 and continuing with an upward slope for every five year cohorts. [129-130] This study used the NIH definition for ED and inquired about activity the previous four months. The prevalence of ED before the age of 61 years in the continental northern European studies were generally quite low except for the study mentioned above. In a recent study by Corona 8 centers from the European Union participated in the study 9. [135] (See Table 6C). Prevalence rates tripled from the decades in the 40’s to 50’s and doubled for each succeeding 10 year cohort. Moreira’s study from the UK and Europe did not stratify for age and reported a prevalence rate for ED of about 18%. [96]

In two studies from the United Kingdom not stratified for age prevalence rates were quite different although similar ages (18-75 years were reported), 8.8% and 26% respectively. [78, 81, 119] Dunn’s study asked for lifelong compared to last three months prevalence for ED and the rates increased for the former to 39% from 26%. [78, 119] In the other two studies from the United Kingdom, both derived again from general practice groups there was a marked difference in prevalence rates for ED although for one group the definition was for complete erectile failure and one was difficulty in attaining and maintaining an erection and were stratified for different age ranges. The prevalence rates for the stricter definition ranged from 7 to 22% for the three periods stratified from age 55 to 70 years of age. [127] For the less strict definition prevalence rates ranged from 9 to 79% from four decades reported, ages 40-79 years. [117]

In the four studies from the Netherlands stratification by age was different in all papers but in general prevalence rates for ages before 60 were in the teens and increased after that for each age period quoted up to age 70 where rates varied from 26 to 42%. [79, 100, 122-125, 131] In the Korfage study age stratification ranged from three to eight years and was reported for different age groups beginning with age 58 and ending with age 78 years. For the five different age groups prevalence rates varied from 12 to 26.3%. [100]

In the three studies from France two were non randomized, the study reporting on ages 18 to 69 years was 7% prevalence rate and the study reporting on ages 40 to 80 years was 15%. [68, 134] In the study stratified for age by decades beginning at age 50 the prevalence rates were 20%, 33%, and 38% for each of the ensuing decades. [116] Of the 3 studies from Germany one was not reported stratified for age but reported a 7.9% prevalence rate for ED over the last year for ages 40-80 years. [87] The two studies stratified by age showed prevalence rates in the teens for those 49 years and younger. For each ensuing decade though rates were half as much in the Braun study compared to the May study. [121, 132] In the two studies from Spain, the one not stratified for age showed a prevalence rate of ED of 12.7% for ages 40-80 years. [88] In the stratified for age study rates were low until the decade of 60-70 years were the rate of 21% was reported. [126] In the single study from Belgium the rates doubled every decade from 40 to 69 years from 19.4% to 65.9%. [128] In the study from Croatia the prevalence rate for ED was low before age 50 but stayed about 18% from ages 50 to 69 years and almost doubled to 38% age 70 and beyond. [91] In the single study from Portugal prevalence rates for ED were high beginning with 30% for the 40 to 49 year decade to 50% to 70% for the next two decades. [133] For the single Italian study rates were very low before age 50 but were reported as 16%, 27% and 48% for the three decades beginning at age 50 years. [120] In the single Turkish study the unstratified for age prevalence rate for those 15 to 60 year of age was almost 60%. [90]

There were seven studies from Latin America, almost all from Brazil. (See Table 6D) In the single report from three non Brazilian countries, Columbia, Ecuador, and Venezuela, the prevalence rates for each of four decades beginning at age 40 and ending as age 79 from each of the three countries were almost the same with a 33 to 38.5% for the first decade, 40-50% for the next, increasing by about 25% for the 60-69 years of age decade to 73-75%, increasing about another 5% until age beyond 79 where rates ranged from 84 to 93%. [140] In the 6 studies reporting on more than 300 patients, the prevalence rates for ED were not stratified for age in one study and the prevalence rate in that study was 13.1% for ages 40-80 years. [86] The four random population and community based population studies reported prevalence rates for ED in the teens before age 50, varying from low of about 12% to 22% in the decade of 50-59 (with one exception mentioned in the
next sentence), increasing from about 32% to 58% in the decade ages 60 to 69 years. [136, 138,139, 141] In one study of 2000 men prevalence rates were much lower than the other random population studies using the IIEF as defining ED from 0.2% beginning with age 20-40 years of age, 1% for those 41 to 50 years of age, about 3% for 51 to 60 years of age and 7% in those greater than 60 years of age. [141] In a study of 965 men participating in a free screening program for prostate cancer, ages 45 to 90 years using IIEF-5 of scores below 21 as defining ED rates of prevalence for the disorder were much higher in this group from almost 37% for those 40 to 49 years of age, increasing by 5.5% for the next decade and by just beyond 20% for those 60 to 69 years of age. For those 70 to 79 years of age the rate was 79.4% and 100% for those 80 and above. [137] Rates were higher when IIEF scores were used to define ED.

In the studies from the United States, (see Table 6E), the methods used and populations varied but two of the studies showed fairly consistent prevalence rates for the various ages, the Massachusetts Male Aging Study (MMAS) and the study from Ansong. [26, 28, 142-143] The Laumann data included men who were younger and reported less than half the prevalence rate for the men 50 to 59 years of age compared to the other two studies from the United States. [20] The Olmsted County study from the United States also showed a lower prevalence rate by a large amount for the ages 40-49 and half the prevalence rate for the decades 60-69 years but similar rates for the decades 70-79 as the MMAS data. [77] In the 3 studies reported from North America that were not part of the last chapter two were not stratified for age and prevalence rates were 16 and 22.5% for ages 40 to 80 years of age. [95, 98] One study reported prevalence data from a survey of health professionals and semistratified by age with the following prevalence rates for those less that 60 years of age, those 60 to 69 years of age, those 70 to 79 years of age and those greater than 79 years of age of 10, 26, 50 and 60% respectively. [145]

There are 6 studies classified as world-wide reports. (see Table 6F) The first was a study by Rosen et al that included the US and 6 European countries. The prevalence rates were stratified for three decades beginning with age 50 years and through age 80 and were about 31%, 55%, and 76% respectively. The overall rates were similar for all countries and Europe only. [80] Nicolosi et al compared prevalence rates in Brazil, Italy and two Asian regions in 40 to 70 years of age. These were not age stratified and the prevalence rates of 15 and 17% were similar for the non-Asian studies and were higher in Asia, 22.4% in Malaysia and 34.4% in Japan. [146] Rosen et al in a second world-wide study again compared prevalence rates in the US, Brazil, and Mexico as well as 5 European countries. Including all of the countries the prevalence rates for ED were stratified by five decades and a single six year group of 70-75 years of age. Rates were in the teens for the three decades beginning with age 20 through age 49 years. For the next two decades beginning with age 50 to 69 years prevalence rates of 22 and 30% were reported with a prevalence rate of 37% for the six years of 70 to 75. Overall prevalence rate was 16% and the individual rates from the seven countries except the US were below this rate with the overall prevalence rate of ED in the US of 22%; half again the total group rate and double to 8% above the other countries. [147] In a second study from Nicolosi et al regional prevalence rates for age 40 to 80 years from around the world were reported. Rates were stratified for age for all of the countries and were low before age 60, were reported as 15.2% for the seventh decade of life and 22% above age 70 years. The regional prevalence rates were similar for all of the regions and ranged from 8 to 15% except for Southeast Asia where the prevalence rate was almost double to 22%. [85] Shabsig et al reported in 2005 non-stratified for age prevalence rates for ED from a large number of men from the US and five European countries. The rates for France, Italy, and Spain were similar, 12 or 13 %, while the UK, Germany, and the US were higher, 19, 22, and 25% respectively. [146] In the same year Laumann reported prevalence rates in a large number of men from various regions of the world. The rates were 13 to 14% in Northern Europe, Southern Europe, Central/South America, and the Middle East. In non-European West the rate was higher at 21% but again as shown above in the Nicolosi studies the highest prevalence rates for ED were in two regions in Asia, 27% in East Asia and 28% in Southeast Asia. [149]

The same tools and methods were used in a United States study and a Japanese survey. [77, 107] Thus these two could possibly provide for the best comparison between two cultures. The Japanese study showed almost double the prevalence rate for the four decades reported on compared to the American study. In contrast, the study from Thailand showed half of the prevalence rate for the age group 40-49 years compared to the Japanese study but almost equal rates for the other older decades reported.

One important issue to be addressed in future research is the validity and reliability of self-report data on ED generated in response to a single question (e.g., the NHSLS’s [20] question, “During the last twelve months has there been periods of several months or more when you...had trouble achieving or maintaining erection?”) when compared to results from the well used validated, multi-item International Index for Erectile Function (IIEF), [30] which is, of course, also a scale based on self-reports. The question of
which of the two instruments may be more useful and accurate for large population studies remains controversial. A good correlation of each criterion in population samples has been reported. [28] A single self-assessment direct question to evaluate ED was applied to the population-based samples of the MMAS follow-up evaluation, in addition to the Brief Male Sexual Function Inventory (BMSFI) and the IIEF. Prevalence was similar to that determined on the IIEF, agreement was moderate (0.56 to 0.58) and association with previously identified risk factors were similar for each classification. The single question correlated well with these other measures (r= 0.71 to 0.78, p<0.001). However the incidence of subjects not classified due to missing data was 9% on the MMAS single question, 8% on the BMSFI, and 18% on the IIEF. Based on these data, the direct self-assessment question may be a practical and accurate for large population studies remains practical tool for population studies, in which detailed clinical measures of ED are impractical.

The Global Survey of Sexual Attitudes and Behavior (GSSAB) [85, 149] have reported prevalence data based on two items, the first item corresponding exactly to the NHSLS question while the second asks if the respondent has reported a problem of achieving and maintaining an erection for two months or more, he is then asked, “how often would you say this has occurred during the last 12 months?” The choices are either occasionally, sometimes, or frequently. The GSSAB regarded only respondents reporting periodic, i.e. sometimes or frequently, difficulties as indicating moderate or severe ED. Across 7 world regions, between 22% and 44% reported only having occasional problems with ED of several months duration. These respondents were excluded from the prevalence estimates of having ED. Various systematic review of population-based estimates of sexual dysfunction note the considerable variation in the items asked to establish the presence of ED in the respondent (see Table 6A-F) and the resulting difficulties posed in establishing the comparability of the estimates across studies. [7, 60] It is imperative that research evaluating the relative efficacy of different measurement strategies be undertaken to establish recommended “best practice” for future studies. Consideration of “best practice” should be mindful that useful epidemiological data can often be generated with brief questions that would not be especially effective in identifying more narrowly defined clinical conditions.

In summary, the prevalence of erectile dysfunction on a world wide basis shows a great deal of variation but the way the information is collected, the way the population is sampled, the tools used for the survey, and, most importantly, the way ED is defined vary greatly. Below the age of 40 years the prevalence is 1-10%. In the decades from 40-49 the prevalence ranges from 2-9% to as high 15%. The 50-59 year age group showed the greatest range of reported prevalence rates. Most of the world show a rather high rate from 20-40% for the ages 60-69 years, some increasing after age 65 years, except for most of the Scandinavian reports where the age of 70 years and older is the decade of major prevalence rate change except the one report from Finland that showed high rates beginning at age 50. [129-130] Almost all of the reports show high prevalence rates for those men in their 70’s and 80’s, ranging from 50 to 100% prevalence of ED in these decades.

**Recommendation 5.**

- There is a need for more prevalence and incidence data studies on sexual dysfunctions in men and women from Africa, India, and Asia. **Grade C.**

**Recommendation 6.**

- Prevalence and incidence studies need to be more parallel in data collected and meet as many standards as possible [7]- duration for disorder screened for should be at least three months or more. Researchers should include severity scales for the disorder in the survey. **Grade C.**

**Recommendation 7.**

- There is a need to study the effect of excluding non-sexually active individual from the prevalence data reports. **Grade C.**

**h) Concurrence of sexual dysfunction**

Both in the descriptive and analytical epidemiological literature there is very little on simultaneous occurrence of different sexual dysfunctions within and across genders. In French men, aged 18-69, it has been reported that 7% of those with manifest ED also are early ejaculators. [150] In an older sample (50-78 year olds) from the Netherlands about 50% of the men with early ejaculation also reported ED. [79] To which extent this simply indicates that incapacity to maintain erection is a sequel to early ejaculation remains to be analyzed. From France it has been reported that 37% of 18-70 year old men with ED have lost their “libido”. [21] It has been found in a Swedish study that within both genders (aged 18-74) nearly all own sexual dysfunctions are closely associated (generally at a p level of < 0.001). [19] The only exception is that for the men with early or delayed ejaculation quite logically were not significantly correlated. Moreover, a high degree of cross-gender concurrence was found. In fact all women’s dysfunctions studied were closely (p <0.005- 0.001) coherent with all male partners’ functions/dysfunctions as perceived by the women. Men’s sexual dysfunctions had precisely the same close associations with men’s perceptions of their female partner’s functions/dysfunctions. These findings firmly suggest that it is important to think in terms of sexual partner relationship, none the least in
therapy-pharmacological or psychotherapeutic. [151] Laumann et al also examined the co-occurrence of dysfunctions for the set of dysfunctions discussed in the latent class analysis, but the actual percentages of overlap were not given in the article. [21]

g) Sexual dysfunctions and personal distress:
It is of paramount importance to know to what extent sexual dysfunctions are accompanied by distress.

Commonly overall level of sexual distress is nowadays measured by one single question or by an aggregative questionnaire such as the FSDS (the Female Sexual Distress Scale) [34, 70]. Given the close coherence of different sexual dysfunctions – intrapersonal as well as interpersonal – we have here chose to focus on the extent to which specific dysfunctions lead to dysfunctional distress (personal problems). Among women and men with manifest dysfunction per se generally less than half experience that it is accompanied by manifest personal distress (Table 7). Moreover, only small minorities of those with mild/sporadic dysfunction report manifest distress. In Sweden 26% and 17% of women and men reported at least one distressing self or partner's sexual dysfunction. However, among the manifestly personally distressed, the vast majority were not satisfied with their sexual lives. This can be compared with the sexual satisfaction rate of 55% in the total population. [19] In general agreement with this and defining sexual distress (one overall pluri-item aggregated variable) using the FSDS [71] have found that 22% of women in the USA aged 18 and above reported sexual distress. This is about half of the 43% who had an – age adjusted – sexual dysfunction. However, these authors did not explicitly ask for distress caused by specific sexual dysfunctions. Measuring women's sexual distress using the FSDS, Rosen et al [152] have reported that among women with low sexual desire level of distress decreased with higher age and those in partner relationship had relatively high level of distress as had those with arousal and orgasmic dysfunctions. Furthermore Bancroft et al., [153] found that neither relative frequency of sexual thoughts, frequency of orgasm, nor lubrication problems were predictors for women having significant or manifest versus no, or mild versus no distress concerning their own sexuality. They further reported that the best predictor of sexual distress was relatively low emotional well-being. In reasonable consensus with other studies Öberg and Fugl-Meyer [154] confirmed that low level of satisfaction with partner relationship is closely associated with women's manifestly distressing dysfunction of sexual interest, lubrication and orgasm. However, the causality is unclear. Thus, a distressing sexual dysfunction may be caused by a disharmonious partner relationship but a sexual dysfunction may contribute to a not satisfying partner relationship.

V. ANALYTICAL EPIDEMIOLOGY

1. RISK FACTORS FOR WOMEN

In this part, we shall first address women’s sexuality in relation to health issues. Subsequently findings relating social and demographic factors to sexual function will be discussed. Besides the investigations referred to, we have not been able to locate reliable and reasonably evidence-based investigations of risk factors for women's sexual functions. Thus, the need for more research concerning women’s sexuality must be underlined. When dealing with risk factors, co-morbidities and socio-demographic items, descriptive epidemiology gives best evidence. However, analytical epidemiology may be an adequate way to identify the relative risk of sexual dysfunction caused by (sets of) medically or psychologically identified particular diagnostic categories.

Recommendation 8:

There clearly is a need for more analytical epidemiological studies about women's sexual dysfunctions. Grade C.

a) General Health-related risk factors

Richters et al [37] found that, compared with women with excellent health, those reporting good, fair or poor health were more likely to have a sexual dysfunction. Significant odds ratios were 1.9, 3.1 and 5.7 for those with good, fair or poor health, respectively. Simultaneously Laumann et al. [20] and Fugl-Meyer & Fugl-Meyer [65] reported that less-than good health leads to greater risks of sexual dysfunctions concerning desire/sexual interest and genital pain. Self-reported health and levels of physical activities have been confirmed to be an important correlate of sexual function, as more orgasm problems were found among women who reported no physical activity [154], and higher level of sexual desire among those who reported higher self-perceived health and more physical exercise. [74] Perceived poor health was also a predictor for women’s sexual desire, arousal, orgasm and dyspareunia. [70, 71, 154]

b) Diabetes

Kadri et al [24] in their descriptive epidemiological study of Moroccan women reported (univariate) significant associations for diabetes with orgasmic dysfunction, dyspareunia and sexual aversion. Also Danish women with diabetes have been found to have
low sexual desire significantly more often than non-diabetic women [74]. In a well-controlled age matched analytical study Enzlin et al. reached the conclusion that sexual problems are frequent in women with diabetes mellitus. Among the sexual function variables, “libido”, lubrication, orgasm and genital pain only decreased lubrication was significantly (univariately) associated with being diabetic. [155] Moreover, women with “more” diabetic complications reported significantly more sexual dysfunctions. However, more recent large epidemiological studies conducted on women representative of the US 2005 census, Brazilian women, and Australian women, did not find a significant relationship between diabetes and desire, arousal, or orgasm. [37, 70, 156-157]

d) Urinary tract diseases

Stress urinary incontinence has been found by Osborn et al. [64] to negatively influence all aspects of women’s sexual function (sexual interest, desire, arousal, lubrication, orgasm) and to be significantly
correlated with dyspareunia and vaginismus. In a small scale analytical investigation [160] urinary stress incontinence was (unvariably) significantly associated with sexual interest, lubricative insufficiency, orgasmic dysfunction and dyspareunia. Along these lines, Laumann et al. found that having urinary tract symptoms were predictors of lubrication insufficiency, orgasmic dysfunction, and dyspareunia while ever having had STI (sexually transmitted infections) was a negative predictor for sexual interests and for lubricative function [20].

e) Gynaecological factors

Hysterectomy has in a few epidemiological studies been found to affect women's sexuality. Dennerstein et al. [73] found that 16% of surgical menopausal women had low sexual desire compared to 7% of menstruating women and the former being more likely to feel distressed. Hormonal therapy improved levels of desire but did not change distress. Furthermore, Shifren et al. [70] reported, despite desire, arousal and orgasm function were lower among women who were hysterectomized. Similarly, McPherson found that sexual arousal, but not vaginal dryness, was impaired in women who received hysterectomy as compared to women with oophorectomy. [161]

f) Psychiatric/psychological factors

There is little doubt that part of the psychological distress experienced by individuals with mood or anxiety disorders affects sexual function. Unfortunately, research on the epidemiology of sexual dysfunction has yet to provide information on the commonality between psychological vulnerabilities that are associated with sexual disorders. By latent class analysis Laumann et al. [20] deduced that emotional problems or stress are sizeable predictors of low desire, arousal disorder and sexual pain (all three defined according to the DSM-IV).

Ten years ago Dunn et al [119] demonstrated significant likelihoods (Odds ratios ranging from 1.8-4.5) depression and anxiety to predict all their investigated parameters: arousal, insufficient lubrication, orgasmic dysfunction and dyspareunia. Accumulating evidence [64, 70-72, 74] confirmed these associations between anxiety and depression with sexual dysfunction. An interesting study by Sievert et al [162], however, with a response rate of only 29%, found that loss of desire for women under the age of 40 correlated with depression symptoms; for women in the age-cohort 40 to 60 with menopausal symptoms and for those older than 60 with somatic and psychological problems – a mutual denominator could be mood changes/depressive symptoms.

The effect of different antidepressants giving negative “changes in sexual function” were, by Clayton et al [163,], found to be significantly more likely to occur (Odds ratios 2.2-2.9) with SSRIs (selective serotonin re-uptake inhibitors) or venlafaxine than with buprion or netazodone in women and men on monotherapy. Moreover, the WHO collaboration center for international drug monitoring has reported that out of a total of nearly 215,000 reported adverse effects of antidepressant during the period 1968-1997, 5000 were sexual in nature. [164] Using the somewhat outdated response cycle phase definitions, about 1500 adverse reactions were related to each of the “desire” and “excitement phases”, while 200 occurred during the “phase of orgasm”. The most typical female SSRI adverse reaction was orgasmic dysfunction. Although the sheer number of reports to the WHO is great, these anecdotal reports cannot be taken as evidence.

g) Social stressors as risk factors

Some epidemiological investigations have addressed the impact of sexual abuse on women’s sexual behaviour and it has been clearly shown that women’s current sexual life can be detrimentally influenced by abuse. [20, 38, 74, 119, 165, 166] Studies that ask people to self-identify as sexual abuse survivors usually report lower rates of sexual abuse as compared to studies that utilize behavioural definitions. [167] Having ever been sexually forced by a man predicts low levels of desire and greater arousal disorder in American women. Also, having ever been sexually harassed predicted arousal disorder and sexual pain [20]. In Sweden, 12% of 18-74 year old women had at some time of their life been sexually abused [165]. Women with a history of sexual abuse had a significantly higher number of sexual dysfunctions than had women with no history of abuse and nearly all different types of sexual abuse were significantly (univariately) associated with orgasmic dysfunction. Having been genitaly abused was also significantly associated with low level of sexual interest. Satisfaction with sexual life was lower in those who had been abused and, in particular, if abused more than once. Furthermore, data from the same representative Swedish sample showed that obesity was not associated with a history of sexual abuse and sexual satisfaction. In Moroccan women [24] having been sexually abused negatively influenced sexual interest. Interestingly, only one study reported rates of sexual function among men with a history of child sexual abuse [38] and they found a less strong relationship between sexual abuse and sexual function compared to the relationship observed in women.

Incidentes of emotional and physical abuse during childhood are highly coremorbib with a history of sexual abuse and some studies have found initial evidence of a stronger relationship between emotional and physical abuse and sexual function as compared to sexual abuse [168]. No epidemiological studies that
we know of have examined this research question which requires the simultaneous assessment of different types of childhood trauma along with measures of sexual function.

Being single is (univariately) associated with dysfunctions of sexual interest, vaginal lubrication, orgasm and with dyspareunia [65]. Low levels of sexual interest, arousal, orgasm and also dyspareunia are significantly most common in women with marital difficulties [64, 119]. There is a close relationship between male partner’s sexual dysfunctions and women’s own dysfunctions; particularly if distressing [19]. Furthermore, low levels of overall sexual satisfaction and satisfaction with partner relationship predict low level of satisfaction with life as a whole. (See Table 7) In a large-scale-analytical epidemiological investigation of a gynaecological sample, Raboch and Raboch reported that a number of “intra-familiar” aspects of life (early loss of mother and father, not having a happy childhood, having three or more siblings or not having a happy marriage) univariately were significant features of women with orgasmic dysfunction, in particular if the dysfunction caused personal distress [169]. In Morocco, relatively low education is common in women with low level of sexual interest [24]. This is also the case in the USA [20] and in Eastern Europe [169] for orgasmic dysfunction and, additionally, in the USA for dyspareunia [20]. In the USA women with more than 20% financial household decrease during the year prior to the investigation have low level off interest and lubrication and also relatively high prevalence of dyspareunia [20]. Furthermore, stress at work or unemployment have been reported to accompany low sexual desire in women [170,171] but was associated with a higher desire of foreplay in French women. [171]

2. RISK FACTORS FOR MEN

a) Age, Health and Social Related Risk Factors

Less than good overall health is likely to concur with men’s low level of sexual interest/desire and with ED [20, 65]. Furthermore, Laumann et al [20] identified a (significant) odds ratio of 2.4 for the likelihood of poor to fair health being a predictor of early ejaculation. Also Richters et al [37] reported that Australian men who are not in excellent or good health are most likely to have a sexual dysfunction (not further specified). Having been sexually touched before puberty predicts lower level of interest/desire (odds ratios 2.2), ED (odds ratios 3.1) and early ejaculation (odds ratios 1.8). [20] Moreover, men who ever have forced a woman sexually are more likely (odds ratios 3.5) to have ED than are those who never have done so. Neither of these two descriptive investigations has found ejaculatory disturbance correlates of sexual abuse. Both in the USA [20] and in Sweden [65] partnerless men are more likely to have low levels of sexual interest/desire and of ED than are those who have a steady partner relationship. In the USA relatively low level of educational attainment is associated with early ejaculation. [20]

The Health Professional Follow-up Study (HPFS) is a cohort of male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians in the United States who responded to a mailed questionnaire in 1986 (original response rate 32%). This U.S. study of prevalence and risk factors for erectile dysfunction found a 10-fold difference in relative risk for erectile dysfunction associated with older age, regardless of health status or previous erectile function. [145] Follow-up questionnaires were mailed every two years. At the time of the 2000 questionnaire, 43,235 men, age 53 to 90 years, were alive and actively participating in the study. The questionnaire was mailed up to four times to non-respondents with a response rate of 79%. This group of 31,742 health professionals, with no known history of prostate cancer, ranged in age from 53 to 90 years at the time of the 2000 questionnaire. Men in the oldest age group were less likely to be married, smoke, or engage in physical activity and were more likely than younger men to have comorbid conditions. When men with prostate cancer were excluded, the age-standardized prevalence of erectile dysfunction in the previous 3 months was 33%. Men with a healthy lifestyle and no chronic disease had the lowest risk for erectile dysfunction; the greatest difference was seen for men 65 to 79 years of age. Comorbid conditions, such as diabetes, cancer, stroke, and hypertension, were also associated with increased risk for erectile dysfunction, whereas physical activity, leanness, moderate alcohol consumption, and not smoking were associated with decreased risk. Men included in this study had lower rates of obesity and less diabetes than same-age men in the general population. In addition, participants in our study were more likely to be white, have higher educational attainment, have higher incomes, and have better health care access than similar-age men in the general population. Therefore, the findings probably reflect a more favorable profile for sexual function across the life course compared with the general population. The study found an inverse association between physical activity and erectile dysfunction. The study also found that younger men (<60 years of age) benefit more from exercise than older men (>80 years of age).

The National Social Life, Health, and Aging Project (NSHAP) is a nationally representative US probability sample of 1,550 women and 1,455 men aged 57-85 at the time of an interview. In this report the weighted response rate was 75.5%. [172] Data on sexual problems were collected through seven dichotomous response items inquiring about sexual problems experienced over several months during the previous 12 months. Items asked included lack of interest in
sex, arousal problems, too early climaxing, inability to obtain an orgasm, pain during sex, unpleasurable sex, and performance anxiety. There was little if any increase in sexual problems with age for either gender except for orgasm and erectile problems in men- both positively correlated with age. Hispanic women reported (OR=2.4) more reports of sexual pain compared to white women. Black men are more than twice as likely to report lack of sexual interest and premature climax (OR 2.3 and 2.90), and almost four times (OR=3.8) likely to report lack of sexual pleasure as white men. Lack of pleasure is sharply lower among widowed or never married (OR=0.1) than married men while divorced and separated men report twice as likely complaints (OR=2.0). Reports of anorgasmia and lack of sexual pleasure decline with men’s higher education in contrast to erectile problems which are sharply elevated (OR=1.9) among men with some college education. Health conditions strongly affect the likelihood of sexual problems in women but less among men, except an association between any lifetime history of STD’s and non pleasurable sex (OR=5.4) and between urinary tract syndrome and erectile problems (OR=3.7). Poor mental health is associated with both women’s and men’s reports of sexual problems; anxiety raising lack of sexual pleasure for men and women and depression selectively associated with men’s anorgasmia and erectile problems. Finally, satisfaction in a relationship was associated with fewer sexual problems. In the healthier, older respondents age patterns suggested maintenance of sexual capacity rather than decline. Increasing biological age does not result in more sexual problems for either sex except for men’s erectile and orgasmic problems. Sexual problems among the elderly seemed more a response to stressors in multiple domains of life from physical health to features of an intimate relationship.

Most epidemiological studies on ED underrepresented minority groups. In a cross-sectional population-based survey conducted between May, 2001 and January, 2002 facilitated equivalent representation was achieved for non-Hispanic whites (N=901), non-hispanic blacks (N=596) and Hispanic males (N=676) 40 years and older by using targeted phone lists to oversample the minority. [173] Overall prevalence rate for ED was 22%; 21.2% for whites, 24.4% for blacks and 19.9% for Hispanics, all categories increasing with older age. Overall sampled ED probability increased with diabetes, hypertension, and moderate or severe lower urinary tract symptoms (LUTS); in whites >70 years of age and diabetes; in blacks with severe LUTS; in Hispanics greater than age 60, moderate LUTS, hypertension, and depression. Probability of ED decreased with level of exercise, higher level of education overall; in blacks with exercise, good relationship quality and lower level of alcohol intake; in Hispanics with high school or college education.

Cross-sectional analysis of data from 2126 adult male participants in the 2001-2002 US National Health and Nutrition Examination Survey (NHANES). Erectile dysfunction assessed by a single question during a self-paced, computer-assisted self-interview. These data are nationally representative of the noninstitutionalized adult male population in the US. [174] The overall prevalence of erectile dysfunction in men aged 20 years and greater was 18.4% (95% confidence interval [CI], 16.2-20.7), suggesting that erectile dysfunction affects 18 million men (95% CI, 16-20) in the US. The prevalence of erectile dysfunction was highly positively related to age but was also particularly high among men with one or more cardiovascular risk factors, men with hypertension, and men with a history of cardiovascular disease, even after age adjustment. Among men with diabetes, the crude prevalence of erectile dysfunction was 51.3% (95% CI, 41.9-60.7). In multivariable analyses, erectile dysfunction was significantly and independently associated with diabetes, lower attained education, and lack of physical activity.

The National Health and Nutrition Examination Survey collect data by household interview. The sample design is a stratified, multistage, probability sample of clusters of persons representing the civilian noninstitutionalized population. Data include medical histories in which specific queries are made regarding urological symptoms (including ED). [175] These items were selected for analysis in 3566 men, 20 years and older. In men 20 years and older, ED affected almost 1 in 5 respondents. Hispanic men were more likely to report ED (odds ratio [OR], 1.89), after controlling for other factors. The prevalence of ED increased dramatically with advanced age; 77.5% of men 75 years and older were affected. In addition, there were several modifiable risk factors that were independently associated with ED, including diabetes mellitus (OR, 2.69), obesity (OR, 1.60), current smoking (OR, 1.74), and hypertension (OR, 1.56).

In the Boston Area Community Health (BACH) Survey ED was assessed in 2,301 men aged 30-79 using the 5-item IIEF-5 (defining ED as a score ≤16). [176] Overall prevalence of ED was 20.7% with a higher rate among blacks (24.9%) and Hispanics (25.3%) compared to whites (18.1%), even after adjusting for age, comorbid conditions, and behavioral risk factors. However after controlling for socio-economic factors the association between race/ethnicity and ED disappeared.

b) Smoking or Other Tobacco Use

It is logical to assume that erectile function, a process which relies on normal arterial vascular performance to operate correctly, would be adversely affected by cigarette smoking. A recent review on cigarette
smoking and erectile dysfunction appeared in 2008. [177] In that article epidemiological and clinical data as well as a discussion of causative factors are well reviewed. In a previous literature review, McVary et al presented the results of an exhaustive review of the literature conducted by the Subcommittee on Smoking and ED of the Socioeconomic Committee of the Sexual Medical Society of North America. [178] These authors found strong indirect evidence that smoking may affect erections. Their conclusions were: “Available evidence on the association of smoking with ED is not complete insofar as association is likely due to the consistency of the relationship of smoking and endothelial disease, and the strength of the association of ED with other endothelial disease”.

Tengs and Osgood performed a complete Meta analysis of available literature over the last 20 years prior to 2001 by searching MEDLINE to identify the prevalence of smoking among impotent men. [179] These authors reviewed over 1000 articles and identified 19 that reported the smoking habits of 3819 men. They found that 16 of these articles, including the 6 largest studies, found the prevalence of smoking to be higher than in the general population. Their meta-analysis revealed that 40% of impotent men were current smokers, which they compared to 28% of men in the general population. These authors concluded that: “Based on almost 2 decades of evidence, tobacco use is an important risk factor for impotence. Anti-tobacco advertisements featuring impotence as a reason to avoid or cease tobacco use are well grounded in scientific fact”.

In the previous consultation there were two articles cited that did not find increased risk for ED in association with smoking. Mak et al performed a population-based study in Belgium. [128] These investigations interviewed a random sample of the population, which included 799 men aged 40 – 70 years. They did not find a correlation between smoking and ED, either in current smokers or in ex-smokers. Similarly, Morillo et al reported on the prevalence of ED in Columbia, Ecuador and Venezuela. [140] This study questioned 1946 randomly selected men aged 49 and older. Using univariate analysis, the authors did not find any association of cigarette smoking with ED.

There were two studies in cross-sectional populations and one in a special clinical population of diabetics included in the last consensus chapter that found a positive correlation between smoking and ED. Miron et al performed a cross-sectional study on the prevalence and risk factors for ED in the general population in Italy. [180] This random sample included 2010 men from the practices of 143 general practitioners. The researchers found that current smokers had an odds ratio of ED of 1.7 (95% confidence interval 1.2-2.4) compared to never smokers. Ex-smokers had an odds ratio of 1.6 (95% confidence interval 1.2-2.3). The authors also found the association of smoking and ED risk to be present in men without a history of any cardiovascular disease, cardiopathy, hypertension diabetes and neuropathy. Nicolosi et al studied the epidemiology of ED in four countries. [146] The countries that were included in the study were Brazil, Italy, Japan and Malaysia. From each country, a random sample of approximately 600 men between the ages of 40 and 70 were interviewed. The authors found an odds ratio of ED of 2.12 (95% confidence interval 1.26-3.56) in men who smoke >30 cigarettes/day compared to men who did not smoke. Bartolotti et al reported on 9670 diabetic men who were categorized as: never smokers (30%), current smokers (30%), or ex-smokers (40%). [181] These participants were randomly selected from 178 different diabetic centers in Italy. The effect of age was considered when the results were analyzed. These researchers found that current smoker had an odds ratio of ED of 1.4 (95% confidence interval 1.3-1.6) compared to never smokers and ex-smokers had an odds ratio of 1.5 (95% confidence interval 1.3-1.6) compared to never smokers. The authors further found that in ex-smokers, the risk of ED was inversely related to the number of years since the patient quit smoking.

A recent epidemiological study of high evidenced-based criteria attempted to identify the association between cigarette smoking and ED and further analyzed the data by adjusting for presence or absence of cardiovascular disease. [182] The Western Australia Men’s Health Study (WAMHS) is based on a stratified sample of the male population obtained from the Western Australia (WA) electoral roll for June 2001. This publication was based on 1,580 participants who had returned their questionnaires and included smoking data and year of birth (89.3% of those returning the questionnaire). The report demonstrated statistically significant increases in the odds of ED among current smokers compared with never smokers even after adjustment for age and cardiovascular disease. Although not statistically significant, the corresponding odds among ever smokers and former smokers were also increased implying a possible adverse effect of previous smoking on erectile function. Cardiovascular disease did not confound the relationship between smoking and ED. This study also suggested that cessation of smoking before middle age may avoid the increase in the risk of ED.

Most studies who report on the association of smoking and ED contain populations with other diseases that are clear risk factors for ED. However, a study of 7,684 Chinese men showed that smoking was associated with ED in men without clinical vascular disease. [183] The same study also demonstrated increased odds of those men who smoked more than 20 cigarettes per day. A. dose
related association has been also reported in other studies. [184, 185] It has also been shown that the magnitude of the association between smoking and ED decreases across increasingly older age groups, suggesting that smoking may have a more apparent impact on erectile function in young rather than older smokers. [186]

Thus it would appear that the preponderance of evidence available at this time would identify cigarette smoking as an independent risk factor for ED. We have, on the other hand, not identified descriptive or analytical literature which links smoking to other male sexual dysfunctions or to any female sexual dysfunctions. Those of us who are clinicians, should use and expand this information to enlighten our patients and to encourage them to add ED to the long list of reasons why they should strive to quit smoking.

c) Diabetes Mellitus

From the Netherlands, Enzlin et al reported that men with complications of type I diabetes had significantly greater prevalence of decreased desire than had those without complications [187]. This was also the case for prevalence of orgasmic dysfunction. Diabetes mellitus has also been associated with retrograde and anejaculation. [188]

Erectile dysfunction has been reported to occur in at least 35-90% of men with diabetes mellitus with the onset of ED occurring in an earlier age (10 to 15 years before) than those without diabetes mellitus [189-202]. In the MMAS study, the age-adjusted probability of complete ED was three times higher in men who reported having treated diabetes mellitus than those without diabetes. [26]

Weinhardt and Carey in 1996 published a comprehensive review of empirical literature, regarding the prevalence of ED among men with diabetes mellitus; they suggest that 26-35% of diabetic men will develop ED. They present an excellent discussion of the methodological limitations of published research and make suggestions for changes to produce more reliable and useful information [203]. Whitehead and Klyde reviewed a large amount of the associations between ED and diabetes mellitus in their literature review of 1990 [189]. Some of their observations are reported in Table 8.

In a separate paper from the Health Professionals Follow-up Study (HPFS) included in the prevalence of ED table, Bacon et al report on the association of type and duration of diabetes with ED in this large cohort of men [204]. Men with diabetes had an age-adjusted relative risk of 1.32 (95% CI 1.3-1.4) for having ED compared to men without diabetes. Men with type 2 diabetes had an increasingly greater risk of ED with increased duration since diagnosis, particularly for men diagnosed >20 years previously. In 178 diabetic centers in Italy, data was collected using interviews regarding erectile dysfunction in 9,868 men [205]. The patients ranged in age from 20 to 69 years. The prevalence of ED was 35.8% for the entire group, ranging from 4.6% for men 20-29 years of age to 45.5% for men 60-69 years of age. For men with insulin dependent diabetes mellitus, diabetes present for over ten years, with fair or poor control based on glycosylated hemoglobin 7.5-9% and > 9% respectively, those managed with agents other than diet control, and history of diabetes mellitus-related arterial, renal, or retinal disease and neuropathy and those who were smokers, all showed a higher odds ratio for ED.

A subset of 1,010 of these men from the Italian group above without ED at baseline were followed prospectively for 2.8 years to determine the incidence of ED associated with diabetes [206]. The crude incidence rate was 68 cases per 1000 men years (95% CI 59-77). The incidence of ED increased with increasing age, duration of diabetes, and deteriorating metabolic control. The rate was higher for type 2 than in type 1. The relative risk increased

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Table 8. Associations of Diabetes Mellitus (DM) with Erectile Dysfunction

| - Erectile Dysfunction is usually present within 10 years of diagnosis of DM |
| - Usually occurs at a younger age group in insulin dependent DM |
| - ED may be first sign of DM in as high as 12 % of cases in males |
| - Poorly controlled DM may produce a reversible temporary ED once controlled |
| - ED in almost all patients with DM related neuropathy |
| - DM macrovascular complications related to neuropathy |
| - DM microvascular complications related to duration of DM and glycemic control |

also with obliterative arterial disease of the lower legs, ischemic heart disease, renal disease, autonomic neuropathy, sensation and motor neuropathy, and diabetic foot and retinal disease. The Massachusetts Male Aging study reported ED incidence of 51 cases/1000 man years [28]. Also, the incidence rate of erectile dysfunction is higher for each decade of diabetic men compared to non-diabetics, up to twice expected in the general population without diabetes mellitus.

Diabetic men with sexual dysfunction, including ED, are older and have a longer duration of diabetes [199, 200, 204, 205]. ED in men with diabetes is more severe and associated with poorer quality of life [175, 194] and poor glycemic control [200]. Hyperlipidemia, hypertension, and obesity are conditions common in diabetic men and also independent risk factors for ED.

Interestingly, Gazzaruso et al. [207] reported that ED itself could be considered the most efficient predictor of silent coronary artery disease in a diabetic population, independently of glycometabolic control and ED severity. In particular, among a consecutive series of 160 subjects with apparently non-complicated type 2 diabetes, they demonstrated that the prevalence of ED was 7-fold higher (35% vs 7%) in subjects with silent coronary artery disease. Similar results were confirmed during longitudinal studies by the same group [208] and other authors. [209] Accordingly, Corona et al. demonstrated that penile vascular insufficiency was inversely related to the risk of silent coronary artery diseases in the diabetic population. [210]

In a recent publication, Rosen and others report an analysis of risk factors in a subset of 373 men of the look AHEAD trial of type 2 diabetes [199]. Of these 373 men 268 were sexually active (68.7%). About 75% of these 373 men had mild, moderate, or severe ED using the erectile function domain of the IIEF (65% of the sexually active men). Of the sexually active men 42.5% had consulted with a physician about sexual problems. Only 7.3% of the sexually active men had severe ED. Risk factors influencing ED were the following: the existence of metabolic syndrome, hypertension history, and other cardiovascular disease. Men with improved levels of fitness were about 40% less likely to have ED. Cardiorespiratory fitness was measured by a symptom-limited graded exercise treadmill test to voluntary exhaustion [199].

d) Obesity metabolic syndrome and erectile dysfunction.

Until the last decade, the risk associated with overweight and obesity had been widely underestimated. Large prospective epidemiological investigations including the Framingham [211], the National Health and Nutrition Examination Surveys [212] and the Prospective Cardiovascular Munster studies [213] have clearly demonstrated that overweight and obesity are independent factors associated with an increased mortality in men and that this is due largely to coronary atherosclerosis or other cardiovascular diseases. Moreover, the same studies have shown that the prevalence of obesity has dramatically increased both in the US [211, 212] and Europe [213] creating a new important burden for the medical community.

The link between obesity and male potency dates back to the Byzantine era, when it was thought that a large stomach impaired a man’s ability to have sexual intercourse. [214] So far, however, the association between obesity, sedentary lifestyle and erectile dysfunction (ED) has not been completely clarified. [215, 216] Baseline data from the Massachusetts Male Aging Study (MMAS) failed to find any association between BMI and ED. [26] More recently, cross-sectional analysis of data from the NHANES survey [174], involving 2126 non-institutionalized men representative of the US adult male population, demonstrated an attenuated association between obesity and ED after adjustment for cardiovascular risk factors. However, longitudinal studies have clearly demonstrated a direct association between these conditions at baseline and the subsequent development of ED. [49, 217] In particular, the Health Professionals Follow up Study [145], including 22,086 US health professional men, showed that after a 14-year follow-up study period, ED was most likely to occur in men who were obese (OR=1.7 [1.5-2]) and who lived a sedentary lifestyle (OR= 0.7 [0.7-0.8] for subjects with physical activity greater than 32.6 vs. less than 2.7 METs/week). In addition, prospective data from the MMAS demonstrated that cigarette smoking and BMI significantly predicted the risk of developing ED even after controlling for confounding factors. [28, 218]

Yet how obesity affects ED is not entirely clear. Early endothelial dysfunction and impaired nitric oxide synthesis, necessary for stimulating smooth muscle relaxation and increased blood flow which is in turn necessary for erection, have been considered the major associated pathogenetic issues. [215-216, 219-220] Corona et al. [214] recently confirmed this hypothesis in a large cross-sectional trial including 2,435 male patients seeking treatment at an outpatient clinic for sexual dysfunction between 2001 and 2007. The results of this study showed that obesity was significantly associated with a higher physical contribution to ED, while there was no difference seen among relational or psychological determinants. As the severity level of obesity increased, penile blood flow decreased (one half of patients with morbid obesity had pathological penile blood flow). In addition, as previously reported [215-216, 219-220], an inverse association between testosterone levels and BMI was also found. In these
patients, hypogonadism can exacerbate sexual dysfunction because of its typical symptoms, such as decreased sexual desire and mood disturbances [214-216, 219-220]. This evidence might be a useful motivator for men to improve their health-related lifestyle choices. Accordingly, Esposito et al. [221] in a randomized trial in obese men, has shown that decreasing BMI and increasing exercise significantly improved ED in approximately a third of cases suggesting that lifestyle changes can reverse ED. Kratzik et al [222] demonstrated that the risk of severe ED is decreased by 82.9% for males with physical activity of at least 3000 Kcal/week. In addition, the same authors reported that an energy expenditure of as little as 1000 Kcal/week significantly reduces the existing risk of ED. Some examples would be bicycling 4 miles (6.4 km) in 15 minutes, social dancing for 30 minutes, running 1.5 miles (2.4 km) in 15 minutes or gardening for 30-45 minutes. [222]

Furthermore, a Mediterranean diet based on olive oil as the major fat source and including more fish, legumes, vegetables and fruits has been recommended as an extremely successful and conservative way to treat obesity since the time of Greco-Roman writers. [223] A large body of evidence has demonstrated that a greater adherence to a Mediterranean diet is associated with a significant improvement in health status, as well as a significant reduction in overall and cardiovascular disease mortality. [224] Hence, in line with these data, the protective role of a Mediterranean diet on erectile function is not surprising. [225] In addition, both clinical and experimental studies have confirmed that combining physical exercise with the reduction of caloric intake provides additional benefits to erectile function. [226]

Recently, it has been reported that central obesity (high waist circumference) may be a better predictor of increased cardiovascular risk than obesity per se [227]. Although this issue is under debate, Cornier et al [228] demonstrated that waistline should be considered at least the best predictor of medical care costs. Central obesity is a key element of metabolic syndrome (MetS), a cluster of metabolic abnormalities related to a state of insulin resistance and an increased risk of developing cardiovascular and metabolic diseases [216, 227]. Although several definitions for MetS have been proposed [216], the criteria defined by the National Cholesterol Education Program-Third Adult Treatment Panel (NCEP-ATPIII) are the most widely used in clinical practice and research. Recently it has been demonstrated that not only the individual components of MetS but also MetS itself is significantly associated with ED. [215-216, 229-230] In addition, prospective data from the Massachusetts Male Aging Study in a population-based cohort observed at three different time points over approximately 15 years showed that ED could also be predictive of MetS with an unadjusted relative risk of 1.35. [231] The prevalence of ED in subjects with MetS ranges from 27% [232] to 80% [233] strictly associated with the number of MetS components and the endothelial function impairment. [215-216, 229-230]

In particular, among subjects with ED, those with MetS are characterized by the worst erectile function, (essentially due to impairment in penile blood flow) and report a prevalent difficulty in obtaining vs. maintaining erection, a gradual onset of the disorder, and a decreased number of nocturnal erections, all of which were demonstrated to be associated more with an organic than a psychogenic origin of ED. [234-236] Corona et al., [234-236] demonstrated that elevated blood pressure and hyperglycaemia, which are well known cardiovascular risk factors, are associated with impaired penile vascular flow to a greater extent than the other components of MetS. The association between hypogonadism and MetS is emerging even in subjects with ED. [215-216, 219-220, 229-230] Abdominal adiposity and hyperglycaemia [215-216, 219-220, 229-230] represent the most important factors involved in the pathogenesis of hypogonadism in MetS. The presence of hypogonadism in men with MetS increased symptoms of sexual dysfunction such as low sexual desire. [215-216]

**Recommendation 9:**

There is still a question whether obesity and the metabolic syndrome per se are additional risk factors for erectile dysfunction or that the diseases cardiovascular and diabetes themselves that are part of these conditions are the risk factors that account for this association. Further research is needed to answer this question. Grade C.

c) Cardiovascular Disease and Hypertension

Endothelial dysfunction is a condition present in many cases of erectile dysfunction and thus there is a common etiologic pathway for other vascular disease states, such as cerebrovascular accidents, myocardial infarction, heart disease, hypertension, hyperlipidemia, low serum levels of high density lipoproteins (HDL), arteriosclerosis, and peripheral vascular disease and thus an association with these other conditions is to be expected. Wabrek and Burshell reported that 64% of 131 men, aged 31 to 86 years, hospitalized for acute myocardial infarction were impotent. [237] Sjögren and Fugl-Meyer reported an 18% prevalence of ED in 49 men before experiencing a myocardial infarction compared to a prevalence of 45% after the event, with a 43% new onset or increase in ED in this group of men. [238] These authors also found that low level of sexual desire increased after myocardial infarction from 14% to 35% and orgasmic problems from 4%
to 25%. In fact 21% reported anorgasmia after the myocardial infarction. In another study ED was present prior to myocardial infarction (MI) in 64% of 131 men and before coronary bypass surgery in 57% of 130 men [239]. In still another study of 132 men attending day case angiography, 40% had experienced ED before their coronary diagnosis had been made. [240] In addition, Montorsi et al. [241] demonstrated that, in subjects with angiographically document coronary artery disease, ED becomes evident prior to angina symptoms in almost 70% of the cases, with a mean interval of more than three years. Accordingly, Thompson et al. [242] in the Prostate Cancer Prevention Trial, reported that incident ED was associated with a 25% increase in risk of subsequent CV events, during a nine year follow-up, after an adjustment for confounders.

Treated heart disease (worse in smokers), treated hypertension (again, worse in smokers), and low serum levels of HDLs were significantly correlated with impotence in the MMAS report. [26] Values of HDL more than 90 mg/dL were associated with no probability of complete ED and conversely when the level of HDL dropped to 30 mg/dL the probability of complete ED was 16%. Complete ED was present in 15% of men with treated hypertension and this incidence was associated with the duration and severity of the hypertension in the MMAS report, as well hypertension increasing the age-adjusted incidence of ED. In another study the prevalence of ED was not increased among hypertensive and pre hypertensive men compared with normotensive men aged 25-40 years. [243] These authors concluded that it takes years for hypertension to cause ED in this generally healthy and younger group of men. Wei et al [53] found that a high level of total cholesterol and a low level of HDL are important risk factors for ED. In an analysis of the two MMAS studies of 1987-89 and 1995-97, it is suggested that ED and coronary heart disease share some behaviorally modifiable determinants in men who are free of manifest ED or predisposing illness at baseline. [244]

Since the last publication of this chapter there has been a stress on the association of cardiovascular disease and risk factors and ED. It is now thought that ED may be a harbinger of silent coexistent or subsequent coronary artery disease. [245, 246] Almost all of the cross-sectional studies tabulated in Tables 6A-F that collected data on coexistent cardiac disease or risk factors found increased prevalence of ED compared to those without these risk factors.

In a recent cross-sectional observational study the intimate nexus between ED and cardiovascular disease was presented. [247] In a group of 1,514 men with an age range of 20-99 years cardiovascular risk factors were more prevalent with increasing age and among participants with ED and severe ED. The age-adjusted odds of ED were significantly higher among men with hypertension (OR= 1.47), ischemic heart disease (OR=1.8), and stroke (OR=1.47). With these latter three conditions and peripheral arterial disease in combination in patients grouped together as cardiovascular disease the odds ratio was 1.85. The age-adjusted odds for severe ED (IIEF-5 <8) was 2.62 in men with peripheral vascular disease with no significant odds ratio for ED in general (IIEF-5< 22). When diabetes mellitus, hypertension, and hyperlipidemic were present in the same patient the odds ration of ED was 3.21. The authors concluded that the relevance and importance of careful cardiovascular risk evaluation in men with ED could not be overemphasized. The authors also emphasized that the associations described in this paper are cross-sectional and that data concerning the interval between the onset of ED and the diagnosis of significant cardiovascular events or recognition of biomedical risk factors were unable to be addressed thus making the temporal relationship between ED and cardiovascular disease and risk factors unanswered.

**Recommendation 10:**

Although the association of ED and Cardiovascular disease and risk factors are well established there is a need for longitudinal studies in patients who have manifest ED or cardiovascular disease and do not have the opposite manifest associated condition in order to establish a temporal relationship between these two entities. **Grade C.**

**I) Hormonal or Endocrine**

The effect of androgens on desire/interest and sexual behavior is well established but few reports show direct end organ, corpora cavernosa, dependency on androgens, except the early growth and development of the male reproductive tract. [248-250] Carani et al [251] did show increased rigidity as measured by rigi-scan in eugonadal men treated with androgens but no change in frequency of NPT associated events nor duration of circumference change, suggesting an enhancement of corpora cavernosal function in response to androgens. In a study by Becker et al, [252] systemic and cavernous plasma levels of testosterone were found to be elevated during erection and with flaccidity and detumescence states, cavernous levels were significantly lower than systemic levels suggesting corporeal binding of testosterone in the cavernous spaces.

Primary or secondary hypogonadism is often associated with erectile failure but not always. This may be due to a low threshold of androgens necessary for cavernosal tissue function, perhaps even at levels that can be maintained by the adrenal androgens in the face of lack of testicular androgens. [253, 254] Hormonal dependency for erection seems to vary for erections produced by different situations,
during rapid eye movement sleep, with visual sex stimulation, or fantasy or sexual situation induced erections. [255-257] Severe low levels are necessary to suppress sleep-related erections, with moderate low levels affecting sexual situation with partner erections, and erections induced by visual sex stimulation not showing much androgen dependency. An article that demonstrates this last point and also the variation in androgen dependency for different types of erection was that by Greenstein et al in 1995. [258] Four, all who had surgical castration, of sixteen men who were surgically or medically castrated, had erection produced by a visual sexually stimulated film, and none were able to have erectile activity in a partner sexually induced situation. These four men had significantly, but yet still at castrate levels, higher levels of testosterone than the men unable to respond to the visual stimulation. Similarly Bancroft and Wu [259] had shown that androgen replacement in hypogonadal men improved erectile response to fantasy (as well as reported sexual acts per week at home) but erections in response to erotic films were not significantly different from normal controls either before or after androgen treatment. Another study showed the futility of using testosterone therapy in those patients with testosterone in the low range of normal to improve erectile function and suggests that testosterone has to be at extremely low levels to effect sexually related erections or nocturnal sleep erections. [260]

As far as epidemiological studies go, the MMAS study constitutes the largest male endocrine database available, by including reliable measurement of 17 hormones. Interestingly, testosterone (total, free, or albumin bound) or dihydrotestosterone (DHT) levels did not significantly correlate with erectile dysfunction. Of the 17 hormones measured, none, with the exception of dehydroepiandrosterone sulfate (DHEAS), correlated with erectile dysfunction. DHEAS levels of 0.5 mgm/ml were associated with a high probability of complete ED (16%) compared to DHEAS levels of 5 and 10 mgm/ml (6.5% and 3.4% respectively). [26, 254] However probabilities of complete impotence increased as DHEAS levels decreased while the overall and moderate ED probabilities remained unchanged. Such patterns support the hypothesis that minimally impotent men may become completely impotent if their DHEAS levels decrease from 10 to 0.5 mgm/ml level. Despite this evidence, Placebo controlled, randomized double blind studies have shown that DHEA administration is not useful for improving sexual dysfunction in men. [261, 262]

The weak relationship between low T and ED is supported by results from both human and animal studies. [263, 264] Rhoden et al [265] on a consecutive large series of almost 1000 elderly subjects, with or without ED, have documented a lack of association between T and International Index of Erectile Function (IIEF-5).

Severe hyperprolactinemia (PRL > 735 mU/L or 35 ng/mL) but nor milder form has a negative impact on sexual function, impairing sexual desire - as well as erectile function - and testosterone production. [266-268] In particular, it has been reported that in subjects with sexual dysfunction, a severely reduced libido is associated with a 10-fold increase in the prevalence of severe hyperprolactinemia. [270] A PRL-induced hypogonadism could explain, only partially, this association [266-268] since PRL plays also a direct role in the control of male sexual desire. Accordingly in hypogonadal subjects with hyperprolactinemia, prolactin-lowering drugs are able to restore both testosterone levels and libido [268], while testosterone replacement therapy is not as effective. [270] The relationship between hyperprolactinemia and erectile function is under debate. Some Authors have suggested a possible pathogenetic link between severe erectile dysfunction (ED) and severe hyperprolactinemia [271] although even negative associations have been reported. [269, 272] In addition, controlled studies evaluating the effect of dopamine agonists on ED subjects with hyperprolactinemia were inconclusive. [268]

g) Urinary tract diseases and Lower Urinary Tract Symptoms (LUTS)

Chronic renal failure is a risk factor for ED. [273] There were two high Prins score studies that looked at ED in patients seen in dialysis clinics and rates for ED were high for all ages almost all above 50% however stratified. [274, 275] In the USA general urinary tract symptoms predicted ED (odds ratio: 3.1), but not other investigated parameters (desire, ejaculation) of male sexual function. [20] These findings principally agree with those of Blanker et al from the Netherlands. [79] The latter also, in their sample of 50-78 year old men identified lower urinary tract symptoms (LUTS) as concurrent with ejaculatory dysfunction – defined as no ejaculation or significantly reduced ejaculatory volume - The odds ratios for the likelihood of moderate and severe LUTS as compared with no such symptoms to concur with ejaculatory dysfunction being as high as 3.8 and 7.8, respectively.

A number of studies from clinical and community populations have shown that the prevalence of ED and reduced sexual desire along with other types of sexual dysfunction is greater in men with LUTS. [276-282] Most of these studies have also shown that the presence of LUTS is an independent risk factor for sexual dysfunction. Moreover there is a positive correlation between severity of LUTS and severity of ED. [276, 277, 279, 281] Decreased sexual satisfaction as well as sexual activity are associated with increasing severity of LUTS. [276, 277] Recently there was a report in the literature
of the first multinational population-based study to evaluate the relationship among those with overactive bladder (OAB) and ED, and also sexual quality of life. [283] 502 cases of OAB were matched with 502 controls. Reduced sexual activity was 14% in cases versus 4% in controls. Those with OAB were significantly more likely to have ED than were controls (OR 1.5). Significantly more of those with OAB (15%) reported decreased enjoyment of sexual activity because of urinary symptoms relative to controls (2%). The perceived impact of OAB on the frequency of sexual activity, sexual enjoyment, and satisfaction appeared most pronounced in cases with urinary incontinence.

An excellent epidemiological study from Finland established the bothersomeness of LUTS symptoms and the prevalence of ED. [284] The target population were samples from Tampere and surrounding municipalities in Finland in 1999. Cohorts of men born in 1924, 1934, and 1944 comprised those studied. Adjusted odds ratios of ED were 2.6 for men with LUTS total scores of 11-19 compared to those without LUTS and 4.4 for those with scores of 20 or more comparing the two groups. For bother scores even low bother were significantly associated with ED.

**h) Other Chronic Diseases**

Polyneuropathy, which commonly involves autonomous dysfunction is another source of sexual dysfunction, particularly ED and ejaculatory dysfunction [285]. Thus, Vardi et al reported a 38% coincidence of polyneuropathy and ED in diabetics and a 10% coincidence of the two in non-diabetics. [286] Among other neurological conditions which may lead to male sexual dysfunctions are Parkinson’s disease. In these patients, decreased sexual desire and ED are common for still unknown reasons. [287-289] However, treatment with dopaminergic substance have been observed to increase level of interest/desire. Even the pathogenesis of the often reported ED is to date unclear. There is good clinical evidence that other chronic neurological disorders may affect sexual function. Thus, in seizure free periods, epilepsy can be associated with reduced sexual interest/desire and with ED. [285, 289] In a review article of genitourinary conditions associated with patients with multiple sclerosis the incidence of ED was reported to be 40-80%, usually occurring a half decade to a decade after onset of the progressive disorder. [290] In multiple sclerosis, ejaculatory dysfunction may, according to clinical reports, prevail in about 50% as the disorder progresses. [289]

In the USA Monga et al [291] In a retrospective study found a three fold increased prevalence of low sexual desire after stroke. Others have identified clearly smaller post-stroke changes in sexual interest/desire. [292, 293] In some contrast there appears throughout the clinical literature to be consensus that between half and two thirds of male stroke patients develop ED. Both early and delayed ejaculation have been described to emerge after stroke; but within in a very wide latitude. [291, 292] To which extent the profound sexual dysfunctions in these patients mainly are results of poor coping or are mainly somatogenic still remains to be elucidated.

Erectile dysfunction occurs in 90% of patients with multiple system atrophy, being the first symptom in 37% of the cases. [294] Other diseases and chronic disorders reported to have a risk for ED include sleep apnea, chronic obstructive lung disease [295], scleroderma [296], and Peyronie’s disease. [297] In a recent epidemiologic study of 70 patients who were candidates for a liver transplantation 52 (74%) had ED using IIEF-5 criteria. [298] This article is a good review of previous studies of this same link and discussion of the possible etiologic reasons for this association along with a review of effect of coexistent other medical conditions and social factors effecting this association.

Fitzgerald and others [299] remind all of the need to be aware of the effect of chronic disease on all urologic disorders including LUTS and ED. In bivariate analyses, most urologic and sexual symptoms were associated with type II diabetes, cardiac disease, hypertension, and depression. However, in multivariate models adjusting for all four illnesses, gender, race/ethnicity, age, alcohol intake, smoking, physical activity, and body mass index there were fewer significant associations. It was found that all urologic symptoms were significantly related to at least one illness, with depression increasing the odds of all urologic and sexual symptoms studied. Urinary tract specialists and sexual health professionals should consider factors outside the urinary tract that may be contributing to urologic symptoms. It remains unknown whether treatment of medical and psychological illnesses can result in meaningful improvement in urologic symptoms, or conversely, whether urinary tract symptoms can provide valuable insight into an individual’s overall health status.

**i) Surgery and Trauma**

Spinal cord injury patients are obviously at an increased risk for erectile and ejaculatory (anejaculation) dysfunctions with central induced erectile activity possible in those with lower spinal cord injury and reflexogenic erection possible in those with upper cord injury. Besides leading to fertility problems (the incidence of male spinal cord injury peaks at ages 15-30) these dysfunctions are among the most pronounced problems for the future quality of life in the quadriplegic or paraplegic men (for an overview see reference [285]). There is – to some extent anecdotal – data showing that both
men and women with complete spinal cord injury rostrally to peripheral genital innervation levels can experience orgasm elicited by stimulation of non-genital body areas and the majority of the men seem to have only minor dysfunction, if at all, concerning sexual interest/desire. Surgery or trauma affecting any level of neurologic control of erection or that interfering with the arterial supply of the corpora cavernosal tissue are unquestionably risk factors for erectile dysfunction. DePalma has reviewed the impact of vascular surgery on ED.\[300\]

From clinical experience, it is well established that ED and anejaculation are common after prostatectomy. There is, however, astonishingly little epidemiological data on this subject. Some four years ago Stanford et al \[301\] reported a high incidence (about 60\%) of post radical prostatectomy ED; whether or not the surgical intervention had been nerve-sparing. Other reports show higher retention of erectile activity after bilateral nerve sparing surgery in the younger male and in those with strong erectile activity before the surgery \[302, 303\]. Radiation therapy to the pelvis also is a source of damage to nerves involved in erectile and ejaculatory functions \[304\] while sexual functions remain stable after treatment for benign prostatic hyperplasia. \[305\].

Schrader et al in 2 studies showed a weak association between some parameters of erectile function and bike riding. \[306, 307\] In the first study 17 bicyclist men were compared to 5 non-cycling controls with nocturnal penile tumescence studies (NPT). The only difference between the groups was a statistical difference in the percentage of sleep time erections, 27.1 ± 9.7\% vs 42.8 ± 17.56 (p=.008). \[306\] Although traditional seats seem to clearly produce sensory deficits from prolonged bicycle riding, ED defects are weakly supported by evidenced based data. In the second study from Schrader et al, data regarding erectile function was available for 64 to 70 of 90 men who were studied at baseline, at which time traditional bicycle seats were used compared to using a no- nose saddle. This was a non-group controlled study with each man serving as his own control over the six months of the study. IIEF-5 was statistically better after 6 months (score of 29.12 vs 29.61 p= 0.015) – 72.7\% of officers scored a perfect 30 at baseline compared to 84.9\% at 6 months. No changes were noted in NPT data. \[307\]

\textbf{j) Psychiatric/psychological risk factors}

It is well established that disorders of the psyche may concur with male sexual dysfunction. There is valid epidemiological data on this subject. In the USA \[20\] emotional problems or stress were significant predictors of low level of desire (odds ratios 3.2), ED (odds ratios 3.6) and early ejaculation (odds ratios 2.3). The association of ED with depression is well established. \[26\] Using the Hospital Anxiety and Depression Scale (HAD) \[308\] Dunn et al \[119\] found that anxiety, but not depression, significantly predicted early ejaculation. Suppression and expression of anger indicate higher probabilities of moderate and complete ED \[26\]. Independently of medication, Araujo et al \[142\] demonstrated that depression is closely associated (odds ratios 2.0) with ED and as discussed elsewhere in this chapter many antidepressants may lead to sexual dysfunctions. This is particularly true for SSRIs, which are nowadays used for delaying early ejaculation.

\textbf{k) Medications and Recreational Drugs}

Erectile dysfunction due to prescription medications is sometimes difficult to prove and is probably often under-reported. In the MMAS, a statistically significant correlation between ED and vasodilators, anti-hypertensives, cardiac and hypoglycemic agents was noted. \[26\] However when the second analysis of the population was made in 1995-97, adjustments for comorbidities and health behaviors attenuated some medication associations with ED with only nonthiazide diuretics and benzodiazepines remaining statistically significant for association with prevalent ED. \[309\] Meinhardt and his co-authors have reviewed the influence of medication of erectile dysfunction in some detail. \[310\] Major classes of prescription drugs commonly reported to be associated with ED are histamine-2 receptor antagonists, hormones, anticholinergics, psychotropics and certain cytotoxic medications. Whether one type of anti-hypertensive agent is less likely to be associated with ED than another is difficult to pin down since the prevalence of ED is often an association with the hypertension condition as well. This debate is well discussed in two articles. \[311-312\] In an experimental rodent animal model of hypertension, data suggested that renin-angiotension system inhibition by enalapril, an angiotension converting enzyme inhibitor, may at least partially normalize penile vascular structure. \[313\] Calcium channel blockers and alpha adrenergic blocker theoretically may be the best alternatives, along with the angio-tension converting enzyme inhibitors, in attempting to reverse ED when associated with other anti-hypertensive agents. Rosen and others review sexual dysfunction problems with the selective serotonin reuptake inhibitors (SSRIs). \[314\] Trazadone is one antidepressant that is unlikely to be associated with ED and in fact has a risk of associated priapism. \[317\] In general, it is suggested that antipsychotics with strong alpha-1 receptor affinity properties be considered as substitutes for other prescription psychotropic drugs associated with ED. Life style related risk factors for ED include chronic alcoholism and chronic use of marijuana, codeine, meperidine, methadone and heroin. \[315\]

There are three recent reviews of the effects of psychiatric drugs on sexual function \[316-318\]
Tricyclic antidepressant and mono-amine oxidase inhibitors have been shown to be associated with delayed ejaculation in double-blind studies [319, 320]. Similarly, studies have shown that selective serotonin reuptake inhibitors (SSRIs) as well as venlafaxine are associated with anorgasmia and decreased libido. There is some evidence that a small number of men may experience erectile dysfunction as the result of SSRI therapy. [321, 322] Duloxetine [323], bupropion [324] and nefazodone [325] have low rates of sexual dysfunction. Most studies are consistent in finding that traditional antipsychotic drugs (for example, haloperidol, thioridazine) are associated with high rates of ejaculatory delay, decreased libido and/or erectile difficulties. [326] Risperidone also has a high rate of sexual dysfunction. [327] Quetiapine and olanzapine, appear to have lower rates of sexual side effects. [328] Most of the antipsychotic drugs and some antidepressants have been reported to be associated with priapism in isolated cases. The largest number of case reports concern thioridazine and trazodone. [329]

Corona et al. recently explored the relationship between the use of selective serotonin reuptake inhibitors (SSRIs), non-SSRIs antidepressants and benzodiazepines (BDZ), hormonal parameters and reported sexual dysfunction on consecutive series of 2040 attending their unit for sexual dysfunction [330]. The current use of SSRIs was associated with a 1.7 fold risk for any degree of hypoactive sexual desire (HSD), while the risk increased to two-fold when moderate/severe HSD was considered. Patients reporting the use of SSRIs showed lower frequency of intercourse and higher sense of guilt with masturbation. In addition, the use of SSRIs was associated with a significant impairment of erectile function and 3.4 fold risk of delayed ejaculation. Conversely, a lack of significant association was observed among BDZ or non-SSRI antidepressant users and all the aforementioned life-stressors and relational parameters.

I) The effects of modification of risk factors

Using data from the reassessment (1995-97) of a portion of the population without ED at baseline in the original MMAS study population (1987-89), an attempt was made to assess the effect of modification of certain risk factors associated with ED as decreasing the incidence of ED in this population. [331] Other chronic disease states were not present in this population at baseline, including men treated for heart disease or diabetes, history of prostate cancer, or those with incomplete data regarding chronic disease risk factors. The results of this analysis showed that a change in smoking status or change in heavy alcohol consumption did not decrease the incidence of ED. The average age at baseline in this population was 52 years of age and changes in tissue may not have been possible to reverse by middle age changes. Men originally obese at baseline seemed to have a higher incidence of ED regardless of the follow-up status. Sedentary behavior status was associated with developing ED with the highest risk of dysfunction for those who had maintained a sedentary life-style. The lowest level of risk for ED, for all factors analyzed, was in those subjects who initiated physical activity after qualifying as sedentary at baseline. Increasing physical activity, even in these men in their 40’s and 50’s, is effective for reversing other cardiovascular disease risk associations and this study seems to demonstrate a similar benefit for decreasing the chance of developing ED. Another lesson to be taken from this study is that modifiable risk factors may require earlier intervention than middle age.

There a very few data that support the notion that treatment of lifestyle risk factors may improve ED. Esposito et al [332], in 2009 published a prospective behavior modification study in which 209 subjects were randomly assigned to one of two treatment groups. 104 men randomly assigned to the intervention program received detailed advice about how to reduce body weight, improve quality of diet and increase physical activity. The control group of 105 subjects was given general information about healthy food choices and general guidance on increasing their level of physical activity. IIEF-5 scores were similar for both groups at the onset of the study. At baseline 35% of the subjects and 38% of the control group had normal erectile function. After two years these figures were 58 subjects in the intervention group and 40 subjects in the control group showing a significantly (P=0.015) improvement in erectile function. The conclusion of this study was that it was possible to achieve and improve erectile function in men at risk by means of non-pharmacological intervention aiming at weight loss and increasing physical activity.
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Committee 3

Psychological and Interpersonal Dimensions of Sexual Function and Dysfunction

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Psychological and Interpersonal Dimensions of Sexual Function and Dysfunction

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A. INTRODUCTION

To most individuals, it seems obvious that psychological and interpersonal factors play a major role in both the etiology and maintenance of sexual problems. The ways in which love and affection are expressed in one’s family of origin, the unique and sometimes traumatic sexual experiences one has growing up, the religious, cultural and societal messages one receives about sex from peers, teachers, relatives and the ever-increasing impact of the media on one’s beliefs and behavior clearly play a role in shaping attitudes and promoting sexual health or dysfunction. More significantly, individual vulnerability to sexual disruption stems from personality and constitutional/biological dispositions to psychiatric and medical illness, medication, surgery as well as the inability to develop and sustain intimate relationships.

This chapter will review the most significant psychological and interpersonal dimensions contributing to sexual health. Other chapters will provide more of a focus on the biological aspects of sexual function and dysfunction. We will consider the predisposing, precipitating, maintaining and contextual factors involved in sexual dysfunction as well as the success of conventional and newer techniques of psychological treatment in the alleviation of these disorders. Finally, we will recommend a treatment model that offers a greater likelihood of success- an integrated biopsychosocial model that fully acknowledges the dynamic interplay between our mind and bodies.

There is a dearth of high level evidence-based studies in this area. The observations concerning developmental factors impeding or facilitating sexual health are primarily theoretical, clinical and anecdotal- with the emphasis on accounting for dysfunctional rather than healthy sexuality. Finally, there is a paucity of well-controlled, large-scale outcome research documenting the efficacy of sex therapy.

I. THE INHERENT TENSION BETWEEN EVIDENCED-BASED RESEARCH AND PSYCHOTHERAPY

It must be noted at the outset that there is an inherent tension between evidence-based medicine and the art and science of psychotherapy/sex therapy. Psychotherapy, as it is generally practiced, is more relational, symbolic and dynamic than other fields of medicine or therapy. The relationship style and personality of both the practitioner and the patient contribute significantly to treatment outcome as well as the therapeutic process itself. Other factors that cannot readily be quantified or manualized and contribute to positive outcomes [1] include such things as the placebo factors that enhance hope and expectancy [2], extra-therapeutic factors such as client motivation and chance events (e.g., meeting a new partner), relationship comfort between the client and therapist and finally, the degree to which the model and structure of therapy conform to the client’s expectations.

Laboratory research is important, but does not easily translate into clearly prescribed clinical interventions that enhance sexual life. Having an array of evidence-based behavioral interventions that enhance sexual function and facilitating sexual health are primarily theoretical, clinical and anecdotal- with the emphasis on accounting for
Sexual dysfunction is typically influenced by a variety of predisposing, precipitating, maintaining and contextual factors [3] (See Table 1). Predisposing factors include both constitutional and prior life experiences that contribute to a person’s vulnerability for dysfunction. Predisposing factors are quite varied and may include a history of childhood or adult sexual abuse or violence, anatomical deformity, chronic illness, etc. However, these factors alone are rarely sufficient to create sexual dysfunction [4].

Precipitating factors include those more immediate factors that can propel a person from adequate response to dysfunctional response. They include such things as separation or divorce, a humiliating sexual experience, a mutilating surgery and biological events such as illnesses, or medications or surgeries with sexual side effects.

Maintaining factors such as relationship conflict, loss of sexual confidence, performance anxiety, and lack of privacy or medications that negatively affect sexual function may prolong and exacerbate problems, irrespective of the original predisposing or precipitating conditions.

Contextual factors encompass the present day stresses and demands that impinge on the individual or couple. These include such diverse issues as serious financial struggles, unemployment, fatigue from childrearing, or the burdens of caretaking for a sick parent, child or partner, etc. They also include environmental factors such as partners working different shifts and not having sufficient privacy. The contextual issues are usually fleeting but can become chronic and do impact on sexual function. Each of these domains contributes to both the individual’s and the couples’ ability to sustain an active and satisfying sexual life or to develop and maintain sexual dysfunction.

1. PREDISPOSING FACTORS - CONSTITUTIONAL FACTORS

Constitutional factors are inborn biological and psychological traits that influence sexual interest levels and response tendencies. They may be created by genomically-based anatomical, hormonal, vascular and neurological characteristics. How constitutional factors lead to variations in desire, arousal, orgasm and pleasure from sex is not known with any precision, yet research suggests that each of these factors can either enhance or impede later sexual performance and satisfaction. For example, intersex children who are born with ambiguous genitalia are likely to experience more sexual problems in later life than those children born with normal genitalia [5].

2. PREDISPOSING FACTORS - DEVELOPMENTAL AND FAMILY OF ORIGIN CONTRIBUTIONS

Psychological development is an on-going process...
that begins before birth and continues throughout life. Over time, individuals either develop or fail to develop numerous sexual and interpersonal capacities, including the ability to love. The developmental processes that organize healthy sexuality, while not clearly understood, do not appear to be sexual per se. The quality of attachments to parents, and the ability of caretakers to identify and satisfy the child’s needs interact with constitutional and temperamental forces to foster sexual comfort and identity [6]. In fact, our understanding of sexual development is conceptual and descriptive and is largely devoid of sophisticated evidence-based studies.

**a) Gender identity development**

Each child develops a gender identity—that is, a sense of self as either a boy or a girl and an increasing preference for play, dress, and peer companionship that is perceived by adults as typical or atypical for a child of that gender. Gender conformity throughout childhood is an early developmental marker for adolescent heterosexuality [7]. Childhood gender nonconformity predicts adolescent and adult homosexuality with greater accuracy in boys than it does in girls [8]. Erotic fantasy often appears in the 10th year of life in both genders [9]. These fantasies reflect the formation of the child’s gender identity, sexual orientation and their preferred sexual “script” e.g., what the individual wants to do with another and what they want done to them [10]. Sexually atypical adolescents may become gay or lesbian and in extreme instances may be diagnosed as having a gender identity disorder (transsexualism) or a paraphilia (such as voyeurism, exhibitionism, fetishism, sadism, masochism, pedophilia) [11]. Although there is much speculation about the specific developmental factors that organize children’s gender identity, orientation, and sexual

<table>
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<th>Table 1: Etiological model for understanding sexual function and dysfunction</th>
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<td>2. Hormonal irregularities</td>
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<td>3. Temperament, e.g., shyness vs. impulsivity; inhibition/excitation</td>
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<td>4. Physical resiliency</td>
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<td>5. Personality traits, e.g., obsessive-compulsive vs. histrionic</td>
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<td><strong>B. DEVELOPMENTAL FACTORS (PARTIAL LIST ONLY)</strong></td>
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<td>2. Infertility or post-partum experiences</td>
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<td>3. Humiliating sexual encounters/experiences</td>
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<td>4. Depression/anxiety</td>
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<td><strong>III. MAINTAINING FACTORS (PARTIAL LIST ONLY)</strong></td>
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<td>1. Ongoing interpersonal conflict</td>
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<td>2. Stress- emotional, occupational, personal</td>
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<td>3. Acute/chronic illness/health problems</td>
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<td>4. Medications, substance abuse</td>
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<td>5. Loss of sexual self-confidence, performance anxiety</td>
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<td>6. Body image concerns</td>
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<td><strong>IV. CONTEXTUAL FACTORS (PARTIAL LIST ONLY)</strong></td>
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<tr>
<td>1. Present day stresses and demands- financial burdens, unemployment, caretaking of parents, children or partner, fatigue from childrearing</td>
</tr>
<tr>
<td>2. Environmental constraints- lack of privacy, time, partners working different shifts</td>
</tr>
<tr>
<td>3. Repeated unsuccessful attempts to conceive children, artificially assisted attempts to conceive</td>
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</table>
scripts, research has been unable to clarify these developmental processes precisely [12].

b) Trauma- Event and process based trauma

Two types of developmental factors are thought to increase the likelihood of sexual dysfunction: event-based trauma (single episode) and process-based trauma (ongoing interactions or behaviors) with caregivers [13]. It is reasonable to assume that the remote influences that create sexual dysfunction during the adult years do so by triggering old trauma/ or anxiety-laden memories, which in the present, are experienced as sexual anxiety.

What follows are two examples of developmental experiences that influence sexual behavior; the first is an example of an event-based trauma, the second of a process based, conflict.

If a 12-year-old girl is raped by a stranger, a decade later when she participates in an entirely consensual sexual intimacy, she may be too frightened to enjoy her sexual experience. We label her childhood victimization as a traumatic developmental factor contributing to, or causing her adult sexual dysfunction. The terror she experienced during the rape may not have been sufficiently processed, understood or resolved. She is not free to enjoy present-day desired sexual experiences because of remnants from the past trauma.

A man avoids sexual intercourse with his wife because he prefers the “safety” of masturbation. Growing up, he experienced his mother as intrusive and over-bearing. He recognizes the hostility he bears toward his mother, but is unable to appreciate that his avoidance of his wife is related to his inability to psychologically separate his wife from his critical mother.

Most predisposing factors to sexual dysfunction are not event-based. Rather, they are process-based, typically involving the ongoing relationship with one’s caretakers. For instance, growing up with parents who express no warmth, do not touch their child affectionately, and refuse to acknowledge his/her feelings can inhibit healthy intimate relationships as an adult as well as undermine the child’s self-respect. Negative relationships in childhood may delay or inhibit healthy adult sexual development.

Clinicians elucidate the developmental factors that predispose a patient to current sexual dysfunction on a case-by-case basis. Our ideas tend to be based on retrospective patient self-reports [14] and are not “evidence based”. Nonetheless they seem helpful in illuminating both the patient’s and clinician’s understanding of the problem. Event and process based trauma may explain what enables one person who has suffered adverse circumstances such as unemployment, marital conflict, or an affair, to become dysfunctional while others under similar circumstances do not.

c) Puberty

Despite the long-held assumption that puberty provides the crucial trigger for the onset of sexual feelings, more recent research suggests that it is the maturation of the adrenal glands and secretion of adrenal hormones around age 10 that appear to be associated with the development of sexual attraction, thoughts and emotions which get shaped by cultural expectations of sexuality [12]. For both girls and boys, there is a positive correlation between plasma testosterone levels and increased interest in sex, although this association is more dramatic in boys than in girls [15].

As their bodies are changing during adolescence, boys and girls receive multiple cultural messages about how men and women do (or should) express, experience and manage their sexual feelings. Notions of men as “naturally” sexually aggressive and women as “naturally” passive may be socially reinforced with the consequence that both boys and girls follow prescribed sociosexual scripts, i.e. men are sexual initiators and women are sexual gatekeepers [16]. Social pressures appear to have a more significant influence in determining the sexual behavior of young women than young men. In fact, women are considered to be more “erotically plastic” than men and hence to be more amenable to gender and sexual cultural prohibitions and expectations [17]. This may help explain why women tend to have a higher incidence of sexual problems as adults than do men [18].

d. Impact and initiation of first intercourse

Although age of first intercourse and the emotional aspect of the experience are thought to contribute to later sexual functioning, research to date on how the sexual debut relates to adult sexual functioning has been limited and contradictory. Woo and Brotto [19] studied Euro-Canadian and Asian-Canadian university students. In the overall sample, older age of first intercourse was associated with more sexual problems as an adult, including more sexual infrequency, sexual avoidance, and non-sensuality. Among the women, Asian-Canadians reported higher scores on the Vaginismus and Anorgasmia measures, whereas the ethnic groups did not differ on the male-specific measures of sexual complaints.

Udry and Billy [20] sampled 1400 Caucasian adolescent virgins and studied which hormonal and social variables predicted the initiation of adolescents’ sexual activity. They found that for males, free testosterone level rather than social variables was correlated with the initiation of first coitus, while for females, hormones had no direct effect but most of the social variables did. These included their friends’ sexual activity, grades, deviance, religiosity, sexual permissiveness, parents’ educational level and locus of control.
In a qualitative study of adolescent girls' first intercourse, Thompson [21] found that the majority of girls in her research remembered their first coital experience as painful and unpleasant. In response, many girls decided to postpone further intercourse for one or more years. The girls who remembered and interpreted the experience positively had mothers who had talked to them about their sexuality in positive ways, had encouraged them to pay attention to their own desire (or lack of it) and had socialized them to expect satisfying sexual experiences. While the relationship of negative first experiences to the development of later sexual problems has not been well researched, it is an area that merits attention. Clinically, it is often reported that traumatic or humiliating sexual initiation and coitus may be associated with later sexual anxiety, aversion and difficulties.

3. SEXUAL ABUSE AND SEXUAL DYSFUNCTION

Childhood sexual abuse, a significant contributing factor to sexual dysfunction, may even be more difficult to discuss with patients than a current sexual problem. It is important to ask about sexual abuse because of its impact not only on gynecologic complaints but also on adult mental health symptoms.

Recent studies have demonstrated child sexual abuse survivors report a lifetime history of multiple exposures to various trauma and higher levels of mental health symptoms. Sexual violence is associated with increased risk of posttraumatic stress disorder and depression [22]. The influence of early sexual abuse on later adult sexual functioning has been found to pertain in particular to problems in sexual desire, arousal, orgasm and sexual pain.

Meston et al. [23] showed that the relationship between child sexual abuse and negative sexual affect was independent from symptoms of depression and anxiety, suggesting that the impact of child sexual abuse on sexual self-schemas may be independent from the impact that the abuse may have in other areas of the survivor's life. In a review article on factors predisposing women to chronic pelvic pain, sexual abuse was associated with dyspareunia and also to non-cyclical pelvic pain [24].

Rellini [25] attempted to create a theoretical model of understanding the sexual problems of women who experienced childhood sexual abuse (CSA). When exposed to sexual stimuli, CSA survivors experienced more inhibitory responses and less excitatory responses than women in a control group. Conversely, in situations when sexual stimuli were not present, CSA survivors showed a greater excitation of sexual responses than women in the non-CSA group. Additionally, CSA survivors showed a potential difficulty inhibiting intrusive sexual thoughts.

One of the major problems in studying CSA is the lack of agreement on the definition and description of sexual abuse. Definitions of sexual abuse vary considerably across countries, cultures and research articles. Without understanding the “meaning” of the behavior to the individuals involved, its putative impact on later sexual function and dysfunction cannot be fully appreciated. For instance, sibling “incest” may or may not be considered normative, depending on the cultural context.

In a well-conducted epidemiological study of sexual well-being in sexually abused Swedish women, Oberg, Fugl-Meyer and Fugl-Meyer [26] defined abuse as forced situations or acts that were perceived as sexual and 11 different abusive acts, ranging from forced exhibition of one's genitals to vaginal intercourse. The national representative sample consisted of 1,335 Swedish women aged 18-74. Twelve percent of Swedish women reported being abused at least once during their lifetime, with the most common types of abuse being vaginal penetration and genital manipulation by the perpetrator. About half of the abused women had been abused more than once. Nearly all types of sexual abuse were significantly associated with orgasmic problems, and the women who had experienced forced vaginal penetration, genital manipulation, cunnilingus or being forced to perform fellatio also had a lower level of sexual interest than non-victims of abuse. Fellatio and genital manipulation were significantly associated with a higher prevalence of vaginismus. Those who had been sexually victimized more than once had significantly lower levels of sexual interest and anorgasmia than women who had been abused only once. Moreover, 81% of the women who had been abused more than once reported one dysfunction. Finally, sexually abused women had lower levels of sexual well-being than non-abused women.

In a recent follow-up study of the long-term impact of CSA, 77 sexually abused and 89 comparison women (mean age = 20.41, SD = 3.38) were assessed 10 years after disclosure in a longitudinal, prospective study [27]. These investigators found that abused women were more preoccupied with sex, younger at first voluntary intercourse, more likely to have been teen mothers, and endorsed lower birth control efficacy than comparison participants.

The impact of sexual trauma on male sexual function has received relatively little attention, and there is some inconsistency in the studies reported to date. Although studies comparing the impact of victimization in men and women show a greater effect in women [28, 29], negative consequences have been found in men as well. In a questionnaire study of 301 men in a nonclinical sample, sexual victimization, sexual abuse and dysfunctional family background were predictive of premature ejaculation and sexual desire disorder. However, long lasting
adverse familial relationships had a greater impact on these disorders than sexual abuse per se [30]. Methodological factors that may affect outcome in these studies have included the definition of sexual abuse [31], whether or not an age discrepancy between offender and victim is required in defining childhood abuse [32], and whether sexual abuse has occurred as a single incident or as repeated victimization [33].

Sexual abuse is considered a salient risk factor for later adult sexual dysfunction, increased prevalence of high-risk sexual behavior and increased adult psychopathology [34, 35]. For instance, a recent study [36] of 1490 women revealed that one-third were survivors of sexual abuse involving penetration. Overall, regression analysis indicated a significant relationship between early sexual abuse and later participation in risky sexual behavior as an adult. The earlier that the abuse occurred, the greater impact it had on the likelihood of engaging in adult risk-taking sexual behaviors. Since child and adolescent sexual abuse is a global phenomenon with equal incidence reported in such diverse countries as Brazil, Chile, Mexico, Israel, Palestine, Sierra Leone, South Africa, Sweden and Switzerland, it is important to screen for its presence during the initial evaluation of both men and women [35, 37-41]. Observing or being the recipient of physical violence during childhood is another risk factor for sexual dysfunction. It has been related to a heightened neurophysiological response to perceived threat (startle response), disruption of trust, and impairment in self-esteem and personal autonomy [42]. Not only do many young people live with violence in intimate relationships, but youth everywhere are exposed to media images of violent situations in which people abuse power and control. These early experiences may predispose individuals to later difficulties with intimate relationships [43].

Chronic and troubling dyspareunia was reported by 37% of a sample of 409 women with a past history of sexual coercion and physical partner abuse and 75% reported various sexual dysfunctions [44]. Notably, only a small number of women had ever discussed these concerns with their physician [45].

4. BODY IMAGE AND SEXUAL FUNCTION

Body image appears to be an important factor contributing to sexual self-confidence for both men and women. It may function as a predisposing, precipitating or even maintaining factor for the development of sexual difficulties since it impacts both early experiences, (e.g., of being teased), and later sexual experiences with partners.

Men tend to worry about penis size, while women tend to worry about body shape and weight. Many women are sexually self-conscious and many avoid sex when they feel overweight or physically undesirable. Often, these feelings are not based on objective fact, but rather rigid (Western) standards, culturally imposed, about the importance of being young, thin and beautiful. There is little empirical research examining the degree to which an excessive focus on body image interferes with, or contributes to sexual dysfunction, per se, but clinical observations suggest that these preoccupations serve as a distraction during sexual exchange.

Changes in the appearance of one's body have also been linked to changes in sexual response. For example, female patients who have undergone treatments involving body – altering surgeries (e.g. for cancer) show a decrease in sexual arousal and interest post-surgery. Women who have undergone psychotherapy for eating disorders that include body – altering components (e.g. weight loss) show enhanced sexual responses following treatment[46].

Faith and Schare [47] examined the relationship between excessive self-focus on bodily appearance and sexual function. They found that negative body image was related to lower levels of sexual experience when sexual attitudes and knowledge as well as global psychological adjustment were held constant. This was an observational study using measures of general body image and sexual experience rather than a well-controlled study.

It should be noted that cultural standards of female beauty and desirability vary considerably cross-culturally. While thinness is socially valued in Western countries, more full-bodied women are considered sexually desirable in other regions of the world. Comfort and self-acceptance with one's body, irrespective of the degree to which it mirrors cultural stereotypes, is believed to be a salient contributory factor to overall sexual health and function.

5. VULNERABILITY AND RISK FACTORS INFLUENCING SEXUAL HEALTH & DYSFUNCTION

Space does not permit a thorough inventory of all of the many constitutional and developmental factors that may predispose an individual to later sexual problems. Suffice it to say that an individual's vulnerability to later sexual dysfunction is determined by the ratio of risk vs. protective factors as well as their personal resiliency. In general, one's vulnerability to sexual dysfunction is increased by having more risk factors lasting for longer periods accompanied by greater coercisiveness than a single negative or traumatic episode [48].

Resiliency is a psychological attribute that describes the individual's ability to cope with significant adversity or stress in ways that are not only effective, but result in their enhanced ability to confront and master future adversity [49]. When stress factors are greater than the individual's protective factors, then even resilient individuals may be overwhelmed and develop sexual problems.
Recent advances in immunology and neuroscience are elucidating the links between emotions and disease, between the brain and the immune system and the mind and body. “With sophisticated new genetic and mathematical modeling techniques, we can determine what part of our stress responsiveness we are born with, and how much is under environmental control. These sorts of theories will help us understand not only the reasons for individual differences in stress responsiveness, but will also point the way to develop new behavioral strategies that can change the set point of different individual’s stress responses [50].”

6. SUMMARY OF IMPACT OF PREDISPOSING CONDITIONS ON SEXUAL DYSFUNCTION

Negative developmental experiences such as problematic attachments, neglectful or critical parents, restrictive upbringing, sexual and physical abuse and violence, traumatic early sexual experiences as well as a variety of constitutional vulnerabilities are associated with a greater prevalence of sexual dysfunctions and difficulties in adult life. While some individuals appear less vulnerable and more resilient in the face of stressors, others are more susceptible. More research is needed on factors that increase personal resiliency and contribute to the development of healthy sexuality.

C. PRECIPITATING FACTORS

Precipitating factors are those that trigger sexual problems. For any single individual, it is impossible to predict which factors under what circumstances may impair sexual desire or performance. Nonetheless, an individual’s vulnerability to a particular set of circumstances can precipitate sexual dysfunction. For instance, suffering humiliation from one’s spouse may cause one man to lose his erection while another man may be unaffected. Similarly, in response to the discovery of a partner’s infidelity, one woman may lose sexual desire while another may become more sexually driven. While initially a precipitating event may be problematic and distressing, it need not necessarily lead to a diagnosable dysfunction long term. However, repetitive problematic sexual experiences damage self-confidence and ultimately are pathogenic for sexual dysfunction, even in reasonably resilient individuals. Often, there is not a clear distinction between either predisposing and precipitating factors or precipitating and maintaining factors. As a predisposing factor, anxiety can increase an individual’s vulnerability to sexual dysfunction. It can also serve as a maintaining factor leading to sexual avoidance or arousal inhibition.

Partners’ physical, emotional and sexual health can affect the sexual and emotional health of the other partner. Therefore, partner issues function as precipitating and maintaining factors. The following section explores this topic in detail and also provides a review of the relationships between anxiety, depression, sexual confidence and sexual dysfunction.

I. ROLE OF THE PARTNER

Studies have begun to clarify the dynamic and reciprocal relationship of one partner’s sexual function, sexual satisfaction, physical and mental health to the other partner’s sexual health and satisfaction. The partner’s role as a precipitating or maintaining factor has been overshadowed by focusing on individual medical or psychological factors or the impact of the quality of the relationship upon sexual function. This section will review the findings on partner issues as precipitating and maintaining factors in male and female sexual dysfunction. Two caveats: 1) we recognize that not all sexual behavior occurs in relationships and 2) the data are derived solely from studies with heterosexual couples. Clearly, more research is needed with gay/lesbian couples to characterize the influence of the each partner on the other’s sexual function and satisfaction.

1. SEXUAL FUNCTION AND SATISFACTION IN PARTNERS OF MEN AND WOMEN WITH SEXUAL DYSFUNCTION

a) Erectile dysfunction (ED)

Several randomized, placebo-controlled trials of men with ED who are treated with phosphodiesterase type 5 inhibitors (PDE5i’s) have evaluated the sexual function of female partners at baseline and end of treatment (see Table 2) [51-53]. Fisher et al. studied 293 women whose male partners had ED and were receiving either vardenafil or placebo [54]. Following the onset of ED 36% of women reported a decrease in sexual desire; 31% noted that their ability to experience orgasm declined; 46% had decreased sexual satisfaction and; the frequency of lovemaking also significantly decreased. Greenstein et al. [55] evaluated 113 female partners of men with ED attending a sexual dysfunction clinic. Fifty-five percent of these partners reported having some form of sexual disorder, mostly orgasmic problems and decreased sexual desire.

Shabsigh et al. [56] investigated the prevalence of female sexual dysfunction (FSD), urinary symptoms, and depressive symptoms in female partners of men presenting with ED. Women completed the Brief Index of Sexual Function for Women, Centers for Epidemiologic Studies-Depression, (CES-D), a demographics questionnaire and general medical questionnaire. Of the 50 women who completed the questionnaires, sexual dysfunction symptoms included: anxiety/inhibition (26%), hypoactive sexual
Table 2: Impact of erectile dysfunction on the female partner

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N of subjects</th>
<th>Methods</th>
<th>Summary results</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher, 2005</td>
<td>293 partners</td>
<td>Internet questionnaires, frequency sexual activity, sexual experience before and after development of partner’s ED and with PDE5</td>
<td>Sexual frequency and sexual satisfaction less frequent after ED. Women with partners who were currently using PDE5 inhibitors had a more satisfying sexual experience than those whose partners did not use a PDE5 inhibitor.</td>
<td>2</td>
</tr>
<tr>
<td>Goldstein, 2005</td>
<td>229 couples</td>
<td>Randomized, double-blind, placebo-controlled Vardenafil/Placebo trial FSFI, mSLQQ-QOL for female partners</td>
<td>Vardenafil increased multiple domains of women’s sexual function, except pain and a marked improvement in sexual quality of life of female partners</td>
<td>1</td>
</tr>
<tr>
<td>Fisher, 2005</td>
<td>197 couples</td>
<td>Randomized, double-blind, placebo-controlled Vardenafil/Placebo trial FSFI, Question QOL</td>
<td>Vardenafil increased QOL and each FSFI domains. Partners’ total mSLQQ-QOL score in the vardenafil group was double of the placebo group</td>
<td>1</td>
</tr>
<tr>
<td>Huntermark, 2007</td>
<td>96 couples</td>
<td>Randomized, double-blind, placebo-controlled Vardenafil/Placebo trial Dyadic Adjustment Scale</td>
<td>No difference between the 2 groups with regard to relationship functioning</td>
<td>1</td>
</tr>
<tr>
<td>Chevret-Méasson, 2009</td>
<td>57 couples</td>
<td>Prospective, open-labeled clinical trial Sildenafil, context close to routine clinical practice Index of Sexual Life, EDITS-Partner</td>
<td>ISL sexual life satisfaction score was low at baseline and increased with a highly significant change in each domain: desire, satisfaction with her sexual life, general life satisfaction</td>
<td>2</td>
</tr>
<tr>
<td>Heiman, 2007</td>
<td>155 couples</td>
<td>Randomized, double-blind, placebo-controlled Sildenafil trial 1/ FePEDS Q3 2/SFQ, FSFI, EDITS-Partner</td>
<td>Greater improvement in Q3 in sexual function. And in Sexual satisfaction measures The interdependence of sexual function and satisfaction between members of couple is demonstrated</td>
<td>1</td>
</tr>
<tr>
<td>Cayan, 2004</td>
<td>87 with partners 38 ED partner 13 ED partner treated sildenafil 17 penile prosthesis</td>
<td>Female sexual function evaluated with FSFI. Men evaluated with IIEF</td>
<td>After treatment of male ED, significant improvement in sexual arousal, lubrication, orgasm and satisfaction in female partners</td>
<td>4</td>
</tr>
<tr>
<td>Conaglen H, 2008</td>
<td>100 couples</td>
<td>Sildenafil or tadalafil for a 12-week phase, followed by another 12-week period using the alternate drug. Female partners interview at baseline, midpoint, and end of study</td>
<td>79.2% of the women preferred their partners’ use of tadalafil, while 15.6% preferred sildenafil. Women’s reasons are: relaxed, satisfying, longer-lasting sexual experiences</td>
<td>4</td>
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</tbody>
</table>
desire (20%), arousal/lubrication difficulty (30%), orgasmic difficulty (24%), dyspareunia (18%), and sexual dissatisfaction (34%). Urinary symptoms of frequency and urgency were reported by 36%. Depressive symptoms were present in 44%.

Goldstein et al. [57] reported that after men received 12 weeks of treatment with vardenafil, the female partners demonstrated significant improvements in total Female Sexual Function Index (FSFI) score as well as sexual desire, subjective arousal, lubrication, orgasm and satisfaction sub-domain scores. Chevret-Measson et al. [53] reported significantly improved scores on the Life Satisfaction Scale for women whose male partners were receiving sildenafil. Similar improvements in female partners sexual function, treatment satisfaction and sexual satisfaction following the man’s treatment with PDE5is are described by others [58-60]. Chevret-Measson [53] suggested that studies much closer to “real life” and clinical practice with a broader population than men and their partners in clinical trials are necessary to assess the global therapeutic approach in a context close to normal practice.

b) Premature ejaculation

The impact of premature ejaculation (PE) upon partners was documented by Riley and Riley in a retrospective audit of their medical records [61]. Approximately 50% of female patients with sexual problems, such as ‘not enjoying sex’ or anorgasmia, had partners with PE either at the onset of their problem or at some time in the relationship. Hartmann et al. [62] reported that 27% of dysfunctional men, including those with PE, were unsure of the capacity and frequency of their partners’ orgasm, compared to 4% of functional men. In contrast to Riley and Riley and Hartmann studies, Byers [63] and Revicki [64] found less impact of PE on female partners sexual function although all studies found women had diminished sexual satisfaction.

c) Female sexual dysfunction

Witting and colleagues [65] investigated the association between female sexual dysfunction, distress and partner compatibility. The two main complaints of women were “too little foreplay” (42%) and “partner is more interested in sex than you” (35%). The women experiencing distress on the Female Sexual Distress Scale (FSDS) or having a sexual dysfunction as determined by the FSFI reported more incompatibility with their partner compared with functional women.

Jodoin[66] asked 46 male partners of women with provoked vulvodynia to complete the Attributional Style Questionnaire-Partner Version, Brief Symptom Inventory, Dyadic Adjustment Scale, Sexual History Form and Global Measure of Sexual Satisfaction. The men’s global and stable negative attributions were related to lower sexual satisfaction whereas, higher levels of internal and global attribution were associated with men’s poorer dyadic adjustment. Additionally, all 4 negative attribution dimensions and higher levels of women’s pain intensity predicted increased levels of psychological distress in men.

Speckens et al. [67, 68] investigated female partners of men with ED where no organic cause could be found and partners of men with organically based ED. They compared the partner’s views on the relationships, sexual function, sexual attitudes, and psychological adjustment. Vaginismus and dyspareunia which preceded the onset of ED were more common in the partners of men with nonorganic ED as were relationship problems. The authors concluded that female sexual dysfunction, high sexual interest and relationship problems contribute to the onset, exacerbation and maintenance of non-organic ED.

The associations between desire discrepancies and sexual and relationship satisfaction in heterosexual dating couples (N = 72) were examined by Davies et al. [68]. Women whose sexual desire level was lower than their partners’ endorsed lower levels of relationship adjustment relative to women whose desire was either greater than or similar to their partners’.

d) Impact of illness on partner sexual function

Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) is a common condition in men involving pelvic pain and sexual dysfunction. Smith et al. [69] sought to identify potential predictors of sexual and relationship function among couples with CP/CPPS, and to examine associations among pain, sexual, and relationship variables. Men completed the International Index of Erectile Function (IIEF) and a subscale of the Multidimensional Pain Inventory. Female partners were administered to the FSFI, and all participants received the Golombok-Rust Inventory of Sexual Satisfaction and the Dyadic Adjustment Scale. Couples’ sexual function, sexual satisfaction, and relationship adjustment were all significantly associated. Patient sexual function was predicted by patient sexual satisfaction and female sexual function, whereas female sexual function was predicted by female sexual satisfaction and patient relationship adjustment. Pain severity significantly predicted sexual and relationship functioning among couples. However, multiple regression models revealed that sexual and relationship variables were the strongest predictors of patient and partner functioning, over and above pain severity.

Harden et al. [70] sought to examine how quality of life, self-efficacy and appraisal of the illness experience vary among men with prostate cancer and their partners according to age. They divided the sample into three categories: middle age (50-64); young-old (65-74); and old-old (75-84). Middle aged spouses reported the most distress related to sexual changes in their husbands. Spouses in both
the middle age and old-old group had more bother related to hormone therapy than the young-old spouses. Couper et al. [71] performed a review of the literature from 1994-2005 regarding psychosocial factors impacting the patient and partner. They found that partners report more distress than patients, yet believe that patients are the more distressed. The focus of concern of patients is on their sexual function which not shared to an equal degree by their partners.

McCabe et al. [72] examined the impact of multiple sclerosis (MS) on sexuality and relationships among 111 males and females with MS. The results indicated that MS had a negative impact on sexual functioning among men and women: only 35.4% of men and 20.4% of women were not experiencing any form of sexual dysfunction. The most common dysfunction for men was ED, and for women was hypoactive sexual desire. Surprisingly, the majority of men and women did not express concern about their sexual problems. Perhaps they accept these problems to be an inevitable consequence of developing MS. McCabe [73] examined the difference in sexual dysfunction between 381 people with MS and 291 people from the general population. Males with MS demonstrated higher levels of sexual dysfunction than males in the general population; however the only difference between females with MS and those from the general population was that MS females reported higher levels of numbness in their genital area.

These studies consistently demonstrate the interdependence of sexual function between partners. Specifically, they suggest that dysfunction in one partner tends to cause problems for the other and that improvement in function in one partner tends to have a positive effect on the other. The data strongly argue that clinicians take a biopsychosocial approach to the treatment of sexual dysfunctions and include evaluation of the partner if possible.

II. THE ROLE OF ANXIETY IN SEXUAL FUNCTION AND DYSFUNCTION

Anxiety played a significant role in early psychodynamic formulations of sexual dysfunction and later became the foundation for the etiological concepts of sex therapy established by Masters and Johnson [74] and Helen Kaplan [75]. Kaplan believed that sexually related anxiety became the final common pathway through which multiple psychopathogens led to sexual dysfunction.

1. RESEARCH STUDIES ON ANXIETY AND SEXUAL FUNCTION

The role of anxiety as a key etiological agent in the genesis of sexual disorders has been examined in several clinical studies as shown in Table 3. A review by Norton & Jehu [76] reported high levels of anxiety in sexually dysfunctional individuals [77-84], which varied in amount and quality. Some studies found higher levels of sexually related anxiety, but no differences in social or general anxiety [81, 82, 85, 86].

a) Anxiety and female sexual dysfunction

The relationship between anxiety levels and female sexual dysfunction has not been extensively studied. While most of the existing research has focused on anxiety in women with diagnosed sexual dysfunction, other research has studied the incidence of sexual difficulties in women with anxiety disorders compared to non-anxious women.

Murphy and Sullivan [87] compared sexually aversive women to sexually functional women and found that the aversive group experienced heightened levels of ‘acute’ anxiety related both to sexual and non-sexual spheres. In addition, the sexually aversive women reported difficulty with identity, self-acceptance and feelings of inadequacy in most psychosocial areas. Leiblum et al. [88] found that women with persistent genital arousal (PGA) were more likely than non-PGA women to experience a range of anxiety symptoms (e.g., panic attacks, obsessive compulsive disorder).

Kaplan [89, 90] believed that performance anxiety was the critical element in sexual avoidance, which reached panic proportions for some individuals. She reported that a significant number of ‘sexaphobic’ patients had a dual diagnosis of sexual and panic disorder. In fact, women with panic disorder have been found to have lower sexual desire than healthy controls [91].

Campillo et al. [92] compared anxiety and depression levels in women with and without sexual disorders and found higher levels of trait anxiety and depression in the sexually dysfunctional women. Trudel et al. [93] examined the role of anxiety, depression and marital adjustment in 20 couples with low desire in one or both partners. The results indicated that the sexually dysfunctional subjects had low levels of depressive mood but moderate levels of anxiety.

b) Anxiety and male sexual dysfunction

Feil and Richter-Appelt[86] compared beliefs and anxiety in ED patients and sexually functional men and found that men with ED reported a significantly higher degree of sexual anxiety but no difference in general or social anxiety. In addition, the subjective feeling of efficacy and personal competency was lower in the ED group.

In another study [94], 41 ED-patients completed the State-Trait-Anxiety-Index (STAI) and the International
Table 3: Empirical studies on the relationship between anxiety and sexual dysfunction:

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Methodology</th>
<th>Results</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper, 1968</td>
<td>77</td>
<td>&quot;Impotent&quot; and ejaculatory disorders patients treated for 1 year</td>
<td>37% were rated cured or improved. Anxiety was most prominent in acute onset erectile dysfunction and premature ejaculation.</td>
<td>2</td>
</tr>
<tr>
<td>Cooper, 1968</td>
<td>79</td>
<td>Examined men with diagnoses of 'impotence' or ejaculatory disorder and investigated them clinically and with a neuroticism scale</td>
<td>While patients with premature ejaculation had the highest anxiety scores, the scores for all groups fell within the normal range. 'Neurotic anxiety' was a significant factor in minority of sexual dysfunctions.</td>
<td>2</td>
</tr>
<tr>
<td>Cooper, 1969</td>
<td>78</td>
<td>Examined prevalence of 'coital anxiety' in patients with sexual dysfunctions in a psychiatric clinic with self-rated levels of anxiety and relation to the first manifestation of the sexual symptoms</td>
<td>94% experienced some degree of coital anxiety which was interpreted as causal. Coital anxiety was seen as a special form of anxiety with only weak association to other 'neurotic' anxieties.</td>
<td>2</td>
</tr>
<tr>
<td>Derogatis, 1979</td>
<td>80</td>
<td>Forty-seven male and 40 female dysfunctional patients were evaluated on the Derogatis Sexual Functioning Inventory (DSFI) and compared to a group of 200 functionals</td>
<td>Both male and female patients showed higher levels of psychological distress and dysphoric affect than normal. The most pronounced elevations were found on depression and anxiety.</td>
<td>3</td>
</tr>
<tr>
<td>Kockott, 1980</td>
<td>81</td>
<td>Examined 42 patients and 24 controls with semi-standardized interviews and 5 psychological scales</td>
<td>In subjects with situational erectile dysfunctions high levels of anxiety were found. The results demonstrated an important functional role of anxiety in the maintenance of sexual dysfunctions.</td>
<td>2</td>
</tr>
<tr>
<td>Kockott, 1980</td>
<td>82</td>
<td>Examined psychophysiological parameters upon viewing of an erotic film in 42 patients and 24 controls</td>
<td>In patients with primary psychogenic erectile dysfunction, all parameters were lower than in the controls indicating that anxiety may act detrimentally on genital arousal parameters.</td>
<td>2</td>
</tr>
<tr>
<td>Munjack, 1978</td>
<td>83</td>
<td>Personality profiles of ejaculatory dysfunction patients were measured on various standardized inventories and compared to a group of normal controls.</td>
<td>Both premature and retarded ejaculators were found to be more anxious, depressed and psychologically disturbed.</td>
<td>2</td>
</tr>
<tr>
<td>Munjack, 1981</td>
<td>84</td>
<td>Personality profiles of erectile dysfunction patients were measured on various standardized inventories and compared to a group of psychiatric patients and a group of normal controls.</td>
<td>Results showed that sexually dysfunctional patients were more pervasively disturbed than control subjects. While depression scores were significantly higher, anxiety scores were not conclusively elevated on all scales, but only on a subset.</td>
<td>2</td>
</tr>
<tr>
<td>Fahrner, 1983</td>
<td>85</td>
<td>41 female and 45 male sexual dysfunction patient’s levels of social insecurity and self-uncertainty were measured on two standardized psychological inventories</td>
<td>Results indicated that general nonassertiveness is not a common symptom of sexual disorders. Rather, insecurity is restricted to specific areas relevant to sexual functioning.</td>
<td>3</td>
</tr>
</tbody>
</table>
Table 3: Empirical studies on the relationship between anxiety and sexual dysfunction (continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Methodology</th>
<th>Results</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feil, 2002&lt;sup&gt;26&lt;/sup&gt;</td>
<td>90</td>
<td>The relationship between erectile functioning, self-esteem, and general sexual skills was determined in a group of sexually dysfunctional patients and compared to normal controls.</td>
<td>Significant differences with respect to beliefs concerning control and personal competency which proved to be lower in dysfunctional subjects. Sexually dysfunctional men also had higher levels of anxiety pertaining specifically to sociosexual situations, but did not exhibit higher levels of general insecurity.</td>
<td>3</td>
</tr>
<tr>
<td>Murphy, 1981&lt;sup&gt;87&lt;/sup&gt;</td>
<td>20</td>
<td>Twenty women diagnosed as sexually aversive and 35 controls were compared on the dimensions anxiety, self-concept, and sociosexual information with a battery of psychological inventories.</td>
<td>The groups differed significantly on anxiety and self-concept profiles indicating that sexually aversive women experience higher levels of anxiety and have more difficulty with identity and self-acceptance.</td>
<td>3</td>
</tr>
<tr>
<td>Lieblum, 2007&lt;sup&gt;249&lt;/sup&gt;</td>
<td>156</td>
<td>Women were recruited for a web-based study of persistent sexual arousal (PGA).</td>
<td>Women with PGA compared to non-PGA women were more likely to be depressed and more anxious, report panic attacks and obsessive compulsive symptoms.</td>
<td>2</td>
</tr>
<tr>
<td>Kaplan, 1995&lt;sup&gt;161&lt;/sup&gt;</td>
<td>414</td>
<td>Summarizes the sexual dysfunction diagnoses and associated disorders of all 5,580 patients seen in the human sexuality programs in which the author was involved between 1972 and 1992.</td>
<td>Of the 414 patients that met the criteria for sexual aversion disorder, 35% had concomitant diagnoses of anxiety disorder. The incidence of anxiety disorders in the remaining diagnostic groups was 10%.</td>
<td>3</td>
</tr>
<tr>
<td>Van Minnen, 2000&lt;sup&gt;91&lt;/sup&gt;</td>
<td>27</td>
<td>The sexual functioning of 27 women with panic disorders was compared to the sexual functioning of 17 women with obsessive-compulsive disorders and 34 controls on a number of self-report instruments.</td>
<td>Both patient groups were found to have lower sexual desire and lower frequency of sexual contact and in anxiety patients, hypoactive sexual desire or sexual aversion disorders were more frequent than in controls. Patients with anxiety disorders are more at risk of sexual dysfunctions and do not corroborate the findings from experimental studies that anxiety may facilitate sexual arousal.</td>
<td>2</td>
</tr>
<tr>
<td>Campillo, 1999&lt;sup&gt;92&lt;/sup&gt;</td>
<td>200</td>
<td>The study evaluated the hypothesis that sexual disorders are significantly related to emotional problems. 200 sexually dysfunctional women were compared with 184 controls on two standardized psychological inventories.</td>
<td>Significantly higher levels of depression and trait anxiety in the patient group, associated to sexual fears, lack of sexual information, or sexual traumas.</td>
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<tr>
<td>Trudel, 1997&lt;sup&gt;93&lt;/sup&gt;</td>
<td>20</td>
<td>Twenty couples with low desire problems were compared with 20 control couples on several psychological measures including the Beck Depression Inventory and an anxiety scale (IPAT).</td>
<td>The low desire subjects showed normal levels of depression and moderate levels of anxiety.</td>
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<td>Mallis, 2002&lt;sup&gt;94&lt;/sup&gt;</td>
<td>41</td>
<td>Patients with erectile dysfunctions (ED) were administered the State-Trait-Anxiety-Inventory (STAI) and underwent a clinical psychiatric evaluation.</td>
<td>Results showed that 93.5% had noticeable state anxiety and 90.5% elevated trait anxiety. While there was no significant relationship between ED severity and state anxiety, patients with severe ED had higher levels of trait anxiety.</td>
<td>3</td>
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<tr>
<td>Author</td>
<td>N</td>
<td>Methodology</td>
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<tr>
<td>Mas, 2002</td>
<td>78</td>
<td>The influence of personality characteristics on the erectile response to intracavernosal injections was determined in 78 patients with erectile dysfunctions.</td>
<td>Trait anxiety as measured by the STAI proved to be a highly significant predictor of the erectile response, even when controlling for the severity of the ED.</td>
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<tr>
<td>Corona, 2008</td>
<td>1388</td>
<td>This study was designed to examine the relationship between psychiatric symptoms and ED among men presenting for treatment of ED.</td>
<td>The findings demonstrated that depression was associated with hypoactive sexual desire (HSD), whereas high levels of obsessive-compulsive symptoms were associated with a lower prevalence of HSD.</td>
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<td>Lykins, 2006</td>
<td>1062</td>
<td>The association between depressed mood and sexual interest assessed in 663 college females, and the results compared to the association among 399 college men.</td>
<td>Most women experienced a negative association between depression/anxiety and sexual function. A small number experienced a positive association. In general men were more likely to demonstrate a positive association between negative mood and sexual functioning.</td>
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<tr>
<td>Sugimori, 2005</td>
<td>1419</td>
<td>The study was designed to determine the relationship between ED and depression/anxiety among 1419 Japanese men aged 40-64 years.</td>
<td>There was a strong association between depression and ED among men from 45-54 years, and between anxiety and ED for men from 50-54 years.</td>
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<tr>
<td>Rosen, 2008</td>
<td>107</td>
<td>Eleven studies related to management or treatment of premature ejaculation were reviewed to determine the psychological factors associated with the disorder.</td>
<td>The evidence suggests that PE is associated with negative psychological and quality of life consequences for the man, as well as having negative associations with his relationship.</td>
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<tr>
<td>Beggs, 1987</td>
<td>19</td>
<td>In 19 sexually functional women, genital sexual arousal during sexual anxiety stimuli was compared to sexual arousal in response to sexual pleasure stimuli.</td>
<td>Results showed significant increases in genital arousal in both conditions, but increases in the pleasure condition were significantly greater than those in the anxiety condition, thus providing support for a functional role of anxiety in sexual dysfunction.</td>
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<tr>
<td>Palace, 1990</td>
<td>16</td>
<td>In 16 sexually dysfunctional women and 16 controls, the effects of sexual anxiety on physiological and subjective sexual arousal were determined under 2 stimulus conditions: an anxiety-evoking and neutral-control preexposure stimulus, each paired with a sexually arousing stimulus.</td>
<td>Anxiety preexposure enhanced genital, but not subjective, arousal in both groups. Functional subjects reported higher levels of genital arousal in both conditions. The results suggest that anxiety may enhance sexual arousal through the facilitation of sympathetic activation.</td>
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<tr>
<td>Meston, 1995</td>
<td>35</td>
<td>The effects of sympathetic activation following acute exercise on physiological and subjective sexual arousal in women</td>
<td>In 35 sexually functional women, the effects of acute exercise on physiological and subjective sexual arousal were determined. Acute exercise significantly increased genital responses to an erotic stimulus, thus providing support for a facilitatory role of sympathetic activation for female sexual arousal.</td>
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<tr>
<td>Meston, 1996</td>
<td>36</td>
<td>The study examined the time course of the effect of acute exercise on female sexual arousal in a group of 36 sexually functional women.</td>
<td>While acute exercise had no effect on sexual arousal 5min post-exercise, it significantly increased genital arousal after 15min and yielded marginal increases at 30min post-exercise. There were no effects of acute exercise on subjective arousal.</td>
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<tr>
<td>Meston, 1998</td>
<td>20</td>
<td>In 20 sexually functional women, the effect of the alpha and beta-adrenergic agonist ephedrine on genital and subjective sexual arousal was examined.</td>
<td>The results indicate that ephedrine significantly increased physiological, but not subjective, responses to erotic stimuli and seems to be able to facilitate the initial stages of physiologic arousal in women.</td>
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</table>
Index of Erectile Functioning (IIEF). The majority of men had high levels of state anxiety as well as trait anxiety, but only trait anxiety correlated statistically with the severity of the erectile disorder. The authors concluded that anxiety as a personality factor could act either as an etiological substrate of ED or as a precipitant for this dysfunction.

With the same questionnaire, Mas et al. [95] examined the influence of personality factors on the erectile response to intracavernosal injections in 78 patients. When controlling for the severity of the ED through IIEF-scores, trait anxiety proved to be a highly significant predictor of injection efficacy. A number of recent studies have supported these associations between ED and anxiety [96-99]. There have been few recent articles that have examined the relationship between anxiety and other types of male sexual dysfunction. However, Althof and Rosen [100] concluded in their review article that the evidence that was available suggested a relationship, not necessarily causal, between anxiety and PE.

c) Summary: Anxiety in sexually dysfunctional men and women

From these results it can be concluded that the majority of sexually dysfunctional individuals exhibit heightened levels of anxiety suggesting a central role of anxiety in the subjective experience and maintenance of sexual disorders. Correlational evidence exists for the relationship between ED and anxiety. However this does not imply causality. It is also not clear if it is generalized anxiety, or anxiety that is more closely related to the sexual content that is more strongly related to sexual dysfunction in men and women.

2. THEORETICAL EXPLANATIONS OF HOW ANXIETY INTERFERES WITH SEXUAL PERFORMANCE

The central role of anxiety reported by sex therapists has been challenged by a number of sophisticated laboratory studies aimed at unraveling the sequence of cognitive-affective processes during sexual arousal in dysfunctional and functional men and, to a lesser extent, women. In these studies, anxiety is induced either by shock threat or by performance demand, sometimes combined with a special distraction condition. Sexual arousal is assessed with psychophysiological (penile tumescence or vaginal photoplethysmography) and subjective (lever, questionnaires, rating scales) measures. Special attention is paid to differences between sexually functional and dysfunctional subjects. Subsequent studies also examined the role of sympathetic activation (SNS activation) such as exercise or other conditions.

Laboratory data indicate that the sexual arousal process operates differently in sexually functional and dysfunctional subjects [101]. Contrary to the findings from clinical studies that indicate an inhibition effect of anxiety, the laboratory evidence has indicated that anxiety (as induced in the lab setting) either facilitates or does not affect sexual arousal in functional subjects. The evidence for sexually dysfunctional subjects is mixed.

Barlow [102] has offered a theoretical model explaining why anxiety may operate differentially in functional vs. dysfunctional individuals. His model emphasizes the role of cognitive interference in male sexual dysfunction. In general, what appears to distinguish functional from dysfunctional responding is a difference in selective attention and distractibility. What sex therapists consider performance demand, fear of inadequacy or spectatoring are all forms of situation-specific, task-irrelevant, cognitive activities which distract dysfunctional individuals from task-relevant processing of stimuli in a sexual context [103].

In summary, the cognitive-information processing models of sexual anxiety assert that sexual arousal is dependent upon ‘task-relevant’ processing of a sexual stimulus. In sexually dysfunctional subjects, sexual stimuli induce a performance demand, which in turn leads to a shift of attentional focus away from the sexual content of a situation, inhibiting arousal.

Lab studies show that subjective and physiological sexual responses are influenced by different mechanisms. Anxiety influences genital responses, but not subjective responses. Attentional focus seems influential in cognitive processing [104].

a) The laboratory evidence for women

For women, the relationship between anxiety and sexual performance has received limited research attention. However, the literature that is available suggests that activation of the sympathetic nervous system (including anxiety provoking stimuli) facilitates genital sexual arousal in sexually functional women and in women with low sexual desire (but not in women with orgasmic disorder) [105-110]. Overall, the evidence for the role of anxiety in sexually dysfunctional women is mixed, with the suggestion that it is more negative than facilitory [111].

Table 3 summarizes the significant clinical implications of anxiety as it relates to sexual behavior.

3. IMPLICATIONS

The laboratory studies on the relationship between anxiety, distraction, general sympathetic activation and sexual response have convincingly shown that anxiety is not universally disruptive to sexual functioning. In addition, results indicate that the anxiety – sexual response relationship is complex and that the term ‘anxiety’ is too broad for
comprehensively describing the variety of factors that can disrupt sexual arousal and functioning. The available evidence indicates that the level and the nature of anxiety and its history are important determinants. Whereas moderate levels and relatively ‘safe’ settings may catalyze sexual arousal, higher levels, less feelings of personal control or a longer history of anxiety very likely impair sexual functioning [91].

III. DEPRESSION AND SEXUAL FUNCTION

The relationship between depression and sexual functioning is of considerable interest to clinicians and researchers since both affective and sexual disorders are highly prevalent, are believed to exhibit a marked co-morbidity and might even share a common etiology [112, 113]. It is generally agreed that the relationship between depressive mood and sexual dysfunction is bi-directional and further complicated by the sexual side effects of antidepressants [114]. Depression has a powerful impact on all aspects of male and female sexual response: desire, arousal and orgasm. Examining sexual function in 134 depressed men and women who were not taking antidepressant medication, researchers reported that 42% of the men reported a decrease in sexual drive; a similar percentage had a decrease in interest in sexually explicit material, sexual fantasies and masturbation. Twenty-six percent of the men were not sexually active in the month prior to assessment. Of those who were sexually active, 34% stated that their erection was less vigorous, 46% were unable to sustain an erection, 12% reported PE and 23% reported delayed ejaculation [115].

1. DEPRESSION AND SEXUAL FUNCTION IN MEN AND WOMEN

The most common sexual pattern associated with depression is loss or reduction of sexual interest and/or sexual arousal. Beck [116] found low sexual interest in 61% of severe depressives compared with 27% of non-depressed controls. Both Derogatis et al. [117] and Schreiner-Engel and Schiavi [118] examined the prevalence of acute psychiatric symptoms and lifetime psychopathology in men and women with different sexual dysfunctions. Derogatis conducted a psychiatric interview and administered the Symptom Checklist 90 Revised (SCL-90R) to a sample of 325 patients (199 men and 126 women). Men with ED had specific elevations on the depression dimension of the SCL-90R. Similarly, anorgasmic women and women with sexual pain disorders also had major elevations of the SCL-90R depression scale reflecting dysthymia and feelings of self-deprecation.

Schreiner-Engel and Schiavi [118] studied the lifetime history of psychopathology in patients presenting with desire disorders. Forty-six subjects (22 men and 24 women) were compared to 36 matched controls, utilizing clinical interviews, SCL-90-R and an instrument assessing lifetime affective and schizophrenic disorders. Although none of the patients manifested any clinical affective disorder at the time of assessment, the proportion of low desire patients with histories of major and intermittent depression was almost twice as high as that of control subjects. Moreover, in 88% of the men and 100% of the women, the initial depressive episode almost always preceded or coincided with the development of inhibited sexual desire. Hayes et al. [119] also found that depression was a strong predictor of arousal and orgasmic dysfunction among women. Interestingly, Lykins et al. [98] found that depression was more strongly associated with lower sexual desire in men than in women. Schreiner-Engel and Schiavi [118] suggested that a past history of depression may contribute to the pathogenesis of low desire or that both disorders result from the same underlying condition.

One of the most recent and intriguing studies looking at the relationship between depression and sexual function in women was that of Frohlich and Meston [120]. These researchers studied 47 college women with low Beck Depression Inventory (BDI) scores (non-depressed) and compared them to 47 women with clinically significant BDI scores. Results showed that the depressed group reported more desire for solitary sexual activity, e.g., masturbation than did the control group but there was no difference in the two depression groups in desire for sex with a partner. The depressed group reported a higher frequency of problems with arousal, orgasm and pain, less satisfaction, and less pleasure. The authors speculated that greater desire for masturbation in the depressed women’s group might reflect the wish for a reliable form of pleasure. It remains to be established whether similar results would be obtained with a population of male students.

Table 4 provides an overview of the studies that have been conducted looking at sexual dysfunction in men and women.

2. DEPRESSION AND ERECTILE DYSFUNCTION

Many of the recent studies have focused on the association between depression and ED. Data from the Massachusetts Male Aging Study [121] showed that depression and anger were highly correlated with ED. Nearly all men with symptoms of major depressive disorder (MDD) had some degree of ED[122]. Based on logistic regression analyses that controlled for other potential predictors of ED, moderate-to-complete ED was 1.82 times more likely in those who exhibited depressive symptoms compared to those who did not.
## Table 4: Empirical studies on the relationship between depression and sexual dysfunction

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Methodology</th>
<th>Results</th>
<th>Level of Evidence</th>
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<tr>
<td>Kennedy, 1999(^{15})</td>
<td>134</td>
<td>Examined sexual function in depressed men and women not taking antidepressant medication</td>
<td>42% of the men reported reduced sexual desire, 46% erectile problems, 12% experienced PE and 23% experienced retarded ejaculation.</td>
<td>3</td>
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<tr>
<td>Beck, 1967(^{16})</td>
<td>966</td>
<td>A depression inventory was administered to 966 psychiatric patients and the incidence of 'loss of libido' was determined in relation to the degree of depression</td>
<td>Loss of libido was found in 27% of nondepressed patients as compared to 61% of patients with severe, 58% with moderate, and 38% with mild depressive symptoms. Loss of libido correlated highly with loss of appetite, and loss of interest in other people.</td>
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<tr>
<td>Derogatis, 1981(^{17})</td>
<td>325</td>
<td>The lifetime history of psychopathology in 22 male and 24 female low desire patients was compared to 36 matched controls on various measures.</td>
<td>Abnormal levels of psychological distress and between one third and one half of the sample were assigned psychiatric diagnoses. Men with ED had specific elevations on the depression scale. Women complaining of anorgasmia and sexual pain disorders also exhibited marked signs of depression and self depreciation.</td>
<td>3</td>
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<tr>
<td>Schreiner-Engel, 1986(^{18})</td>
<td>46</td>
<td>The lifetime history of sexual dysfunction underwent a psychiatric evaluation and completed a symptom checklist (SCL-90-R).</td>
<td>None of the patients showed any clinical affective disorder, the proportion of patients with histories of major and intermittent depression was twice as high as that of controls. In 88% of men and 100% of women, the initial depressive episode preceded or coincided with the development of low desire. Results suggest a common etiology of both disorders.</td>
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<tr>
<td>Hayes, 2008(^{19})</td>
<td>356</td>
<td>Study was designed to estimate prevalence and factors associated with FSD in Australian women.</td>
<td>Low desire was more frequent in women in relationships for 20-29 years. Depression was associated with low arousal and high distress.</td>
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<tr>
<td>Frolich, 2002(^{20})</td>
<td>94</td>
<td>Compared sexual function among 47 women with depressive symptoms not receiving medication to 47 aged matched controls.</td>
<td>Women with depressive symptoms reported more problems with sexual desire, arousal, orgasm, pain, and less sexual satisfaction and pleasure.</td>
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<tr>
<td>Feldman, 1994(^{21})</td>
<td>1709</td>
<td>Normative data on the prevalence of ED, and its physiological and psychosocial correlates in a general population are provided. The Massachusetts Male Aging Study was a community based, random sample observational survey of noninstitutionalized men 40 to 70 years old conducted in the Boston area. A self-administered sexual activity questionnaire was used to characterize erectile potency.</td>
<td>The combined prevalence of minimal, moderate and complete impotence was 52%. The prevalence of complete impotence tripled from 5 to 15% between subject ages 40 and 70 years. Subject age was the variable most strongly associated with impotence. After adjustment for age, a higher probability of impotence was directly correlated with indexes of anger and depression.</td>
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<tr>
<td>Araujo, 1998(^{22})</td>
<td>1265</td>
<td>Data from the Massachusetts Male Aging Study were reanalyzed to determine if ED is associated with depressive symptoms.</td>
<td>After controlling for potential confounding variables, nearly all men with symptoms of major depressive disorder were found to have some degree of ED. Moderate to complete ED was almost twice as likely on those who exhibited depressive symptoms, indicating a robust and independent relationship between depression and ED.</td>
<td>2</td>
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<tr>
<td>Shabsigh, 1998(^{23})</td>
<td>120</td>
<td>120 men who presented with either ED only, BPH (benign prostatic hyperplasia) only, or with both problems were screened for depressive symptoms.</td>
<td>Patients with ED (either alone or in combination) were 2.6 times more likely to report depressive symptoms than patients with BPH only. ED patients with depressive symptoms also had lower libido. It was concluded that ED is associated with high incidence of depressive symptoms, regardless of other variables such as age or comorbidities.</td>
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<td>Strand, 2002(^{24})</td>
<td>120</td>
<td>120 ED patients were screened for depressive symptoms which were determined either categorically (DSM-IV diagnosis of depressive disorder: yes or no) or dimensionally as the score on the Brief Symptom Inventory (BSI).</td>
<td>Results showed that only a subset of patients (12%) fulfilled the categorical diagnosis of depressive disorder. When measured dimensionally with the BSI, however, the patients had significant elevations of depression and other dysorphic affects indicating a significant degree of emotional distress.</td>
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Assalian writes that men with ED may become depressed because of their sexual dysfunction and because of the secondary effects that ED may have on the relationship [123]. In men who present with one of these two problems it is crucial to ask about the other because of their frequent coexistence. The effective management of depressed men with ED often involves treating both conditions concurrently.

Shabsigh et al. [124] studied 120 men who presented to a urologic clinic with ED, benign prostatic hyperplasia (BPH), or both. Rates of depression in the ED group, the ED and BPH group, and the BPH group alone were respectively 54%, 56% and 21%. Patients with ED and depression were more likely to discontinue (intracavernosal injection or vacuum) treatment than ED patients without depressive symptoms. In a later review, Shabsigh et al. [125] stressed that ED and depression have a significant negative impact on the quality of life of patients and their partners.

Strand et al. [126] screened a cohort of 120 men who sought evaluation at a sexual behaviors clinic for depressive symptoms which were determined either categorically (DSM-IV diagnosis of depressive disorder: yes or no) or dimensionally as individual scores on the Brief Symptom Inventory (BSI). Utilizing DSM-IV criteria for depression, only a small, but by no means insignificant, subset of men (12%) qualified for a diagnosis of depressive disorder, but when distress was measured dimensionally the group demonstrated significantly elevated levels among all dimensions, including depression. These results indicate high levels of emotional distress in ED patients similar to those found by Derogatis et al. [117]. Sugimori et al. [99] found that among middle aged men (45-59 years) there was a strong association between ED and depression. Corona et al. [96] demonstrated that among men, depression was also related to low levels of sexual desire.

Seidman [127] suggested that ED and the accompanying psychosocial distress may stimulate the development of depressive illness in vulnerable individuals, or that depression might cause ED. It is likely that the relationship between depression and ED is bidirectional.

Finally, the results of a large-scale study of 4557 depressed patients in France found high rates of sexual dysfunction [128]. Patients with DSM-IV major depressive episodes but no previous diagnosis of sexual dysfunction were studied. Evaluation included both questionnaire (the Arizona Sexual Experience Scale) and physician observation. Overall, the researchers found that 35% of the participants spontaneously reported sexual problems and 69% indicated problems when asked by the physician. The frequency of sexual dysfunction was higher in patients treated with antidepressants than in untreated patients (71% and 65% respectively).

3. SUMMARY

In summary, the empirical evidence confirms a prominent role of depression in sexual dysfunction. While the exact direction of causality is difficult to ascertain, the data not only indicate a close correlational relationship between depression and sexual disorders but also support a functional significance of mood disorders in causing and maintaining sexual dysfunction. Compared to functional controls, sexually dysfunctional men and women exhibit both higher levels of acute depressive symptoms and a markedly higher lifetime prevalence of affective disorders. All of the studies reported have been at levels 3,4 and 5 of evidence and consequently, more randomized controlled research is needed.

Further, we recommend that assessment of anxiety and depression should be included as part of the initial evaluation in individuals presenting with sexual complaints and dysfunctions. An attempt should be made to ascertain whether the anxiety/depression is a consequence or a cause of the sexual complaint. If a pre-existing acute depression exists, it should be treated along with the sexual problem. Some research suggests that relief of the sexual problem is associated with relief of depression [129]. The role of anti-depressants and anti-anxiety medications as contributory factors to the sexual dysfunction should be evaluated and if implicated, a change in medication(s) may be indicated.

IV. OTHER PERSONALITY FACTORS AND SEXUAL FUNCTION/DYSFUNCTION

Hoyer et al. [130] reported on the relationship between patients seeking treatment for mental health concerns and sexual dysfunction at an outpatient clinic. Pre-treatment, of the 451 patients seeking psychotherapy, mostly for anxiety and depression, 68% of females and 54% of males reported at least one sexual complaint. Following treatment that did not focus on sexual dysfunction, those in remission, or those who had a positive response to therapy, demonstrated a 26% reduction in sexual symptoms. Patients who did not respond to therapy had a 4% reduction in sexual symptoms. The authors suggest that clinicians treating patients with anxiety and depression be aware of the high rate of sexual dysfunction and consider augmenting treatment by also treating their sexual dysfunction.

1. OBESSIVE-COMPULSIVE DISORDERS AND SEXUAL DYSFUNCTION

There are a few reports examining the association between obsessive-compulsive disorder (OCD) and sexual dysfunction. Independent studies [131-134]
suggest that approximately 50% of individuals with OCD report sexual problems and that 60% to 73% of OCD individuals are dissatisfied with their sexual lives.

While Van Minnen and Kampman [91] believe that OCD develops as a reaction to severe sexual conflicts within the patients or in their family of origin, Staebler et al. [134] did not find any differences in the sexual history of OCD patients or patients with panic or depressive disorders.

A variety of research studies suggest that OCD may be a specific risk factor for sexual difficulties. For instance, in a descriptive study of 44 OCD patients, Rasmussen and Tsuang [133] reported that 32% had sexual impulses that conflicted with their values. In a comparable study, 36% of the sample patients had sexual obsessions [131]. A recent study of women with persistent genital arousal disorder (PGAD) found that they were more likely than non-PGA women to evidence high levels of panic attacks and OCD [88]. Corona et al. [96], in contrast, found that high levels of OCD symptoms were associated with a lower prevalence of HSDD in men. Clearly, more research is needed to better understand the role of OCD in the development and maintenance of sexual dysfunction in men and women.

2. HISTRIONIC PERSONALITY DISORDERS AND SEXUAL DYSFUNCTION

There is a marked lack of research regarding the sexual attitudes, behavior, and relationships of patients with histrionic personality disorders. Apt and Hurlbert [135] compared a sample of women with histrionic personality disorder (HPD) with a matched sample of controls (aged 24-31 years). Women with HPD were found to have significantly lower sexual assertiveness, greater erotophobic attitudes toward sex, lower self-esteem, and greater marital dissatisfaction. They also had significantly greater sexual preoccupations, lower sexual desire, more sexual boredom, greater orgasmic dysfunction, and were more likely to enter into an extramarital affair. Apt and Hurlbert concluded that, although these patients are inordinately concerned with their physical attractiveness and sexual appeal, their sexual behavior varies widely and tends to run the gamut from unresponsive to promiscuous.

3. BORDERLINE PERSONALITY DISORDER AND SEXUAL DYSFUNCTION

Similar to the study above, Hurlbert [136] found that women with borderline personality disorder showed higher sexual self-esteem and sexual assertiveness compared to controls but also a greater likelihood of having extra-marital affairs. Sensation seeking, often associated with narcissistic personality disorders, has been associated with increased sexual desire and arousability but is not associated with marital/sexual satisfaction [135].

4. SUMMARY: SEXUAL DYSFUNCTION IN OBSESSIVE-COMPULSIVE, BORDERLINE AND HISTRIONIC PERSONALITY DISORDERS

It appears that personality disorders are often associated with difficulties in intimacy, sexual desire, and pair-bonding. However, the empirical evidence is too limited to draw conclusions regarding causal relationships between any specific personality disorder and sexual dysfunction. The available information consistently indicates higher levels of psychological distress and a substantial overlap with symptoms of mental disorders in sexually dysfunctional patient samples. The problems most often identified in sexually dysfunctional individuals are mood and anxiety disorders, and deficits in self-esteem and self-regulation, with some studies indicating that women are more affected by these factors than men.

However, conclusions based on the data currently available are seriously limited on methodological grounds. A wide array of heterogeneous instruments ranging from unvalidated global measures of psychopathology to more refined and validated instruments including interviews have been used to establish diagnostic criteria. In addition, in some studies, mixed diagnostic groups and small samples were used, while others did not employ matched control groups.

5. OTHER PRECIPITATING FACTORS FOR SEXUAL FUNCTION AND DYSFUNCTION

In addition to the disorders described above, there is a wide array of precipitating factors that may “tip the balance” from satisfactory sexual function to dysfunction. Among these factors (but by no means all) are life stage stressors such as childbirth, infertility, divorce or loss, unemployment, extra-relationship affairs, humiliating or traumatic sexual experiences, partner sexual inadequacy or clumsiness and most significantly, relationship discord. Space limitations preclude a discussion of all of these factors, so we will focus on the most important, namely interpersonal and relationship contributions.

6. ANGER ASSOCIATED WITH SEXUAL DYSFUNCTIONS

In assessing individuals and couples with sexual problems, clinicians often identify the presence of anger in the individuals and relationship. Kinsey
pointed out the striking similarities between the physiological responses during sex and the bodily reactions that accompany the experience of anger [137]. This similarity was also noted in primate studies where MacLean [138] showed that sexual and aggressive responses are in extremely close proximity to each other in the limbic system of the brain. Several clinicians speculated that sexual dysfunction may be a means of expressing anger at the partner [139, 140]. Additionally, Kaplan [75] stated that the partner rejection, power struggles and sexual sabotage create dysfunction rather than pleasure. Sex therapy cannot be conducted separately from an examination of the couple’s hostility. Exploration of anger must be pursued if treatment is to be successful in the longer term [141].

D. INTERPERSONAL DIMENSIONS OF SEXUAL FUNCTION AND DYSFUNCTION

Clinically, it has been observed that sexual problems are sometimes the cause and sometimes the result of dysfunctional or unsatisfactory relationships. These observations generally stem from clinical data rather than controlled research with community samples. Often it is difficult to determine which came first— a non-intimate and non-loving relationship, or low sexual desire and/or performance problems leading to partner avoidance and antipathy. The research literature is conflicting, and often difficult to interpret since couples begin therapy with varying degrees of relationship satisfaction or dissatisfaction. An early study found that sexual and relationship satisfaction were independent domains [142] (see Table 5). Heiman et. al. [142] reported that sexual satisfaction remained intact in a non-clinical sample of 110 couples even when a sexual dysfunction was present, although the majority of the research literature shows a correlation between sexual problems and relationship problems.

Most studies that have examined the impact of interpersonal issues on sexual function have used a correlational study design rather than randomized controls trials, limiting the extent to which causative statements and generalizations may be drawn.

I. RELATIONSHIP DYNAMICS AND SEXUAL DYSFUNCTION IN MEN AND WOMEN

McCabe and Cobain [143] found that global deficits in the current relationship were more likely to occur among sexually dysfunctional women than sexually functional women, but found no differences between the two groups in communication or number of arguments. These authors believe that women who are in poor relationships may express their lack of relationship satisfaction by avoiding sexual interactions and restricting their range of sexual experience and intimacy. Among men, however, relationship problems did not appear significantly related to sexual dysfunction, but the level of arguments did. Men with HSDD evidenced more difficulties than non-HSDD men in their level of relationship functioning by demonstrating increased arguments and lower sexual satisfaction. Donahue and Carroll [144] reported similar findings: female clients with HSDD demonstrated lower levels of relationship satisfaction than male clients with HSDD. Kelly et al. [145] also found that among couples where the female was experiencing orgasmic disorder, the couples experienced poorer communication than control couples who did not experience any sexual dysfunction. Roffe and Brit [146] found evidence for high levels of hostility among couples seeking sex therapy. They also found that lack of expressiveness and low levels of affection within the relationship contributed to sexual dysfunction. Although there has been limited research conducted on the relationship of men with PE, Rosen and Althof [100] found that PE impacted on both the men and their partners. The impact of sexual dysfunction on the relationship is well illustrated in a study conducted by Oberg and Fugl-Meyer [147], who found that the major predictors of female sexual dysfunction were dissatisfaction with the relationship and partner sexual dysfunction.

An interesting finding by Smith et al. [69, 148] was that the partners of men with Chronic Prostatitis/Chronic Pelvic Pain Syndrome also experienced low levels of sexual functioning and sexual satisfaction, as well as poor relationship functioning. In fact, male sexual functioning significantly predicted the sexual functioning of their female partner. Atwood et al. [149] also emphasized the importance of the couple relationship in both the development and maintenance of ED. Clinicians and researchers have noted that these relationship problems are often not well addressed in the resolution of sexual dysfunction in both men and women [150].

There are methodological problems associated with most of the research exploring the interaction between sexual and relationship function and satisfaction. Many of the studies consist of small, non-representative samples, lack a no-treatment control group, provide inadequate assessment of the specific sexual dysfunction(s) and fail to adequately assess the couple’s relationship. More significantly, it is difficult to determine to what extent the sexual complaints led to lower relationship satisfaction or the conflict in the relationship resulted in poorer sexual function and satisfaction. Finally, the reported association between relationship maladjustment and sexual dysfunction is confounded in studies of “clinical populations” rather than population-based studies.
Table 5: Studies on interpersonal dimensions of sexual function and dysfunction

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Subjects</th>
<th>Treatment Method</th>
<th>Summary of Study Findings</th>
<th>Evidence Based Medicine Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heiman, 1986</td>
<td>110</td>
<td>Survey of non-clinical respondents</td>
<td>Sexual and relationship functioning are independent domains</td>
<td>3</td>
</tr>
<tr>
<td>McCabe, 1998</td>
<td>343</td>
<td>Compared 114 dysfunctional males and 84 dysfunctional females with 43 functional</td>
<td>Dysfunctional females were more likely than functional females to experience negative events</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>males and 102 functional females on individual and relationship factors.</td>
<td>in adolescence, poorer relationship and more negative attitudes to sex. Dysfunctional</td>
<td></td>
</tr>
<tr>
<td>Donahey, 1993</td>
<td>66</td>
<td>Hypoactive sexual desire men were compared to women in relation to psychological</td>
<td>Women were more likely to experience problems in relationships and psychological</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and relationship functioning.</td>
<td>functioning compared to men.</td>
<td></td>
</tr>
<tr>
<td>Kelly, 2006</td>
<td>47 couples</td>
<td>Compared (a) couples with no physical problems, females had sexual problems, (b)</td>
<td>Group b evidenced poorer communication patterns in their relationship than either of the</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>couples with no physical or sexual problems, (c) couples with physical and no sex</td>
<td>other two groups.</td>
<td></td>
</tr>
<tr>
<td>Roff, 1981</td>
<td>492</td>
<td>246 couples seeking sexual dysfunction therapy were compared on their marital</td>
<td>Three types of marital interactions were identified: high hostility by wife or husband,</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>interactions</td>
<td>inhibited response by husband, affection expressed by both partners</td>
<td></td>
</tr>
<tr>
<td>Oberg, 2005</td>
<td>926</td>
<td>Survey of non-sexually active Swedish women aged 18-65 years in a heterosexual</td>
<td>Low levels of satisfaction with the relationship and male sexual dysfunction predicted</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>relationship</td>
<td>sexual dysfunction in the female partner</td>
<td></td>
</tr>
<tr>
<td>Smith, 2007</td>
<td>75 couples</td>
<td>Compared sexual and relationship functioning of 38 men with Chronic Prostatitis/</td>
<td>Men with CP/CPPS evidenced higher sexual dysfunction than control men partners of men</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic Pelvic pain Syndrome and their partners to 37 control men and their partners.</td>
<td>with CP/CPPS reported more sexual pain vaginismes and depressive symptoms than control</td>
<td></td>
</tr>
<tr>
<td>Pietropento,</td>
<td>400</td>
<td>Physicians were surveyed to determine the prevalence of inhibited sexual desire</td>
<td>There was considerable disagreement in the prevalence of ISD, but there was a general</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>among their patients.</td>
<td>consensus that ISD was associated with the quality of marital relationships.</td>
<td></td>
</tr>
<tr>
<td>Herlbert, 1993</td>
<td>57</td>
<td>Compared the effectiveness of two group interventions using orgasmic training in</td>
<td>The treatment was generally found to be effective for both treatment groups; the couples</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>the treatment of hyoactive sexual desire: women were assigned to women only group,</td>
<td>only group showed some evidence of greater improvement than the women only group.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>couples group, or wait list control group.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zimmer, 1987</td>
<td>48</td>
<td>Compared the effectiveness of sex therapy alone, sex therapy and marital therapy</td>
<td>Both treatment groups showed improvement in their sexual symptoms. However, the</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>to a control condition.</td>
<td>combined sex and marital therapy group demonstrated the greatest improvement.</td>
<td></td>
</tr>
<tr>
<td>Macphee, 1995</td>
<td>98</td>
<td>49 couples where the woman was experiencing ISD were assigned to either Emotion</td>
<td>The group receiving marital therapy made modest improvements in their levels of sexual</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>focused Therapy group or a control group.</td>
<td>desire and reductions in levels of depression. Lower initial levels of marital distress</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>resulted in greater treatment gains.</td>
<td></td>
</tr>
</tbody>
</table>
Table 5: Studies on interpersonal dimensions of sexual function and dysfunction (continued).

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Subjects</th>
<th>Treatment Method</th>
<th>Summary of Study Findings</th>
<th>Evidence Based Medicine Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stuart, 1987</td>
<td>90</td>
<td>Compared 59 married women with inhibited sexual desire to 39 married women with normal sexual desire.</td>
<td>The ISD group demonstrated poorer functioning in the areas of sexual history, marital, functioning, and other aspects of sexual functioning.</td>
<td>3</td>
</tr>
<tr>
<td>Trudel, 2005</td>
<td>80</td>
<td>Evaluated differences in dyadic adjustment between 20 couples with HSD, and 20 couples without this condition.</td>
<td>HSD was found to be associated with a range of relationship problems, but causality could not be determined.</td>
<td>3</td>
</tr>
<tr>
<td>Hurlbert, 2005</td>
<td>66</td>
<td>Evaluated whether relationship dynamics or other aspects of sexual functioning predict sexual desire and psychosocial functioning among 66 women with hypossexual desire.</td>
<td>Relationship factors were strongly associated with sexual desire and psychosocial functioning. Other aspects of sexual functioning were strongly associated with psychosocial functioning.</td>
<td>3</td>
</tr>
<tr>
<td>Leiblum, 2002</td>
<td></td>
<td>Review of literature related to the experience of sexual dysfunction among menopausal women.</td>
<td>Lack of sexual desire is the most common sexual complaint among post-menopausal women. This may be due to biological changes, as well as psychological and relationship factors.</td>
<td>4</td>
</tr>
<tr>
<td>McCabe, 1997</td>
<td>343</td>
<td>198 dysfunctional men and women were compared to 145 functional men and women in relation to their levels of intimacy and quality of life.</td>
<td>Dysfunctional men were lower than functional men for all aspects of intimacy; this difference only applied for social and recreational intimacy among women. Quality of life was lower for dysfunction women than functional women. This difference did not apply to men.</td>
<td>3</td>
</tr>
<tr>
<td>Davies, 1999</td>
<td>72 couples</td>
<td>Sexual desire discrepancies and their relationship to sexual and relationship functioning were examined in 72 dating couples.</td>
<td>Women whose sexual desire was lower than their partners’ evidenced lower levels of relationship adjustment compared to women with the same or higher levels of sexual desire compared to their partner.</td>
<td>3</td>
</tr>
<tr>
<td>Klusman, 2002</td>
<td>1865</td>
<td>Survey of German students aged 19-32 who were involved in a heterosexual, steady relationship. Investigated the relationship between sexual motivation and length of relationship.</td>
<td>Sexual activity and satisfaction decline with length of relationship in both men and women; sexual desire declines in women; desire for tenderness declines in men but increases in women.</td>
<td>3</td>
</tr>
</tbody>
</table>
II. RELATIONSHIP DYNAMICS AND HYPOACTIVE SEXUAL DESIRE

HSDD is one of the most perplexing, prevalent and etiologically complex of all the sexual dysfunctions. It is generally found to be more common in women than in men [151-153]. In men it is often confounded with arousal and erectile problems, making it difficult to determine the primary diagnosis. There is a considerable overlap between desire, arousal and orgasmic difficulties for both men and women.

Interpersonal factors are frequently cited as one of the causal determinants of low sexual desire. Social-developmental theories e.g., Scharff’s [154] object relations perspective; differentiation theories; (e.g., Schnarch [155]), and cognitive behavioral theories (e.g., Pridal & LoPiccolo [156]), address the role of relationship factors as either inhibiting or facilitating the experience of sexual desire.

Most theories describe HSDD as emerging from an interaction between individual and dyadic characteristics. Notable examples are Talmadge and Talmadge’s [157] relational model, and Rosen and Leblum’s [158] sexual scripting paradigm. Zilbergeld and Ellison[159] and others [155] have theorized that sexual dysfunction, particularly HSDD, serve as a “distance regulator” in a relationship. If a couple is fearful that too much intimacy will lead to fusion and lack of individual differentiation, one or both partners may attempt to create distance, often through sexual apathy. Even approaches that do not view relationship issues as central to sexual desire recognize the role of the current relationship in maintaining the individual determinants of the disorder [160].

It is generally agreed that, at the very least, the cooperation of the partner without HSDD is essential for the successful treatment of desire disorders [161]-[162]. In fact, 73% of surveyed physicians endorsed the belief that sex therapy or psychotherapy with both members of the couple is the best form of treatment for most cases of inhibited sexual desire[163]. Further, there is empirical evidence indicating that sex therapy with the couple is more efficacious than treating the HSDD patient alone [164], that combined marital and sex therapy approaches are more efficacious than sex therapy alone for couples with HSDD [165], and that women with HSDD show modest improvement in desire and other aspects of sexual functioning following brief marital therapy [166].

There is research supporting the observation that low sexual desire is associated with lower levels of relationship satisfaction and adjustment, both for individuals with low desire and their partners [167]. For example, couples with HSDD have poorer levels of dyadic adjustment than couples without HSDD [168]. Similarly, Trudel, Landry and Larose[93] found that compared to controls, couples in which one partner was diagnosed with HSDD obtained lower adjustment scores on the Marital Happiness Scale. Hurlbert et al. [169] found that the relationship between HSDD and relationship functioning was stronger for women than for men.

A large scale health and sexuality survey of 2,050 pre-, peri-, and postmenopausal women between the ages of 20-70 found that those women who reported lowered levels of sexual desire also reported more relationship dissatisfaction, lower frequencies of sexual activity, fewer orgasms and more distress [170].

McCabe [171] observed that individuals with HSDD reported lower levels of intimacy and lower satisfaction with the quality of the intimacy in their lives than controls. Davies et al. [172] examined discrepancies between partners’ levels of sexual desire, and found that for both husbands and wives, individuals who felt that there was a discrepancy between their own and their partner’s desire reported lower relationship satisfaction.

In stable long-term relationships, sexual frequency declines over time, although satisfaction may continue to remain high. Even among young adults, sexual frequency declines over time. Klusmann [173], for example, reported changes in sexual interest in students between 19 and 32 years of age who were in “steady partnerships.” He found that both sexual activity and sexual satisfaction declined over time but that desire decreased only in women. Desire for tenderness decreased in men but increased in women over that period.

III. THE IMPACT OF RELATIONSHIP THERAPY ON SEXUAL DYSFUNCTION

Wiederman [174] suggests that treatment focused solely on the sexual dysfunction is likely to fail if the underlying relationship dynamics are ignored. He maintained that without treating the problematic relationship, enhanced sexual function is likely to be temporary or that other psychological symptoms in one or both partners will develop in order to maintain homeostasis. At present, there is limited empirical research to either support or refute this view.

In a comprehensive review of treatments for sexual dysfunction, Besharat [175] highlighted the importance of communication and conflict resolution strategies as well as resolution of systemic issues in the relationship. While there are conflicting findings, the preponderance of evidence suggests that therapy, which specifically addresses relationship
issues, will be more successful than therapy that only focuses on the resolution of the sexual dysfunction. The existing research supports the observation that the quality of the relationship plays an important role in the outcome of sex therapy [176].

Stravynski et al. [177] conducted a study to determine if treatment outcome for sexually dysfunctional men differed depending upon whether therapy focused on sexual problems, interpersonal issues, or a combination of both. The results demonstrated that a focus on the interpersonal issues was more effective than the other two treatments. Although the combined treatment was more effective at post-therapy and at six months follow-up than the interpersonal therapy, by the one-year follow-up there were no differences between the levels of sexual dysfunction for these two groups. This finding would suggest that, in the long-term, the most important focus of therapy for sexual dysfunction is on developing interpersonal skills and resolving relationship problems. In a subsequent study of sexually dysfunctional women, Stravynski et al. [177] found that treatment focusing on the resolution of sexual problems or relationship problems were equally effective compared to a control condition in resolving sexual problems at both post-treatment and 12 month follow-up. Kilmann et al. [178] also found that relationship adjustment was the strongest predictor of successful treatment outcome among men with erectile dysfunction. Similar findings were obtained among sexually dysfunctional women [179].

In contrast to the above findings, Hawton, Catalan, and Fagg [180] found that the quality of the couples' relationship was not related to successful treatment outcome for women presenting with low sexual desire. The most important predictor of success was the male partner's motivation to obtain a successful outcome at the beginning of therapy.

The role of the partner in the treatment outcome of sexually dysfunctional couples is clearly illustrated in a study by Hirst and Watson [181]. These authors found that good outcomes following treatment were obtained for dysfunctional individuals without partners, or for those individuals whose partners agreed to participate in therapy, whereas substantially poorer outcomes were obtained for those individuals whose partners did not participate in treatment. Consistent with the importance of the partner in treatment outcomes, Sand et al. [182] found that men with ED rated their relationship with their partner higher than many other aspects of their lives (e.g., employment, material possessions). These findings highlight the importance of interpersonal relationships in managing ED.

In a series of case studies, Leiblum [183] and Althof [184] both found that although oral medication (e.g., sildenafil citrate) may assist a man in obtaining an erection, the use of this intervention was unlikely to lead to a satisfying sexual relationship unless relationship issues were also addressed. These issues include feelings of insecurity that develop as a result of the sexual dysfunction, as well as anger and disappointment. Returning to an active sexual life after an extended period of sexual abstinence requires more than medication alone. Leiblum and Althof [184] highlighted the importance of obtaining a thorough assessment and treatment of both the interpersonal and sexual relationship as well as including the partner, where possible, in the therapy process.

While the evidence is not conclusive and the studies cited are not randomized controlled trials but primarily Level 3, 4 and 5 research, the findings demonstrate a significant relationship between sexual and relationship functioning. While it is impossible to determine cause and effect relationships with any certainty, the literature suggests better long-term outcome when relationship issues are treated and resolved.

Whether the relationship problems preceded the development of the sexual dysfunction, or vice versa, it would appear that the most effective form of intervention is to treat both the relationship and sexual difficulties. If this does not occur, the problem that is not addressed may continue to influence the other area that is the focus of treatment, and so eventually undermine the treatment process. Clearly, more rigorous controlled studies need to be conducted to determine the validity of this argument more conclusively.

E. LOVE AND INTIMACY

It would be neglectful to discuss psychological and interpersonal contributions to sexual function and dysfunction without including some references to the importance of love and intimacy. While cultures vary enormously in the degree to which they consider love important for marriage, or even, the importance of love at all in interpersonal committed relationships, most individuals in Western countries believe that emotional intimacy and feelings of love enhance and sustain sexual satisfaction and pleasure.

There is little or no empirical research on this topic, so the comments that follow are based on clinical observation rather than scientific data.

It is clear that love implies different meanings to different individuals [6]. Some of the meanings include the following:

- Love is a label for the transient emotions that bring together various degrees of pleasure and interest between two individuals.
- Love is an idealized ambition e.g. To have mutual respect, reliability, fidelity,
intimacy, sexual pleasure, and a comfortable balance of individuality.

- Love is a commitment. Typically, love involves the commitment of two people to honor and cherish each other throughout life’s vicissitudes.
- Love is an idealized internal representation of the partner. When a person falls in love and continues to be happy with a partner, an internal image of the beloved is created and reinforced. This internal idealized image enables an individual to deal with a partner when he or she is behaving badly or when disappointments ensue.
- Love is a “deal” with a person who possesses desired and desirable assets.
- Endearing words of love are often expressed when a person wants to have sex.

While not typically discussed in scientific discourse or evidence-based research, love is a vital ingredient for many individuals in fostering and maintaining strong and satisfying interpersonal and sexual intimacy. Mechanistically treating sexual problems without considering or discussing the quality of caring and love between partners is usually unsuccessful, if not immediately, then over time.

### F. MAINTAINING FACTORS FOR SEXUAL DYSFUNCTION

While the predisposing and precipitating factors that have been reviewed are important to assess, they may not be responsible for the chronic nature of a sexual problem. It is the maintaining factors that are responsible for transforming disappointing or episodic sexual failures into chronic dysfunction. Examples of maintaining factors include the following: performance anxiety, loss of sexual confidence, guilt, inadequate sexual information or stimulation, psychiatric disorders, relationship discord, loss of sexual chemistry, fear of intimacy, impaired self-image or self-esteem, restricted foreplay, and poor communication. The factors that maintain sexual dysfunction may not be the ones that initially predisposed or precipitated the initial sexual failure. However, by the time individuals present for treatment, the maintaining factors may be more disruptive to therapeutic outcome than those that initially predisposed the person to develop the sexual dysfunction. A case illustration may illuminate this point:

A 34-year-old woman complains of an inability to become both physically and subjectively aroused during sexual intercourse with her male partner of two years. Assessment reveals an early history of father-daughter incest, which, however, appeared to have been satisfactorily resolved during her late adolescent years. She enjoyed good sexual response during early courtship with both her present partner and previous partners. However, her current partner is often demeaning and critical of her body shape and weight and so, she has become quite self-conscious during love-making. This has led to distraction during sex, which further interferes with her sexual response, which then becomes a point of contention between them. Anticipation of critical comments from her partner leads to performance anxiety and further inhibits her response creating a downward spiraling negative cycle.

### I. PERFORMANCE ANXIETY

Early etiological theories [74] regarded performance anxiety as the crucial pathogenic factor for maintaining sexual difficulties. Performance anxiety is the fear of future sexual failure based on previous failures- a common maintaining contribution for almost all male and female sexual dysfunctions. Many theorists consider performance anxiety to be the central causal factor interfering with sexual arousal since it serves as a distraction from sensual feelings, undermines sexual self-confidence and ultimately, contributes to sexual avoidance.

### II. SEXUAL CONFIDENCE

An important aspect of the psychological response to sexual dysfunction is the extent to which the man or woman lost, or in some cases never achieved confidence in both their capacity to function sexually, as well as the extent to which they perceive themselves to be a sexual being. This is given the umbrella term of "sexual confidence", and the limited literature that has evaluated this important concept is outlined below.

Althof [185,186] described one of the goals for psychotherapy for both men with ED and PE to be the enhancement of his sexual confidence. He suggested that although there are now medical treatments for PE, it is important to address the psychological factors associated with this condition, one of which is the level of the man’s diminished sexual confidence. Perelman [187] also noted the reduction in sexual confidence that is associated with PE, and emphasized the importance of addressing the man’s confidence in his sexual functioning in therapy.

Men receiving sildenafil or tadalafil for the treatment of ED reported significantly improved sexual confidence following treatment [188-191]. Additionally, Phelps, Jain, and Monga [192] found that a combination
treatment with sildenafil and a psychoeducational intervention was more likely than sildenafil alone to increase the man’s sexual confidence as well as his satisfaction.

The above findings demonstrate the importance of considering sexual confidence in the treatment of both ED and PE among men. It is possible that medical treatments may increase the level of a man’s sexual confidence, but it would appear that psychological interventions may be necessary for many men to restore their confidence in their sexual functioning.

No studies were located on the association between female sexual dysfunction and the levels of sexual confidence. However, it is highly likely that sexual dysfunction is strongly associated with a reduction in a woman’s level of sexual confidence, and so this dimension of psychological functioning should be targeted in therapy.

### III. OTHER MAINTAINING FACTORS

Space precludes a discussion of all the maintaining factors that may be responsible for turning an acute problem into a chronic one. Suffice it to say that maintaining factors include those present conditions that enhance or impede sexual comfort and intimacy. In particular, anxiety, depression and confidence, as well as problems in the relationship, which are factors that have been discussed elsewhere in the chapter, are likely to be responsible for maintaining sexual dysfunction in both men and women. Maintaining factors include immediate contextual factors that influence sexual spontaneity, as well as partner-related factors such as sexual technique and absence of sexual dysfunction. It is obvious that there is reciprocity in partner-related sexual activities such that a problem in one partner may trigger problems in the partner and vice versa. It is therefore essential to assess how sexual partners mirror each other in terms of desire, arousal and satisfaction.

### G. HOW SUCCESSFUL ARE WE IN CHANGING DYSFUNCTIONAL SEXUAL BEHAVIOR?

### I. THE CHALLENGE OF OUTCOME RESEARCH IN SEX THERAPY

Sex therapy outcome studies are notoriously difficult to design and conduct. The challenge facing researchers is not only to design studies that meet the highest level of evidence-based medicine but to also demonstrate regard for the complexity of sexual life. A narrow mechanistic focus on genital function/dysfunction or successful performance fails to encompass the broader variables that constitute patient and partner sexual satisfaction and dysfunction and disease-specific quality of life (QoL) [184, 193]. As such, in some newer models of sexual response [194], psychological and relational components play a more significant role than previously was the case. For these reasons the use of validated tools such as the IIEF and the FSFI in the measurement of any changes during sex therapy is likely to have only limited value due to the narrow focus and specific items measured by the instruments. An example of incorporation of a psychological construct of perceived control over ejaculation has recently been determined as central to measuring benefit in men treated with a new compound dapoxetine for rapid ejaculation [195]. A recent systematic review of published self-report outcome measures of sexual function concluded that of the 23 self-report measures identified, only 14 could be judged reliable and valid measures, of which only two met ‘superior’ psychometric standards [196]. The use of target symptoms identified by the individual at the onset of sex therapy may likewise restrict the capacity for the researcher to identify the change processes which may occur during therapy.

Understanding and measuring changes in the flexibility of cognitive and behavioral coping processes which may be facilitated within sex therapy may be more appropriate outcome measures [197]. Additionally, QoL variables encompass relational, self efficacy/confidence, emotional and sexual satisfaction and pleasure. Thus, outcomes conceived solely in terms of women’s facility in achieving coital orgasm, men’s prowess at delaying ejaculation, the buckling force of an erection, blood flow through the clitoris and vagina, or the frequency with which partners bring their bodies together are far too restrictive outcome criteria. Sexuality outcome studies must assess the complex interplay between the biological, emotional, psychological and relational components of individual’s and couples’ lives [198].

For example, intracavernosal injection of vasoactive substances is an efficacious treatment in terms of inducing erection. However, the high-dropout rate, up to 60%, suggests a lack of treatment satisfaction [184]. Which clinical endpoint(s) should be used to assess treatment outcome? Should it be continued use of the treatment, efficacy in achieving or maintaining firm erections, sexual or relational satisfaction or partner sexual or QoL variables?

Chronic illnesses can disrupt QoL through adverse effects on sexual function which may long term or irreversible. As such, pharmacological treatments may have limited effectiveness for some chronic illnesses (e.g. diabetes).
There is also disagreement as to what defines a good treatment outcome even when function-oriented criteria are employed. For instance, in treating female anorgasmia, what defines success—achieving orgasm once, achieving orgasm from manual or oral stimulation some specified percentage of occasions, achieving coital orgasm with or without clitoral stimulation, etc? And, what constitutes success in treating erectile dysfunction—the ability to consummate intercourse (which is a distinctly heterosexual goal but which ignores a wide segment of the population, namely gay and auto sexual men) or the degree of penile rigidity?

The CORE Outcome Measure (CORE-OM) [199] is a 34-item questionnaire designed to measure a pan-theoretical ‘core’ of clients’ global distress, including subjective well-being, commonly experienced problems or symptoms, and life/social functioning. The main purpose of the tool is to offer a global level of distress which is expressed as the average mean score of the 34-items that can be compared with clinical thresholds before and after therapy to help determine clinical and reliable change. A recent study concluded that the psychometric properties of the CORE-OM are reproducible in a psychosexual population [200]. Finally, the emphasis on frequency counts of various sexual acts or initiations as a primary outcome measure is also questionable since it ignores both positive changes in sexual satisfaction and physical and emotional intimacy.

II. WHY IS THERE A PAUCITY OF WELL-CONTROLLED SEX THERAPY OUTCOME STUDIES?

Fundamentally, it appears that there are two primary explanations for the dearth of well-controlled sex therapy outcome studies. The first is that they are labor intensive and unfortunately, are not considered a priority by governmental granting agencies. Moreover, because there is no incentive for pharmaceutical companies to fund purely psychological treatments, this source of funding has been unavailable. The second reason is that the incredible success of Masters and Johnson’s [74] original treatment program made it seem as though we had found the “holy grail.” Never before or since has such a large-scale study reported such a highly successful post-treatment and five year follow-up of 792 men and women been achieved (with an overall reported failure rate of only 15%). For several decades, the field relied primarily on their treatment approach and few innovations were forthcoming [201]. Unfortunately, no other clinical study or center has been able to replicate Masters and Johnson’s impressive success either short- or long-term.

III. METHODOLOGICAL PROBLEMS IN SEX THERAPY OUTCOME STUDIES

Outcome studies in psychotherapy are lacking [202] and those in sex therapy pose some unique challenges. Spence [203] criticizes sex therapy outcome studies because often they: 1) employ small sample sizes; 2) do not use experimental control groups (waiting list, no treatment, attention placebo controls); 3) lack random allocation to conditions; 4) fail to offer clear cut definitions of diagnostic criteria to permit replication; 5) generally do not include assessments of long-term outcome; and 6) do not adequately describe the therapy method utilized.

Heiman and Meston [204] further criticize sex therapy studies for failing to utilize treatment manuals, which are considered prerequisites for designating a treatment as “well-established” using the American Psychological Association (APA) standards. This failure to describe a standardized manualization of interventions remains problematic because of the difficulty of reproducing interventions in subsequent investigations [205] and especially in sub-populations. Additionally, the effectiveness to the patient of any intervention may depend on the skills of the clinician delivering the intervention which is in turn influenced by previous training and on-going supervision of the individual sex therapist.

Psychometrically sound measurement instruments has, until recently, been lacking in the majority of outcome studies, thereby raising questions about the validity of the reported results. Many studies employ self-report instruments or patient diaries that lack validation or clinical judgments made by un-blinded clinicians.

The few studies that have reported long-term follow-up suffer from serious problems of sample attrition. Thus, the generalizations stemming from these studies may represent a biased subset of the total population.

Changes to the delivery of care will also influence the need for both improvement and choice of outcome measure. For example, studying the use of bibliotherapy [206, 207, 208] Hunot and Wylie [208] carefully designed evidence-based self-help tools [209] and internet delivery of sex therapy [210-213]. Finally, the overlap between different sexual dysfunction diagnoses can make comparisons across studies and treatment interventions difficult.

In past research, patients were often diagnosed with one dysfunction based on the belief that sexual dysfunctions were discrete disturbances in the sexual response cycle. There is currently recognition of the fact that there is considerable overlap among sexual...
disorders [153, 214]. There also remains an absence of clear consensus concerning core definitions [215]. This lack of clarity and overlap between diagnostic categories must be methodologically or statistically controlled in order to assess the impact of any intervention on the disorder under study.

Despite all of these shortcomings and difficulties, there is suggestive data indicating that sex therapy can be quite helpful in ameliorating male and female sexual dysfunctions. Further, there is no evidence against the efficacy of psychotherapy when applied to appropriate clinical populations [216].

H. PSYCHOLOGICAL TREATMENT OF SEXUAL DYSFUNCTIONS-GENERAL FORMULATIONS

Masters and Johnson’s groundbreaking contributions recounted in Human Sexual Inadequacy [74] described their innovative format of employing mixed-sex co-therapy teams working with couples in a quasi residential setting with daily individual and conjoint treatment sessions. Basic treatment elements included an emphasis on sensate focus exercises and the elimination of performance anxiety. Masters and Johnson recommended beginning with non-sexual touching and then, in a desensitization paradigm, moving on to more genitally focused caressing. By emphasizing the non-demand nature of the sensual exchange, Masters and Johnson sought to eliminate performance pressure.

Masters and Johnson’s treatment method was an expensive, therapist intensive, impractical model to reproduce. Therefore modifications of their treatment format were investigated to ascertain if similar results could be achieved with more conservative, conventional outpatient treatment models. Clinicians examined the impact of single therapist versus co-therapy teams, weekly versus daily treatment sessions and group formats versus individual/couple sessions. The results indicated that couples did as well when seen on a weekly basis and by a single therapist [217-219]. Two studies examined whether matching the gender of the therapist with the gender of the symptom bearer would result in improved outcome; no differences were found [217, 220].

Researchers also examined the efficacy of individual versus group treatment formats. Group formats were advantageous because they were less costly in terms of therapist time, provided patients with the knowledge that they were not alone in their suffering, offered peer support, and allowed patients to learn from the experiences of others. Additionally, competition within the group motivated patients to change behaviors and desensitized them to discussions of their private sexual lives [203]. However, the use of groups in sex therapy has been limited because of organizing and scheduling difficulties as well as finding enough patients with the same disorder available for treatment at the same time. One recent Cochrane Database systematic review to evaluate the effectiveness of psychological interventions for the treatment of ED found 11 RCT's and evidence that group therapy improved ED [221, 222]. Further a combination of sildenafil and psychotherapy together showed significant improvement in erectile function and decreased discontinuation from treatment. Drop out from therapy and lack of end of treatment therapy measures, regardless of whichever measure is used will further distort the reporting of change – beneficial or otherwise from sex therapy.

More recent approaches to sex therapy have included cognitive-behavioral interventions focused on challenging or correcting maladaptive cognitions, behavioral techniques such as desensitization and assertiveness exercises, family of origin and psychodynamic explorations exploring the role of past developmental experiences on present behavior and systemic and couples therapy.

The following sections will review the outcome of psychological and sex therapy on female and male sexual dysfunction.

I. TREATMENT OUTCOME FOR FEMALE SEXUAL DYSFUNCTIONS

In this section, treatment outcome will be described for both the recognized DSM-IV-TR and recommended new diagnostic categories of female sexual disorders, namely, hypoactive sexual desire disorders, female sexual arousal disorder (which includes genital arousal disorder, subjective arousal disorder, combined genital-subjective arousal disorder and persistent genital arousal disorder), orgasmic disorder and sexual pain disorders. Each of these dysfunctions can be further categorized into acquired and lifelong specifying whether they began after a period of normal function (acquired type) or have been present throughout the woman’s sexual life (lifelong). Heiman [223] and Heiman and Meston [204] have published comprehensive reviews of much of the evidence-based research looking at the prevalence, etiological factors and treatment outcome for the various female dysfunctions. In the last edition of this volume, Althof, Leiblum, et. al. [224] provided a more current update and evaluation of the literature on female sexual dysfunctions. This section will summarize the treatment outcome studies for female sexual dysfunction that have been conducted both in the past and most recently.
I. SEXUAL DESIRE DISORDERS

There is a dearth of efficacy data on the psychological treatment of sexual desire disorders, despite the fact that hypoactive sexual desire is the most common female sexual complaint [225]. There is no shortage of published descriptions of psychological treatments [155, 226], but most however, do not meet contemporary standards for evidence based research. Consequently, most of the studies reviewed here are of Levels 3, 4 and 5 evidence.

Sexual desire is difficult to define and difficult to measure. Does one count sexual frequencies of various sexual behaviors or attempt to assess the degree of internal motivation to engage in sexual activity? Do we tally sexual fantasies or frequency of various sexual behaviors as a proxy measure of desire or interest? And, perhaps more importantly, what should be considered indicative of a successful treatment outcome? Greater frequency of sexual behavior? More pleasurable activity? Partner or self satisfaction with the degree, intensity and frequency of sexual exchange? Less subjective distress about the level of desire? Changes on a validated assessment instrument?

Basson [227] and others [228, 229] have argued that many women never report spontaneous desire yet can become readily aroused with effective stimulation or the wish to be intimate with a partner. Basson believes that lack of responsive desire is more likely to be a marker of HSDD than spontaneous desire. She [227] postulated that many women in established relationships engage in sex from an initial stance of sexual neutrality and then, with increasing amounts of arousal, begin to experience desire. Often, desire is triggered by a variety of internal motivations or external reinforcements rather than intrinsic physical tension although for women in new relationships, desire may be experienced more spontaneously. It must be acknowledged that the motivations or incentives to either initiate or respond to a sexual request or overtire are extremely varied. In an interesting research study conducted by Meston and Buss [230] with 1,549 undergraduates, the researchers and their students identified hundreds of reasons for engaging in sex, but were able to categorize them into four main factors and 13 subfactors. The four main factors were Physical, Goal Attainment, Emotional and Insecurity. The Physical subfactors encompassed stress reduction, pleasure, physical desirability and experience seeking. The Goal Attainment subfactors included resources, social status, revenge and utilitarian. Emotional subfactors included love and commitment and expression. And finally the three Insecurity subfactors were self-esteem boost, duty/pressure and mate guarding. Obviously, knowing that a sexual experience has occurred tells us nothing about either the desire accompanying it, or the diverse and not necessarily sexual motives for engaging in it!

There is little agreement about what constitutes normal desire in women of various ages given the hormonal variations accompanying different life stages. Consequently, there is little agreement as to what constitutes a sexual desire disorder as opposed to normative changes in sexual interest over the female life-cycle [229]. While situational and acquired loss of desire is characteristic of many life stages, e.g., pregnancy and child-rearing, generalized and chronic lack of desire is more resistant to intervention and suggests a different etiology.

Hawton and his colleagues [231] conducted a prospective, non-controlled study of a community sample of couples who underwent a modified Masters and Johnson treatment program. Sexual desire problems seemed to be alleviated largely or completely in 56% of the couples following treatment. However, in follow-up, 1 to 6 years after treatment termination, 75% of the sample had relapsed. In a subsequent review of the efficacy of sex therapy for sexual dysfunctions, Hawton [218] noted the variable outcome that is often found across studies. He observed that outcome is worse when the male partner is the identified HSDD patient and has low motivation to engage in treatment than when the female partner is the target of treatment.

Hurlbert [232] investigated the viability of orgasm consistency training for the treatment of female HSDD. Women were randomly assigned to group treatment with either standard sex therapy interventions or the addition of orgasm consistency training (directed masturbation) in addition to sensuality exercises, communication training and education. Post-treatment and follow-up at 3 months suggested that there was greater improvement in the orgasm consistency group although both groups demonstrated greater sexual arousal and assertiveness as well as greater sexual satisfaction.

The efficacy of cognitive-behavioral therapy for women with HSDD has been reported in two studies. McCabe [233] found that of the 43% of women complaining of HSDD who underwent 10 sessions of CBT, 54% had the same complaint following treatment. Treatment in this case consisted of 10 sessions of a cognitive behavioral therapy. The program included interventions designed to enhance communication between partners, increase sexual skills and reduce sexual and performance anxiety. Overall, improvement was noted for 44% of the women. The findings are limited, however, in that many of the women had multiple sexual dysfunctions and there was no control group.

In a study by Trudel et. al. [234] comparing cognitive behavioral interventions specifically developed to address desire disorders with a control condition, 74%...
of the low desire women no longer met diagnostic criteria for HSDD after 12 weeks of group therapy and these effects were said to be maintained at a 1-year follow-up assessment. Compared to the control group, CBT resulted in significant improvement in quality of sexual and marital life, sexual satisfaction, perception of sexual arousal, sexual self-esteem and less depression and anxiety.

The most recent and promising group treatment for women with sexual desire complaints is employs a three session mindfulness-based psychoeducational intervention [235, 236]. “Mindfulness” is described as “relaxed wakefulness” or “non-judgmental, present-moment awareness” and is derived from Buddhist meditation [237]. In a small study of 26 women with complaints of either desire or arousal problems, Broto, Basson and Luria [235] reported significant improvement in sexual desire on the Female Sexual Function Index (FSFI) and a reduction in sexual distress with just three 90 minute psychoeducational sessions spaced two weeks apart. The psychoeducational intervention consisted of a variety of cognitive-behavioral exercises targeted to sexual arousal and desire complaints (e.g., body image distortion, maladaptive beliefs about sexuality, relationship distress, etc.) but most importantly, mindfulness exercises along with homework assignments involving reading, self-observation, behavioral exercises and couple communication. The most positive changes were noted in the 8 women with a prior history of sexual abuse. These authors suggest that mindfulness techniques might be especially helpful in altering the activity of the middle prefrontal cortex which consists of brain areas which are activated when a reflective state is achieved and prior expectations, automatic thoughts and emotional reactions are reduced.

At this time, most of the large-scale funded research seeking to enhance female sexual desire have focused on pharmacological interventions, eg., bupropion or libanserin [238, 239] or hormonal treatments such as androgen supplementation delivered via gels, creams, patches, pills or injections [240-242]. Recently there have been randomized, double-blind, placebo-controlled studies investigating the long-term treatment of a testosterone patch on women’s sexual desire and arousal. Several of these studies have found small changes in the number of satisfying sexual events, improved sexual satisfaction, and diminished distress with androgen treatment [240, 243]. A review of this research is beyond the focus of this chapter and may be found later in this volume. Unfortunately, there are no studies comparing hormonal supplementation with other pharmaceutical compounds, sex therapy or couples’ therapy and none looking at the impact of combined treatment. Combination therapy with both medical and psychological interventions has the potential to address the multiply-determined biopsychosocial issues that contribute to the development and maintenance of HSDD. This is an area that warrants well-controlled research with different populations of women, both pre- and post-menopausal.

### I. SEXUAL AROUSAL DISORDERS

To date, there are only a few published outcome studies specifically focusing on the psychological treatment of female arousal disorders. This is partly attributable to the historical lack of attention paid to arousal disorders per se as well as to the described co-morbidity of female sexual disorders. Recently, there has been considerable interest in female sexual arousal disorder because of the success of vasoactive agents in the treatment of male erectile disorder [244-246].

Although not officially adopted at this time, a recent consensus conference composed of experts in women’s’ sexuality proposed a new nomenclature for diagnosing women’s sexual disorders generally, and arousal disorders in particular. Four sub-types of arousal disorders in women were identified: genital sexual arousal disorder, subjective sexual arousal disorder and combined genital and subjective arousal disorder. Additionally, a disorder involving excessive and persistent genital arousal was identified, persistent genital arousal disorder (PGAD), which is characterized by insistent feelings of genital vasocongestion and throbbing in the absence of conscious desire, genital arousal unrelieved with orgasm, genital arousal unrelated to sexual desire, genital arousal which is intrusive or unwanted, and genital arousal which is at least moderately distressing [247-249]. To date, most of the treatment of PGAD has consisted of single case reports involving either discontinuation of medications that appeared to be associated with the onset of symptoms, mindfulness and distraction based interventions, pelvic floor therapy, or surgery for anomalous blood flow conditions [250, 251].

While most of the treatment studies involving complaints about sexual arousal have focused on the use of hormonal supplementation, e.g. estrogen or androgen replacement for deficient lubrication or sensation, there are a few recent studies exploring the use of psychological treatments for increasing subjective sexual arousal. For example, the psychoeducational group treatment model used to treat women with sexual desire complaints (described above) was also found to be effective for the treatment of arousal difficulties in women with gynecological cancer [236, 252]. In this small group intervention, three sessions focusing on cognitive and behavioral therapy with education and mindfulness training was employed. Women completed questionnaires and had a physiological measurement of genital arousal both at the start
and end of the therapy. The investigators reported a positive effect on sexual desire, arousal, orgasm, satisfaction, sexual distress, depression and overall well-being and a trend towards significantly improved physiological arousal.

III. ORGASMIC DISORDERS

According to the DSM-IV, female orgasmic disorder is defined as the “…delay in, or absence of, orgasm following a normal excitement phase….” although what constitutes a normal excitement phase is uncertain [253]. Summarizing several studies, Haavio-Mannila and Kontula [254] reported that women experience orgasm only 40 – 80% of the time, regardless of the method of stimulation. The absence of orgasms during intercourse does not constitute a genuine sexual dysfunction [255, 256]. The overlap between desire, arousal, and orgasm difficulties in women further complicate differential diagnoses.

No single factor has been shown to be strongly related to orgasmic response and dysfunction in women [257]. In general, women with orgasm difficulties tend to experience more sex guilt [258, 259], tend to be less sexually assertive [260, 261], and endorse more negative attitudes towards sexual activity and masturbation [143, 145]. Women with orgasmic difficulties have been found to be less aware of physiological signs of arousal and orgasm [255, 262]. Heiman and Grafton-Becker [257] noted that anorgasmic women often fear loss of control during orgasm.

As with other sexual dysfunctions, female orgasmic disorder can be divided into lifelong and acquired subtypes. Different treatment approaches have been shown to be effective for the two subtypes. Directed masturbation training is most efficacious for lifelong and generalized orgasmic problems [204]. This treatment involves self-stimulation in which the woman becomes more aware of the type of stimulation needed to increase her arousal and pleasure and subsequently generalizing this to partner sexual situations. Heiman and Meston [204] noted that across all studies involving nearly 600 women seen for between 6-14 treatment sessions, directed masturbation alone was superior to systematic desensitization and directed masturbation with sensate focus was more effective than sensate focus alone [263-273]. Women with acquired and situational female orgasmic disorder tend to be more distressed about and less satisfied with their overall relationship [178, 274, 279]. Consequently, treatment often includes some combination of education, sexual skill training, couples’ therapy, masturbation and non-demand touching exercises, as well as interventions to address body image concerns and negative sexual attitudes.

Many investigations highlighted the importance of couples’ treatment along with sex therapy for the resolution of these problems. Women with acquired and situational female orgasmic disorder tend to be more distressed about and less satisfied with their overall relationship [178, 274, 279]. Consequently, treatment often includes some combination of education, sexual skill training, couples’ therapy, non-demand touching exercises as well as interventions to address body image concerns and negative sexual attitudes.

In the McCabe [233] study cited above, of the 36 women (67% of the initial sample of 54 women) presenting with anorgasmia who completed treatment, successful outcome was achieved with 89%. Heiman [223] notes that “treatments for primary anorgasmia appear to fulfill the criteria of “well-established” whereas situational anorgasmia studies fall into the “probably efficacious” group.

It should be noted that the relative failure of reported treatments of coital anorgasmia may be due to misdiagnosis. A major difficulty with past definitions of orgasmic disorder was that women who were
diagnosed with female orgasmic disorder may well have been more accurately diagnosed with a sexual arousal disorder, that is, a lack of sufficient physical or subjective arousal which obviously impeded orgasmic attainment. In fact, the more accurate diagnosis for many of the women in earlier research would be female sexual arousal disorder rather than orgasmic dysfunction [280].

IV. SEXUAL PAIN DISORDERS: DYSPAREUNIA AND VAGINISMUS

The sexual pain disorders tend to be quite prevalent, although they often go unreported since some women tolerate uncomfortable sexual exchange for months or even years without seeking assistance. Coital pain has been estimated to affect about 15% of American women according to the recent large-scale survey of sexual health [151].

The definition of dyspareunia recommended by the consensus conference on women's sexual disorders (2001) is "persistent or recurrent pain with attempted or complete vaginal entry and/or penile vaginal intercourse". Although included as a sexual dysfunction in the DSM-IV, Binik and his collaborators have long argued that dyspareunia should be classified as a pain disorder rather than a sexual dysfunction since pain is the most salient aspect of the syndrome [281].

Etiologically, a host of psychological factors have been associated with the complaint of dyspareunia but it is difficult to determine which is the cause and which is the effect of living with a chronic pain disorder [282]. Among the psychological concomitants that have been researched are: childhood sexual trauma, phobias, hostility, and in particular, reports of anxiety and depression. Even depression scores are associated with greater pain complaints. Relationship discord is frequently reported. There are also a large number of organic conditions that can either cause or maintain sexual pain: physical factors such as infection, hymenal scarring, STD's, pelvic inflammatory disease and most especially, neural and pelvic floor contraction are often instrumental in the genesis of the problem. Pelvic floor massage with an experienced massage therapist in addition to cognitive education, relaxation training, self-insertion exercises and sensuality training are included in treatment programs. The repeated experience of pain with sexual intercourse typically leads to increased genital muscle tension which further exacerbates existing pain by adding muscle pain to the original pain interfering with penetration and reducing genital blood flow[283]. Catastrophizing thoughts and hypervigilance as well as performance anxiety only make matters worse.

Treatment of dyspareunia ideally requires a multidisciplinary approach involving a physician, a pelvic massage therapist, and a psychotherapist. Treatment focuses on learning techniques for reducing or coping with the pain as well as dealing with catastrophic thoughts, anticipation of pain and avoidance of all sexual exchange. Biofeedback, vaginal and/or pelvic massage, tricyclic anti-depressants, Xylocaine before intercourse, sensuality exercises, avoidance of perfumed or irritating products, a low oxalate diet and relaxation techniques have all been tried, with varying degrees of success. Education about vulvodynia in general, and vulvar vestibulitis in particular, has been found helpful as well as cognitive restructuring and sex therapy with both partners.

The most well controlled study of women with vulvar vestibulitis was reported by Bergeron et. al. [284], who compared biofeedback, cognitive-behavioral therapy and vestibulectomy in a randomized series of 78 patients. While all three groups reported improvement in symptomatology post-treatment and at 6 month follow-up, vestibulectomy resulted in approximately twice the pain reduction as compared with the other two treatments. The authors concluded that vestibulectomy was superior to the two psychological interventions, although it did not significantly change the frequency of intercourse or other psychosocial variables. In a 2.5 year follow-up study of these women [285], 51 of the 78 women from the original study were reassessed. The investigators completed a gynecological exam, a structured interview and validated pain and sexual functioning measures. There were less pain complaints at the 2.5 year follow-up than at the 6 month follow-up and there were no differences on the sexual measures at 6 months or at 2.5 years follow-up. Of significance, higher pre-treatment pain intensity was associated with poorer treatment outcome at the 2.5 year follow-up for all interventions- vestibulectomy, biofeedback, and cognitive-behavioral therapy.

Vaginismus has been diagnosed as persistent or recurrent difficulties to allow vaginal entry of the penis, a finger, and/or any object, despite the woman's expressed wish to do so. There is variable (phobic) avoidance and anticipation/fear of pain [280] associated with this disorder. It is usually treated through a combination of relaxation exercises and in vivo graduated self-insertion of dilators of increasing size [286]. Typically, education about the female anatomy as well as Kegel and puboccygeal exercises are part of treatment along with more psychodynamic exploration of the genesis and meaning to the woman of vaginal penetration. While Masters and Johnson [41] reported a 100% success rate in their treatment of 29 women, more recent investigators have noted somewhat less positive outcome, although most studies concur in finding behavioral desensitization ultimately successful with motivated women [287].
<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>N</th>
<th>Treatment Method</th>
<th>Results</th>
<th>Evidence Grade</th>
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</thead>
<tbody>
<tr>
<td>Cooper, 1970</td>
<td>50</td>
<td>In vivo desensitization, sex therapy, psychotherapy. No control group</td>
<td>The results indicated a 50% improvement in sexual functioning post-therapy</td>
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<td>DeAmicus, 1985</td>
<td>22</td>
<td>Sensate focus, directed masturbation, sensual awareness, communication training, modification of sexual behaviors. No control group</td>
<td>There was a 64% - 76% improvement in sexual functioning at post-treatment, and this was maintained at follow-up</td>
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<td>Heiman, 1983</td>
<td>41</td>
<td>Cognitive behavioral therapy, communication training, directed masturbation, sensate focus, systems conceptualization. Wait-list control group</td>
<td>There was a 15% to 40% improvement in sexual functioning at 3 months follow-up</td>
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<td>Kilman, 1986</td>
<td>55</td>
<td>Group couples communication skills &amp; sex education vs. group couples sexual skills. These two groups compared to a control group</td>
<td>The results demonstrated 25% improvement in sexual functioning for both treatment groups at post-test. These results were maintained at 6 months follow-up</td>
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<tr>
<td>Kuriansky, 1982</td>
<td>19</td>
<td>Systematic desensitization, directed masturbation &amp; assertiveness training for the treatment condition. No control group</td>
<td>The results demonstrated an improvement of 95% in levels of sexual dysfunction a post-therapy, and 84% at two year follow-up</td>
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<td>Meston, 2007</td>
<td>1549</td>
<td>Evaluated the extent to which 237 reasons for having sex were rated by 1549 undergraduate students as having led them to have sexual intercourse</td>
<td>The main reasons for having sex were physical pleasure, to obtain resources, for lover, to boost self-esteem, a sense of duty and to guard one’s partner. Men were more likely to endorse physical reasons and women were more likely to endorse romantic reasons</td>
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<tr>
<td>Hawton, 1986</td>
<td>14</td>
<td>Treatment program was a modified Masters and Johnson therapy program. No control group</td>
<td>Sexual desire programs were resolved in 56% of the couples. However, 1-6 years follow-up, 75% of the sample had remitted</td>
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<tr>
<td>Hurlbert, 1993</td>
<td>39</td>
<td>Group intervention including orgasm training was compared to group intervention alone for women with HSD</td>
<td>Both groups of women made improvements in 2 of the 4 sexual behavior measures. The women who received orgasm training showed greater sensual arousal and sexual assertiveness at post-treatment and follow-up</td>
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<td>McCabe, 2001</td>
<td>200</td>
<td>Evaluated the effectiveness of individual CBT for the treatment of sexual dysfunction: 95 males, 105 females. No control group</td>
<td>After therapy, respondents experienced lower levels of sexual dysfunction, more positive attitudes to sex, and fewer aspects of their relationship affected by their sexual dysfunction</td>
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<td>Trudel, 2001</td>
<td>74</td>
<td>74 couples where one partner experienced HSD were randomly assigned to a 12-week CBT program (n = 38) or a wait list control group (n = 36)</td>
<td>The treatment group evidenced lower levels of HSD, as well as improved cognitive, behavioral, and marital functioning. These results were largely maintained at 3 months and 12 months follow-up</td>
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<tr>
<td>Author &amp; Year</td>
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<td>Brotto, 2008</td>
<td>26</td>
<td>A mindfulness based, 3 session group treatment for women with sexual desire or</td>
<td>The group treatment improved levels of sexual desire and sexual distress, as well as subjective sexual arousal (not objective arousal). Women with a history of sexual arousal made the best improvements.</td>
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<td>arousal disorders. No control group</td>
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<td>Brotto, 2008</td>
<td>22</td>
<td>A three session CBT combined with psychoeducation program was used to target</td>
<td>Treatment resulted in improvements in sexual desire, arousal, orgasm, satisfaction, sexual distress, depression and overall well-being.</td>
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<td>female sexual arousal disorder among women who had been treated for cervical</td>
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<td>cancer. No control group</td>
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<td>Segraves, 2001</td>
<td>51</td>
<td>51 women with HSD were treated with placebo (4 weeks) followed by bupropion</td>
<td>29% of women responded to treatment with bupropion SR, with increases in sexual arousal and improved sexual desire. There was no response to placebo.</td>
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<td>sustained release (SR) (8 weeks)</td>
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<td>Barbach, 1974</td>
<td>83</td>
<td>Group treatment for 83 preorgasmic women using masturbation training. No control</td>
<td>91.6% experienced orgasm using masturbation at post-treatment.</td>
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<td>group</td>
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<td>Deeks, 2001</td>
<td>304</td>
<td>Sexual function was assessed in 120 premenopausal, 76 perimenopausal and 108</td>
<td>Age was a better predictor of sexual satisfaction than menopausal status; sexual dysfunction was better predicted by menopausal status than age.</td>
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<td>postmenopausal women</td>
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<td>Bergeron, 2008</td>
<td>78</td>
<td>Women with dyspareunia due to vulvar vestibulitis were allocated to one of three treatment</td>
<td>All groups showed improvement in pain, psychological adjustment and sexual function; the vestibulectomy group showed greatest improvement.</td>
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<td>groups: group CBT, surface electromyographic biofeedback or vestibulectomy</td>
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<td>Ter Keule, 2007</td>
<td>117</td>
<td>Participants with lifelong vaginismus were allocated to either 3 months CBT</td>
<td>Treatment led to an increase in intercourse frequency, a decrease in fear of intercourse, and an improvement in non-intercourse penetration behavior.</td>
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<td>treatment (n = 81) or a control group (n = 36)</td>
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<td>Sarwer, 1997</td>
<td>730</td>
<td>Behavioral sex therapy for 365 married couples with a range of sexual dysfunctions. No control group</td>
<td>Success rate was 65%, with few drop-outs. Amount of sensate focus in last week of therapy was the strongest predictor of success.</td>
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<td>Smith, 2008</td>
<td>25</td>
<td>Evaluated the effectiveness of a group CBT and bibliotherapy program for women</td>
<td>The women demonstrated significant improvements in their FSFI scores at post-therapy, as well as improvements in most FSFI domain scores.</td>
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<td>with sexual dysfunction. No control group</td>
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<td>Leiblum, 1977</td>
<td>16</td>
<td>Group directed masturbation therapy program. No control group</td>
<td>The results demonstrated an 80% improvement in sexual functioning during masturbation.</td>
<td>3</td>
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<td>LoPiccolo, 1972</td>
<td>8</td>
<td>Directed masturbation treatment program. No control group</td>
<td>The findings demonstrated a 100% improvement in functioning during masturbation and a 75% improvement during coitus.</td>
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<td>McGovern, 1975</td>
<td>12</td>
<td>Treatment program that focused on sexual and communication skills, anxiety</td>
<td>The findings demonstrated a 100% improvement in sexual functioning for all women with primary inorgasmia, but not for those with secondary anorgasmia.</td>
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<td>reduction, and directed masturbation. No control group</td>
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</table>
A recent study reported considerable efficacy with the use of cognitive-behavioral therapy on women with life-long vaginismus [288]. In this Dutch study, women with primary vaginismus were allocated at random to a 3 month CBT (N=81) or a waiting list control condition (N=36). The primary outcome measure was full vaginal penetration by the partner. A reduction in scores on a fear of coitus and non-coital penetrative behavior instrument were also assessed. Treatment resulted in an increase in intercourse, a decrease in fear of coitus and an enhancement of successful non-coital penetration behavior compared to the no treatment condition. No particular treatment predictors were identified but the authors concluded that behavioral techniques such as gradual exposure, aimed at decreasing avoidance behavior and penetration fear, were effective interventions in resolving lifelong vaginismus. Chapter 25 in this volume provides a comprehensive overview of the etiology and treatment of sexual pain disorders.

V. PSYCHOLOGICAL TREATMENT WITH MIXED FEMALE SEXUAL DYSFUNCTIONS

In what was described as a “field trial” of the effectiveness of behavioral treatment for sexual dysfunctions, Sarwer and Durlak [289] reported the outcome with 365 married couples presenting to an outpatient sexual therapy clinic with a variety of sexual dysfunctions. Interventions included sexual education, communication skill training and body-touching exercises over a period of seven weeks. Treatment outcome was evaluated by the clinician as being either successful or unsuccessful-successful if the primary sexual complaint had abated by the end of treatment with no new problems developing and the couple had engaged in intercourse once in the last 3 weeks of therapy. Given the loose definition of success and the methodological shortcomings in both problem definition and outcome, it is still encouraging to find that the authors reported overall success for 65% of the couples with few dropouts. Moreover, outcome did not vary significantly as a function of diagnosis, gender or even history of sexual abuse. Surprisingly, the best predictor of successful outcome was the amount of sensate focus exercises completed in the last week of treatment rather than the nature of the dysfunction or the prior history of sexual abuse.

A more recent study investigated the impact of a psychoeducational group on women with varying sexual concerns [290]. In this study, 25 women between the ages of 25-70 completed a demographic and baseline FSFI questionnaire indicative of sexual dysfunction. Significant improvement was found in one or more FSFI domains and in the total FSFI score at the conclusion of the group intervention.

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>N</th>
<th>Treatment Method</th>
<th>Results</th>
<th>Evidence Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>McMullen, 1979</td>
<td>60</td>
<td>Directed masturbation and bibliotherapy compared to directed masturbation and videotape</td>
<td>There was a 66% improvement in the sexual functioning of the group that received bibliotherapy with masturbation compared to 50% improvement for masturbation and the videotape. Results were better for functioning during masturbation compared to coitus</td>
<td>2</td>
</tr>
<tr>
<td>Masters, 1970</td>
<td>342</td>
<td>Sensate focus, couples therapy, systematic desensitization, sex education and communication training</td>
<td>There was no control group for this study, but the success rate ranged from 77% - 83%. The follow-up success rate after 5 years was 82%</td>
<td>3</td>
</tr>
<tr>
<td>Obler, 1973</td>
<td>37</td>
<td>Systematic desensitization with videotape vs. psychoanalytic treatment with videotape vs wait list control group</td>
<td>The following improvements were made for each of the treatment groups at post-therapy: systematic desensitization: 85%, psychoanalytic treatment: 23%, and wait list control group: 23%</td>
<td>2</td>
</tr>
<tr>
<td>Schneidman, 1976</td>
<td>20</td>
<td>Masters and Johnson treatment approach. No control group</td>
<td>Sexual dysfunction was reduced by 55% during masturbation, but only 5% with coitus at post-therapy. The results for masturbation improved to 70% at 6 months follow-up</td>
<td>2</td>
</tr>
</tbody>
</table>
Based on clinical observation and experience as well as some empirical research, Hawton [219] and others [152] have identified a variety of factors that appear to be related to more positive outcome with psychological treatment interventions: the motivation for success of both partners, relationship satisfaction and compliance with homework assignments. Conversely, four variables have been identified with treatment dropout: 1) lower socio-economic status, 2) the male partner’s lower or lack of motivation for treatment, 3) a conflicted partner relationship and 4) poor progress by the third treatment session.

Overall, psychological interventions utilizing sensate focus exercises, directed masturbation and cognitive-behavioral interventions have been highly successful in treating primary orgasmic dysfunction and somewhat less effective in treating coital anorgasmia. Treatment outcome with desire and arousal disorders and sexual pain complaints is more variable since these problems can co-occur and a variety of contextual factors can interfere with outcome. However, several recent studies utilizing a small psychoeducational group treatment format consisting of mindfulness and cognitive behavioral interventions have been promising for women with sexual desire and arousal disorders. Treating the contextual and relationship issues that inevitably accompany these problems is crucial, however, for long-term improvement.

**J. PSYCHOLOGICAL TREATMENT OF MALE SEXUAL DYSFUNCTION**

This section will review the existing psychological research on male sexual dysfunction. While the majority of current research tends to focus on pharmacological interventions, this is no way obviates the critical importance of psychological and interpersonal interventions. In fact, the future will hopefully focus on combined and/or integrated treatments. These ideas will be discussed in the following sections.

**I. SEXUAL DESIRE DISORDER**

There are no reports solely on the psychological treatment of men presenting with HSDD [291]. Some men with HSDD are included in studies of men and women presenting with mixed sexual dysfunctions but the small numbers of these men does not lend itself to a careful outcome analysis. In medical practice, HSDD is often misinterpreted as ED, and treated as such. The lack of public education on sexual health issues, the myth that men are always motivated to be sexual, the insufficient sexological knowledge of health-care providers, and the lack of tools to comprehensively assess male HSDD, comprise causative factors of this misconception, which may partly explain the high proportion of failures of treatments for symptomatic ED.

It is likely that the etiology of HSDD is multifactorial. Hormonal, medication side effects, mood and interpersonal issues may all play a role in the development and maintenance of this problem. For the therapeutic management of HSDD, either pharmacological or psychological treatments have been tested, but factorial designs to investigate the differential contributions and interactions of both approaches have not been reported [291]. Moreover, there is a paucity of evidence-based interventions for psychogenic hypoactive sexual desire disorder in either sex [292].

**II. PSYCHOTHERAPY OF ERECTILE DYSFUNCTION**

The prevalence of ED ranges between 10% [293] and 52% [294] and has a significant impact on the man, couple and relationship. Different age distributions and concomitant medical conditions, as well as methodological differences, may explain much of the variance in reported prevalence rates. The biopsychosocial model is helpful in understanding the etiology of ED which can be due to multiple organic causes such as illness, medication and surgery (e.g., diabetes, hypertensive medication, and post-radical prostatectomy) in combination with psychological and relational issues (performance anxiety, depression, and relationship concerns). Etiological factors may change with time, disease processes can improve or worsen, damaged nerves may heal, medications can be started or discontinued and psychological and interpersonal issues can wax and wane leading to different etiological configurations of ED over time.

Psycho-sexological literature has made an important contribution in ED description, etiology and diagnosis, but it lacks large, randomized and controlled studies demonstrating the efficacy of the psychotherapeutic treatment (see Table 7) [295, 296]. As noted by The National Institutes of Health Consensus Conference on ED [297], “outcome data of psychological and behavioural therapy have not been quantified, and the evaluation of success of these treatments is poorly documented”.

Psychological treatment of ED consists of a variety of interventions including: psychodynamic interpretations regarding transference or anxiety, systemic desensitization, sensate focus, couples therapy, behavioral assignments, sex education, communication and sexual skills training, and masturbation exercises. However, it is not clear which
<table>
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<tr>
<th>Author</th>
<th>N</th>
<th>Methodology</th>
<th>Results</th>
<th>Evidence Level</th>
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<tr>
<td>DeAmicis, 1985&lt;sup&gt;273&lt;/sup&gt;</td>
<td>38</td>
<td>38 couples who had been treated with cognitive/behavioural therapy, sensate focus, sexual skills training, sensual awareness training for sexual dysfunction, 3 years previously was determined by a self-report assessment battery. No control group</td>
<td>Men with ED reported significant improvement in their ability to maintain erections during intercourse but not to achieve erections prior to intercourse (66% success rate post treatment; 52% 3 years follow-up)</td>
<td>2</td>
</tr>
<tr>
<td>Hawton, 1986&lt;sup&gt;221&lt;/sup&gt;</td>
<td>140</td>
<td>Prospective study of the long-term outcome of 140 couples who had entered sex therapy (Masters and Johnson co-therapy model). No control group</td>
<td>Positive long-term outcome for ED.</td>
<td>2</td>
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<tr>
<td>Hawton, 1995&lt;sup&gt;219&lt;/sup&gt;</td>
<td>0</td>
<td>A review of the literature concerning the application and outcome of sex therapy (Masters and Johnson co-therapy model) and other treatments for sexual dysfunction (Sex education &amp; psychotherapy)</td>
<td>Less is known about the effects of treatment of individuals without partners, bibliotherapy and combining sex therapy with marital therapy and with physical methods of treatment.</td>
<td>2</td>
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<tr>
<td>Heiman, 1983&lt;sup&gt;218&lt;/sup&gt;</td>
<td>19</td>
<td>15-session weekly treatment was compared with a 15-session daily treatment. (Cognitive Behavioural Therapy, sensate focus, communications training, systems conceptualization) No control group</td>
<td>The outcome of daily v weekly treatment was generally not different, with only some indication of better results for erectile failure when treated in the weekly mode. (65 – 70% success rate post-treatment; the same % after 3 months follow-up)</td>
<td>3</td>
</tr>
<tr>
<td>Kilman, 1987&lt;sup&gt;178&lt;/sup&gt;</td>
<td>16</td>
<td>Men with secondary ED and their partners were included in three treatment groups (Communication Technique Training, Sexual Technique Training, Combination Treatment). All couples participated in their respective formats in twice-weekly sessions for a total of 20 hours.</td>
<td>All three treatment groups obtained substantial gains so that between-format differences were not statistically significant. Subject variables which predicted success/experience ratio gains included age of the male partner, perceived level of relationship adjustment, and the male partner’s success/experience ratio prior to treatment. (81% success rate post-treatment, the same % after 6 months follow-up)</td>
<td>3</td>
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Table 7. Psychotherapy outcomes studies for the treatment of erectile dysfunction (Continued).

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<th>Author</th>
<th>N</th>
<th>Methodology</th>
<th>Results</th>
<th>Evidence Level</th>
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<tr>
<td>Levine, 1978&lt;sup&gt;295&lt;/sup&gt;</td>
<td>16</td>
<td>16 couples, the men had chronic secondary psychological impotence. They were evaluated, treated (Sensate focus and conjoint psychotherapy), and followed up by the same sex therapist. Pre- and post-therapy Sexual Interaction inventories were administered as measures of therapeutic effectiveness. No control group</td>
<td>By the end of treatment 6 men of the 16 were consistently potent and 4 were potent at least half of the time. Of the 11 men who had improved, 10 demonstrated considerable instability in erectile functioning over 1-year follow-up (38% success rate post-treatment, 6% over 1 year follow-up)</td>
<td>3</td>
</tr>
<tr>
<td>Masters, 1970&lt;sup&gt;24&lt;/sup&gt;</td>
<td>245</td>
<td>Quasi-residential, daily combination of individual &amp; conjoint treatment, sensate focus, sexual skills and communication training</td>
<td>No results available</td>
<td>2</td>
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<tr>
<td>Obler, 1973&lt;sup&gt;265&lt;/sup&gt;</td>
<td>27</td>
<td>Systematic desensitization and assertiveness training compared to psychoanalytic oriented group treatment</td>
<td>The results indicated that the desensitization technique was significantly more successful in eliminating sexual dysfunction and reducing associated sexual and social anxiety than the comparative group</td>
<td>3</td>
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<tr>
<td>Takefman, 1984&lt;sup&gt;296&lt;/sup&gt;</td>
<td>16</td>
<td>Sixteen couples were randomly assigned to one of two treatment conditions. The first group treated with sensate focus &amp; communication training. Couples in the second group were assigned only the communication training</td>
<td>Both treatment groups reported significant improvement in several measures of erectile functioning, general sexual functioning, and marital adjustment.</td>
<td>3</td>
</tr>
<tr>
<td>Wylie, 1997&lt;sup&gt;253&lt;/sup&gt;</td>
<td>23</td>
<td>Treatment outcome was studied in 37 couples who entered modified modern sex therapy and behavioural system couples therapy for male erectile disorder. No control group</td>
<td>Significant improvements in target symptoms, questionnaire scores, including the GRISS, and frequency of attempts at sexual activity were recorded. (87% success rate post-treatment, the same % after 6 months follow-up)</td>
<td>2</td>
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<tr>
<td>Althof, 2004&lt;sup&gt;299&lt;/sup&gt;</td>
<td>0</td>
<td>The authors outline the goals of psychotherapy for ED and discuss the factors that make psychotherapy effective.</td>
<td>Successful sexuality outcomes require attending to the complex interplay among biologic, psychologic and relational components of individual’s and couple lives.</td>
<td>4</td>
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of these interventions in combination or alone has the greatest efficacy. Clinical experience highlights that these interventions help the patient and/or couple to improve their relationship and sexual life. Men with acquired ED demonstrated more gains than men with life-long ED [186].

Hedon [298] offers three recommendations regarding anxiety and the treatment of ED: 1) to fully explain ED to patients to reduce worry related to lack of knowledge; 2) to reassure the patients that their problems are not unique and that they can be overcome; and 3) to propose positive action to assist the patient and his partner in resolving the ED.

The paper by Althof and Wieder [299] describes the four goals of psychotherapy for ED: 1) seeking to reduce or eliminate performance anxiety; 2) understanding the context in which men/couples make love; 3) implementing psycho-education and modification of sexual scripts; and 4) to identify and reduce the resistances to premature discontinuation of pharmacotherapy.

Sex therapists play an important role in assessing and treating the emotional, cognitive and interpersonal components that are associated with erection difficulties, whether these be causes of the condition, consequences of the condition, or both [300]. In a recent study [301] alexithymia levels were found to be correlated with the severity of erectile dysfunction, as measured by the International Index of Erectile Function (IIEF). These data confirm the importance of the emotive dimension in human sexuality, in particular of the individual capacity to feel and communicate emotions. The limited imaginative activity of alexithymic subjects can also be reflected in a lack of sexual fantasies, considered central to human sexuality.

Masters and Johnson [74] reported initial failure rates of 41% and 26% for lifelong (primary) and acquired (secondary) ED, respectively. Their two to five year follow-up of this cohort indicated sustained gains. In a review of studies of the treatment for ED, Mohr and Beutler [302] wrote that the component parts of these treatments typically included behavioral, cognitive, systemic and interpersonal communication interventions. Averaging across studies, it appears that approximately two-thirds of the men suffering from erectile failure will be satisfied with their improvement at follow-up ranging from months to six years. These studies utilized either a couples or a group format. The duration of couple’s therapy ranged from 4 to 20 weekly meetings. Group therapies met weekly for 10 to 20 sessions. All forms of intervention except biofeedback, pelvic muscle floor exercises and hypnosis were equally effective in producing sustained change.

Wylie [303] reported on a prospective study of 23 couples where the man presented with ED. Utilizing a combination of modified sex therapy and behavioral system couple therapy, 87% of men demonstrated improvement in their sexual symptom within six sessions of treatment. Moreover, the improvements were found in men’s sexual confidence and frequency of sexual activity and pleasure derived from sexual activity. The gains were sustained at the six-month follow-up. Wylie [304] has also provided a non-systematic review considering different published studies regarding various types of sex therapies. These data can be characterized as uncontrolled, unblinded trials. The conclusions from this review are consistent with the findings outlined above.

There are few controlled reports on individual therapy for single men, except for that of Reynolds [305] who highlighted the difficulties of treating men without partners. All studies with long-term follow-up have found a tendency for men to relapse. Hawton [231] noted that recurrence of or continuing difficulty with the presenting sexual problem was commonly reported by 75% of couples; this caused little to no concern for 34%. Patients indicated that they discussed the difficulty with the partner, practiced the techniques learned during therapy, accepted that difficulties were likely to recur, and read books about sexuality.

Melnick et al [221] conducted a meta-analysis of the effectiveness of psychological interventions for ED compared to oral drugs, intracavernosal injections and vacuum pumps. Only 11 randomized or quasi-randomized trials involving treatment of 398 men could be found in the literature. These 11 trials employed multiple psychological techniques. The authors concluded that group therapy significantly improved erectile function and demonstrated greater efficacy than men in a control group. Men randomized to receive psychotherapy plus sildenail showed significant improvement of ED and were less likely than those receiving only sildenail to discontinue treatment. No differences were found between psychological intervention and men receiving either injection or vacuum pump therapy.

More recent research has shown that ED has a significant negative impact on both the man and his partner. Loss of penile rigidity can have a profoundly adverse effect on a man’s psychological well-being and may be associated with behavioural changes such as the avoidance of intimacy that can impair their general relationship [306]. Couples who have been sexually abstinent for several years often adapt to life without sex. The Index of Sexual Life (ISL) developed by Chevret et al. [52] indicated that the partners of men with ED reported a significantly decreased sexual drive and sexual satisfaction, compared with partners of men without ED. Fisher et al. [54] in the Female Experience of Men’s Attitudes to Life Events and Sexuality (FEMALES) study reported a decline in sexual desire, arousal,
orgasm frequency and satisfaction among female partners of men with ED, compared with their sexual functioning before their partner developed ED. Studies have shown that the participation of the partner supports the adherence to therapy, and her involvement facilitates successful long term ED therapy. These studies suggest that women should be included in ED treatment if possible [307, 308]. Moreover, the presence of the couple ensures not only the restoration of erectile function but improves the sexual quality of life of both partners [308].

1. RELAPSE PREVENTION

The concept of relapse prevention has generally not been incorporated into sex therapy. In the past, the patient and therapist reached a mutual decision about when to terminate, worked toward that goal and ended treatment on a set date. Patients could, of course, re-contact their therapist for additional treatment if problems returned.

To prevent relapse, McCarthy [309] has suggested that therapists schedule periodic “booster or maintenance” sessions following termination. Follow-up sessions have been recommended in order to resolve “glitches” that have interfered with progress.

III. PSYCHOTHERAPY WITH PREMATURE EJACULATION

The Global Study of Sexual Attitudes and Behaviors suggest a global prevalence of PE of approximately 30% across all age groups [293] and which, according to some authors, has a greater impact on QoL and sexual enjoyment than ED [100, 185, 310].

Researchers have described the different forms, pathogenesis and diagnosis of PE as well as its treatment, especially pharmaceutical. A recent report by the International Society for Sexual Medicine (ISSM) established a contemporary, evidence-based definition of lifelong PE [311]. The Committee proposed that lifelong PE should be defined as a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy.” The panel of ISSM researchers concluded that there are still insufficient published objective data to propose an evidence-based definition of acquired PE [311]. This definition identifies the areas to assess, namely, short intravaginal ejaculation latency time (IELT), lack of control and distress for both partners [312, 313]. McMahon et al. [311] suggested that acquired PE might point to a psychogenic etiology, while lifelong PE might have an organic etiology, although further evidence remains to be gathered to support this assumption.

Althof [314] has reviewed the different psychotherapies for PE, from the pioneering “stop-start” techniques of Semans [315] to the “squeeze technique” of Masters and Johnson. After such initial approaches, successive sex therapies have focused mainly on subjective aspects of the life of both the patient and his partner, as well as on their relationship.

Present day psychotherapy for rapid ejaculation is an integration of psychodynamic, systems, behavioural, and cognitive approaches within a short-term psychotherapy model. The guiding principles of treatment are to learn to control ejaculation while understanding the meaning of the symptom and the context in which it occurs [316, 317].

Thus, besides teaching self-control techniques to delay ejaculation, modern psycho-sexual therapies try to achieve the following aims: 1) to help the patient recover his self-confidence and confidence in his sexual performance; 2) to reduce performance anxiety; 3) to increase communication between the partners; and 4) to resolve interpersonal issues that precipitate and maintain the dysfunction. In addition, psychotherapists seek to modify rigid sexual repertoires, and help the couple remove barriers to intimacy.

The majority of psychotherapy treatment outcome studies can be characterized as uncontrolled, unblinded trials; none meet the requirements for high level evidence-based studies. The literature is comprised of reports on small to moderately sized cohorts of subjects who received different forms of psychological interventions with limited or no follow-up. In most studies, active treatment was not compared to placebo, control or wait list groups [316].

The biopsychosocial perspective has introduced a non-linear epistemological model. It is necessary to view the individual as a multidimensional (biological, psychological and social) unique being and definitely overcome the mechanical-medical and linear approach which, referring to an eighteenth-century metaphor, sees the body as a machine.

Since the early 1970s, an array of individual, conjoint, and group therapy approaches employing behavioural strategies such as stop-start [315] have been used to treat rapid ejaculation [75, 309, 318-320]. Table 8 summarizes the initial and long-term efficacy of psychological interventions for rapid ejaculation.

Masters and Johnson reported on 432 men who were seen in their quasi-residential model utilizing multiple treatment techniques including the squeeze technique in combination with sensate focus and interpersonal therapy. Failure rates of 2.2% immediately after treatment and 2.7% at the five year
follow-up were documented [74]. Other researchers have been unable to replicate Masters and Johnson’s success rates. For instance, only 64% of men in Hawton’s study were characterized as successful in overcoming their premature ejaculation [3].

Cognitive behavioral therapy [321] as well as multimodal psychodynamic and behavioural treatments [13, 322] are described in review papers; however, there are no documented carefully controlled outcome studies that examine the efficacy of these methods. Minimal therapist contact, defined as between 4 to 15 brief weekly telephone contacts, with bibliotherapy has also been found to lead to successful outcomes [323]. This finding may not hold for more complex situations that involve relationship and communication difficulties (see Table 8).

Psychosexual-behavioral therapy for PE can also be delivered in group format or through bibliotherapy [324]. Although initial rates of success of psychosexual-behavioral therapy have been very high, more recent rates are more modest and range between 60% and 90% [325]. Further, these rates are not sustainable and may fall to 25% three years after therapy [325]. Such observations are not surprising since many of the studies have pooled patients with different PE categories (lifelong and acquired), age groups, levels of general and sexual anxiety, sexual experiences and somatic vulnerabilities (such as tactile and/or CNS hypersensitivities) [325].

In a recent study by De Carufel and Trudel [326] the aim was to compare the efficacy of a new functional-sexological treatment for PE with a behavioral treatment (squeeze and stop-start techniques). They also compared the two treatments against a wait list condition. The results showed that there was a significant change between pre-treatment and post-treatment and between pre treatment and follow-up in the two treatment groups. For the wait list control group, changes were not significant (see Table 8). Additionally, hypnosis has been utilized in the treatment of PE. This treatment approach focuses not only on the symptom, but has a more holistic focus [327].

When utilizing pharmacotherapy for PE, clinicians may also utilize brief, targeted psycho-educational interventions, called coaching [185, 187, 328, 329]. Coaching can help clinicians treat that component of PE not addressed by pharmacotherapy by targeting obstacles to affective sexual activity including: restrictive sexual patterns, avoidance of sexual activity and an unwillingness to discuss sex with a partner. The goals of coaching are to identify and resolve the patient’s resistance to medical therapy, reduce or eliminate his performance anxiety, help him gain or regain sexual confidence and modify his maladaptive sexual “scripts”. Coaching can be conducted by a non-mental health professional but it requires time, interest, some training in sex therapy and sensitivity; in addition, they should compile a list of appropriate therapist referrals.

Psycho-dynamically oriented therapists view the dysfunction as a metaphor in which the man/couple is trying to simultaneously conceal and express conflicting aspects of themselves or the relationship. In symbolic terms, the dysfunction contains a compromised solution to one’s life dilemmas. Alternatively, behavior therapists understand the dysfunction as a conditioned response or a maladaptive response to interpersonal or environmental occurrences [316].

Donahuey and Miller [1] reported that regardless of the therapeutic modality (individual, couple or group therapy), or the specific therapeutic goals, there are several common factors that make psychotherapy effective: 1) empowering the patients to experience themselves as having the ability to create change and impact contextual factors; 2) the patient/therapist relationship is critical to successful therapeutic outcome. The therapist must be able to assess and accommodate to the patient’s readiness for change and provide a safe and empathic environment where the patient can explore obstacles, choices and meanings of his psychological and behavioural dilemmas; 3) the role of hopefulness and realistic expectancy should be provided in psychotherapy [316].

Therapy should be tailored for each patient, as one treatment does not fit all. Each treatment option should be discussed with the PE patient including the success rate and possible adverse effects such that the patient participates in the decision-making. This will improve compliance and success of therapy [312].

Taylor and Simonelli [330, 331] report on alexithymic patients who had “coexisting” PE. Generally it was the partner who asked them to seek professional help. This situation may result in a lack of the man’s intrinsic motivation which leads to his adopting a passive role in the therapeutic process, limiting the effectiveness of treatment. The man’s passivity in the clinical relationship and the therapist’s emotional reactions (feelings of impotence, discouragement, anger) evoked by the alexithymic relationship style may reproduce what happens in the dynamics of the couple and in this sense it may be a valuable starting point for the psychotherapist [330, 331].

**IV. DELAYED EJACULATION**

Delayed Ejaculation (DE), alternately known as retarded or inhibited ejaculation has a relatively low prevalence rate rarely exceeding 3% [151, 332, 333]. Recently however, there has been greater interest in
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<th>Author, Year</th>
<th>N</th>
<th>Methodology</th>
<th>Results</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>De Amicis, 1985</td>
<td>20</td>
<td>20 couples who had been treated with cognitive/behavioural therapy, sensate focus, sexual skills training, sensual awareness training for sexual dysfunction, 3 years previously was determined by a self-report assessment battery. No control group</td>
<td>Data from men with PE revealed some immediate significant post-therapy gains which were not sustained at 3-year follow-up</td>
<td>2</td>
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<tr>
<td>Hawton, 1986</td>
<td>14</td>
<td>Prospective study of the long-term outcome of 14 couples who had entered sex therapy (Masters and Johnson co-therapy model). No control group</td>
<td>Long term outcome was often poor for PE</td>
<td>2</td>
</tr>
<tr>
<td>Hawton, 1995</td>
<td>0</td>
<td>A review of the literature concerning the application and outcome of sex therapy (Masters and Johnson co-therapy model) and other treatments for sexual dysfunction (Sex education &amp; psychotherapy)</td>
<td>Less is known about the effects of treatment of individuals without partners, bibliotherapy and combining sex therapy with marital therapy and with physical methods of treatment.</td>
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<tr>
<td>Heiman, 1983</td>
<td>21</td>
<td>15-session weekly treatment was compared with a 15-session daily treatment. (Cognitive Behavioural Therapy, sensate focus, communication training, systems conceptualization) No control group</td>
<td>Treatment was successful in producing statistically and clinically significant changes in the target 15-session weekly treatment was compared with a 15-session daily treatment. (Cognitive Behavioural Therapy, sensate focus, communication training, systems conceptualization) No control group latency to ejaculation.</td>
<td>2</td>
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<tr>
<td>Lobtiz, 1982</td>
<td>6</td>
<td>Behavioural approach. Premature ejaculation is treated through a retraining program, as modified by the use of the &quot;squeeze&quot; technique. The sex research program has developed clinical innovations to facilitate changes in sexual behavior. No control group</td>
<td>The Sex Research Program has experienced generally good results in the treatment of PE. The success rate is six out of six</td>
<td>4</td>
</tr>
<tr>
<td>Masters, 1970</td>
<td>186</td>
<td>Quasi-residential daily combination of individual &amp; conjoint treatment, sensate focus, squeeze technique, sexual skills &amp; communication training</td>
<td>Failure not of 2.2% after treatment and 2.7% at the 5 year follow-up</td>
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this dysfunction with suggestions that the prevalence may be higher than initially reported [151, 332]. The dysfunction appears moderately and positively related to age. The etiology and pathophysiology are incompletely understood and there are no evidence based treatments reported for this dysfunction [334, 335].

In terms of the psychological underpinnings of DE, there are three very different perspectives. The first posits that delayed ejaculation is due to the man’s not receiving sufficient physical stimulation. An alternative perspective is that the man is insufficiently mentally aroused even though he has an adequate erection. Finally, the third perspective focus on the stimulation the man has become accustomed to receiving through his idiosyncratic masturbatory practices and that these sensations are not reproducible when engaged in partner sexual behaviour.

The available literature concerning the psychological treatment of DE is almost entirely anecdotal with small numbers of patients in each report[336]. Men suffering from delayed ejaculation may benefit from different psychological approaches including: sex education, reduction of goal oriented anxiety, increased and more genital focused stimulation and sex therapy. Richardson reviews the following treatment techniques for DE [337]: viewing erotic films, sex play, erotic fantasies, sexually stimulating literature or magazines, and masturbatory exercises [338, 339]; meditative relaxation therapy or hypnosis combined with psychotherapy [338].

In a meta-analysis, Munjack and Kanno report the success rate for sex therapy of DE ranges between 42% and 82% [340]. A distinguishing characteristic of men with DE and one that has implications for treatment is that they usually have little or no difficulty attaining or keeping their erections: in fact they are often able to maintain erections for prolonged periods of time. Yet, despite their good erections, they report low levels of subjective sexual arousal and pleasure, at least compared with sexually functional men [341]. Similar to men with other types of sexual dysfunction, men with DE demonstrate high levels of relationship.
distress, sexual dissatisfaction, anxiety about their sexual performance, and general health issues significantly higher than sexually functional men. Along with other sexually dysfunctional counterparts, men with DE typically report lower frequencies of coital activity [342].

Bancroft perceives men with DE as having inadequate physical stimulation and recommends the use of, 'vigorous stimulation using a lubricating jelly or cream to overcome the block' [343]. Men are first stimulated to ejaculate extra-vaginally with gradual introduction of intercourse and vaginal ejaculation.

Perelman focuses on the men’s idiosyncratic masturbatory practices and seeks to instruct these men in more conventional masturbation that more closely mimics sensations derived from intercourse [329, 332, 342, 344]. As characterized by Perelman, masturbation serves as a “dress rehearsal” for sex with a partner. By informing the patient that his difficulty is merely a reflection of “not rehearsing the part he intended to play,” the stigma associated with this problem can be minimized and cooperation of both the patient and partner can be evoked. The goal of most current therapeutic techniques for DE (either primary or secondary) is not merely to provide more intense stimulation, but rather to stimulate higher levels of psychosexual arousal and, eventually, orgasm within the framework of a satisfying experience.

Hawton discusses that during masturbatory exercises with the partner, the man must be trained to concentrate on genital stimulation [339]. He also recommends the male-superior position as he postulates that this often facilitates ejaculation. Hawton, Bancroft and Winzce recommend the use of vibrator to increase sexual arousal [256, 339, 343].

Self-stimulation techniques incorporating fantasy can be used to achieve incremental increases in arousal. Fantasy can help block inhibiting thoughts, often a significant step that might otherwise result in interference with the progression of sexual arousal. Additionally, an important component in the treatment of any type of DE is the removal of “demand” or “performance” anxiety [256].

Jannini perceives the delay in ejaculation as mirroring the men’s over controlled personality organization [345]. That is in life these men show little emotion and seem over controlled. They also discuss the role of men’s fear of impregnating his partner or contracting sexually transmitted diseases as interfering with arousal and ejaculation. If the clinician suspects the patient’s DE is related to fear of conception, he may inquire about the patient’s ability to experience a coital ejaculation with contraception (including condoms) but not during “unprotected” sex. Such a “test” can serve as a powerful diagnostic indicator: Resolving this issue typically requires individual consultations with the man and occasionally with the partner [334].

Whether related to fertility or not, the man’s anger (expressed/unexpressed) toward his partner may be an important intermediate causational factor and must be ameliorated through individual and/or conjoint consultation. Anger acts as a powerful anti-aphrodisiac, and while some men avoid sexual contact entirely when angry at a partner, others attempt to perform, only to find themselves only modestly aroused and unable to maintain an erection/and or reach orgasm [334].

As treatment progresses, interventions may be experienced as mechanistic and insensitive to the partner’s needs and goals. In particular, many women respond negatively to the impression that the man is essentially masturbating himself with her various body parts, as opposed to engaging in the type of connected lovemaking she may prefer [334]. Therefore, the formation of a strong therapeutic alliance where the aims are clearly discussed and shared within the couple is fundamental to avoid poorer treatment prognosis.

The biopsychosocial model is helpful in understanding the etiology of male and female sexual dysfunctions and provides a useful paradigm for developing comprehensive treatment interventions. There is a dearth of knowledge concerning male HSDD and delayed ejaculation and there is an enormous need for controlled trials in these areas. The psychological literature has made important contributions in ED description, etiology and diagnosis and development of validated clinical outcome measures. The uncontrolled trials regarding psychotherapy for ED demonstrate modest to good success; however, large, randomized controlled studies demonstrating the efficacy of the psychotherapeutic treatment need to be undertaken. Similarly, several uncontrolled trials support psychological intervention as helpful for PE yet there remains a need for large, controlled trials using validated outcome measures.

### K. INTEGRATING MEDICAL AND PSYCHOLOGICAL TREATMENTS FOR SEXUAL DYSPNFUNCTION

Combination or integrated therapy is an exciting concept that has the potential to significantly advance the manner in which men, women and couples receive treatment for sexual dysfunctions [328, 346-349]. Combining medical and psychological interventions harnesses the power of both treatments to enhance efficacy, increase treatment and relational satisfaction, and decrease patient discontinuation. Previously, combination therapy, alternatively called coaching or integrated therapy has been successfully employed in the treatment of
depression, childhood anxiety, schizophrenia, and posttraumatic stress disorder [350-352]. It is also an important aspect of treatment for diabetes and breast cancer because psychosocial support is a crucial component of care giving.

Combination or integrated treatment is the logical extension of the biopsychosocial model. It addresses the relevant biological/medical as well as psychosocial issues that predispose, precipitate and maintain sexual dysfunction. Too often, medical treatments for sexual dysfunction, those approved and those off-label, are narrowly or mechanistically directed at sexual function alone and fail to address the salient psychosocial issues (see Table 9). Likewise, psychological intervention alone may be time consuming, costly and fail to yield rapid symptom amelioration. For example, PDE5is for ED are generally efficacious in 70% of men with ED; yet, 60%-70% of individuals fail to continue treatment. In response to this surprisingly high discontinuation rate, clinicians developed medical and educational strategies to “optimize” PDE5i treatment which focused on patient education, dose optimization, need for sexual stimulation, and follow-up [353-355]. However, none of these “treatment optimization” proposals addressed any of the crucial psychosocial issues such as: restarting a sexual life after an extended period of abstinence, partner resistance, partner concerns or dysfunction, lack of confidence and performance anxiety, depression, relationship issues, men with unconventional sexual scripts and unrealistic expectations. These factors are likely to be present in men, even if the ED was initially due to organic causes because of the number of years that men generally take to seek treatment for their ED. Combination therapy would include all the medical optimization recommendations while simultaneously addressing the psychosocial barriers that hinder treatment efficacy, satisfaction and compliance. These psychosocial interventions are also well placed to address partner issues that may impede that treatment process.

Combined or integrated treatment paradigms challenge traditional sex therapy practices. They provide a venue where the psychosocial factors that precipitate or maintain sexual dysfunction can be identified, acknowledged and addressed while the patient simultaneously makes use of and has success with a variety of efficacious medical treatments for sexual dysfunction.

An emerging body of evidence strongly supports the value of combination treatment. There are however, several important questions that require further clarification as regards combination therapy: 1. What is the best theoretical model for combination therapy? 2. Who delivers the care (nurse, social worker, psychologist, or, physician)? 3. Where is the intervention performed (medical clinic vs. mental health office)? And, 4. Are the medical and psychological treatments concomitant or stepwise [328]?

From experience, we know the traditional referral of patients from a primary care, urological, or gynecological specialist to a sex therapist is fraught with difficulties. For a variety of reasons (stigma, cost, insurance issues, lack of motivation, etc.) patients rarely follow through. The rule of thumb is that only 10% of referrals present for a first visit with a sexual counselor. Additionally, sex therapists are a rare commodity. Many patients are not willing to pay for these services and/or cannot commit to treatment over a period of several months.

One solution to the problem of resource availability, time, and money would be to offer the initial services at the site of the primary care or specialty physician. Onsite intervention would allow more individuals to have access to sexual health education and intervention. In a “one-stop shopping” model, patients could see the physician and the person designated to do the psychosocial intervention (this may or may not be one and the same person). This eases the time and financial burden on the patient and might serve as an additional income stream for the practitioner. To take a lesson from the behavioral medicine interventions, this would require sexual experts to train physicians and other health care workers in assessment, education, and rudimentary psychological intervention. The conceptual model would guide these caregivers to recognize when more intensive psychological treatment is required and to appropriately refer. Or, in the future we may witness the establishment of comprehensive sexual health centers that include specialists (urologist, gynecologist, cardiologist, internist/family practice specialist, endocrinologist, mental health clinicians) from multiple disciplines working together as teams under one roof offering a more integrated level of care.

I. REVIEW OF COMBINED THERAPY TREATMENT EFFORTS

This section will review studies describing combined medical and psychological treatments for men with ED. While there are articles on combination therapy for PE they are not evidenced based. Additionally, medical treatments for FSD have lagged behind those for men and thus there is scant literature on combination therapy for women with low desire, arousal or orgasmic dysfunction. Given the multiply determined nature of FSD it is likely combination medical and psychological therapy will ultimately be of significant benefit to women as well. There are descriptions of combination therapy of female pain disorders; however, this will be discussed in Chapter 25.
<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Summary of study findings</th>
<th>Level of Evidence</th>
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<tr>
<td>Abdo, 2008</td>
<td>120</td>
<td>120 men with psychogenic ED were randomly assigned to 3 groups- 1. group counseling plus sildenafil; 2. sildenafil only; 3. group counseling only. After 3 months, compared to baseline, all 3 groups had improved SHIM scores. The combined therapy group had the highest post-therapy scores on the SHIM and the MSQ.</td>
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<td>Althof, 2007</td>
<td>0</td>
<td>Review of combination medical and psychological interventions for sexual dysfunctions. Also offers suggestions for care delivery and a proposal for levels of psychological intervention.</td>
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<tr>
<td>Aubin, 2009</td>
<td>44</td>
<td>44 couples were randomly assigned to receive sildenafil alone or sildenafil plus 8 sessions of couples’ therapy. The couples plus sildenafil group had a greater number of improved and maintained sexual function and cognition domains for both partners from pre- to post-treatment than the sildenafil only group.</td>
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<tr>
<td>Bach, 2004</td>
<td>6</td>
<td>In couples where sildenafil was successful in creating erection but the couple was not satisfied with their sexual lives the author examined the effect of supplementing treatment with a various psychoeducational strategies. Five of six men evidenced increases in sexual satisfaction and the frequency of intercourse after adding the manualized treatment with minimal therapist contact to the use of sildenafil. They maintained these gains at an average of 6 months post-treatment.</td>
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<td>Banner, 2007</td>
<td>57</td>
<td>53 men with psychogenic ED and their partners were randomized into 2 groups: 1. cognitive behavioral sex therapy (CBST) plus sildenafil and 2. sildenafil only. After 4 weeks, CBST was added to the sildenafil only group. Authors established IIIEF erectile function and sexual satisfaction domain scale criteria. At 4 weeks, 48% and 66% of combined therapy (CBST) group vs. 29% and 38% of sildenafil only group met success criterion. At 8 weeks, 66% and 75% of original CBST group and 58% and 45% of the new combined group met success criterion.</td>
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<tr>
<td>Chen, 2002</td>
<td>41</td>
<td>Forty-one men treated with a combination of Viagra and a vacuum device reported higher satisfaction than with each treatment alone on the IIEF questions and/or domains.</td>
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<td>Colson, 1996</td>
<td>1001</td>
<td>A three-phase treatment protocol learning to use self-injection therapy alongside cognitive restructuring and sensate focus led to full recovery with satisfactory sexual intercourse with complete discontinuation of injection therapy in 50.7% of patients compared to 24.5% of cases where injection therapy was given alone. Injection therapies that facilitate erections such as moxisylyate were better suited for combination with CBT than prostaglandin or Papaverine.</td>
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<td>Hawton, 1995</td>
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<td>There is a need for integrated approaches to male sexual dysfunction whereby patients can be assessed in clinics staffed by urologists, psychologists or psychiatrists, and others specialized in sexual medicine.</td>
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<tr>
<td>Hartmann, 1993</td>
<td>68</td>
<td>A combination of psychosexual and self-injection therapies can be a promising therapeutic option. Negative predictors included partner problems, premature ejaculation, reduction of sexual desire and smoking; positive predictors are predominantly organogenic impotence, employment of auto-injection therapy, adequate sexual stimulation by partner.</td>
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<td>Kaplan, 1990</td>
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<td>The use of sex therapy techniques which were originally developed to overcome resistances to the behavioral modification of sexual symptoms, is effective in helping some of the patients overcome their resistances to pharmacotherapy.</td>
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<td>Kingsberg, 1998</td>
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<td>Sex therapy may be required to treat a sexual dysfunction or to manage a chronic physical problem that requires a change in the person or couple’s typical sexual repertoire.</td>
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<td>Leiblum, 2002</td>
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<td>Whilst medication (sildenafil) is extremely effective in restoring erectile function, it is often necessary to ensure the partner is actively involved in treatment since many men are in relationships characterized by sexual apathy, avoidance and/or relationship conflict.</td>
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<tr>
<td>Author</td>
<td>N</td>
<td>Summary of study findings</td>
<td>Level of Evidence</td>
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<td>Lottman, 1998†</td>
<td>195</td>
<td>Four groups – ICI, patients dropping out after ICI in the trial dose phase, patients on other treatment, patients following first counseling renounced treatment. Fifteen patients had the effect of ICI treatment in combination with short-term psychological counseling. No significant difference is found in marital satisfaction between the four groups. In the ICI plus treatment group providing information about factors that contribute to erectile function and enabling couples to communicate about sexual problems were the most important factors to increase efficacy of ICI treatment.</td>
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<td>McCarthy, 1998†</td>
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<td>Case studies illustrating the successful integration of sildenafil into a comprehensive treatment plan</td>
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<tr>
<td>Melnick, 2005†</td>
<td>30</td>
<td>Randomly assigned men to 3 groups- 1. group counseling plus sildenafil; 2. sildenafil only; 3. group counseling only. After 6 months, compared to baseline, all 3 groups had improved IIEF scores. Utilizing the criterion of normalization of IIEF scores only the combined and psychotherapy only groups showed statistically significant improvement.</td>
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<td>Perelman, 2005†</td>
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<td>Review of combined medical and psychological interventions for sexual problems.</td>
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<tr>
<td>Perelman, 2006†</td>
<td>0</td>
<td>Theoretical paper proposing that combined medical and psychological treatment for premature ejaculation is frequently the best approach.</td>
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<td>Phelps, 2007†</td>
<td>83</td>
<td>Men randomly assigned to 2 groups. The first received one 90 minute psychoeducational intervention and sildenafil, and the second received only sildenafil. After 24 weeks both groups demonstrated significant improvement on the IIEF. However, the EDITS treatment satisfaction total score for the combined group was significantly higher than the sildenafil only group.</td>
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<td>Rosenstock, 1999†</td>
<td>15</td>
<td>Brief sex therapy described as facilitative in men with functional erectile capacity and who were given sildenafil and brief sex therapy sessions.</td>
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<td>Segarves, 1999†</td>
<td>2</td>
<td>The first case report of sildenafil being used to successfully reverse anti-psychotic induced sexual dysfunction. The second case is the first report of sildenafil in combination with behavioral therapy for erectile dysfunction.</td>
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<tr>
<td>Segenreich, 1994†</td>
<td>125</td>
<td>Psychotherapy and VCD’s in men with differing etiologies for ED led to improvements in objective parameters of sexual functioning including NPT, penile brachial index and maximal penile rigidity regardless of whether or not they were seen with their wife. Improvement in subjective parameters such as spontaneous erections and adequate coitus without the vacuum device was seen where the wife attended.</td>
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<td>Tita M, et al, 2006</td>
<td>57</td>
<td>57 post prostatectomy and cystectomy men randomized into 2 groups- 1. ICI plus sexual counseling and, 2. ICI only. Over the course of the 18 months, men also received a trial of sildenafil. At the 3- and 18-month follow-up, compared to the ICI only group, the combined group achieved significantly higher erectile function, desire, orgasm, and satisfaction scores. Additionally, the combined group manifested a lower discontinuation rate and was able to achieve good quality erections with lower doses of medication. More men in the combined group responded to sildenafil than men in the ICI-only group.</td>
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<td>Turner, 1989†</td>
<td>15</td>
<td>A single successful pharmacologically induced erection administered in the doctor’s office was not effective in producing improvement in patients with psychogenic erectile dysfunction when it was not accompanied by psychological counseling.</td>
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<td>Wylie K, 2003†</td>
<td>45</td>
<td>84% of couples reported improvement after psychotherapy and vacuum device compared to 60% who reported improvement after couples psychotherapy alone in a cohort of patients diagnosed with predominant psychogenic MED (and who chose couples psychotherapy).</td>
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</table>
Abdo et al. and Melnick et al. [221, 356, 357] together and independently, have a series of articles that compare combination sildenafil and group counseling to group therapy or sildenafil treatment alone. Abdo et al. [356] randomly assigned 120 men with psychogenic ED to one of three experimental conditions: in Group 1, participants received 3 months of weekly group psychotherapy plus sildenafil; in Group 2, they received only sildenafil; and in Group 3, they received only weekly group counseling. The initial dose of sildenafil was 50 mg; however, it could be increased to 100 mg. At the end of 3 months, compared to baseline, all three groups demonstrated significant improvement in post-treatment Sexual Health Inventory for Male (SHIM) scores. The combined therapy group had the highest post-therapy scores on the SHIM and the Male Sexual Quotient measure compared to the other two groups.

Melnik and Abdo [357] randomly assigned men with psychogenic ED to one of three experimental groups. In Group 1, participants received 6 months of theme-based psychotherapy plus sildenafil 50mg; in Group 2, they received only 50 mg of sildenafil; in Group 3, they received only theme-based sexual counseling. At the end of 6 months, compared to baseline, all three groups demonstrated significant improvement in post-treatment International Index of Erectile Function (IIEF) scores. However, utilizing the criterion of normalization of IIEF scores (EF domain ≥26), only the combined and psychotherapy only groups demonstrated statistically significant improvement.

The authors explained the results in terms of psychotherapy encouraging patients to understand the emotional component of their condition, helping them to strengthen their commitment to the change process, to become more deeply involved, and to benefit from treatment. Psychotherapy also promoted more realistic and positive sexual expectations instead of expecting automatic, autonomous erections.

Aubin et al [358] reported on 44 couples who were randomly assigned to receive sildenafil alone or sildenafil plus 8 sessions of couples’ therapy. Sexual and couple outcome variables included: the IIEF and FSFI, four sexual cognition scales, Dyadic Adjustment Scale, and two emotional and sexual intimacy scales of the Personal Assessment of Intimacy in Relationship questionnaire (PAIR). The main study hypothesis of greater treatment gains for the combined vs. drug-only treatment in all domains of sexual function, cognition, and couple relationship was partially supported. The couples plus sildenafil group had a greater number of improved and maintained sexual function and cognition domains for both partners from pre- to post-treatment than the sildenafil only group. Regardless of treatment condition, men obtained improvements in five out of six domains of sexual function. However, during the follow-up phase, men in the sildenafil only group showed decreased sexual function in four out of six domains, whereas men in the combined treatment group maintained treatment gains in all sexual function domains. Women in the combined group obtained a greater number of improved sexual function and cognition domains than women in the sildenafil only group. There were comparable gains in sexual intimacy for women in either group.

Phelps, Jain, and Monga [192] highlighted the value of combined therapy in a study where the psychological intervention consisted of a one-session psychoeducational meeting. The authors compared two groups of men: The first received combined treatment with one 90 minute session psychoeducational intervention and sildenafil, and the second received only sildenafil. The initial dose of sildenafil was 50mg with titration allowed to 25mg or 100mg. The psychoeducational group included information about sexual function, clarified their treatment expectations, suggested communication exercises and provided references for self-help books. After 24 weeks of treatment, there were no differences in the IIEF scores between the two groups: Both demonstrated significant improvement. However, the EDITS treatment satisfaction total score for the psychoeducational intervention group was significantly higher than the sildenafil-only group.

Banner and Anderson [359] randomized 53 men with psychogenic ED and their partners into 2 groups: 1) combined sildenafil and cognitive behavioral sex therapy (CBST) and, 2) sildenafil only. After 4 weeks, CBST was added to the sildenafil only group. The authors fashioned criteria for success that included the IIEF erectile function and sexual satisfaction domain scores >19 and ≥6 respectively. At 4 weeks, 48% and 66% of combined therapy (CBST) group vs. 29% and 38% of sildenafil only group met success criterion. At 8 weeks, 66% and 75% of original CBST group and 58% and 45% of the new combined group met success criterion for EF and sexual satisfaction respectively.

Bach et al. [360] examined the effect of supplementing sildenafil treatment with a range of different strategies in men where the sildenafil was effective in creating erection, but the men and their partners were not satisfied with their sexual lives. There were several unique aspects to this study including: an assessment of the impact of combination therapy on partners; minimal contact with the therapist, and the use of a treatment manual. The treatment manual consisted of: 1) psychoeducation regarding sexual dysfunction and normative sexual functioning, 2) information on various factors affecting sexual arousal, 3) discussion of typical reactions to sexual problems, 4)
recommendations for optimizing conditions in which sexual activity occurs, 5) strategies for improving communication, and 6) instructions on the use of behavioral strategies such as sensate focus. Each week participants were asked to read assigned chapters from the manual and to complete the corresponding exercises. They would have weekly telephone contact with the therapist.

Five of six men evidenced increases in sexual satisfaction and the frequency of intercourse after adding the manualized treatment with minimal therapist contact to the use of sildenafil. They maintained these gains at an average of 6 months post-treatment.

Three articles have addressed combined treatment with intracavernosal injection therapy (ICI). Lottman, Hendricks, Vruggnik, and Meuleman [361] compared a small group of men receiving ICI plus three sessions of counseling at weeks 0, 6, and 12, with a larger cohort of men receiving ICI without counseling. During the trial dosing phase, there were no differences in discontinuation patterns. From the trial dosing phase forward until the 6-month follow up, no additional patients discontinued treatment in the combined therapy group. In contrast, the discontinuation rate after the trial dosing phase in the ICI-only group was 60%. Patients reported that counseling increased their knowledge about factors contributing to erectile dysfunction and improved their ability to communicate about their sexual interest and desires. Through counseling they felt more comfortable talking about feelings and thoughts concerning sexual problems.

Hartmann and Langer [362] described an integrated treatment program involving injection therapy and sex counseling. They concluded that a combined approach was more beneficial to men with primarily psychogenic ED and that improvement could occur only in the absence of partner problems or premature ejaculation.

In a more recent study, Titta et al. [363] reported on a group of non-nerve sparring radical retropubic prostatectomy and cystectomy patients receiving ICI who were randomized into two groups. The first group received ICI plus sexual counseling, while the second group received only ICI. Patients were followed for 18 months after initiating ICI. Over the course of the 18 months, all men also received a trial of sildenafil. In these patients, there were no differences between the groups on baseline IIEF or postsurgery scores. At the 3-month and 18-month follow-up, compared to the ICI only group, the counseling plus ICI group achieved significantly higher erectile function, desire, orgasm, and satisfaction scores. Additionally, the counseling plus ICI group manifested a lower discontinuation rate and were able to achieve good quality erections with lower doses of medication. Finally, more men in the sexual counseling group responded to sildenafil than men in the ICI-only group.

Combined treatment utilizing vacuum tumescence therapy and counseling was reported by Wylie et al. [364] who randomized 45 patients with primarily psychogenic ED into two groups. The first group participated only in couples therapy, whereas the second was instructed in the use of a vacuum device while simultaneously receiving couples therapy. Improvement was reported by 84% of the combined group, but by only 60% of the therapy-only group. The authors suggested that early combination treatment of couples therapy and a physical treatment, such as a vacuum device, may lead to a more beneficial response than psychotherapy alone. They also highlighted the importance of demonstrating potential benefits from a physical intervention early in therapy and suggested that delaying the demonstration of such benefits to the patient may have a negative impact on treatment outcome.

Whether using oral medication, intracavernosal injection or vacuum pump therapy for ED, these studies all suggest that combining medical and psychological treatments for ED improves the efficacy of the medical treatment and promotes greater treatment satisfaction and decreased discontinuation rates than medical treatment groups alone. The benefits of the psychological intervention appear to be educational, motivational and help men/couples to sort through some of the psychosocial obstacles that impede successful and satisfying treatment outcomes.

L. SEXUAL COUNSELING ON THE INTERNET

Sex therapy on the Internet is a controversial notion. There are several ethical and professional challenges to be overcome; nonetheless use of the Internet poses several advantages for patients that include: easy accessibility, anonymity, practicality, and reducing embarrassment or humiliation in obtaining treatment. It additionally removes the barrier of geographical isolation and therapist’s availability during business hours. Internet psychotherapy has been successfully used to treat panic disorder, social phobia, depression and recurrent headache [365-368]. Therapists may find that lack of visual contact and physical proximity to the patient may result in not detecting the subtle and not so subtle visual and auditory cues. There are also professional issues including liability, consent and conducting treatment in states or countries where the clinician is not licensed. From a physician’s perspective there are also multiple concerns regarding prescribing medication over the Internet without physically examining the patient or gathering a detailed and accurate medical history.
There are six papers that examine the benefits of providing Internet treatment to individuals with sexual problems [369-372]. All are exploratory in nature, and report on small samples of patients. Three of the six focus on treatment of men with ED; the other three include men with PE and women with sexual dysfunctions.

In a pilot study with 8 subjects, Hall examined online sex therapy for men and women with a diverse range of sexual dysfunctions including: anorgasmia, vaginismus, dysparuenia, premature ejaculation, delayed ejaculation and erectile dysfunction [369]. The number of email sessions ranged between 2 to 23. Online therapy began with patients completing the Problem Evaluation Form which solicited sexual history and information about the specific dysfunction. Based on the patient's responses to the form the online therapist devised a treatment plan. At the conclusion of treatment patients completed an online evaluation form.

Online therapy improved sexual function significantly, much, slightly in 2, 3 and 2 patients respectively. Two patient's sexual function remained the same. All 8 patients reported an improved self awareness and 6/8 said their sexual knowledge improved. Obviously, this was an uncontrolled study using unvalidated questionnaires with a very small number of patients. However, it was designed as a pilot study and suggests that Internet sex therapy may benefit some patients.

Leusink and Aarts [370] investigated the effectiveness of electronic consultations to 219 men suffering from ED. Unlike the previous study after completing an online history form the authors provided prescriptions for PDE5i’s as well as suggestions for psychological interventions. The IIEF and General Assessment Question (GAQ) were given pre and post online therapy and response to both were compared. Eighty-one percent of men reported improved erectile function at the conclusion of their econsultation. This study did not include a comparison group, making it difficult to assess whether similar outcomes would have been achieved following face-to-face consultation, or might have been due to spontaneous recovery.

McCabe and Price [371] evaluated the effectiveness of an Internet-based treatment program for ED and compared a combined medical and psychological Internet intervention to only an psychological Internet intervention. Each arm of the study received the same psychological treatment intervention. Outcome measures included the International Index of Erectile Dysfunction, Self Esteem and Relationship Questionnaire, Kansas Marital Satisfaction Scale, Index of Sexual Satisfaction and World Health Organization Quality of Life BREF. The psychological intervention was a cognitive-behavioral intervention targeted to resolve psychological and relationship factors related to ED. The Internet program called Rekindle consisted of three treatment components: sensate focus, communication exercises and unlimited email contact with a therapist. Subjects and their partners were encouraged to spend approximately 2 weeks completing each of the five treatment modules. The entire Rekindle Internet program took 10 weeks to complete.

The purpose of email contact (unlimited) was to resolve any individual or relationship problems that the men experienced as a result of the sensate focus or communication exercises. Improvements in erectile function were significantly greater among men who completed the program compared to those who received no treatment. Rekindle was not associated with significant improvements in orgasmic function, sexual desire and overall satisfaction.

Both the combined therapy and psychological intervention only groups demonstrated improvements in sexual function from pretest to post-test. There were no significant differences between either treatment. Similarly, compared to baseline, at the end of treatment both groups demonstrated significant improvements in relationship satisfaction. The authors suggest that in cases where ED is more severe or has been established for a significant period of time, a more intensive Internet intervention may be necessary. Additionally, they point out that when other comorbid sexual dysfunctions are present, or when the level of discord within the general relationship is high, Rekindle may also need to be supplemented with additional treatment.

McCabe et. al. [372] completed another study where they compared the Rekindle program to a no treatment control group. After completion of the study subjects in the control arm could participate in the treatment arm. Men in the treatment arm reported improved erectile function and relationship satisfaction in contrast to men in the control group. The sexual gains of men in the Rekindle group remained stable for 3 months following the termination of treatment. While the second study employed a control group and utilized validated outcome measures the numbers of subjects enrolled in the study was relatively small (12 in Rekindle; 19 in the control arm) and there was no involvement or data from partners.

In a wait-list controlled, randomized study, van Diest and van Lankveld et. al. studied the impact of Internet counselling on men with ED and PE [373, 374]. Forty-nine men and 32 men with ED and PE respectively completed 3 months of treatment as well as two follow-up assessments at 3 and 6 months. The unique aspect to van Lankveld’s protocol was that patient’s were required to pay for treatment. The protocol employed validated measures to assess outcome including the IIEF, Golombok Russ
Inventory of Sexual Satisfaction (GRISS), Global Endpoint Question (GEQ) and the confidence scale of the Self Esteem and Relationship Questionnaire (SEAR). Internet treatment was modelled after Masters’ and Johnson techniques such as sensate focus and augmented by cognitive behavioral interventions. Additionally, when deemed appropriate PDE5i’s, clomipramine, SSRI’s or topical anaesthetic cream was prescribed.

In participants with ED, erectile functioning and overall sexual satisfaction improved significantly; however, the results of treatment for PE men was not superior to wait list controls. Treatments gains were maintained at follow-up.

The use of the Internet shows promise for offering therapeutic interventions to patients suffering from sexual dysfunctions. However more work remains to be done in terms of extending the Internet offerings to larger and more diverse populations of subjects and providing extended follow-up of the stability of the changes. Additionally, the aforementioned challenges of protecting patient’s privacy, consent and concerns with liability need to be addressed.

M. CONCLUSIONS AND RECOMMENDATIONS

Despite the numerous studies cited in this chapter, the predominant levels of evidence tend to fall between systematic reviews of cohort studies (level 2) to expert opinion without explicit critical appraisal (level 5). The complexity of sexuality, whether normal or dysfunctional, is created by the interaction of the forces of culture, individual development, individual psychology, interpersonal relationships and biology. There is no sexual behavior, solitary or partnered, that is not shaped in some way by each of these five influences.

Advances of medical and psychological therapies for sexual dysfunctions need to be perceived through this intricate biopsychosocial web. The biopsychosocial model provides a compelling reason for skepticism that any single intervention—i.e. a PDE5 inhibitor, supraphysiological doses of a hormone, processing of childhood victimization, marital therapy, pharmacotherapy of depression, etc. can by itself be sufficient for most patients or couple’s experiencing sexual dysfunction. This is especially true since sexual behavior most often occurs in a dyad with two individuals who bring their unique histories, inhibitions and motivation to the treatment.

The goal of treatment is the restoration of lasting and satisfying sexual function. Clinical work demands that the therapist works to understand all of the forces that caused the problem even as they are providing treatment. This requires the therapist to conceptually identify and separate the predisposing developmental factors from the precipitating factors from the contextual factors from the factors that maintain the symptom.

While the committee recognizes the reality that all physicians and mental health professionals do not have the same ability to work with biological, cultural, interpersonal, and individual psychological contributions to a given dysfunction, we urge all professionals to guard against simplistic thinking about the cause and treatment of any of these problems. We conclude this chapter by offering the following recommendations:

1. There is a vital need for collaboration between clinicians in the evaluation, treatment and education surrounding sexual dysfunction. Each discipline has something to contribute to patient care.
2. In many cases neither psychotherapy alone, nor medical intervention alone, is sufficient for the lasting improvement of sexual problems.
3. The adoption of the biopsychosocial model that includes predisposing, precipitating, maintaining and contextual factors. Such a model leads to a comprehensive understanding of the sexual problem and serves as a roadmap for thoughtful treatment.
4. More research is needed on factors that increase personal resiliency and contribute to the development of healthy sexuality.
5. Clinicians need to carefully assess patient’s presenting with sexual disorders for the presence of depression and design studies to determine if there is a causative link between depression and sexual dysfunction.
6. Population based studies of the interpersonal relationship dimension and sexual dysfunction are needed.
7. Large scale, randomized, controlled studies employing validated outcome measures and long-term follow-up for the psychological treatment of male and female sexual dysfunctions need to be conducted.
8. Research is needed to identify the best models for conducting combined and/or integrated treatments for sexual dysfunction.
9. Professional organizations need to develop guidelines for Internet treatment of sexual dysfunction.
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Committee 4

Ethical, Socio-cultural and Educational Aspects of Sexual Medicine

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INTRODUCTION TO THE CHAPTER

The Ethical, Socio-cultural and Educational Aspects of Sexual Medicine Committee will be comprised of three separate essays describing the elements listed in the Committee’s title. Because the topics Committee was assigned were diverse, the Committee members chose to submit the content as separate contributions, focusing on more specific points related to each of the three topics above.

The sections will include:

I. EDUCATIONAL ASPECTS OF SEXUAL MEDICINE

II. ETHICAL PERSPECTIVES IN SEXUAL MEDICINE

III. SOCIO-CULTURAL ASPECTS IN SEXUAL MEDICINE
I. EDUCATIONAL ASPECTS OF SEXUAL MEDICINE

S. Parish, J Dean

1. INTRODUCTION

In modern society there are many educational needs regarding sexuality and the clinical management of sexual concerns, problems, and disorders. This discussion will focus on the current state of sexual health education in physician undergraduate, graduate, and postgraduate medical education. We will also provide a summary of current standards for developing curricula and defining competencies in sexuality education.

a) Need for Improved Sexual Health Education

There has been an increasing awareness regarding sexual health in recent years, and more public attention has been focused on sexual problems, such as erectile dysfunction (ED). However, despite increased professional awareness and increasing demand from patients, ED remains under-diagnosed and under-treated by doctors across the world. This is also true for other male sexual dysfunctions, as well as dyspareunia and disorders of desire in women.[1] Only 25% of U.S. primary care physicians actually take a patient's sexual history, citing lack of training as the most common reason for not doing so.[2,3,4]

Both patient's and physician's acknowledge the lack of discussion of sexuality in clinical settings and thus under-diagnosis of sexual problems. Patients want to discuss sexual issues, but perceive significant barriers. For example, in one study, 71% of surveyed patients felt their physician didn't have time, 68% didn't want to embarrass physician, and 76% believed no treatment was available.[5] Patients report non-empathetic judgmental responses, physician discomfort, concerns regarding privacy, and a lack of cultural sensitivity. Many patients do not have confidence in their physician's skills in managing sexual problems and do not believe they would receive effective treatment. An international study of 27,500 men and women revealed that half of all sexually active participants had at least one sexual problem; but only 19% had sought medical care, and only 9% reported being asked about sexual health in the previous 3 years.[6] Most patients (over 90%) believe that it is a physician’s role to address sexual health concerns and are grateful when their doctor initiates the discussion.[7]

b) Physician Barriers

Physicians report numerous barriers to addressing sexual problems including: insufficient knowledge about the diagnosis of sexual function and dysfunction; inadequate training in communication skills; lack of information about treatment options; apprehension that their inquiries may offend the patient; low recognition that healthy sexual activity is important; time constraints; inadequate reimbursement, lack of privacy, cultural, and language barriers, and personal discomfort about sex including language, ageism; and the assumption that all people are married, heterosexuals, and monogamous.[8] Physicians may have difficulty remaining objective and separating their personal views from those of their patients.[9] Physicians in training may have limited sexual experience, unresolved issues regarding their own sexuality, or concern about developing sexual feelings toward patients.

In several studies physicians reported gender as a significant barrier to sexual history taking. In one survey of a multidisciplinary practice, male and female physicians reported significant discomfort interviewing patients of opposite sexes.[10] and in
a course on ED, dealing with communication and management strategies, female physicians report more perceived difficulty as compared to their male colleagues.[11]

c) Detection of Hypoactive Desire and Related Female Sexual Problems

Sexual problems in women are common. In the recently published study Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE), almost half (43.1% age adjusted estimate) of women had some sexual problem. Low desire, present in 37.7% (age adjusted estimate) of subjects, was the most common sexual problem observed. Sexually related personal distress was present in 22.8% of subjects, and a sexual problem with associated personal distress was present in 12.0% of women.[12] Despite this substantial prevalence, the majority of physicians rate their knowledge of FSD as only fair to poor; and their level of comfort parallels their self-assessed knowledge. In a systematic survey of an academic primary care clinic in which half of potential subjects responded, 90% of clinicians reported little confidence in making the diagnosis of Hypoactive Sexual Desire Disorder (HSDD). 90% of physicians had not screened a patient for HSDD. Faculty were more confident than residents.[13]

In a recent fax/ e mail study of a random sample of practicing physicians that used a case vignette-based survey, 21% of OB/GYNs and 38% of primary care physicians reported that they were not at all confident about treating HSDD. In multivariate analysis, low confidence was associated with perceived time constraints, the perceived lack of effective therapy, fewer years in practice and fewer patients who presented with distressing sexual problems per week. Female PCPs were less confident than males about their ability to treat HSDD, an observation not reported in OB/GYNs. Respondents also cited perceived time constraints and lack of therapeutic options as barriers to initiating discussions about sexual health. Respondents believed that medical and residency education provided inadequate training for sexual history taking, however participation in continuing medical education and practice experience were associated with greater confidence in the multivariate analysis.[14] The many significant barriers to providing effective care for women’s sexual health are poorly and variably addressed by existing curricula and educational programs.[15]

d) Screening and Detection of Sexual Problems

Clinicians infrequently screen for sexual problems, so detection rates are consequently low. If practitioners do take sexual histories, they most commonly focus on sexually transmitted disease risk assessment and prevention and/or contraception rather than sexual problems. Improving screening procedures does improve recognition. In a frequently cited study in which clinic physicians were trained to take a screening sexual history, 53% of the patients reported a sexual problem.[7 Most] (91%) of the patients said they considered questions about sexuality to be an appropriate part of the interview. Training in sexual health screening increases detection, which satisfies patients.

e) Physicians’ Desire for Sexual Health Education

In the ED course discussed above, physicians’ previous training in communication skills was reported as the strongest predictor for sexual history taking.[11] While physicians typically do not receive adequate training in sexual medicine and sexual history taking, they believe that they should address sexual problems and that they need more training. Practicing physicians can gain increased comfort and experience in managing sexual problems by incorporating routine sexual health questions into their practice, by addressing the barriers discussed above, by sharing cases with colleagues, and by exploring their own attitudes toward sexuality.[9]

As we will discuss, physician education, targeted at improving skills, increasing knowledge, and encouraging awareness of personal biases, is the key to minimizing obstacles that interfere with doctors optimally addressing sexual health.

2. CURRENT STATE OF UNDERGRADUATE SEXUAL HEALTH EDUCATION

The majority of medical students believe that sexual history taking will be an important part of their future clinical practice; however, between 42-62% of U.S. medical students feel that the training on sexuality they received in medical school is inadequate.[16] Studies assessing curricula at individual institutions have demonstrated that students receive a broad range of non-standardized training. More controversial topics in sexual health have even less favorable representation. For example, of the 82 U.S. medical schools that responded to a survey (65% of the 126 schools surveyed), 8 faculty reported that they had no teaching on gay and lesbian issues.[17] Cultural influences on sexual practices do not appear to be addressed in most sexuality curricula.

The most comprehensive recent information about the status of undergraduate sexual health education is reported in a recent survey on sexual health training in medical schools in the USA and Canada.[18] In this survey 141 medical schools were contacted, and 101 valid responses were returned. The survey asked about the type of educational experiences, whether they were mandatory or elective, whether they were designed by single or multiple disciplines, and the number of course hours dedicated to human
sexuality. The questionnaire also assessed specific content areas, as well as exposure to and training in clinical settings addressing sexual problems. Additionally, the survey assessed the availability of continuing medical education (CME) programs in sexual medicine and related topics.

A total of 84 respondents (83%) reported using a lecture format for sexuality education. Two thirds of the schools used a multi-disciplinary approach to teach sexual health, and three quarters of the schools reported Psychiatry as the most frequently involved discipline. The majority (54%) of the schools provided 3-10 h of education. The curricula of 96 respondents included causes of sexual dysfunction (94%), its treatment (85%) altered sexual identification (79%) and issues of sexuality in illness or disability (69%). Only 43 (42%) schools offered clinical training programs that focused on treating patients with sexual problems and dysfunctions; and 56 (55%) provided the students in their clerkship with supervision in dealing with sexual issues.

In a survey of 25 UK medical schools’ teaching on erectile dysfunction (ED) to undergraduates, only 9 indicated that the subject was covered in their curriculum; and only 5 reported providing significant exposure within an integrated program of teaching on sexuality. The others stated that ED is covered by a 30-60 minute lecture, either during urology or gynecology rotations.[19]

A global survey was conducted through a collaboration between ISSIR (Int. Soc. for Sexual and Impotence Research), WHO, and World Federation of Medical Education (WFME). The report concluded that approximately 30% of medical schools have no educational program in human sexuality or sexual medicine and that 50% have less than 10 hours teaching, mostly related to reproduction. The disciplines most involved in teaching are Gynecology, Psychiatry and Urology; and only 15% of schools have more than 20 hours of teaching with multidisciplinary involvement.[19]

**a) ISSR/ISSM Curriculum in International Undergraduate Sexual Health Education**

In response to the survey described above, the ISSIR educational committee (www.issir.org) recommended a globally applicable curriculum (www.med-sexedu.net) calling for an intensified global strategy in the future teaching of medical doctors in Sexual Medicine. In 2005 the International Society of Sexual Medicine (ISSM) chartered an education committee that was charged with reviewing curriculum at 1,700 medical schools worldwide. The committee then initiated the creation of a structured, multidisciplinary, medical school curriculum with modules pertaining to sexual medicine that could be adapted to suit different cultural needs. Although the curriculum is still under development, when available these modules could be distributed to medical schools for direct use or as a basis for independent curriculum development. In addition to the teaching materials, a 20-30 hour program (available electronically) is to planned to assist in faculty training and development.[20]

**b) New Developments in U.S. Undergraduate Medical Sexual Education**

A number of medical schools have made improvements to their sexual health education programs. Several models described below incorporate a multi-disciplinary approach to enhance trainees’ attitudes, knowledge, skills, and overall comfort in managing sexual health problems. Table 1 outlines the elements including attitudes, knowledge, and skills training that have been addressed in sexual health curricula. A variety of innovative teaching methods are described in the examples below.

Case Western Reserve University School of Medicine described the implementation of a “comprehensive, cross-disciplinary and innovative curriculum that is based on three primary objectives for teaching sexual health: attitude change, behavior change and knowledge acquisition.” [21] Attitude change is accomplished by promoting students’ awareness of their own attitudes toward sexuality and exposure to normal variations of sexuality. Behavior change is being addressed by enhancing communications skills “regarding all aspects of sexual functioning.” Knowledge acquisition involves a multi-disciplinary approach to all aspects of sexual health, including topics such as biology; sexual development; and sociologic issues such as the impact of ethnicity, race, culture, and economic status on sexual health. Strategies to incorporate the sexual health content include faculty development to enhance sexual communication skills; additional didactic sessions; case-based learning; standardized patient (SP) interviews; testing using multiple choice questions; assessment of students’ attitudes using the Sex Knowledge and Attitudes Test (SKAT); and the creation a sexual health website.

The enhanced curriculum at Case Western also employed Objective Structured Clinical Exams (OSCEs), including both sexual health content in existing stations and stand-alone stations. An OSCE is a timed, multi-station examination in which learners perform tasks such as interviews, physical exams, and counseling with SPs in realistic settings. At each station learner performance is evaluated with specific checklists or global rating scales, completed by faculty proctors and/or SPs.[15]

The University Of Massachusetts Medical School implemented curricular enhancements throughout the four years. These include an elective reflection session regarding students’ reactions to the dissection of the female pelvis during the first year anatomy course; an elective session on the
“Medical Risks of the Gay, Lesbian, Bisexual and Transgendered Community”; and a multi-disciplinary one-week elective women’s health course for fourth year students.[22]

Other educational initiatives in sexual medicine include student-initiated programs. Useful learning methods included discussions with fellow students, interactive presentations with faculty, patient panels, didactics, and teaching peers.

c) New Developments in International Undergraduate Sexual Medicine Education

Some innovative model curricula have emerged from medical schools in the United Kingdom (U.K). The University of Cambridge instituted role-playing mock clinic scenarios, which allows students to empathize with the patient, and discover and test beneficial behaviors.[23] The University of Cambridge also conducts a session dedicated to increasing awareness of homosexuality. During the session students explore internalized prejudice by brainstorming all the slang terms they know relating to homosexuality and then reflecting on them silently.

Another medical school in the UK, Leicester-Warwick Medical School, initiated a course designed to aid the students in recognizing their attitudes and values toward sexuality.[24] Methods include desensitization, problem solving and reflection. Students address their embarrassment with sexual topics, including becoming familiar with slang and medical terms in a safe environment in which they might rehearse their reactions and responses.

3. CURRENT STATE OF U.S. GRADUATE MEDICAL EDUCATION

Sexual health training in graduate medical education is understudied and largely unaddressed. According to Rosen et al, “Residency training in sexual medicine has been largely neglected, with little attention given to educational curriculum development or implementation; and few programs have training in sexual problem management across disciplines or subspecialties (e.g. family medicine, internal medicine, OB-GYN, urology, and psychiatry).[25]

a) Accreditation Standards for U.S. Undergraduate and Graduate Sexual Health Education

The Liaison Committee on Medical Education (www.lcme.org) determines accreditation standards for medical schools. The curricular requirements related to sexual health are general and include learning about: behavioral subjects; communication skills, medical consequences of common societal problems, such as abuse; diverse cultures and belief systems, and gender biases. The Accreditation Council for Graduate Medical Education has outlined residency program training requirements for all disciplines (www.acgme.org). Sexual medicine requirements are also very general. Internal Medicine residents should receive “instruction and clinical experience in the prevention, counselling, detection, diagnosis, and treatment of gender-specific diseases of men and women.” Family medicine guidelines call for the “teaching of human sexuality.” Pediatrics requirements mandate learning about sexual abuse, and male and female reproductive health including sexuality, pregnancy, contraception and STDs. Urology requirements include training in sexual dysfunction. OB-GYN residents should receive training in contraception, infertility, menopause, high-risk sexual behavior, as well as specific sexual medicine skills such as sexual history taking and psychosexual counseling. Psychiatry guidelines are vague, addressing issues of gender, race, ethnicity, socioeconomic status, religion/spirituality, and sexual orientation (knowledge and attitudes).[15]

Both the LCME and ACGME now require performance-based assessment to document the acquisition of competencies. They require direct observation of live patient encounters; SPs and OSCEs are the preferred or next best method for assessing many clinical skills. These principles of competency evaluation have not yet been directly applied to sexual medicine skills; in order to meet contemporary standards, the discipline of sexual medicine will need to incorporate these educational approaches into new curricular efforts.

b) New Developments in Residency Sexual Health Education

Few residency training programs have described innovations in sexual health education. The Robert Wood Johnson Medical School (RWJMS) has been an internationally recognized model for comprehensive sexual health education for medical students since 1973. Using a small group interactive format, the course seeks to provide a culturally diverse and patient-centered approach’ focusing on three components: (1) integration of didactic and attitudinal learning; (2) multidisciplinary approach to sexual problems; (3) clinical skills, including communication skills and sexual history taking (http://www2.umdmj/hspweb). A similar model was developed for residents, incorporating the three components into a half-day program for senior house staff from RWJMS-affiliated residency programs in multiple specialties, including 46 internal and family medicine, psychiatry, geriatrics, OB-GYN, urology, and pediatrics residents.[25] Methods included didactic presentations on sexual dysfunction, physician and patient panels, an audience response system with feedback, and interviewing skills practice.
4. CURRENT STATE OF POST-GRADUATE SEXUAL HEALTH EDUCATION AND CME PROGRAMS

Less than half (44.6%) of the North American medical schools who responded to the 2003 survey discussed above offered continuing medical education (CME) programs for professionals interested in sexuality related topics.

In response to the increasing demand and interest, some organizations, composed of practicing physicians in one or several disciplines, now offer lectures, workshops, and longer courses on the evaluation and treatment of sexual dysfunction. Organizations that have provided these courses include the American College of Physicians (ACP) (representing general internists and subspecialists), the American Academy of Family Physicians (AAFP), the American Psychiatric Association (APA), the North American Menopause Society (NAMS), and the American Urological Association (AUA). Academic societies, such as the Society for General Internal Medicine (SGIM), offer workshops geared toward clinician educators that address both clinical care and teaching strategies. In the last decade multidisciplinary, specialized organizations such as the International Society for the Study of Women’s Sexual Health (ISSWSH) have been sponsoring meetings that are dedicated to sexual health research and educational courses designed to enhance clinical care.[15] Other international organizations, such as the Latin American Society for Sexual Medicine (SLAMS), have also offered sexuality courses on the Internet. Also, post-graduate sexual education commonly occurs through the establishment of preceptorships, other formal arrangements and consultations, direct observation of sexual health specialists, and networking.

Industry sponsored CME programs consist of symposia at professional meetings, teleconferences, and internet-based training programs on sexual health problems. Teleconferences include interactions with live speakers in conjunction with slide presentations on clinical assessment and management. Web-based resources include case-based formats and video demonstrations of skills such as sexual history taking and communication, as well as ED management. The intervention employed an array of instructional methods including didactics, tutorials, video-based dramatization, group scripted role-play demonstration with participant discussion and decision-making and individual role-play practice. Standardized questionnaires demonstrated shifts in physicians’ attitudes toward patient-centeredness and less judgmental attitudes towards patients’ sexuality. Physicians’ self-assessed their knowledge acquisition and rated the efficacy of the course components; participants gave the highest ratings to the tutorial on ED management and the sexual history taking role-play.

Consistent with previously published studies, Athanasiadis and colleagues’ assert the effectiveness of scripted role-plays, combined with interactive small group formats using problem-based learning, for acquiring communication skills for sexual history taking and clinical management of sexual dysfunction.[26] It is important to note that their outcomes solely relied on self-reported changes attitudes, knowledge, and skills, and not on physician self-reported or objective changes in their clinical practice.

The most extensive post-graduate CME program to date was initiated by the European Society for Sexual Medicine (ESSM) in 2007. The ESSM launched the Oxford course, a 2-week residential program of 76 hours of teaching, discussion, and sexual health interviewing and counselling skills training, conducted by international experts, for 29 physicians of 21 nationalities from a wide spectrum of disciplines. This course, described as “an outstanding success,” was designed to be a first effort toward compliance with the “structured teaching requirements” anticipated for professional qualification as a sexual health specialist under the new European Division of Sexual Health.[27]

5. SUMMARY OF SEXUAL HEALTH EDUCATIONAL METHODS

In the examples above, an array of educational methods have been employed to meet the challenges of teaching sexual medicine at all levels of medical education. These and other methods and their benefits are summarized below:
Lectures on sexual health content: instruction by experts on complex biomedical issues

Case-based seminars: interactive, generate adult learning

Workshops and patient panels: exposure to multiple viewpoints

Training in interviewing couples: modelling of complex interaction

Discussion groups: exploration of feelings and self-reflection

Immersion/desensitization: exposure to alternative practices

Scripted Role-Play: observe expert demonstration of interviewing/counselling skills

Role-play (individual): practice eliciting sensitive information in a safe environment (open-ended questions and normalizing statements)

Standard patient scenarios: structured practice with immediate feedback

Observed structured clinical encounters (OSCEs): competency assessment and evaluation

Video review of live encounters: individualized feedback and self-reflection

Clinical and research electives: personalized in-depth exposure

Faculty development: enhance dissemination and multidisciplinary interaction

6. SUMMARY OF DEFICIENCIES IN CURRENT SEXUAL HEALTH TRAINING PROGRAMS

Numerous innovations have occurred in recent years in undergraduate, graduate, and post-graduate sexual health education. Emerging curricula have enhanced training in knowledge, skills and attitudes; and institutions and organizations have employed an array of educational methods. However, standards for curriculum development and the assessment of competencies, such as those developed in the U.S. by the ACGME, have not been adequately employed in sexual health education. Four specific deficiencies can be identified.

(1) Most curricula have consisted of set lectures or seminars. Few programs have employed learner-centered learning, which encourages individual learners’ to self-assess their needs, define personalized goals, and track their progress.

(2) The majority of program innovations have focused on the dissemination of clinical knowledge. Some programs have included skills training; however few have addressed the full spectrum of clinical skills including sexual history taking, physical exam, procedures, behavioral counseling, and medical recommendations. Individualized skills training, combined with immediate feedback, has not been substantially employed.

(3) Evaluation of the efficacy of educational programs has primarily relied upon trainees’ self-report of program efficacy and self-assessment of changes in knowledge, skills, and attitudes. Objective measurement of the performance of clinical skills has not been reported. Although some training programs have employed OSCEs to assess the acquisition of clinical skills, standardized competencies and performance parameters have not been well described.

(4) Objective measures of the impact of graduate and post-graduate physician training in sexual health on patient satisfaction and objective health outcomes are lacking. Follow-up questionnaires documenting changes in clinical practice after sexual health training have not been employed.

Future training programs at all levels of medical education should incorporate standardized measures of skill acquisition with objective patient outcomes into the design of the educational initiative. Objective evidence of the benefits of sexual health education on patient care is necessary to stimulate the development of the field and support the need for more widespread education and training.

7. BARRIERS TO THE IMPLEMENTATION OF SEXUAL HEALTH EDUCATIONAL PROGRAMS

While there have been some substantial advances in the delivery of sexual health education programs worldwide, significant barriers to their implementation still exist. These include:

- Lack of public awareness of the importance of sexual health as a priority
- Lack of governmental and other public funds dedicated to the development of sexual health education programs
- Deficiency of resources in educational settings, such as new textbooks and equipment
- Few hours of dedicated curricular time in medical schools and residency training programs
- Paucity of faculty development programs
- Few well qualified and trained professionals to carry out educational programs
• Lack of widespread access to educational programs

• Lack of attention to sexual health issues across ethnicities, religions, and races

8. MANDATE FOR A UNIVERSAL UNDERGRADUATE SEXUAL HEALTH CURRICULUM

This committee recommends an intensified global strategy in the future teaching of basic sexual health education, as an obligatory part of the learning requirements for physicians. As described above several international organizations have made recommendations through initiatives regarding the development of sexual health curriculum.

Recently, the ISSM Education Committee has initiated the process of recommending a universal curriculum for all medical schools. This committee has targeted three aims that include (i) defining competencies in relevant to sexual health education, including knowledge, skills and attitudes; (ii) creating an effective teaching and assessment process to ensure and demonstrate the acquisition of competencies and impact on patient outcomes; and (iii) designing an implementation strategy that includes dissemination to worldwide medical universities.

Core elements should include:

• Basic knowledge of human sexuality

• Awareness of personal attitudes towards one’s own and other people’s sexuality, which should include a respectful attitude towards persons with different sexual orientations and sexual practices

• Basic skills in identifying, diagnosing, managing and, if necessary, referring to the appropriate professional, sexual health problems

9. RECOMMENDED SEXUAL HEALTH TRAINING FOR POST-GRADUATE PHYSICIANS

This committee promotes the need for the establishment and support of continuing education for established health professionals. This committee also believes that there should be a requirement for physicians specializing in sexology and sexual medicine to undertake a specified training program appropriate to their discipline.

We recommend that the content for such curricula should be similar to undergraduate education, with the addition of issues relevant to the practicing physician (highlighted with an *). A core training program should be based on the best available evidence-based medicine and include:

Knowledge
Anatomy and physiology of the sexual response
Psychology
Biological basis of human sexuality
Sexual development
Sexual identity and orientation
Gender identity
Sexual behavior
Sexual dysfunction
Cross-cultural issues in sexual health
Sex and relationships
Sex and reproductive health
Sex and ageing
Sex and the effect of medical problems and their treatments
Therapeutic interventions for sexual dysfunction
  Medications
  Surgery
  *Office-based counseling
  Sexual psychotherapy
  *Medico-legal aspects of sexuality and sexual behavior
  *Ethical aspects of sexual medicine
  *Sexual research
  *History of sexual medicine

Skills
Communication
  With professionals
  With patients and partners
  *Education
  With professionals
  With patients and partners
Clinical assessment
Clinical management
Clinical governance
  *Administrative skills
  *Research skills
  *Advocacy skills
Such programs, whether at basic level or for
the specialist, should be properly validated and supervised by an appropriate academic authority. In conjunction with universal standards, we recommend the establishment of regional and international centralized infrastructures, which create standards for accreditation, and overseeing of the practice of sexual medicine.

10. CONCLUSIONS

Concordant with major advances in the evaluation and treatment of sexual dysfunction, society has become more willing to recognize sexual problems and discuss sexual health. However, many medical students, house staff, and practicing physicians continue to receive variable, non-standardized or inadequate training in sexual history taking and sexual dysfunction management. The efficacy of these interventions on the acquisition of clinical skills and patient outcomes has not been assessed. Hopefully, existing models have established a trend that will inspire all medical schools to offer mandatory, comprehensive curricula in sexual health education. Graduate medical sexual education is has just begun to address the need to give physician trainees uniform, standardized skills to meet the demands of current clinical practice. Continuing medical education programs are being offered in multiple disciplines and by specialty multidisciplinary organizations. The challenge is to create widely available programs that provide physicians across specialties with the skills needed to meet contemporary patients’ needs in sexual health care.[15]

Table 1. Components of Model Undergraduate Sexual Health Curricula

<table>
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<tr>
<th>Attitudes</th>
<th>Knowledge</th>
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<tbody>
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<td>Self-awareness of own beliefs, values, attitudes</td>
<td>Biology of sexual development on molecular level</td>
</tr>
<tr>
<td>Reflection/ desensitization</td>
<td>Anatomy and physiology of human sexual response</td>
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<tr>
<td>Variations of normal sexual behavior</td>
<td>Psychological influences on sexual development</td>
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<td>Ethical issues</td>
<td>Causes of sexual dysfunction (biological, psychological, social)</td>
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<td>Impact of medical illness, treatment, medications</td>
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<td>Sexual health in adolescence</td>
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<td>Impact of menopause, aging on sexuality</td>
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<td></td>
<td>Sociologic issues (ethnicity, race, culture, religion, sexual orientation and economic status)</td>
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REFERENCES

II. ETHICAL PERSPECTIVES IN SEXUAL MEDICINE

Leonore Tiefer

1. PATIENT-PHYSICIAN ETHICS

In their classic text, Beauchamp and Childress[1] described a medical ethics framework for patient-physician relations based on four fundamental moral principles: respect for autonomy, nonmaleficence ("do no harm"), beneficence and justice. All the traditional aspects of modern professional medical practice can be seen to derive from one or another of these principles, e.g., mandatory informed consent for treatment and research participation, confidentiality, patient rights protection, access to care, and respect for human dignity. This approach is described in some detail in the ethics and education chapter in the previous edition of this Sexual Medicine text.[2]

The approach based on principles has been used in constructing the ethical codes of many professional medical organizations and has many important applications to the practice of sexual medicine. However, there are some important challenges and supplements to principilism that have particular relevance for sexual medicine.

Challenges to autonomy

It is often said that respect for autonomy is the keystone of contemporary medical ethics. Each patient is respected as a competent individual and given the right to make informed choices about their own health care. However, sexual activity presents certain dilemmas that are almost impossible to resolve using the conventional approach to autonomy and require that we expand our professional outlook.

First, sexuality is a subject about which many—perhaps most—people are very poorly informed due to the widespread absence of comprehensive sex education, the limits on sexual information provided to the public and the abundance of sexual myths.[3] Assuming that a patient needs only to be informed about the specific medical choices relevant to his specific problems ignores the larger context of misinformation and ignorance, and the almost inevitable presence of sexual embarrassment and even shame. Dodds [4] argues, for example, that a person’s “autonomy competency” is limited whenever they are uncomfortable, frightened, experiencing values conflicts, or otherwise compromised, a situation that seems to describe sexuality quite well.

Second, sexual activity usually involves another person and has substantial implications for the physical and psychological health and well-being of that other person. Thus considering only the patient’s autonomy and rights when it comes to sexual health is oversimplified.

Consider the common situation where a man with erectile dysfunction consults a physician but does not bring his wife, whom he says is his only sexual partner. The range of available treatments—sex therapy, medical devices, medications, and surgeries—will all have some impact on his wife. The patient needs information and education about his problem and the available treatments AND his wife needs information and education also. The sexuality knowledge base of both individuals is likely to be limited. Moreover, the wife may have important perspectives to contribute. She may have health issues that would limit her interest in vaginal intercourse. She might be so worried about the impact of the medication, device or surgery on her (often elderly) husband’s health that she is fearful about engaging in sexual relations with him. It is possible that she may feel a more important problem in the couple’s sexual life is being overlooked by the focus of this particular consultation. Research has shown that the information provided by the patient’s wife sometimes changes not only the treatment recommendation but the actual sexual dysfunction diagnosis.[5]

Given these information and relationship issues, the ethical physician will make every effort to involve the patient’s wife in order to educate her, involve her and consider her choices in the matter before a treatment decision is made.

2. ETHICS IN A MULTICULTURAL WORLD

We live in multicultural societies where sexual practices, attitudes and values vary widely, to say the obvious, from the very liberal to the very conservative. A small number of professionals will practice sexual medicine in homogeneous societies, but the rest need training to clarify their own values and learn how to handle the complexities posed by cultural diversity.[6] Professionals without suitable exposure and facility with the subject of human sexualities are likely to feel uncomfortable discussing sexual issues with patients, are likely to make assumptions based on cultural or age-related stereotypes, may take overly brief and medicalized histories, and may feel conflicted about the proper use of resources for patients such as educational books, videos, websites and erotic stores.

Sexual values clarification workshops and trainings are unlikely to be scheduled at medical conferences but sexology groups such as the American Association of Sex Educators, Counselors and Therapists (http://www.aasect.org) have decades-long experience offering workshops addressing professionals’ attitudes and values.

Sexual rights are an important component of
sexual values, and organizations such as the World Association for Sexual Health (WAS) http://www.worldsexology.org/ offer regional congresses that include professional training in sexual rights. WAS has developed documents such as the Declaration of Sexual Rights (approved in 1999) that is now available online in 18 languages (http://www.worldsexology.org/about_sexualrights.asp). Study of this document will enlarge the sexual medicine professional’s sense of the human rights and civil rights perspectives on sexual conduct. Finally, discussions of ethics are part of the trend in cultural competence in health-care delivery.[7] Cultural competence in sexual medicine embraces awareness of linguistic, inter-cultural, intra-cultural, and economic variations, and leads the provider to avoid making assumptions but rather to inquire closely about each patient’s and partner’s sexual beliefs and their origins. It will move the provider away from overly standardized and stereotyped approaches towards assessment and treatment that is truly respectful and patient-centered.

3. ETHICS AND RESEARCH, CONTINUING EDUCATION, PROFESSIONAL ORGANIZATIONS

The past decade has seen an explosion of interest in ethical dilemmas related to the new relationships between healthcare professions and the pharmaceutical industry. This evolving area is especially relevant to sexual medicine because of the strong interest of the pharmaceutical industry in potential markets for sexual dysfunction and dissatisfaction treatments.

A 2009 report by the highly respected U.S. Institute of Medicine (IOM) reviews this area of professional ethics and makes a number of recommendations for reform as regards the relationship between industry and clinical research, education and patient-care. (http://www.iom.edu/CMS/3740/47464.aspx) The IOM’s solution to “disentangling the relationships between doctors and drug companies” (p.1193) includes government-sponsored registries to monitor industry payments, greater disclosure of all professional-industry relationships, and setting limits on industry gifts and payments to health-care professionals.

Rothman and colleagues recently reviewed ethical issues that pertain to professional medical associations (PMAs).[9] PMAs have central roles in defining and advancing health care through conferences, continuing medical education, practice guidelines, codes of conduct, and public advocacy positions. PMAs have been very important in developing the new field of sexual medicine. Rothman and colleagues emphasize that any threats to the integrity of PMAs because of questionable financial links could harm public health and compromise the role of medical professionals.

During the past decade, the relationship between medicine and industry, specifically involving pharmaceutical and medical device companies, has come under intense scrutiny. The overriding concern is that industry ties create conflicts of interest both real and perceived….The problem has exceptional relevance for PMAs because industry funding of their activities, although varying in degrees, is pervasive (ibid, p.1367-8)

After reviewing many areas where industry makes important contributions to medical progress as well as many potential conflicts of interest, Rothman and colleagues conclude with 10 explicit recommendations for PMAs. First on the list is “a complete ban on pharmaceutical and medical device industry funding” for general PMA operational costs (including meetings, research or fellowship sponsorship, journals and practice guideline developments) except for clearly identified marketing opportunities such as journal advertising and exhibit hall fees (ibid., p. 1368). They recommend a variety of ways to pool gifts and grants from industry for research and education that do not identify individual donors or link recipients to specific donor companies.

This new trend towards elimination of conflicts of interest between PMAs and the pharmaceutical industry is relevant for sexual medicine organizations that grew over the past decade largely as the result of industry sponsorship and gifts. Continuing sexual medicine education needs a new paradigm for operations and support that should evolve through industry-independent consensus meetings (as recommended by the IOM).

Conflicts of interest with regard to clinical research design, conduct and publication of results are also being scrutinized as the result of recent industry scandals and changing public values. Recent scandals regarding the suppression of data and ghostwritten articles provoked renewed regulatory attention, but popular awareness had been building around conflicts of interest in clinical research such as publication biases, lack of appropriate controls, and industry-supportive research endpoints. Marcia Angell, leading medical educator and former editor of the New England Journal of Medicine makes some observations that might especially pertain to the current picture in sexual medicine:

Physicians who would be quite skeptical about drug company advertisements and the pitch of sales representatives tend to trust the peer-reviewed medical literature. One result of this bias in the literature is that physicians learn to practice a very drug-intensive style of medicine. Even when lifestyle changes would be more effective... (p.1071) [10]
**Ethical issues regarding sexual pharmaceuticals**

Scientifically tested medical and drug treatments for sexual dysfunctions are relatively recent, although the history of popular sex enhancers or aphrodisiacs stretches back thousands of years. [11] Following the enormous sales success of the first prescription oral drug for erectile dysfunction, Pfizer’s Viagra (sildenafil citrate), many companies became interested in sexual dysfunction and sexual medicine. Since 1998, a few new products have been approved, several have been discontinued while still in clinical trials, and a few older drugs have been approved for sexual indications. More drugs are under development including vascular, hormonal and central nervous system agents.

In addition to the standard approach of drug development, testing, approval, and information circulated to doctors, the sensationalism of sexuality and the huge profits signaled by the blockbuster reception of Viagra have introduced new challenges into the domain of sexual dysfunctions and pharmaceuticals: unlicensed prescribing, off-label prescribing, and advertisement directly to the public.

Fallon [12] has recently reviewed the range of drugs now commonly being prescribed ‘off-label’ for sexual problems, especially for rapid ejaculation in men and desire and arousal complaints in women. He suggests that routine use of such medications is often appropriate and based on reputable published studies. Other independent experts [13] have challenged the widespread use of off-label prescriptions, suggesting “most lacked evidence of clinical efficacy” (p. 1023).

In any case, no one will argue that sexuality pharmaceuticals are among the best-advertised of all drugs in those countries (currently only the USA and New Zealand) that permit direct-to-consumer advertising (DTCA). This situation has introduced numerous problems regarding patient demand, overprescribing, and patients’ miseducation. However, the era of DTCA may be ending, and, with it, some of the ethical dilemmas sexual medicine professionals have faced will subside. However, this arena of practice will continue to offer thorny challenges to all careful practitioners.

**REFERENCES**


**COMMENT**

**Eusebio Rubio-Aurioles**

The committee assignment of reviewing the broad spectrum of topic proved to be a significant challenge that in fact created a longer period of agreement that expected. An unfortunate agreement in the committee was the decision to publish some of the members’ views in an independent way, that is, with the member supporting only what she has to say about the subject.

Although Leonore Tiefer’s statement is highly pertinent and provocative, other members of the committee felt obliged to state specific comments and additions to this contribution to present a more balanced view, since the clear anti-pharmaceutical approach that she chooses is at the same time biased and unbalanced. Also, in some instances the references and commentaries posed are expanded.

The conflict of interest ethical dilemma in sexual medicine is a real one. However, pointing out only the negative aspects of this dilemma might be unfair and unrealistic, especially when the precisely the current level of development of sexual medicine as a field of inquiry, research, medical diagnosis and treatment has had an unprecedented development because of the involvement of the pharmaceutical industry, as the report quoted by Tiefer states:

*Research partnerships among industry, academia,*
and government are essential to the discovery and development of new medications and medical devices that provide improved means for the prevention, diagnosis, and treatment of health problems. Historically, the federal government has taken the lead in supporting discoveries in basic science, whereas commercial firms have focused on the discovery of specific medicines and then their development through clinical trials to the regulatory approval of marketable products (p.97 [1]).

The ethical dilemma posed by the involvement of the pharmaceutical industry should of course be addressed and professional medical organizations, scientific journals and health professionals in general should be aware that profit oriented activities with health professional should always be conducted with the highest scientific standards and in all cases, all levels of possible conflict of interests should be acknowledged.

The comments on off-label use of drugs for sexual dysfunction, as stated by Tiefer, is also unfortunate. One of the most researched uses of off-label medication for sexual dysfunction is the use of Selective Serotonin Reuptake Inhibitors (SSRIs) for the management of premature ejaculation. The review quoted by Tiefer [b], where authors state that off-label used lacks of scientific evidence, does not include the use of ISSR for this off-label indication, therefore, suggesting that the use of off-label medication for the treatment of premature ejaculation lacks scientific evidence is misleading, especially in view of the fact that approval for drugs to treat this condition is still pending in many countries of the world.

The fact that pharmaceutical industry supports continuous medical education activities poses another ethical dilemma. The suggested ban of support from the industry can make sense in areas of the world that have sufficient economic resources as to ask Universities, and government supported agencies to take over the role of promoting continued medical education. However, we have to recognize the in many areas of the world, activities supported by industry are the only ones available to the health professionals. Rather that promoting a generalized ban that would result in a detrimental effect for the underdeveloped areas of the world, a strengthening of the ethical standards in industry supported activities should be encouraged. The pharmaceutical industry has responded to these problems issuing recently a series of modifications to a code of ethics that promotes self regulation of their relations with health professionals (Code on Interactions with Healthcare Professionals, available at http://www.phrma.org/iles/attachments/PhRMA%20Marketing%20Code%202008.pdf)

International proposals for ethics in sexual medicine

The World Association for Sexual Health (WAS) has produced two documents that are highly relevant for ethical considerations in sexual medicine: the WAS Declaration of Sexual Rights and the In 1999, the WAS issued a Declaration of Sexual Rights that includes the basic values that are needed for a healthy sexual development and life. This declaration is reproduced in Box A and is available at http://www.worldsexualhealth.org/sites/default/files/Declaration%20of%20Sexual%20Rights.pdf
Declaration of Sexual Rights

Sexuality is an integral part of the personality of every human being. Its full development depends upon the satisfaction of basic human needs such as the desire for contact, intimacy, emotional expression, pleasure, tenderness and love.

Sexuality is constructed through the interaction between the individual and social structures. Full development of sexuality is essential for individual, interpersonal, and societal well being. Sexual rights are universal human rights based on the inherent freedom, dignity, and equality of all human beings. Since health is a fundamental human right, so must sexual health be a basic human right.

In order to assure that human beings and societies develop healthy sexuality, the following sexual rights must be recognized, promoted, respected, and defended by all societies through all means. Sexual health is the result of an environment that recognizes, respects and exercises these sexual rights.

1. **The right to sexual freedom.** Sexual freedom encompasses the possibility for individuals to express their full sexual potential. However, this excludes all forms of sexual coercion, exploitation and abuse at any time and situations in life.

2. **The right to sexual autonomy, sexual integrity, and safety of the sexual body.** This right involves the ability to make autonomous decisions about one’s sexual life within a context of one’s own personal and social ethics. It also encompasses control and enjoyment of our own bodies free from torture, mutilation and violence of any sort.

3. **The right to sexual privacy.** This involves the right for individual decisions and behaviors about intimacy as long as they do not intrude on the sexual rights of others.

4. **The right to sexual equity.** This refers to freedom from all forms of discrimination regardless of sex, gender, sexual orientation, age, race, social class, religion, or physical and emotional disability.

5. **The right to sexual pleasure.** Sexual pleasure, including autoeroticism, is a source of physical, psychological, intellectual and spiritual well being.

6. **The right to emotional sexual expression.** Sexual expression is more than erotic pleasure or sexual acts. Individuals have a right to express their sexuality through communication, touch, emotional expression and love.

7. **The right to sexually associate freely.** This means the possibility to marry or not, to divorce, and to establish other types of responsible sexual associations.

8. **The right to make free and responsible reproductive choices.** This encompasses the right to decide whether or not to have children, the number and spacing of children, and the right to full access to the means of fertility regulation.

9. **The right to sexual information based upon scientific inquiry.** This right implies that sexual information should be generated through the process of unencumbered and yet scientifically ethical inquiry, and disseminated in appropriate ways at all societal levels.

10. **The right to comprehensive sexuality education.** This is a lifelong process from birth throughout the life cycle and should involve all social institutions.

11. **The right to sexual health care.** Sexual health care should be available for prevention and treatment of all sexual concerns, problems and disorders.

Sexual Rights are Fundamental and Universal Human Rights

Adopted in Hong Kong at the 14th World Congress of Sexology, August 26, 1999

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A relatively short statement of ethical issues related to the practice of sexuality related professions was produced by the World Association for Sexual Health: The WAS Guiding Ethical Principles are available at http://www.worldsexualhealth.org/sites/default/files/Guiding%20Ethical%20Principles.pdf and are reproduced in BOX B
WAS- World Association for Sexual Health [4 ]

Guiding Ethical Principles*

Preamble

In our endeavors to achieve international recognition as the peak reference group for all matters associated with human sexuality, the World Association for Sexual Health (WAS) is committed to ethical practice in all areas. The Guiding Principles have application for clinicians, researchers, therapists, educators, and administrators. WAS acknowledges that most professions enunciate a specific code of conduct for their members, the WAS Guiding Ethical Principles are designed to enhance existing codes and provide guidance in the sensitive area of human sexuality.

The term sexologist implies a professional with specialist knowledge and skills in the area of human sexuality. Sexologists employ their specialist skills as educators, researchers, sociologists, clinicians, counselors, therapists and administrators. These Principles apply to all Sexologists when working within their professional capacity.

Various terms are used throughout this document to describe those persons, whether they be individuals, couples, groups, societies or any other entity, receiving services from or potentially affected by the professional activities of Sexologists. The terms include client, patient, student and research participant. These terms are not exclusive, nor are they intended to be definitive.

These ethical principles are designed to encompass all areas of sexology.

The Foundation Principles

The Code is founded on those principles recognized internationally through the agency of the United Nations, the World Medical Association and other, professional bodies.

The major principles are:

**Autonomy.** The obligation to support the individual’s right to self-governance through free and rational decision making.

**Beneficence** The obligation to act for the benefit of those who request professional services.

**Non-Malfeasance** The obligation to do no harm

**Justice** The obligation to act on the basis of fair adjudication between competing claims.

The Principles

**Principle 1: Sexologists shall have appropriate professional preparation and maintain an ongoing commitment to continuing education. Application:** Sexologists must hold a relevant, recognized professional qualification for their area of practice. It is the Sexologists responsibility to maintain standards of professional education and knowledge, based on current research and the development of procedures and techniques. This should be achieved through regular attendance at continuing professional education programs, professional seminars, meetings, congresses and the reading of appropriate professional literature.

**Principle 2: Sexologists must operate only within their area of professional expertise and competency. Application:** Sexologists should recognize the professional boundaries and the limits of their professional competency. They should declare the parameters in which they work and, where appropriate, refer people to another, appropriately qualified sexologist.

**Principle 3: Sexologists should inform clients, patients and research participants of their professional qualifications and affiliations. Application:** In their place of work, where applicable, Sexologists should display their qualifications in a manner that is readily observable. Qualifications should be from recognized institutions and organizations. Limitation: The display should be professional in nature commensurate with the dignity of the profession.

**Principle 4: Sexologists should uphold and enhance the integrity of the profession. Application:** Sexologists should act in a manner that supports and enhances the integrity of the profession. Thoughtful application of each of these principles achieves this.
**Principle 5: When available, Sexologists should engage in science-based practice** Application: Sexologists should employ techniques and procedures that have demonstrated efficacy, based on appropriate research. *Limitation* In behavioral, clinical or social research, experimental and developing procedures may be employed when the risk/benefit ratio has been carefully assessed and there is full disclosure to the research participant. In education and health promotion innovative techniques may be used giving due regard to the social and cultural context and participants are appropriately informed.

**Principle 6: Sexologists have a responsibility to maintain and enhance the knowledge, health and welfare of their communities** Application: Actions taken on behalf of a client, patient or community may have an undesired affect on others, including groups within a society or the society itself. Sexologists should have regard for the impact of their proposed actions and make a decision based on the greater good.

**Principle 7: Sexologists should exercise respect for colleagues.** Application: Sexologists should act in a manner that does not bring disrepute upon their colleagues or their profession. They should act on principles of fairness at all times and not take actions that undermine individual colleagues. *Limitation:* Where a Sexologist has evidence that a colleague has acted unprofessionally is incompetent or otherwise acting inappropriately, the matter should be first discussed with that colleague and, if necessary, brought to the attention of relevant authorities.

**Principle 8: Sexologists shall not breach the professional relationship.** Application: Within the context of the professional relationship the Sexologist must act with integrity at all times. A Sexologist must not engage in intimate relations with a client, research participant, student or patient, or otherwise place them in a position where the professional relationship is compromised. When the service is of a psychotherapeutic nature a Sexologist should not provide services to a close family member.

**Principle 9 The sexologist shall respect and uphold the autonomy and dignity of those receiving their professional services.** Application: This principle applies irrespective of age, gender, race, ethnicity, educational level, sexual orientation, social circumstances, or political affiliation. It obliges the Sexologist to facilitate the exercise of autonomy through providing necessary and sufficient information to enable rational decision-making. *Limitation:* Individual autonomy is limited by the recognition of the rights of others and the avoidance of harm. It is also limited through the capacity of an individual to make rational decisions on their own behalf. Under such circumstances an advocate may act on behalf of that person. (Appendix 1.)

**Principle 10 The Sexologist shall maintain professional confidentiality** Application: Sexologists should maintain confidentiality at all times. Informed consent must be first obtained prior to disclosing information to third parties. *Limitation:* Under certain jurisdictions there is a legal obligation to report particular activities to certain authorities. The Sexologist is morally obliged to make a reasoned decision as to disclosure. Such decisions should be based on the legal and political circumstances and on what is deemed to be the greater good.

**Principle 11 Where appropriate, the Sexologist should obtain informed consent.** Application: Prior to implementing any action the Sexologist should provide sufficient and necessary information on the recommended activities and alternatives. The possible benefits and risks must be disclosed. The Sexologist may disclose which option is, in their professional opinion, the optimum action within a particular context. *Limitation:* Where the person is not in a position to provide informed consent, an advocate may act on their behalf.

**Principle 12 Sexologists will maintain appropriate records.** Application: Sexologists will maintain records on clients, client groups, patients or research participants. Such records may be used for research purposes when prior, written consent has been obtained.

**Principle 13: Sexologists will provide information on their fee schedule to potential clients** Application: Prior to the provision of services, information on fee schedules, insurance rebates and tax provisions, where relevant.

**Principles for the conduct of ethical research**

**Principle 14: Sexologists shall employ recognized research protocols** Application: All research activities should follow an acknowledged research protocol that is deemed by peers to be appropriate to the nature of the study.

**Principle 15: Sexologists shall employ recognized protocols in the use of human research subjects** Application: The use of human subjects requires adherence to the Helsinki Declaration, which includes the following: informed consent, potential benefit(s) must outweigh potential risk(s), freedom to withdraw without
Prejudice and confidentiality

**Principle 16: Sexologists shall employ recognized protocols in the use of animal research subjects.**  
*Application:* The use of animal subjects requires adherence to the protocol set down for the humane treatment of experimental animals, which includes the following: appropriate housing of the animal subject minimization of pain and discomfort and appropriate disposal at the conclusion of the study.

**Principle 17: Sexologists shall utilize peer review to evaluate their work.** *Application:* Research proposals and research reports should be made available for expert and peer review.

**Principle 18: Sexologists have an obligation to provide support for, or to conduct research and to disseminate findings.** *Application:* Sexologists should contribute to the development of the body of knowledge through the conduct of appropriate research and through dissemination of findings. This applies to adverse outcomes as well as positive one.

*Approved by the WAS General Assembly on July 13th, 2005, Montreal, Canada*
III. SOCIO-CULTURAL ASPECTS IN SEXUAL MEDICINE

Eusebio Rubio-Aurioles

The influence of culture on sexual behavior has been extensively studied and documented. In a classic book reporting the differences on a variety of sexual behaviors comparing information from more than 200 societies “culturally independent” as: “patterned and customary ways of behaving and acting that characterize the members of a society” [5]. Sociology has studied culture in several ways but one of the clearest concepts proposed to study the relationship of culture with human sexual behavior is the concept of “sexual script” that basically proposes that members of a group are prescribed how to behave in terms of what to do, with whom to do it, when and how to do it and with a rationale to do it to have the why [6]. Thus, culture acts through sexual scripts at an individual level.

A large number of anthropological and sociological studies have documented the variability of sexual behavior that can be attributable to culture [7]. While the objective of this review is not to present a full account of the cultural variability of human sexual behavior, there is a need for the clinician working in sexual medicine to be aware of the fact that culture has a very significant impact on how sexuality is understood and experienced in people’s lives. This need is particularly important for practitioners of sexual medicine who serve culturally diverse populations.

I would be out of the scope of this chapter to cover the amount of information which is published that refers to the specific differences among cultural groups. The reader is referred to valuable resources that have summarized the characteristics of different areas and cultural groups around the globe, in particular the work edited by Robert Francoeur and Raymond Noonan [8] with descriptions on the views and ways in which human sexuality is lived on 60 countries and places with information relatively recent, with the additional advantage of having its contents freely available over the internet at http://www2.hu-berlin.de/sexology/IES/xmain.html. A clinician, who finds himself or herself in a situation where he or she is serving a patient from a culture not familiar to him, could find it valuable to review what is available on the particular culture with this resource or others.

Another problem that Cross-Cultural research on human sexual behavior has encountered is the fact that many cultures (i.e. groups of people who were originally isolated in a single cultural milieu) have encountered a process of acculturation that has made that the westernized cultural view of sexuality has been present and absorbed by many societies originally isolated from the mainstream of westernized culture. An attempt to overcome this problem was carried out by a group lead by Murdock and White in 1969 [9] who assembled a sample of culturally “pure” societies with information obtained by a large number of anthropological reports. This sample has been utilized by many researchers to make sense of the variability observed amongst cultures.

One particular review of these attempts merits mention: In 1986, the American sociologist Ira Reiss published a report using the standardized sample of Murdock and White and performed several statistical analyses to attempt to identify culturally variable sexual scripts, and culturally invariable sexual scripts [10]. Reiss conclusion after this analysis was that the following propositions could be held after the analysis: 1. Societies judge stable social relationships as of great importance. 2. Societies view physical pleasure and self disclosure as the building blocks of social relationships. 3. Physical pleasures and self-disclosure are the common outcomes of sexual behavior. 4. Therefore, sexual behavior will be seen as important due to its ability to promote stable relationships. 5. Such stable bonding between genetic males and females produces a context for the nurturance of offspring- 6. Stable heterosexual relationships are the rudimentary bases for husband-wife and parent-child roles; and thus in this sense, kinship an gender roles are derivative from the bonding properties of the sexual relationship. 7. Important social relationships are culturally defined in ways that are intended to institutionalize protective mechanisms and, 8. Therefore, marital sexuality will involve jealousy norms concerning the ways, if any, to negotiate extramarital sexual access without disturbing the existing marriage relationship.

CULTURALLY SUPPORTED SEXUAL PRACTICES THAT HAVE BEEN IDENTIFIED AS HAZARDOUS TO HEALTH.

A number of practices held in areas of the world where culture prescribes what the World Health Organization (WHO) denominates hazardous sexual practices remain in today’s world. Among them, female genital mutilation (FMG), in its various forms and ways of practice, remains a classic example where cultural values collide with the minimum requirements to attain sexual health. Specific recommendations to prevent FMG from occurring have been issued [11]

In addition to FMG practices such as dry sex, where the value of a lubricated vagina is not recognized but dryness is preferred. Vaginal dryness is promoted by certain cultures as means of increasing male sexual pleasure but the health consequences on the female have been documented as deleterious [12].
In any event, the possible conflict between health promoting values and culturally held values continues to pose a big challenge for the promotion of sexual health. In general, it can be said that when a cultural practice challenges the chance of fulfilling a human right, the practice should be revised and perhaps challenged and eliminated.

A PROGRAM FOR CULTURAL CHANGE PROMOTING SEXUAL HEALTH

Recently, the World Association for Sexual Health produced a document where the available evidence was reviewed by a panel of experts from around the globe [13]. Eight cultural changes were identified as necessary to promote a sexually healthy world and they are summarized as follows:

1. Recognize, promote, ensure and protect sexual rights for all

Sexual rights are an integral component of basic human rights and therefore are inalienable and universal. Sexual health is an integral component of the right to the enjoyment of the highest attainable standard of health. Sexual health cannot be obtained or maintained without sexual rights for all.

2. Advance toward gender equality and equity

Sexual health requires gender equality, equity and respect. Gender-related inequities and imbalances of power deter constructive and harmonic human interactions and therefore the attainment of sexual health.

3. Condemn, combat, and reduce all forms of sexuality related violence

Sexual health cannot be attained until people are free of stigma, discrimination, sexual abuse, coercion and violence.

4. Provide universal access to comprehensive sexuality education and information

To achieve sexual health, all individuals, including youth, must have access to comprehensive sexuality education and sexual health information and services throughout the life cycle.

5. Ensure that reproductive health programs recognize the centrality of sexual health

Reproduction is one of the critical dimensions of human sexuality and may contribute to strengthening relationships and personal fulfillment when desired and planned. Sexual health encompasses reproductive health. Current reproductive health programs must be broadened to address the various dimensions of sexuality and sexual health in a comprehensive manner.

6. Halt and reverse the spread of HIV/AIDS and other sexually transmitted infections (STI)

Universal access to effective prevention, voluntary counseling and testing, comprehensive care and treatment of HIV/AIDS and other STI are equally essential to sexual health. Programs that assure universal access must be scaled up immediately.

7. Identify, address and treat sexual concerns, dysfunctions and disorders

Since sexual concerns, dysfunctions and disorders impact quality of life, it is critical to recognize, prevent and treat sexual concerns, dysfunctions and disorders.

8. Achieve recognition of sexual pleasure as a component of holistic health and well-being

Sexual health is more than the absence of disease. The right to sexual pleasure should be universally recognized and promoted.

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Committee 5

Economical Aspects Of Sexual Dysfunctions

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INTRODUCTION

The economical aspects of sexual dysfunctions (SD), primarily erectile dysfunction (ED) has changed significantly over the years. Limited data indicate that the economic considerations in SD therapy continue to increase. There are several reasons for this increase, including greater acknowledgment of the widespread prevalence of sexual disorders, SD's as undertreated conditions, a broader spectrum of individuals at risk, aging of the population with more concern about quality of life, the success of oral therapy and other new therapies under development. The global aging process and dramatic improvements in longevity are expected to strongly influence the economic issues of SD management. However, there are little published data on the economic aspects of SD. Further research is necessary to determine the various components of the economic impact of ED and other SD. Research should also explore cultural and ethnic determinants in the economics of these conditions and societal impact of their treatment. Therefore, studies should be both cross-sectional and longitudinal due to the cumulative effect of SD and the unknown long-term issues such as rates. Cost-effectiveness analyses can be informative because they systematically distill medical decisions down to the quantity and quality of life gained by intervention and may help determine specific algorithms for ED and other SD management including cost. Drug comparative and drug combination studies have shown safety and efficacy of the therapy but more longitudinal studies are needed to further elucidate ineffective and unnecessary expensive combinations. The mission of the Committee on Economical Aspects is to identify, research, summarize and report on all medico-economic issues related to ED and other SD for both male and female. In addition, the Committee is charged to produce observations, conclusions and recommendations regarding the economic aspects. The study of the economics of medical conditions may be performed at different levels, namely;

1. DESCRIPTIVE ECONOMICS

This involves a precise definition of the condition under study, as accurate identification of the disorder and the subject is fundamental in the description of the economic consequences.

2. ANALYTIC ECONOMICS

This involves the search for recognition of trends, correlations, predictors and other statistical indicators. This is important in the understanding of market or consumer behavior and the identification of influencing factors.

3. INTERVENTIONAL ECONOMICS

This involves the planning of an intervention and the investigation of a consumer or market response. This chapter is mainly confined to descriptive and to a lesser extent analytic economics.

I. EPIDEMIOLOGY OF SEXUAL DYSFUNCTIONS

Sexual dysfunctions in both males and females have a substantial prevalence throughout the world. Greater public health awareness surrounding SD, population growth and the global aging population...
will unequivocally continue to increase the prevalence of SD. The population growth and increased life spans predispose more people for SD as longevity allows for more active sex life in couples. Sexual dysfunctions of male and female includes a broad spectrum of disorders. Male SD includes ED, Peyronie’s disease, early (premature, rapid) ejaculation, desire disorder, hypogonadism and priapism. Female sexual dysfunction involves disorders of sexual desire, arousal, orgasm and dyspareunia, which lead to personal distress. Therefore, sexual dysfunction epidemiology can be further appreciated when dissected into both male and female SD.

1. MALE SEXUAL DYSFUNCTION

Even though numerous studies have been published in the last five years on prevalence of ED, limited data is available for the different facets of male SD, thus, this review will mainly focus on ED and premature ejaculation (PE). The first major large-scale community based study of ED in the US was the Massachusetts Male Aging Study (MMAS), which estimated a prevalence of 30 million men for minimal, moderate and complete ED [1] and up to 100 million men worldwide. [2] The Health Professions Follow-up study comprised of more than 31,000 men aged 53-90 years in the United States (US) found that ED ranged from 25% among those younger than 59 years to 61% in those older than 70 years old. [3] The National Health and Nutrition Examination Survey (NHANES) representing both racial and ethnic groups in the US with a sample of 2,126 men from age 20-75 years established an overall ED prevalence rate of 18.4% based on self-reporting of being “sometimes able or never able to keep an erection adequate for sexual intercourse.” In this study an association between age and ED was shown, with prevalence steadily increasing from 6.5% in men 20-39 years to 77.5% in those ≥ 75 years old. Notably, Hispanic men younger than 50 years reported ED at approximately twice the rate of Whites (12.5% vs. 4.9%), after controlling for hypertension, diabetes and obesity which are risk factors for ED. [4]

The Global Study of Sexual Attitudes and Behaviors (GSSAB) was an international survey comprised of 13,618 men in 29 countries that systematically calculated sexual problems among adults aged 40-80 had an overall prevalence of 10%, mainly in Asian countries. [5] Their analysis also showed that ageing effects are quite strong across most regions with respect to erectile difficulties. In all regions, except Central/South America and Southeast Asia, men aged 60-80yrs are significantly more likely to report erectile difficulties than those aged 40-49yrs (OR from 2.7 to 6.9). The Male Attitudes Regarding Sexual Health survey was a nationally representative study of men older than 40 years of age and minority groups. The study estimated the prevalence of moderate or severe ED to be 22% overall. ED prevalence rates were 21.9% among 901 White men, 24.4% for 596 Black men and 19.9% among 676 Hispanic men. [6]

More recently, the National Social Life, Health and Aging Project (NSHAP) with published data from 2005-2006 comprised of 1455 men 57-85 years of age surveyed adults about sexual function and behavior via in-home interviews [7]. Analysis of the data indicated that the most prevalent sexual problem were erectile difficulties (37%), where 90% of these people were bothered by this condition. The likelihood of being sexually active declined steadily with age but yet a substantial number of older men regard sexuality as an important part of life.

Despite variations in definition, methodology and study populations, these studies substantiate the global extent and presence of male SD. The prevalence of ED is not the same in different continents, countries, and ethnic groups. One of the reasons for this difference may be a non-uniform definition of ED. [8-9]

While substantial data exist on the prevalence of ED, there is little knowledge regarding the incidence of drop out from treatment programs or discontinuation of follow-up visits. Approximately 9 to 25% of sildenafil responders discontinued successful treatment because of medication cost. [10] In a recent study conducted by Cooke et al, [11] sildenafil prescriptions were–filled by 51.4% of members in a managed care organization in the first quarter of 2001 but significantly decreased to 13.9% by the fourth quarter. In order to obtain accurate data of ED prevalence, it is important to build homogenous reports with uniform nomenclature regarding definition and severity of ED. The prevalence of ED should always be calculated among groups of the same age range.

The understanding and assessment of premature ejaculation (PE) has increased over the past five years.[12] Although there are varied conceptualizations of PE, the standards committee of the International Society of Sexual Medicine defined lifelong PE as a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy.[13-14] Current data suggest that PE is the most frequent male SD with an estimated prevalence of 20% to 30%.[15] The prevalence of PE varies widely between different countries. The Keele (UK) study reported a prevalence of 18%, with less than 50% of sufferers expressing a desire for treatment. Prevalence in the Middle East and Japan
have rates as high as 45-50%. Past data on the prevalence of PE are varied, once again, in great part owing to the lack of prior standardization of the definition of PE and criteria for patient enrollment in epidemiologic studies.

2. FEMALE SEXUAL DYSFUNCTION (FSD)

Female sexual dysfunction (FSD), a multidimensional medical condition with organic (biological), psychological and social (interpersonal) determinants. FSD has detrimental effects on a woman’s quality of life and also has economical and societal impact. The data derived from the US National Health and Social Life Survey (NHSLS), which evaluated a national probability sample of 1,749 women, is widely cited due its methodological approach. The authors reported that 43% of women are affected by SD. The recent Global Study of Sexual Attitude and Behaviors (GSSAB) international survey of 13,882 women 40-80 years of age found that 39% of women reported a problem with sexual activity. More currently, the NSHAP data of 1550 women 57-85 years old reported that the most prevalent sexual problem was low desire (43%).

The Sexual Function Health Council of the American Foundation for Urologic Disease (AFUD) devised the first consensus-based definition and classification system for FSD. It is disorders of sexual desire, arousal, orgasm and pain that lead to personal distress. Sexual desire disorder include low desire, with a prevalence of 43% of women between 57-85 years of age. Sexual arousal disorders, characterized mainly by vaginal dryness, have been reported in 39% of women. Orgasmic disorder is reported in 34% of women. Sexual pain disorders include dyspareunia and vaginismus, which is reported to have a prevalence of 12.8%.

In conclusion, there is still great potential for advancing our understanding of women’s sexual function. The use of quantitative and validated questionnaires would help to investigate the extent and importance of this emerging problem. Additionally, further research on risk factors, quality of life issues, and development of effective treatment solutions are needed to determine the economic impact of FSD.

II. AGING AND SEXUAL DYSFUNCTION

Aging is a key risk factor for the development of male ED as revealed by the classical work of Kinsey et al, which is the first epidemiological study of male sexual behavior published in 1948. They recruited a total of 15,781 men up to 80 years of age and found a prevalence of erectile dysfunction ranging from <1% for young men to 80% in the uppermost age group. A half of century later, the MMAS reported a similar trend. Specifically, the prevalence of ED increased from 39% in men in their 40’s to 67% for those in their 70’s. The validated questionnaire used in the MMAS was also utilized by a cross-sectional epidemiological study conducted in four different countries (Brazil, Italy, Japan and Malaysia). Collectively, these studies affirm the global extent of ED with an age-dependent increase in prevalence.

A notable aspect of the global aging process is the progressive demographic ageing of the older population itself. For most nations, regardless of their geographic location or developmental stage, the 80 or over age group is growing faster than any younger segment of the older population. The most remarkable increase is expected to occur in Japan, where in 2050; more than 1 in every 3 persons aged 60 or over will be at least 80 years old. In 2050, six countries will have more than 10 million people aged 80 years or over: China 99, India 48, US 30, Japan 17, Brazil 10 and Indonesia 10 million. Together, they will account for 57% of all those 80 or over in the world. The recent UN report showed significant increase in the average life expectancy in the whole world (Fig 1) projecting substantial increase in old men and women with sexual dysfunctions.

Fig. 1 Projections of Populations > 80 y.o.

Since age has been shown to be a significant risk factor for all types of SD, we anticipate an enormous number of patients with ED or SD due to the growing population for those over 80 (Fig. 2).

General practitioners are typically the first point of contact for men experiencing health problems and are a primary source of help for SD. Despite this, many men find it difficult to address this condition in a clinical setting. Recently, Australian prevalence data indicated that while 21% of men aged over 40 years suffer from ED; only 30% discuss their problem with a health professional. Shabsigh and associates reported treatment-seeking behavior in 6 different countries (USA, France, Germany, Italy, Spain and
They found that barriers to addressing ED include patient assumptions that it is a normal part of aging, apprehension discussing sex and fear of a negative response. Therefore, aging itself did not directly increase the cost of ED diagnosis and treatment. We have to estimate the cost by combining the age demographics and the treatment-seeking rate in each country or culture. However, increased acknowledgement and acceptance of SD worldwide, as well as professional cognizance will drive the cost of ED much higher.

III. RISK FACTORS

The United Nations has reported over 374 million men worldwide aged 65 years and older by 2025, an increase of 164 million from the current number. In 2002, the global proportion of men aged over 65 years was 10%; this is set to rise to 20% by 2050. The strong correlation between ED and ageing will inevitable increase the prevalence of ED in the future. Although ED is an age-dependent medical condition, it is also highly associated with co-morbidities such as vascular, hormonal, neural, psychogenic factors and drug adverse effects.

Despite the prevalence and implications of ED on quality of life, current data on ED among the healthy population is scarce, particularly for physiological and psychosocial variables.

1. ERECTILE DYSFUNCTION

Erectile dysfunction is a prevalent condition associated with co-morbid conditions such as diabetes, hypertension, hyperlipidaemia and metabolic syndrome that share an underlying pathophysiology mechanism with endothelial dysfunction. For instance, in a cohort of 1,519 healthy men, those with a total cholesterol >240 mg/dl and LDL of >160 had a 2.7 and 2.6 fold increased risk for moderate to severe ED, respectively. [25] By the same token, in the case of hypertension, analysis of 3,906 men using Sexual Health Inventory in Men (SHIM) questionnaire, (where ED was determined by a SHIM score of < 21) found that about 67% of men with hypertension have some degree of ED. [29] Although ED is a natural consequence of aging, its severity is directly related to vascular risk factors, all of which are associated with endothelial dysfunction.

a) Diabetes

Erectile dysfunction is common in men with diabetes. Prevalence rates range from 20 to 85% in men. Men with diabetes are at a 3-fold risk for ED than those without this health problem. ED affects those with diabetes at an average of 10 to 15 years earlier than the general population regardless of insulin dependency status. [1] In diabetic men, ED may be multifactorial involving possible vascular, neurological and components, any of which as a causal factor significantly impacts the quality of life for these men.

b) Depression

Depression and ED clearly are associated. In the landmark MMAS, men who had untreated depression were almost twice as likely to report ED than men without depression. [1] Of sexual complaints among depressed men, low libido is most prevalent, followed by orgasmic difficulty and finally ED. [26] Co morbid
ED and depression are seen commonly in practice. The association between the two conditions is bidirectional, with each factor reinforcing the other.

c) Cigarette Smoking

The underlying pathophysiology of ED in smoker’s remains poorly understood. However, most investigators still consider smoking as a risk factor for vasculogenic ED. The duration of smoking, the number of cigarettes smoked per day, and the number of years smoking directly correlates with ED and confer not only a higher prevalence but also heightened ED severity [27]. Epidemiological and clinical studies suggest that smoking causes peripheral vascular disease and adversely affects erectile function by impairing endothelium-dependent smooth muscle relaxation. [28] With some studies reporting a dose response pattern [29-30].

d) Alcohol Consumption

Although alcohol is considered to improve erection and sexual drive when utilized in small amounts due to vasodilatory effects and suppression of anxiety, excessive alcohol consumption has long been regarded as a risk factor for ED. In fact, chronic, heavy alcohol consumption may have an irreversible effect on erectile function due to neurological damage. Polsky et al [29] reported a significantly higher OR with >8 drinks/day than 1-7drinks/day (2.09 vs. 1.96) after adjusting age, education levels, presence of diabetes and smoking.

e) Overweight/Obesity

Excess body weight and obesity may increase the risk of ED by 30-90% compared to normal weight subjects. The Health Professionals Follow-up Study reported that men with a BMI higher than 28.7 are likely to carry a 30% higher risk for ED than those with a normal BMI (<25). [3] The 9-year follow-up MMAS reported that body weight was an independent risk factor for ED, with a risk exceeding 90% of controls (OR 1.93 and 1.96).[31] In addition, in a case-control study, compared with age and weight matched control subjects, patients with the metabolic syndrome had higher OR with >8 drinks/day than 1-7drinks/day (2.09 vs. 1.96) after adjusting age, education levels, presence of diabetes and smoking.

2. PEYRONIE’S DISEASE

Peyronie’s disease is a fibrotic disorder of the tunica albuginea of the penis resulting in varying degrees of penile curvature and veno-occlusive dysfunction that leads to sexual dysfunction in some men. Information on the prevalence of Peyronie’s disease is mixed but generally suggests that approximately 5% of men aged 50 years or older will experience this condition. The most convincing population based data was reported by a community, cross-sectional study of 8,000 men from Germany, where 3.2% showed symptoms consistent with the disease. A linear trend was observed for the prevalence of the disorder ranging from 1.5% for men 30-39 years old to 6.5% for men over 70.[33] Similar prevalence was seen among 100 men screened for prostate cancer in Brazil, where 3.7% of men 50 years and older reported symptoms of penile angulation or plaque.[34]

3. PREMATURE EJACULATION

ED and early ejaculation coexist. Poor overall health and/or a simultaneous urological condition increase the risk of premature ejaculation (PE). The NHSLS found that men who self-report “poor to fair health status” have a significantly elevated risk of PE, as well as ED and low sexual desire.[17] Youth as long been postulated as a significant risk factor for PE because some younger men have limited sexual experience. Surprisingly, the NHSLS results showed that younger individuals (18-29 years) do not appear to be at any greater risk for PE than older men, up to 59 years old. PE is likely the only major SD to manifest in healthy young adults and is worth increased efforts for early diagnosis and treatment.

4. FEMALE SEXUAL DYSFUNCTIONS

Female sexual problems do not increase with biological age, unlike in men. The NSHAP data demonstrated a strong relationship of stress, anxiety, depression and poor mental health with women’s endorsement of sexual problems.[9] Additionally, results indicated that certain health conditions strongly affect the likelihood of sexual problems among women. For instance, any life-time history of STDs roughly quadruples women’s odds of reporting sexual pain (OR=3.8) and triples their lubrication problems (OR=3.1). Similarly, lower urinary tract syndrome increases women’s lack of sexual interest (OR=6.5) and lack of sexual pleasure (OR=4.2). Women’s lack of pleasure is also higher among those with poor self-rated physical health (OR=2.7). Relative to white women, Hispanic women reported sexual pain 2.5 times more (OR=2.4) and black women reported 60% lower incidence of lubrication problems. Having some college education lowers women’s performance anxiety by half or more relative to women with less than a high school diploma. Also, women with high school or equivalent education had lower incidence of lack of sexual interest.[35]
IV. IMPACT OF SEXUAL DYSFUNCTION

1. ECONOMICAL

The prevalence of ED is high and is strongly age-related. In 2002, the global proportion of men aged over 65 years was 10%, this is set to rise to 20% by 2025. The projections made in 1998, that a fourfold increase in the ED budget would occur in the next 4 years to 2002, from about $0.9 billion to $5 billion have been proven.[36] The economical impact of any medical condition is not restricted to the cost of diagnosis and management. The impact may include lost time at work, decreased productivity, and the effect on partner, family and co-workers. The impact is further confounded by the correlates of ED, which have high economical implications such as, atherosclerosis, myocardial infarction, diabetes mellitus, hypertension, depression, BPH and prostate cancer.

2. QUALITY OF LIFE

The quality of life for men as it relates to both general and disease specific issues have been evaluated and reported in several studies of prostate cancer and ED.[37-39] In a recent study conducted in France, men with ED that were treated with intracavernous injections (ICI) of prostaglandin E1 (PGE1) reported satisfaction and improved sex life. Assessments were made using validated questionnaire to evaluate overall satisfaction with ICI, impact on quality of life, ease of use, perceived partner satisfaction and quality of erections. The overall satisfaction rate for ICI was 78.3%, 81.1% found the injections easy to use, 86% were ready to recommend ICI to friends, 70.1% had improvements in their sex life, 50% had improved relationships with their partner, 44.8% had improved quality of life and 80.3% had confidence in attempting sexual intercourse.[40] Another recent study of 553 men with ED from the US, Brazil, Mexico, Australia and Japan assessed psychosocial measures after treatment with sildenafil citrate. The IIEF and Self-Esteem and Relationship (SEAR) questionnaires were utilized. The sildenafil group reported significantly greater improvements in self-esteem, confidence, sexual relationship satisfaction and all sexual function domains of the IIEF.[41]

Many studies have used different assessment tools for quality of life issues in men suffering from ED. Various questionnaires are used to ascertain psychosocial factors associated with ED. Despite the methodology or lack of consistent assessment tool, these studies demonstrated significant improvement in quality of life for men with ED.

3. RELATIONSHIP

Erectile dysfunction is a common condition with diverse sequelae affecting men and their partner’s, disrupting their relationship due to a lack of intimacy. The negative impact of ED such as depression, anxiety and low-self esteem seen in these patients can influence their partner’s satisfaction as well. A recent study reported different modalities for organic ED led to couple satisfaction. Approximately 354 couples were classified according to their line of therapy into five treated groups. The Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) and IIEF were used for assessment. Sildenafil citrate-treated group represented the highest mean value of satisfaction domains of IIEF and penile implants group was second. The testosterone group represented the highest mean value for sexual desire. Domains of quality of life were significantly improved among satisfied cases more than unsatisfied subjects after therapy.[42]

The aggregate findings from all these cross-cultural studies highlight the universal improvement in psychosocial function and well-being in men after successful ED treatment.

4. CO-MORBID CONDITIONS

Co-morbid conditions affect erectile function and quality of life, and treatments of these conditions usually improve these issues. Conditions such as arterial insufficiency may predispose men to ED at an earlier stage, thus, PDE-5is have now been implicated as useful therapy for both ED and cardiovascular disease. Sildenafil has been shown to improve cardiac output and cause vasodilation in men with congestive heart failure and pulmonary hypertension also suffering from ED.[43]

V. TREATMENT SEEKING BEHAVIOR

Patterns of help-seeking behavior among men with ED are important to recognize and identify in order to improve access to treatments, and limit the psychological burden. In a study by Moreira et al [44], behavioral factors related to seeking help for ED were identified from the GSSAB international survey in 29 countries among men aged 40-80 years. They found that 77.8% of men sought no professional help or advice for their sexual problems. Only 18% made an attempt to seek medical help. Men from East Asia were the least likely to seek medical help (6.5%), whereas those from South-east Asia were the most likely (22.5%). The most frequent action taken by men was ‘talk to partner.’ Countries from East Asian and Middle Eastern clusters reported the lowest frequencies, while South-east Asia and Southern Europe had the highest frequencies of this action. The frequency of seeking psychological help
(psychiatrist, psychologist or marriage counselor) was low and varied widely among men (2-12%). However, higher frequencies were reported in countries from the Middle East and South-east Asia. As they got older, men from Southern Europe and Central/South America were more likely to seek medical help. Generally, those more likely to seek medical help were respondents who have been asked by a doctor about possible sexual difficulties in a routine visit in the past 3 years or those who think a doctor should routinely ask patients about their sexual function. The most common reasons for not seeking help by 74% of men was that ED is a normal part of ageing. Some felt comfortable accepting this notion. Another 68% didn’t think this was serious or the problem would go away. Similar studies have reported these same beliefs of acceptance and complacency.[45] A Japanese study specifically addressed patient’s attitudes toward ED treatment through a national mail survey sent to married couples 30-79 years of age. Of the 2,034 males that responded to questions about sexuality, 29.9% felt they had ED. Only a small percentage sought treatment, and 4.8% consulted a physician. Reasons for not doing so were cited as ‘not bothered by ED’ or cultural shyness.[46] In a cross-sectional study in Australia, 409 men were evaluated for ED duration and treatment seeking behavior. Their results demonstrated that men with ED of longer duration were more likely to have discussed their ED with their partner and doctor. Also, these patients sought information and treatment for their ED problem. The reason might be that men with a longer duration of ED are more likely to perceive their ED as severe and permanent, thus, lower frequency of sexual activity would make them more willing to seek help for this problem. [47] There is a high level of abandonment of ED medication therapy (50-60%), only few patients appear to remain on oral therapy for more than a year. [48] The reasons for drop-out rates or patient dissatisfaction with oral ED therapy is unclear. However, Kloetz et al [49] reported that patients discontinued treatment due to a lack of opportunity or desire for sex, or that their partner had shown no sexual interest.

It is clear that there are behavioral factors which become barriers as it relates to seeking medical help for ED and other SD in men. These patterns of behavior result in high drop-out rates for therapy and low utilization of medical service. Therefore, further research is warranted in addressing this issue.

### VI. DIAGNOSTIC EVALUATION

The evaluation of any patient with SD should proceed in a stepwise manner. The latest American Urological Association guidelines on ED state that “the typical initial evaluation of a man complaining of ED is conducted in person and includes sexual, medical and psychosocial histories as well as laboratory tests thorough enough to identify co-morbid conditions that may predispose the patient to ED and that may contra-indicate certain therapies.”[50] One important goal of a diagnostic evaluation is to identify any correctable cause of SD. As it pertains to FSD, little standardization of the diagnostic evaluation exists. However, the diagnostic assessment for male sexual dysfunction is well established. The remainder of this section will deal with the evaluation of ED only. Overall, the economic impact of diagnostic evaluation is poorly understood as the data on this topic is approximated and remains speculative.

The diagnostic flow-chart is comprised of three levels ranging in invasiveness and expense. This includes 1) non-invasive 2) semi-invasive 3) invasive tests. The first level consists of history, physical examination and limited laboratory tests. Routine lab tests include blood glucose, lipid panel, and hormonal assessment. A complete medical history and psychosexual assessment may include validated questionnaires, such as IIEF or Aging Male Symptom (AMS). This is followed by a thorough focused physical examination. The accuracy of this initial evaluation to establish a differential diagnosis between organic and psychogenic ED was determined by Davis-Joseph and associates.[51] They concluded that medical history and physical examination had a sensitivity of 95% but specificity of only 50%, which is quite reasonable considering the simplicity and low cost of this evaluation.

Semi-invasive tests include nocturnal penile tumescence (NPT) and rigidity recording, ICI pharmacotesting, and color duplex Doppler ultrasonography (CDDS). The evaluation of nocturnal erectile activity helps to differentiate organic from psychogenic ED. In general, the Rigiscan it is neither sensitive nor specific enough to diagnose ED because of the high incidence of false-negative and false-positive results. This test costs approximately US $140 as reported in CPT (current procedural terminology) codes and insurance reimbursement policy.

Intracavernosal Injection (ICI) testing is useful in the initial evaluation and treatment of ED. It involves a single intracavernosal injection of either 10 or 20mg of a vasoactive agent (prostaglandin E1) and then an assessment of the response. This evaluation costs approximately US $104 as reported in CPT (current procedural terminology) code and insurance reimbursement policy.

Color duplex Doppler ultrasonography (CDDS) can assess penile blood flow. CDDS has been found to be specific and accurate. This study is often
performed in conjunction with a stimulant, such as an injectable, intracavernosal agent (PGE-1) or genital plus audio-visual to overcome anxiety and sympathetic stimulation brought on by the test itself. The cost for the test and necessary drug/stimulant is approximately US $141 as reported in CPT codes and insurance reimbursement policy.

More invasive studies include dynamic infusion cavernosometry/ cavernosography (DICC) and arteriography. DICC were gold standard in the diagnosis of veno-occlusive dysfunction. However, veno-occlusive dysfunction is often a multifocal problem and a result of degeneration of vascular smooth muscle rather than a site specific venous leakage. This evaluation costs approximately US $163 as reported in CPT codes and insurance reimbursement policy. Penile angiography is reserved exclusively for patients who are candidates for penile revascularization (such as patients that suffered trauma or perineal crushing injury). It has limited role in the evaluation of patients with ED.[52]

VII. RESEARCH AND DEVELOPMENT

Research-based and pharmaceutical companies invested $58.8 billion in research and development in 2007, an increase of nearly $3 billion from 2006. The majority of this money was focused on diseases related to hematology/oncology, central nervous system, infection, cardiovascular and endocrinology. The expenditure for the development of products related to the genitourinary system was minimal. The enormous success of the oral ED therapy will be unlikely to stimulate much further development of new drugs. The investigational strategies of gene therapy is promising for future ED therapy as more advancements occur in molecular biology, as well better understanding of the physiology of erection and pathophysiology of ED. The non-pharmacological therapies, such as vacuum erection device and penile implant must be included in the overall analysis of the ED market. While this data is limited, it appears that the annual dollars allocated to R&D for penile implants has remained at roughly the $7 million level.

VIII. COST OF THERAPIES

1. SALES

Worldwide pharmaceutical sales were estimated at $712 billion in 2007, an increase of $178 billion over the past five years. The worldwide growth rates by year in ED therapies are shown in Fig. 3. In addition, Worldwide sales of all ED therapies and PDE5Is is shown in Fig. 4. The United States accounts for 45.9% of global pharmaceutical sales. The total health-care expenditure in the US is expected to reach $4.2 trillion in 2016[53] and pharmaceutical sales are forecast to grow 5.5% next year, which comprise 10% of national healthcare spending. The total market for drugs to treat ED represents a very minute portion of this total. In the US, the PDE-5i accounts for majority of ED prescriptions. Sildenafil sales in 2007 were $1.7 billion, an increase of 6% worldwide compared to 2006.[54] Levitra sales in 2007 were $421 million, a 5.7% increase from 2006.[55] Cialis total revenues were $1.1 billion in 2007, where worldwide sales grew 25% in 2007, driven by increased demand and higher prices. As of 2007, Cialis seem to be gaining market share worldwide.[56] While Viagra held a stronger lead in the US, with 56.6% total market share and sales of $615 million in 2006 according to IMS Health, sales were down 6%. Cialis held 27% of the US market, with sales up 26% to $294 million, while Levitra claimed 13.3% with sales up 30% to $144 million.[57] These big gains for Cialis might be due to the 36 hour effectiveness from a longer half-life of 17.5 hours, compare to 4 and 5 hours for Viagra and Levitra respectively. Additionally, the number of prescriptions filled weekly increased for both Cialis and Levitra but markedly decreased for Viagra between 2004-2005. Cialis 5 and 2.5mg was introduced for daily dosing in Europe and the US in 2007/8 was patients who anticipated more frequent sexual activity. At this stage it is too early to assess the impact of this new formulation. The growth in sales for Cialis, Viagra, and Levitra can be seen in Fig. 5.

In addition, annual US testosterone therapy sales have been going up (Fig. 6). In 2008, Testim sales reached $141M, and Androgel $547M, with overall testosterone market approaching $811M Fig. 7.

2. COST-EFFECTIVENESS

Cost-effectiveness analysis is a welcome addition to the factors that health insurers should consider when deciding what treatments to cover. When sildenafil was introduced to the US market in 1998, it created much ambivalence from the health insurance companies in terms of coverage because they anticipated the likelihood of explosive costs. Health plans have been concerned about the impact of PDE-5i will have on their pharmacy budgets because of the nature of the disease it treats, namely, that ED is a self-reported condition, hence, potentially a large portion of men could seek PDE-5i therapy. However, insurance plans should be cautious of this rationale, since ED has now been proven to be a marker for more serious co-morbid conditions such as cardiovascular disease, diabetes mellitus or the metabolic syndrome. There are limited data on the
newer ED drugs, hence, more attention will focus on sildenail. The introduction of sildenail and growing awareness of ED has yielded an 84% increase in the number of men seeking and using treatments for ED from 1998 through 2002. Within 2 years of the introduction of sildenail, the number of patients visits for the chief complaint of ED increased in Germany (55%), Spain (90%), UK (103%), US (250%) and Mexico (279%). Wilson et al ascribed the rising cost of managing ED in the UK to a 3-fold increase in the number of men presenting to generalists for ED, which eventually were referred specialists under Schedule 11 restrictions. Primary care physicians continue to be the leading prescribers of PDE-5i, accounting for 65%, followed by non-urological specialists (23%) and urologists (17%).

The anticipated economic burden of sildenail has been proven otherwise in several studies. Smith et al used a Markov decision model based on conservative assumptions so that the cost-effectiveness of sildenail would not be exaggerated. They found that the cost-effectiveness of sildenail treatment compared favorably with accepted interventions for other medical conditions, such as coronary artery bypass grafting, renal dialysis and cholesterol-lowering medications. They concluded that sildenail treatment costs about $9000 per quality-adjusted life-year, which is well below the $50,000 threshold often used as a benchmark in such analyses. Recently, Cooke and colleagues assessed the cost and utilization of sildenail in a large managed care organization (MCO) with a quantity of 6 units per 30-day supply for 20,281 members. They reported that the total allowed charges for sildenail pharmacy claims in 2001 were $3.56 million, of which patients paid 26.6% in average cost-share resulting in a net drug cost of $0.18 per member per month (PMPM). The impact of sildenail on the MCO’s pharmacy budget was only 0.5% and 91.7% of members did not exceed their sildenail quantity limit. Another study demonstrated the cost-effectiveness of ED therapy for 285,436 patients from 51 health plans from 1999 to 2001. They reported that health plans spent an average of $83.91 in 1999, $95.41 in 2000 and $119.26 in 2001 on ED care in a patient. The largest category of ED care expenditures was PDE-5i, estimated at 37% of the total cost that amounted to $27.46 in 1999, $32.92 in 2000 and $44.22 in 2001. For other ED therapy 8.45% was spent on testosterone hormone therapy, 3.85% on penile implants, 4.41% on ICI, 2.68% on alprostadil pellet insertion and 0.81% on VED. Notably, PDE-5i had the lowest annual cost per user ($121), while testosterone therapy had the highest $404. The
authors further dissected the average annual cost of ED therapy to demonstrate the minute amount spent by health plans per member yearly.

They reported that health plans spent an average of $0.91 in 1999, $1.03 in 2000 and $1.29 in 2001 per member annually for ED related services and treatments. Of the $1.29 spent in 2001 per member yearly, $0.48 were spent on PDE-5i. When the investigators converted these costs from per member yearly into per member monthly, the average costs were $0.025 in 1999, $0.03 in 2000 and $0.04 in 2001 for PDE-5i.[63] Additionally, 3 studies in abstract form, found lower than expected pharmacy benefit costs associated with adding sildenafil coverage in a managed care drug benefit plan. Lehman et al.[64] discovered that the drug costs PMPM of adding sildenafil coverage to 4 health plans with 15 million members ranged from $0.04 to $0.21. Similarly, Cherayil and colleagues found that sildenafil coverage in a MCO without restriction of quantity was $0.03 to $0.24.[65] When MCOs did impose restrictions on sildenafil quantity per prescription but without prior authorization, drug costs were also lower than expected, at $0.07 to $0.08 PMPM.[66] The aggregate findings of all these findings showed very similar values for ED therapy and supports the notion that coverage of sildenafil is cost-effective. Perhaps, insurance companies who limit or deny coverage for sildenafil may not have based their decisions on empirical cost or cost-effectiveness calculations by several studies. [63-66]

X. ECONOMIC IMPACT

1. THE DESCRIPTIVE ECONOMICS OF ED

The introduction of sildenafil to US commercial markets in 1998 affected the nation immensely. Sildenafil was seen as a palatable oral treatment for ED, where prior therapy was more labor intense but were covered by most insurers. The simplicity of sildenafil and direct to consumer advertising attracted many individuals with ED that were suffering silently. The prevalence of ED in 30 million US men from MMAS and an estimated incidence of 20% increase by 2010 with 921,000 cases predicted annually befuddled the health insurance industry. The combined cost of sildenafil ($10 per pill then) and prevalence data from MMAS initiated immediate reaction from health care providers to reject coverage, demand higher copayments or limit monthly quantity. Similarly in the UK, the prevalence of ED is high and the total expenditure of ED in the National Health System (NHS) further dampened any motivation of sildenafil coverage by insurance agencies. A study conducted in the UK reported that from 1997 to 1998,
the cost of ED in the NHS for 113,600 men was estimated at £53 million.[67] Drugs only accounted for 25% of the total cost and 4% as indirect costs to society due to lost productivity. In essence, the authors concluded that ED imposes a relatively small dent in the economy of UK society. In spite of this, NHS enforced restrictions for ED under Schedule 11 in an attempt to curb expenditure, which ironically increased NHS cost and utilization of all resources including sildenafil. This occurred mainly from a 3-fold increase in the number of men presenting to GPs, who are the referred to specialists under the Schedule 11 restrictions.[60]

Besides the growing prevalence of ED worldwide and reported expenditure in the NHS of UK society that might be seen as costly by most insurers, other factors account for the resistance to reimburse ED therapy. Part of the motivation for denying sildenafil coverage is its classification of a “lifestyle drug”, which is the perception that it doesn’t cure or even treat an illness or disease, and that the function it temporarily restores are not life-threatening or critical enough. As a result of this, most patients are paying full private cost for their treatment which may force them to “prioritize” their medications, especially for critical ones such as lipid-lowering or anti-
hypertensive drugs. However, this rational may have potential ramifications of neglecting serious medical conditions when they present for ED. Available data has now proven the strong association of ED with co-morbidities such as diabetes mellitus, cardiovascular disease, hyperlipidaemia, depression, hypertension and the metabolic syndrome.[26, 31-32] These factors have yet to be established in the cost-effectiveness of ED therapy in the future.

2. UTILIZATION OF HEALTH CARE SERVICES IN ED

Various health care systems have responded differently to the increased demand for oral ED therapy. Most countries, with the exception of the UK and initially, Sweden banned state sponsored prescribing of oral ED therapy. Some, including Holland allowed more expensive injection therapy to be available on the assumptions that the inconvenience would decrease the frequency. The UK NHS treats all drugs equally and therapy has been restricted to patients with certain defined conditions, including severe distress. In Japan, sildenafil was approved for use in 1999 but the government would not reimburse under the NHS. The rationale is that sildenafil improves quality of life but does not cure an underlying condition. In the US, 40% of sildenafil prescriptions are covered by third-party payers and 2% are covered by Medicaid. In a study conducted by Titlow et al [68] they concluded that instead of costs, value judgments seemed to play a central role in drug coverage decisions, which is largely unspoken. The authors discovered that among 53 MCO surveyed, the most common method of controlling sildenafil cost was by limiting the quantity or the duration of its use. Approximately, 64% of MCOs placed limits on sildenafil coverage, 23% did not cover treatment for ED at all, 21% required prior authorization and only 2% covered sildenafil without any restrictions. The Veterans Health Administration (VHA) system manages 5.2 million male patients aged 18 years and older. Nearly 10.5% were dispensed PDE-5i between 2004-2005, a period that coincides with the introduction of vardenafil and tadalafil. In spite of these new oral therapy, sildenafil still comprised 99.53% of all PDE-5i pharmacy claims, followed by vardenafil at 0.46% and tadalafil at 0.01%. However, the aggregation of these data might have influenced the VHA system to replace sildenafil coverage with vardenafil since January 2006. [69] The reason for this is unclear but perhaps it just may be another method employed by a health care system to control pharmacy costs.

Limited access to ED therapy has led to a high price black market, indicating that consumers were willing to pay more than the market price in many countries. These prices range from $20 to $30 per pill in Malaysia, Hong Kong and Thailand but even more in China $50. [70] In the UK, internet sales are illegal for prescription only medication and concerns were raised that the requirement to pay for oral medication may lead to patients with serious co-morbidities, such as ischemic heart disease seeking internet therapy over a comprehensive assessment from their physician. This may have important health economic implications caused by failure to diagnose a critical disease.

3. SD MANAGEMENT COSTS WORLDWIDE

The release of sildenafil to the US commercial market in 1998 has increased the ED market in the US from $100 million in 1995 to $3.1 billion in 2006. In 2003, the market for non-oral (transurethral and injectable) therapy for ED was $85 million worldwide and $32 million in the US. In 2006, sildenafil remained the market leader for ED therapy, with $1.6 billion in sales and represents 58% of all prescriptions and also, representing 3.4% of Pfizer’s total revenue of $48 billion. Cialis is the most recently released ED drug, becoming available in 2003. It differentiates itself by having a significantly longer half-life of 17.5 hours versus 4-5 hours for sildenafil and vardenafil. Eli Lilly had sales of $971 million in 2006, representing 6.2% of their total revenue $16 billion. Levitra in 2006 had the smallest market share of the three drugs, with $464 million in sales, representing 1.1% of Bayer’s total revenue of $43 billion (Fig. 5). Treatments used for ED suggest shifting forms of health care. The use of diagnostic tests markedly decreased, suggesting that the diagnosis of ED is being established by history and physical examination. While the pharmacological therapy with oral PDE-5i has increased tremendously, the market sales of other options (MUSE, alprostadil and prosthesis) has decreased. Although 30 million men are affected with ED in the US, only 22,000 men received penile implants in the US and Europe 2007, which clearly shows a greater preference for the oral agents.[71] Although the utilization of sildenafil continues to grow, the rate of growth has slowed down possibly due to competition from Cialis, deceleration of growth of the ED pharmaceutical market and saturation of a single medication market. Interestingly, known facts about ED as a symptom of hypogonadism and the metabolic syndrome has influenced the sale of testosterone replacement therapy (Androgel). Androgel sales in 2007 were £308 million worldwide, an increase of 25% since 2004.[72] The efficacy and safety of transcutaneous delivery systems accounted for this growth. Although the approved indication is for hypogonadism, the growing prevalence of ED could further impact greater market sales for this treatment. Additionally, the burden of testosterone deficiency that can cause a wide range of symptoms leading to significant morbidity highlights the benefits and cost-effectiveness of testosterone treatment, further driving market sales. The exact cost of FSD is unknown currently because the treatment is complicated by the lack of a single
causative factor, limited proven treatment options, overlap of different types of disorder and limited availability of treatment and limited expertise in the treatment of FSD.[73] The PDE-5i have not been shown to improve diminished desire. Testosterone hormone therapy, topical and systemic estrogen in postmenopausal women and progesterin therapy are the main pharmacological treatment of FSD.

4. FUTURE PREDICTIONS FOR THE SEXUAL DYSFUNCTION MARKET

The burden of diseases associated with ED worldwide will increase with the aging of the male population, increasing prevalence of co-morbid conditions, expanded treatment seeking behavior, costs of pharmaceutical therapy and direct consumer advertising will undoubtedly impact the commercial market for ED. Extrapolating from the prevalence of ED and current utilization trends implies that the cost of treatment worldwide could be tremendous.

There is clear evidence in the literature that demonstrated FSD to be a significant health problem for patients and their partners, yet women may not come forward to discuss it. FSD remains a controversial, complex and under-researched clinical issue. Progress in this field is slow, such that testosterone remains the only treatment specifically approved for the treatment indication of FSD, and this approval is limited to European countries and oophorectomised women. However, there is widespread off-label use by women of testosterone products approved for men and extensive prescriptions of compounded testosterone products for women in clinical practice. In order to accurately assess costs implications for FSD further efforts should include standardized diagnostic and treatment algorithms (pharmacological and non-pharmacological) suitable for clinical practice in addressing the varied symptoms of FSD.

5. PREMATURE EJACULATION

Premature Ejaculation (PE) is believed to be the most common male sexual dysfunction [74] affecting 5-40% of all sexually active men [75]. PE can lead to devastating consequences to the man and his partner, including increased anxiety, lowered self-esteem, impaired quality of life, relationship difficulties, decreased libido, erectile dysfunction (ED), among others. But, despite this and similar to other sexual disorders, very few men with PE look for help from a healthcare professional [74,76]. The lack of a widely accepted definition of PE can also contribute to the under diagnosis of this condition. A recent multinational and large survey, internet-based – PEPA survey – [74] showed that only 9% of men with self-reported symptoms of PE had spoken about this to their doctor and only 4% had talked to a sex therapist or to a psychologist about their condition. Why don’t men seek help for their problem? Possible explanations include:

- No perception of the problem (especially if the partner doesn’t complain)
- Embarrassment to talk about sexuality
- Not knowing which health professionals to consult regarding their PE
- Physicians not prepared or reluctant to talk about sexual disorders
- The lack of an approved medication to specifically treat PE. Pharmacological treatments currently available for PE include:
  - Topical anaesthetics
  - Tricyclic antidepressants
  - Selective serotonin reuptake inhibitors (SSRIs)

Although 60% of men in the PEPA survey were aware of the existence of medications to treat PE, only 13% reported having used them.

The social and personal impact of PE is well established in the literature but very little is known about the economic impact of this condition. Since there is no medications approved to treat PE (other than Dapoxetine in Europe) and the most commonly used drugs are the tricyclic antidepressants and the SSRIs – which are also prescribed for other conditions – it’s impossible to detect whether a prescription was issued for the treatment of PE with these medications. This means we cannot identify the real treatment cost of PE treatment with these compounds and indirect measures can only estimate the true cost. A recently published study [77] had the aim to better understand the health profile and the needs of men who seek help for PE in the US. In this retrospective study, men with PE were compared to non PE men control group, whereby those in PE group were found to consume more medical resources, primarily because of a higher number of physician visits (3.03 for non PE vs. 5.23 for PE group) and greater use of prescription medications. After diagnosis the mean total cost of diagnosis and medication (whether PE or non PE related) decreased by 24% from US$ 1,320 in the year before to US$ 998 in the year after diagnosis. Total diagnosis cost in the year before PE diagnosis was US$ 1,036 per patient and fell 36%, to US$ 630 per patient in the year after diagnosis. It is not known which components of the cost decreased but the total prescription costs in the year rose 37% from the year prior to a PE diagnosis (US$ 283 per patient) to the year after diagnosis (US$ 368 per patient). However, this increased cost associated with the treatment of PE is offset by a large reduction in the per-patient diagnosis costs – the total per-patient costs of diagnosis and treatment decreased by 24% after PE diagnosis (from US$ 1.320 to US$ 998). Among men with PE, the percentage with a prescription for any SSRI more than doubled after their diagnosis, from 21% prior to diagnosis to 54%
after diagnosis. This increase does not correlate with an increase in a co-morbid diagnosis of depression. Prescription for sildenafil rose from 8 to 11% prior and after diagnosis of PE. This increase either does not seem to be correlated to an increase in the diagnosis of ED. Some men may have received both classes of drugs. Total cost for both diagnosis and prescription per patient-year were much greater for men with PE than for controls (PE, US$ 1,320 vs, control US$ 447). Based on regression analysis to account for contributing costs of the top co-morbidities, men with PE had an overall higher total prescription cost per patient per year when compared with the control population (US$ 422 vs, US$ 148, p<0.0001). Men diagnosed with PE were also more likely to be diagnosed with “disorders of the penis”, “hyperplasia of the prostate” and “urinary system symptoms”. Men with PE who have these other conditions appear more likely to seek medical treatment, which presumably provides them with more directed treatment, reducing the number of future visits, and thus, the healthcare costs. Furthermore, the diagnosis of PE is associated with a decrease in treatment costs; therefore encouraging patients to seek a diagnosis if they believe they have PE and asking patients about their sexual health at routine office visits are ways physicians may help to reduce healthcare costs of men with PE.

6. PEYRONIE’S DISEASE

Nelson estimated the US patients of Peyronie’s disease as 4.5 million and depression patients from Peyronie’s disease as 2.16m. [78] From this number they estimated Peyronie’s disease induced depression cost yearly in US 250 million workdays missed, 66 billion of replacement costs for absenteeism, and 2,5 billion in incremental medical costs. If it is applicable to the whole world the cost will be enormous.

Economic impact on relationship and divorce

The direct cost of treating Peyronie’s disease is not reported to have a major economic impact on relationship with partners. The cost of managing Peyronie’s disease-induced depression might have a larger impact on relationship with partner as mentioned above.

7. PRIAPISM

a) Epidemiology

True incidence of priapism is unknown. The first epidemiological study was done in Finland.[79] They reviewed hospital discharge diagnoses from 1975 to 1990. They calculated the incidence rate from 0.34 to 0.52/100,000 person-years in these 10 years if ICI-induced priapism was excluded. A Dutch study followed this. [80] They investigated 145,071 men cohort by using general practitioner research database. They found the incidence rate of 0.9/100,000 person-years annually. If the ICI-induced priapism is included, the rate will be doubled. PGE1 injection is known to induce priapism in 15% and papaverine injection is in 17%. [81] Priapism in sickle cell disease patients has unique clinical manifestations. The life-long prevalence of priapism in SCD patients is believed to be from 29 to 42%. [81] In summary, the incidence rate of spontaneous priapism will be 0.34 to 0.9/100,000 person-years. If ICI-induced priapism is included, this number will be doubled. Moreover in the society where many SCD patients exist this number will increase proportionally.

b) Relationship with ageing

The effect of aging on priapism is not clear.

c) Relationship with other medical risk factors

Genitourinary and hematologic malignancies are known to cause priapism. [81] Many atypical antipsychotic medications are known to cause priapism. [82] Cocaine use is also known to cause priapism. [81]

d) Impact on QoL

British group in SCD and thalassaemia center made a qualitative study by interviewing six SCD-related priapism patients. [83] They found a profound psychological impact on each patient. The patients feel despair, embarrassment and isolation. They could not sleep well since the priapism usually occurs in the night time. This deprivation of sleep cause bad effect on general quality of life. [83] These results might be applicable to patients of other causes.

e) Treatment seeking behavior and patient preference

The aforementioned British study also revealed that the patients don’t seek prompt treatment because of embarrassment or lack of knowledge. [83] The patients do not have enough time to show preference of therapy since they usually receive medical help in ER.

f) Diagnosis

The complete history taking and physical examination of the penis are the key diagnostic tool. Therefore the cost is minimal. To differentiate ischemic type from non-ischemic type the blood gases analysis of corpus cavernosum will be done.[81] This procedure is not so expensive.

g) Research and Development

UCSF group found in hypoxic rat corpus cavernosum the PDE5 expression was significantly reduced.[84]
They postulated that SCD patients may have low PDE5 expression, predisposing them to recurrent priapism. [84] In accordance with this basic data, Burnett gave PDE5 inhibitors to the SCD-induced recurrent priapism patients. [85] Six out of seven patients showed efficacy. Since PDE5i may be effective to priapism, [85] pharmaceutical companies who have PDE5i might invest money to this field.

**h) Cost of therapies**

The sooner a patient seeks medical help, the less invasive treatment, aspiration and phenylephrine injection will be applied. This maneuver is not expensive. If not, the more invasive treatment, shunt surgery will be necessary. The cost of this surgery is expensive. Moreover, if ED is induced, the cost of severe ED treatment will be added to the initial costs.

**i) Similarities and differences between priapism and other condition**

Urinary retention is a urological emergency and cause pain and anxiety in patients. The prevalence of acute urinary retention is 2.2 to 6.8 episodes /1000 person-years,[86] one-hundred times more frequent than priapism episodes. Retention is embarrassing but the patients seek treatment promptly. The cost is very minor since catheterization can resolve the problem quickly. It is desirable to educate primary care physicians to treat priapism easily just like to treat urinary retention.

**j) Economic impact of PD on society, patients, health care providers, insurance**

The sooner the less expensive treatment is available and effective. The education to health care professionals and high-risk groups like SCD patients or patients on ICI program or patients on antychicotic drugs is manadatory. This investment to medical education will cut the cost of the aforementioned treatment.

**k) Economic impact on relationship and divorce**

Complete ED induced by long-time priapism episode might cost expensive ED treatment and big economic burden might cause a big impact on relationship.

**8. FEMALE SEXUAL DYSFUCTION**

**a) Introduction**

Epidemiological studies have shown that FSD is highly prevalent.[87-89] Indeed, the international consensus group estimated that it affects more than 20% of women.[90] HSDD is the most prevalent type of FSD and occurs in both pre- and postmenopausal women.[87-89, 91,92] The European cohort of the Women's International Study of Health and Sexuality (WISHeS) – a cross-sectional study carried out in France, Germany, Italy and the United Kingdom among 2,467 women – found the prevalence of HSDD to range from 7% for pre-menopausal women to 16% for surgically menopausal women in the 20 – 49 years age group.[93] The prevalence among women aged 50-70 years was 9% for naturally postmenopausal women.[92]

It is difficult to estimate the current costs of managing female sexual dysfunction (FSD), although it is acknowledged to have an economical and societal impact. [94] The reason stems from the fact that although 30% of women reported discussing sexual problems with their general practitioner, only 3% had an entry relating to sexual difficulties recorded in their medical records [95]The number of diagnosed cases of female sexual dysfunction therefore remains relatively small and many women remain untreated. The cost of treating FSD is therefore likely to be relatively low when set against its health burden.

It is also important to note that because female sexual dysfunction is often experienced alongside other health problems (e.g. menopausal transition, depression, cancer, diabetes) or secondary to medications (e.g. SSRIs, oral contraceptives) it can be difficult to isolate the costs of treating FSD from the costs of the contributory factors.

**b) Use of healthcare services**

Primary care physicians are often the first port of call for women suffering from sexual problems, especially in healthcare systems where they have a role as a gatekeeper to specialist / secondary care services. Humphrey et al [95] found that general practitioners in the UK see on average 2.6 patients with sexual dysfunction each month, 62% of consultations being related to erectile dysfunction in men. If it is assumed that the remainder of the consultations (38%) are for women, then this would equate to approximately one consultation per month. Assuming a similar consultation rate among the UK’s 42,876 general practitioners [96] (RCGP 2006), would result in approximately 500,000 GP consultations for FSD annually, at a cost of £13.5m to the National Health Service based on a cost of £27 per consultation. [97]

Moreover, physician attitudes and practices regarding HSDD in the primary care setting further adds to the problem. Laumann et al found that 90% of respondents had little confidence in making a diagnosis of HSDD and that 90% had not screened a patient for HSDD.[88] These results are consistent with an earlier international survey of people aged
40–80 years, which found that only 8–10% of subjects had been asked about their sexual health during a routine visit to their doctor.[89]

c) Management Options in FSD

The mainstay of treatment for FSD is psychosexual therapy or counselling. Access to and availability of these services is variable and may be provided within a variety of settings including mental health services and genitourinary medicine (GUM) clinics. Treatment is often funded privately by sufferers limiting access to care to those who can afford it. Services may also be provided by voluntary sector organisations, such as RELATE in the United Kingdom. The fragmented nature of service provision makes it very difficult to estimate the total number of women receiving psychosexual treatment based on currently available data and may explain the low number of consultations recorded in the Hospital Episode Statistics.

Recent study [103] estimated that 152 patients with female sexual dysfunction were seen annually in a single clinic by a multi-disciplinary team of physicians, psychologists and sex therapists. This study estimated an average cost per woman of £472 over a three-month period. This would equate to an annual management cost of £1,888 per woman and a total cost of £286,976 for the estimated 152 women treated (clinic practitioner costs only, not including any medications or referrals to other services). If it is assumed that the 25% of GUM clinics which hold sexual dysfunction clinics [103] see a similar number of patients annually to that reported in Goldmeier et al 2004, and that these patients were to receive similar levels of treatment, this would equate to an annual cost of just under £20 million for FSD services provided by GUM clinics alone [103].

These studies demonstrate that relationship and behavioural interventions are not inexpensive and that relapse rates can be significant. Pelvic pain disorders such as vaginismus and dyspareunia along with sexual aversion disorders are likely to require management along behavioural principles. Guidelines in FSD are likely to suggest that sex therapy and relationship interventions will be important to compliment pharmacological therapies with corresponding increase in the overall cost of care.

d) Pharmacological Treatments

Few pharmacological treatments are currently approved for the treatment of female sexual dysfunction. Hormone replacement therapy (HRT) may be used to treat symptoms of the menopause, including sexual symptoms, although its use has steadily declined since 2002 due to publication of data suggesting that HRT may increase the risk of cardiovascular disease and several types of cancer. The cost of HRT prescribing attributable to FSD is difficult to estimate because sexual dysfunction may be one of several manifestations of the menopause and a formal diagnosis of FSD is unlikely to be recorded by doctors treating a number of menopausal symptoms. Recent trends in the prescribing costs of HRT can be seen in Figure 8.

Since 2007 the testosterone patch, Intrinsa, has been approved in the European Union (but not USA) for the treatment of hypoactive sexual desire disorder in bilaterally oopherectomised and hysterectomised individuals.

Figure 8: HRT prescribing costs
women receiving oestrogen therapy [106]. Approval was based primarily on the results of two six-month, double-blind, placebo-controlled trials: the Investigation of Natural Testosterone In Menopausal women Also Taking Estrogen in Surgically Menopausal women (INTIMATE SM) 1 and 2 trials. [112] The primary endpoint in both trials was total satisfying sexual activity, which increased by 74% (INTIMATE SM 1) and 51% (INTIMATE SM 2) following treatment with Intrinsa® for six months, compared with placebo. [112] In real terms, this equated to 1 additional satisfactory sexual experience per month and this was considered by prescribing authorities insufficient to endorse the prescribing of INTRINSA by physicians, although in some patients the benefit was marked. In both trials, there were also significant improvements in distress related to sexual dysfunction in testosterone- vs. placebo-treated patients. [112]

From start of trial to January 2009, 3,900 women in the UK received at least one prescription for Intrinsa, with an average of 106 days on therapy. This equates to an annual prescription cost of approximately £438,000 [109].

Approximately 4,000 women in the UK received a prescription for other androgens in the year to January 2009 [109], however it is unknown whether these were prescribed for female sexual dysfunction or in connection with other diagnoses. Despite the poor evidence base for the use of the phosphodiesterase inhibitors (PDE5Is) in female sexual dysfunction, there is evidence of some limited use in women. There has been considerable interest in the use of PDE5Is (particularly sildenafil) to treat FSD in antidepressant associated sexual dysfunction. Women consult physicians three times as often as men and are twice as likely to be prescribed antidepressants. Rates of FSD with these medications are reported at 30-70% in the first months of treatment [111] lead to increasing relapse, recurrence, disability and resource utilisation by affected patients. Non adherence to antidepressant therapy in women approaches 70% with sexual side-effects are a major (probably understated) cause of discontinuation. Decreased sexual interest, lack of genital sensitivity and vaginal lubrication: delayed or absent orgasm: dyspareunia; reduced satisfaction and loss of pleasure in sexual relations are all common symptoms. Nurnberg et al[108]investigated 98 pre-menopausal women (mean age 37.1) with previously normal sexual function prior to antidepressant therapy and treated them with 50 or 100mg sildenafil or placebo on demand prior to sexual activity. The investigators found significant improvement in female sexual function (both arousal and desire) scores for sildenafil over placebo and no withdrawals due to adverse events.

Despite this evidence, there appears to be no plan for the manufacturers to seek licence for the use of PDE5Is in women.

1,112 women received a total of 3,420 prescriptions for sildenafil, tadalafil or vardenafil in the year to January 2009. Most of these prescriptions (3,160) were for sildenafil, with 180 and 40 for tadalafil and vardenafil respectively (CSD patient data 2009). Conservatively assuming that each dose was for a single pack containing four tablets of the standard dose, the total cost of NHS prescriptions for phosphodiesterase inhibitors in women would be approximately £73,000 per annum (MIMS 2009).

It is important to note that the above estimates take into account the costs of NHS general practice prescriptions only. In 2008 approximately 3.5% of Intrinsa sales in the UK were in the private market (IMS Exponent data 2008). This proportion may be higher for the phosphodiesterase inhibitors given current NHS prescribing restrictions for men. The above data also takes no account of prescriptions made within the secondary care setting.

For the treatment of Female arousal and orgasmic disorder the FDA licensed EROS, a battery operated clitoral suction device available for $200-250 on physician prescription. EROS has not yet achieved approval in the UK but is available for private purchase at £200. In 2005, an estimated 5M vibrators were purchased in the UK with prices ranging from £2 to £120 [113].

\[e)\] Funding Implications for Pharmacological Preparations

With the exception of the UK, drugs for erectile dysfunction in men have been funded privately. The UK department of health has allowed therapy for men with diabetes, prostate cancer, multiple sclerosis, pelvic surgery and a few rare conditions but also those suffering severe distress. It is difficult to see how such a model could be applied to licensed medication for FSD, as personal distress or relationship difficulty form a pre-requisite for diagnosis. Much negotiation will be required to balance possible gender inequalities with the economic cost of funding new medications for women, which will require regular rather than on-demand dosing. INTRINSA was granted a full licence for a small group of surgically post-menopausal women in the UK and this was always unlikely to result in high health care costs particularly with almost immediate questions on efficacy and long term safety.

\[f)\] Conclusion

It is difficult to paint an accurate picture of the economic costs of female sexual dysfunction for a number of reasons. FSD diagnoses are poorly recorded in NHS datasets. This may be due to clinicians' lack of
familiarity or comfort with FSD as a genuine diagnosis and also to the complex relationships between FSD and common co-morbidities and concomitant medications. In addition, women with FSD are seen by a variety of healthcare professionals, across a variety of settings within both the NHS and private sector. There are no widely followed authoritative UK or European guidelines for the treatment of FSD and women follow a variety of treatment pathways. There is currently no clear referral and commissioned pathways for FSD within the UK. It is clear from the emerging literature that management of FSD could have a significant impact on NHS resources, with the highest costs being associated with general practice consultations and psychosexual consultations within sexual dysfunction clinics. The cost of psychosexual therapy is considerable and relapse rates are high and this needs to be considered rather than a pre-occupation with the more easily measured cost of drugs. At present, spending on pharmacological treatments is relatively low and uptake of new treatments such as the testosterone patch has been relatively limited. New treatments for women will require delicate discussions on what can be funded by health providers particularly in the light of past experiences with drugs for sexual dysfunction in men.

XII. POLICIES REGARDING SEXUAL DYSFUNCTIONS

1. HEALTH INSURANCE

Health coverage in the US is far from universal. Approximately 40% of third party payers cover oral ED therapy. Although SD encompasses different problems, available information from these insurance companies mainly addressed ED and Peyronie’s disease. The specific details covered by each plan vary, however, there are some general guidelines set forth by most of these insurance agencies. For example, Blue Cross/Blue Shield and Aetna policies consider the diagnosis and treatment of ED medically necessary. Their diagnostic workup includes most imaging and lab tests. They share some differences here, Blue Cross require the patient to be at least 18 years old for ED evaluation but Aetna doesn’t specify an age limit. Aetna will cover most diagnostic test, except NPT because of its low specificity, whereas Blue Cross does but only in a sleep lab. As for treatment, most ED therapies are covered, except oral medications (PDE-5i) or limited quantity. Blue Cross covers 6 tablets per month, as well as Cigna, United Healthcare and Kaiser Permanent but Aetna and many others do not. Regarding Peyronie’s disease, Aetna considers surgical correction medically necessary if the patient had significant morbidity for 12 months or more who failed conservative medical treatment.

2. GOVERNMENT

Medicare is a social insurance program administered by the US government, providing health insurance coverage to people who are aged 65 and older, or who meet other special criteria. Prior to January 2007, many Medicare plans limited ED prescriptions to 4 pills per month and usually required prior approval. However, new change went into effect January 2007 to dissolve all coverage in an effort to save millions of dollars a year. While they did not provide statistics on how much Medicare spent on drugs, their decision was due to the Congressional Budget Office estimate that the Medicare coverage would cost $2 billion over a ten year period. Interestingly, the Department of Veterans Affairs covers 4 pills per month, which leads one to question why the federal government support ED drugs for one group of seniors but not for another. The NHS under the UK government limits 1 tablet per week for ED, provided that men met the criteria under Schedule 11 or suffered severe distress from ED.

3. RESEARCH AGENCIES

The National Institute of Health (NIH) organization for research on ED is the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK). The important points they emphasized about ED are as follow: ED is the repeated inability to get or keep an erection firm enough for sexual intercourse, ED affects 15 to 30 million American men, ED usually has a physical cause, ED is treatable at all ages and treatments can include psychotherapy, drug therapy, VED and surgery.

XII. SUMMARY

Review of the economic aspects of sexual dysfunctions reveals the following observations:

1) The global ageing process will continue to influence the high prevalence of SD.

2) The global trend of increasing obesity and metabolic syndrome is expected to result in increased burden of SD.

3) There continues to be many barriers to treatment seeking and access to care. In the light of the established gender difference in treatment seeking and the known higher treatment seeking in women, the introduction of new therapies for FSD is expected to have a substantial impact.

4) Although SD’s are mainly age-dependent conditions, they are associated with many serious
5) The economic impact of SD’s especially ED is further confounded by medical conditions, such as cardiovascular disease, DM, HTN, hyperlipidemia, BPH, prostate cancer and depression.

6) Majority of patients with SD are managed by PCP, followed by specialists.

7) Although limitations exist for oral ED therapy, PDE-5i sales continues to grow.

8) Oral therapy has expanded the patient base for ED.

9) Several studies have reported the cost-effectiveness of PDE5i that health insurers can use as a model to aide decisions about oral ED coverage.

10) Testosterone replacement therapy for male hypogonadism has grown substantially, despite under diagnosis.

11) Testosterone replacement therapy is currently licensed in European Union for FSD/HSDH in surgical menopause. This narrow indication currently limits the economic impact. But, concern exists about efficacy and long term safety.

12) The economic issues of FSD have remained largely unexplored due to the lack of licensed therapies. However, with the advent of new therapies, such as the transdermal testosterone and Flibanserin, the understanding of the economic impact of FSD is expected to improve in the future.

13) HRT for postmenopausal women continues to decline. Nevertheless, this decline may result in unmet need for treatment of menopause related FSD.

14) Very little data is available on the economics of: premature ejaculation and Peyronie’s disease.

15) Health care systems and government agencies remain cautious about coverage of SD therapy. There appears to be significant knowledge needs in such systems and agencies, especially about the link of SD’s to overall health.

16) R&D for pharmacological treatments of male and female sexual dysfunctions continues to expand globally.

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Committee 06

Clinical Evaluation and Symptom Scales in Men and Women with Sexual Dysfunction

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# A. OVERVIEW AND BASIC PRINCIPLES OF CLINICAL EVALUATION IN SEXUAL MEDICINE

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## II. MANAGEMENT PRINCIPLES IN SEXUAL MEDICINE

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1. Development and Role of Self-Administered Scales or Questionnaires (SAQ's)
Clinical Evaluation and Symptom Scales in Men and Women with Sexual Dysfunction


INTRODUCTION

Sexual problems are prevalent in men and women of different ethnic and social backgrounds, ages and health statuses, as shown in numerous recent epidemiological studies [1-6]. These studies have also identified several correlates, major risk factors and associated comorbidities. However, sexual health problems are often neglected in clinical practice [7,8]. Many patients have difficulty discussing their sexual problems or concerns with a physician due to a sense of frustration, confusion, embarrassment or distress; moreover, patients often feel that physicians are reluctant, disinterested, or unskilled in sexual problem management. Such patients' perceptions frequently guide behavior, as clinicians are often reluctant to ask about sexual issues due to their negative attitudes towards sexual issues and concerns, time constraints, as well as a growing knowledge gap between developments in sexual medicine and the clinical skills of practicing physicians [9,10]. The challenge is to create uniform, widely accepted diagnostic and treatment approach for sexual problems and dysfunctions, based on understanding the common language between clinicians and patients. Such a strategy would improve not only doctor-patient communications and treatment outcomes, but most importantly, it would lead to the development of educational materials and curricula to provide practicing physicians across specialties with the needed skills to meet modern patients’ needs in sexual medicine healthcare delivery [11-13].

In that effort, our committee reviewed current literature and have provided basic guidelines for the broad approach for assessing sexual problems in a medical practice setting. Initially, principles of sexual evaluation are presented and a diagnostic and treatment algorithm for all sexual dysfunctions in both genders. A review of current diagnostic approaches for erectile dysfunction (ED) is presented, which this committee has evaluated in the previous Consultation [14]. Other diagnostic approaches are briefly considered and readers are referred to more detailed description in other chapters. Finally, an overview of scales and questionnaires for sexual problems is presented. Accordingly, the chapter is divided into 3 major sections: A. Overview and basic principles of clinical evaluation B. Overview of diagnostic tests for erectile dysfunction and C. Overview of standardized sexual function scales and questionnaires, as well as broader outcome (HQL, treatment satisfaction) measures in men and women.

A. OVERVIEW AND BASIC PRINCIPLES OF CLINICAL EVALUATION IN SEXUAL MEDICINE

Considering clinical evaluation and use of symptom scales in sexual medicine, we should keep in mind the main aspects of human sexuality, as well as the definitions of health, sexual health and sexual medicine, in order to define the scope of the process. It is also essential to consider patients’ rights and the goals of diagnostic procedures; these definitions, which are specified as follows, permit us not only to provide a broad framework of scientific understanding, but also to establish core principles for the development of a simplified and broadly applicable diagnostic and treatment algorithm.

I. DEFINITIONS

The World Health Organization (WHO) has offered widely accepted definitions of health and sexual health, defining also sexual rights.
1. HEALTH

“Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”. Of note, this definition has not been amended since 1946 [15].

2. SEXUAL HEALTH

“Sexual health is a state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity. Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence” [16].

3. SEXUALITY AND SEXUAL RIGHTS

Sexuality is a central aspect of human experience throughout life and encompasses much more than sexual intercourse: sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy and reproduction. Sexuality is influenced by the interaction of multiple factors, including biological, psychological, social, economic, political, cultural, ethical, legal, religious and spiritual, and historical factors. Human sexuality can include multiple dimensions, including thoughts, fantasies, desires, beliefs, attitudes, values, behaviors, practices, roles and relationships. While sexuality can include all of these dimensions, not all of them are always experienced or expressed [16].

According to the WHO declaration, all persons have the right to “seek, receive and impart information related to sexuality, as well as receiving the highest attainable standard of sexual health, including access to sexual and reproductive health care services are fundamental sexual rights. Sexual rights embrace human rights that are already recognized in national laws, international human rights documents and other consensus statements”. The WHO declaration furthermore describes sexual rights as “the right of all persons, free of coercion, discrimination and violence, to: 1) the highest attainable standard of sexual health, including access to sexual and reproductive health care services; 2) seek, receive and impart information related to sexuality; 3) sexuality education; 4) respect for bodily integrity; 5) choose their partner; 6) decide to be sexually active or not; 7) consensual sexual relations; 8) consensual marriage; 9) decide whether or not, and when, to have children; and 10) pursue a satisfying, safe and pleasurable sexual life” [16].

4. SEXUAL MEDICINE

The only available definition of sexual medicine is derived from the European Academy for Sexual Medicine (EASM) [17]: Sexual medicine is the branch of medicine concerned with human sexuality and its disorders. Sexual medicine attempts to improve sexual health through the prevention, diagnosis, treatment, and rehabilitation of conditions or diseases that involve:

- sexual function,
- sexual and/or partnership experience and behavior,
- gender identity, and
- sexual trauma and its consequences.

EASM also emphasized in the definition that “sexual medicine takes into account the individual and couple dimension as well as the knowledge and methods of medical, psychological and social sciences. It recognizes that many of the conditions or disorders may be caused by other medical conditions and/or their treatment” [17].

II. MANAGEMENT PRINCIPLES IN SEXUAL MEDICINE

Three basic principles underlie the management of sexual problems in both men and women; when taken together, these three principles provide a balanced and integrated approach to clinical evaluation and treatment of sexual problems and dysfunctions. These 3 principles are described bellow (Table 1).

**Table 1: Management principles in sexual medicine.**

<table>
<thead>
<tr>
<th></th>
<th>Principles in Sexual Medicine Care</th>
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<tbody>
<tr>
<td>1</td>
<td>adoption of a patient-centered framework, with emphasis in cultural competence in medical practice (CCM)</td>
</tr>
<tr>
<td>2</td>
<td>application of the principles of evidence-based medicine (EBM) in diagnostic and treatment planning</td>
</tr>
<tr>
<td>3</td>
<td>use of a unified management approach in evaluating and treating sexual problems in both men and women</td>
</tr>
</tbody>
</table>

1. ADOPTION OF A PATIENT-CENTERED FRAMEWORK, WITH EMPHASIS IN CULTURAL COMPETENCE IN MEDICAL PRACTICE (CCM)

**a) Patient-centered care**

Traditionally, the dominant model in medicine has been the “disease-centered” approach, which assumes that disease is accounted for by deviations from the norm of measurable biological variables. The “disease-centered” model focuses on medical consultation and establishment of an essentially patriarchal doctor-patient relationship, in which the patient fulfils a passive role and the doctor embod-
ies medical expertise. It aims to measure outcomes in an objective and quantifiable way, while often neglecting that people come to be made well, made whole, to recover the sense of health, of being well [18-20]. This applies particularly in the case of sexual medicine.

Patient-centered care, is an interactive process (Table 2) [18], an approach that consciously adopts the patient’s perspective and respects his or her ideas, feelings, expectations and values, as the physician tries to enter the patient’s world, to see the illness through the patient’s eyes[19]. Patient-centered medicine assumes a holistic approach that takes into account not only the biological dimension of disease, but also its psychological and social implications, in accordance with the definition of health provided by the World Health Organization [20].

b) Cultural competence in medical practice (CCM)

In keeping with the concept of “patient-centered” medicine, it is important for health providers and physicians to offer culturally and linguistically appropriate services to their patients. When patients do not understand what their healthcare providers are offering or telling them, and when providers either do not speak the patient’s language or are insensitive to cultural differences, the quality of health care can be severely compromised [21]. The field of cultural competence focuses on overcoming language barriers, improving communication between culturally competent physicians and patients, understanding patients’ conceptualization of their condition, improving negotiation of approaches that allow for the best option available within the health and social system, and all within the framework of patients’ own worldview. Table 3 [22] summarizes the essential cultural competencies that apply to sexual medicine and should be incorporated in every sexual medicine encounter with a patient.

Cultural competence in sexual medicine is fundamental, as providing culturally competent sexual health services becomes more complex when care providers and patients possess different genders, racial or ethnic identities, countries of origins, social statuses, and sexual behavior patterns.

c) Patient-centered criteria in sexual medicine

In defining patient-centered care in sexual medicine, the following criteria should be considered:

1. **Sexual dysfunction exists only when satisfaction arising from the integrated components of sexual function, e.g. sexual desire, arousal, and orgasm or climax are reduced or absent.**

A person may have a specific dysfunction, such as erectile dysfunction or anorgasmia, but not consider it as a personal and/or relationship problem.

**Table 2: The interactive process of patient-centered care. Adopted from [18].**

<table>
<thead>
<tr>
<th>Interactive components of patient centered process</th>
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</thead>
<tbody>
<tr>
<td>1. Exploring both the disease &amp; illness experience</td>
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<tr>
<td>2. Understanding the whole person</td>
</tr>
<tr>
<td>3. Finding common ground regarding management</td>
</tr>
<tr>
<td>4. Incorporating prevention and health promotion</td>
</tr>
<tr>
<td>5. Enhancing the patient-doctor relationship</td>
</tr>
<tr>
<td>6. Being realistic</td>
</tr>
</tbody>
</table>

**Table 3: Summary of Cultural Competencies. Adopted from [22].**

<table>
<thead>
<tr>
<th>Medical cultural competencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Knowledge of epidemiology and the differential effects of treatment in various ethnic groups</td>
</tr>
<tr>
<td>2. Awareness of how culture shapes individual behaviour and thinking</td>
</tr>
<tr>
<td>3. Awareness of the social context in which specific ethnic groups live</td>
</tr>
<tr>
<td>4. Awareness of one’s own prejudices and tendency to stereotype</td>
</tr>
<tr>
<td>5. Ability to transfer information in a way that the patient can understand and to use external help (e.g. interpreters) when needed</td>
</tr>
<tr>
<td>6. Ability to adapt to new situations flexibly and creatively.</td>
</tr>
</tbody>
</table>

2. **Sexual dysfunctions are essentially self-reported conditions.**

Sexual dysfunctions may have major impact in quality of life and psychosocial and emotional well-being; in some cases there may be no biological findings, although the patient may feel that he/she has a sexual problem, due to interpersonal, psychological or social problems. Therefore, the diagnostic approach has as a primary goal not to prove the existence of the problem, but to unmask the underlying etiology and consequences of the problem, and to consider appropriate management options.

3. **Outcomes assessment should focus not only on reduction of distress or resolution of certain symptoms, but on the overall sexual well-being of the individual.**

2. **APPLICATION OF EVIDENCE-BASED MEDICINE (EBM) IN DIAGNOSTIC AND TREATMENT PLANNING**

a) Why EBM in sexual medicine?

Evidence-based medicine is the integration of best available research evidence with clinical expertise and patient values [23].

Clinical decision-making is guided increasingly by
the results of randomized, clinical trials (RCT’s), prospective patient registries, cohort and case-control studies, meta-analysis and systematic reviews. According to the principles of evidence-based medicine (EBM), clinicians should consider evidence from multiple sources in making a diagnosis and in formulating a treatment plan for each individual. Although not applicable in every case, findings from controlled trials, patient registries and systematic reviews can inform the decision-making process in multiple ways. In selecting among available diagnostic and treatment options, clinicians and patients should both evaluate the potential risks and benefits as determined by the weight of clinical evidence. [24].

Specifically in sexual medicine, where sexual problems are a) not life-threatening, b) involve intimate aspects of people’s life, c) are self-reported conditions, and d) involve treatment options that are multiple and diverse, each patient has the right to be fully informed concerning his or her sexual health status, as well as the evidence-based diagnostic and treatment options that are available, in order to participate actively in the decision-making process. Since it is evident that available treatments and diagnostic approaches for sexual dysfunction are proliferating, the patient should be given every opportunity to choose among available options, and to determine which option fits best to his/her special needs. Patients’ needs vary also in their preference for information and involvement in the decision-making process, and for this reason the approach should be flexible and individualised. This is ultimately why communication is the royal pathway to both evidence-based and patient-centered medicine [25].

b) EBM in diagnostic procedures

Strong consideration should be given to the evidence basis for diagnostic evaluation in each case. The goals of the diagnostic procedures are well defined (Table 4) [26].

Specific tests or procedures should not be recommended without controlled clinical data or research evidence supporting their use. Particularly in the case of costly or invasive procedures, these should not be recommended in the absence of supporting evidence and their applicability to the specific case. Both physicians and patients should be encouraged to consider the available scientific evidence prior to selecting among specific treatments or diagnostic options. Accordingly, this chapter considers the currently available diagnostic approaches for sexual dysfunction in the context of evidence-based literature in support of their use. In conclusion, EBM and patient-centered medicine are viewed as highly complementary and equally applicable in the clinical management of sexual dysfunction.

3. USE OF A UNIFIED MANAGEMENT APPROACH IS RECOMMENDED IN EVALUATING AND TREATING SEXUAL PROBLEMS IN BOTH MEN AND WOMEN.

Gender disparities in sexual medicine have traditionally been a major barrier for women in obtaining adequate clinical services for sexual difficulties or dysfunctions. Gender stereotypes have also hampered understanding and appropriate diagnostic evaluation in women, as terms like “frigidity” have been used indiscriminately in psychoanalysis and other branches of medicine. Fortunately, sexual medicine in recent years has become more aware and sensitive to the need for gender equality and the need for a unified management approach. In the diagnostic algorithm below, we propose a unified, step-wise management approach for both men and women with sexual problems. The proposed algorithm has been based on the algorithm presented by this Committee in the previous Consultation [14].

**III THE ICSM-5 DIAGNOSTIC AND TREATMENT ALGORITHM**

The International Consultation in Sexual Medicine (ICSM) proposes the ICSM-5, as a step-wise diagnostic and treatment algorithm for sexual dysfunctions in men and women (Figure 1). The main goal of ICSM-5 is to unmask the underlying aetiology and/or indicate appropriate treatment options according to men/women’s individual needs (patient-centered medicine), using the best available data from population-based research (evidence-based medicine).

The **first step** includes the **basic evaluation**; medical, sexual and psychosocial history are mandatory for every patient, while focused physical exam and laboratory tests are highly recommended; **step 2** includes the **interpretation of the findings** and identification of needs for specialized tests. In the majority of the patients optional tests are not necessary. In one study (**FIGURE 2**), the impact of the different diagnostic steps on the management strategy for erectile dysfunction has been explored in a sample of 1,276 patients visiting an andrology
outpatient clinic; basic evaluation allowed diagnosis in 79.7% of the patients, therefore specialized diagnostic procedures were necessary in only 1 out of 5 patients [27]. However, physicians may make the final decision either to proceed with specialized tests/referral or to treatment [28]. Step 3 includes patient/partner education, which is of major significance and a necessary prelude for shared decision making. Step 4 includes the development of a mutually-agreed upon treatment plan, equally considering the available treatment options for a certain diagnosis, as well as patients’ needs and preferences. Finally, step 5 refers to the important phase of follow-up, emphasizing that the overall goal of treatment is improvement of patient’s subjective sexual well being and not merely relief of symptoms and/or restoration of sexual function.

**STEP 1: BASIC EVALUATION**

Clinical evaluation for sexual dysfunction has unique
challenges and opportunities that can make the process difficult for some clinicians and underline the need for specific skills, as sexual medicine clinical practice has some unique characteristics (Table 5). Initial assessment of a sexual problem should include sexual, medical, and psychosocial history in every case. Physical examination and laboratory tests are highly recommended if appropriate, but are not always necessary.

Table 5: Unique characteristics of sexual medicine clinical practice

<table>
<thead>
<tr>
<th>Goals of diagnostic procedures</th>
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<tbody>
<tr>
<td>1 Social environment - Cultural competence</td>
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<tr>
<td>2 Physicians’ biases and gender variations</td>
</tr>
<tr>
<td>3 Patients’ embarrassment, lack of knowledge, plethora of misleading info</td>
</tr>
<tr>
<td>4 Couples’ problem</td>
</tr>
<tr>
<td>5 Self-reported initial diagnosis</td>
</tr>
<tr>
<td>6 Health system inadequacies (lack of education –lack of specialized care centers)</td>
</tr>
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</table>

1. SEXUAL HISTORY

A detailed sexual history should be obtained for all patients presenting with a sexual problem. In obtaining a history with men or women with sexual problems, special attention should always be paid to personal, social or cultural sensitivities. Patients may or may not be comfortable with direct inquiry into their sexual function and issues related to sexual problems. The interview should ideally be conducted as a face-to-face interaction with a sympathetic examiner [29]. Attention should be paid to the setting of the interview, in particular the need for privacy and confidentiality, and the clinician should make every effort to ensure patient trust, comfort and openness.

Since the type and duration of the problem is not always apparent at the outset, and since individuals frequently present with one type of dysfunction (e.g. lack of erection, early ejaculation), but may have other sexual or interpersonal problems, a detailed sexual history should always be obtained. While briefchecklists or questionnaires may be of value in the recognition and initial evaluation of a sexual problem, these should not substitute for a detailed sexual history. The examiner should always be attentive to both the intra- and inter-personal aspects of sexual dysfunction. Careful attention should be paid to both the style and content of the initial evaluation. Overall, the clinician should strive to maintain an attitude of comfort and flexibility throughout the evaluation process. Emphasis should be given to the education of physicians to deal with sexual issues and their level of knowledge; alternatively clinicians should refer their patients to specialists.

a) Physician-patient communication

The first step in the evaluation of any patient with sexual problems should be to establish an effective physician-patient-partner relationship. Only by encouraging the patient or the affected couple to discuss their sexual experience, will the physician fully ascertain the patient’s sexual concerns, their feelings and expectations about the sexual problem, and especially their concerns about the condition, its impact on patient’s/partner’s quality of life, and their expectations regarding the therapeutic outcome [30]. A second important focus of a patient-centered approach is the attempt to understand the whole person, including the patient’s culture and background, his/her life setting, family and clues about the sexual partner.

Patients typically desire the doctor to take the initiative in clinical interactions, to use simple and direct language, to be nonjudgmental, caring, and respectful, and to provide clear explanations and allow for questions, to acknowledge and explore the patient’s responses, and to promote an optimistic attitude when possible.

b) The physician-patient barriers: education and communication

It is not uncommon for physicians to be embarrassed, ashamed or reluctant to address sexual issues or concerns of their patients, despite the fact that the most important intervention is simply to ask or bring up the topic [29,31-35]. Several barriers to taking sexual history have been reported (Table 6) [11]. Characteristics identified by physicians as causing discomfort include interviewing opposite gender patients, patients aged less than 18 or more than 65 years, patients whose academic achievement is below college level, and patients who are divorced or single [32]. Training physicians in communication skills has been shown to be fundamental for sexual history-taking and the management of sexual problems, as it improves their level of comfort in dealing with sexual issues. Essentials in education include undergraduate curriculum, sexual medicine courses, psychosocial orientation and modification of physicians’ personal sexual attitudes [9,33-37].

Table 6: Barriers to taking sexual history. Adopted from [11].

<table>
<thead>
<tr>
<th>Physicians’ Barriers asking about sexual history</th>
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<tbody>
<tr>
<td>1 Insufficient knowledge</td>
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<tr>
<td>2 Inadequate communication skills</td>
</tr>
<tr>
<td>3 Discomfort with sexual language</td>
</tr>
<tr>
<td>4 Lack of information about treatment options</td>
</tr>
<tr>
<td>5 Time constraints</td>
</tr>
<tr>
<td>6 Fear of offending the patient</td>
</tr>
<tr>
<td>7 Clinician’s embarrassment about sexuality</td>
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</tbody>
</table>
Typical questions that have been recommended to initiate the sexual history or discussion of sexual issues include: ‘Are you happy with your sexual life?’; ‘Do you have any questions or concerns about sexual matters?’ and concluding with the question ‘Is there anything else about your sexual life that I need to know about to ensure you good sexual health care?’ Listening attentively to one’s patients, male or female, and clarifying their concerns or questions are invariably important elements in defining the nature of the problem, its severity and duration, as well as patients’ motivations for treatment [34-36].

c) ALLOW : Forming a healing physician-patient relationship

In order to establish a holistic physician-patient relationship and to obviate the usual communication barriers, the “ALLOW” acronym (Figure 3) is recommended [38]; it is a 5-step communication plan that enables the clinician to manage sexual issues while recognizing the limitations and varied needs and qualifications of clinicians for managing sexual problems.

The first stage in assessment is represented by the letter “A” - “asking” the patient about sexual function and activity. There are many ways to inquire about sexual problems, for example, when the social history is discussed or a review of systems is performed. The main purpose is to give the patient an opportunity to discuss sexual matters in a non-threatening manner; a statement about the confidentiality of the information being discussed is therefore necessary. The second step is represented by the letter “L” - “legitimizing” the patient’s problem and acknowledging that sexual dysfunction is a relevant clinical issue. In contrast, if the patient perceives that his or her sexual problem is being ignored or dismissed, this can delay or discourage the patient from seeking further help. The third step is again represented by the letter “L” - “limitations” the clinician may bring to the evaluation of sexual problems. These can include lack of knowledge or personal discomfort with discussion of sexual matters, even clinician’s personal values. Based on this self-evaluation by the clinician, the next step may be a referral, as the clinician has done it “ALL” for the patient. Step 4 involves “Opening up the discussion”. The discussion should explore the sexual problem and its context; biological, psychosocial and relationship. The final stage, represented by the letter “W” - “Work together to develop a treatment plan”, involves dialogue with the patient to identify an appropriate goal and mutually acceptable management plan. It is essential at this point for the clinician to evaluate patient and partner’s values and discuss risks and benefits of different treatment options.

d) Screening tools for sexual dysfunction

Sexual problem identification should be regarded as a routine and necessary aspect of medical care for both men and women. This principle is applied to all new patient visits, especially for individuals at risk, such as men or women above the age of 50, patients with chronic illnesses or medical conditions, following major surgery or hospitalization, during major life changes (e.g., divorce, childbirth), as well as during return or follow-up visits for these patients. The depth and extent of sexual inquiry should be individualized, based on the clinical setting, patient characteristics, and type of visit. Screening checklists can provide a valuable resource in identifying and assessing sexual problems in men and women. These simple tools have the obvious benefits of providing validated and cost-efficient identification of the problem, as well as preliminary assessment of current and past sexual functioning. To facilitate initial identification of a sexual problem, two brief screening checklists have been developed by the ICSM committee on diagnosis in the previous consultation [14] and more recently by the Standards Committee of the ISSM. It should be emphasized that, although valuable in recognizing and identifying sexual dysfunction, screening tools should not be substituted for a thorough sexual, medical, and psychosocial history. Moreover, further evaluation of these symptoms is always recommended prior to initiating sexual medicine therapy.

1. THE BRIEF SEXUAL SYMPTOM CHECKLIST FOR MEN (BSSC-M) AND WOMEN (BSSC-W) [14]

This brief checklist consists of 4 simple questions and it is suitable for use in primary care settings, as well as for screening and addresses the patient’s
level of satisfaction with sexual function (the major outcome measure in sexual health) [14]. Additionally, it assesses duration, the type/s of sexual problems experienced, as well as the willingness of the person to discuss the problem with a health care provider. Three of the four questions are common for men and women, while the fourth question (type of problem) is specific for gender (APPENDIX 1 and 2). BSSC has been used in the literature [39], however, validation data are lacking.

2) The Sexual Complaints Screener for Men (SCS-M) and Women (SCS-W)

More recently the Sexual Complaints Screener for Men (SCS-M) and Women (SCS-W) have been developed by the Standards Committee of the International Society for Sexual Medicine [pers comm, H. Porst, Hamburg, Germany] (APPENDIX 3 and 4). The SCS consists of a series of questions concerning sexual experiences during the last 6 months. Validation of the SCS is in process.

e) Differentiating Sexual problems S (sexual) CDDD

Misinformation and ignorance about sexual function and dysfunction are commonplace [40]. Many individuals are misinformed or unaware of basic information about sexuality and reproduction, and have sexual concerns or questions, such as penile size, refractory period after ejaculation, and morning erections for men, while frequency of sexual desire and achievement of orgasm for women are frequent areas of misunderstanding. Misinformation or myths may lead to uninformed sexual decisions with serious consequences, e.g. unintended pregnancy, a sexually transmitted disease or other avoidable problems [41]. Other individuals have specific problems, e.g. situational premature ejaculation, different levels of sexual desire between partners, which may also lead to psychogenic sexual dysfunction or the initial phase of a sexual dysfunction, e.g. change in erection hardness due to mild arterial insufficiency. Sexual dysfunctions are highly prevalent, while disorders that cause sexual problems, e.g. Peyronie’s disease and vulvodynia are also common. During the initial phase of assessment, physicians need to discriminate between such sexual concerns, difficulties, dysfunctions and disorders [41]. It is not uncommon that a sexual concern or worry may be the cause of sexual difficulty, which in some cases may lead to a sexual dysfunction. Conversely, anatomic or medical problems e.g. penile deviation or Peyronie’s disease, may be the cause of difficult sexual penetration and diminished sexual satisfaction, which may lead in turn to relationship problems and concerns about masculinity or femininity. Therefore, it should be acknowledged that sexual inquiry is a dynamic process involving different levels and domains of concern, difficulty and dysfunction (Figure 4) [41].

f) Types of sexual dysfunction: defining the underlying aetiology of sexual dysfunction

It is evident that Step 1 of ICSM-4 diagnostic algorithm has a major goal to identify and characterize the underlying aetiology. The presence or absence of biological findings will be a clear determinant of organic component that may include: a) anatomic (including surgery-related), b) vascular, c) neurogenic, d) hormonal, and e) drug-related. There is increasing awareness and interest in the clinical literature regarding the addition of distress/interpersonal difficulty to the diagnostic criteria of sexual dysfunctions. While most authors recognize the necessity for inclusion of personal or interpersonal distress for both men and women, others present evidence that some persons with sexual dysfunction are not distressed by it [42]. A classification of the degree of distress associated with dysfunction can be described as Type II and III sexual dysfunctions as follows:

- not significant mental (cognitive) or emotional (affect) distress: resolution of the main symptom (e.g. restoration of erections) will adequately diminish mental and/or emotional distress.
- significant mental (cognitive) or emotional (affect) distress: resolution of the main symptom (e.g. restoration of erections) will not diminish mental and/or emotional distress. In this case, complementary psychotherapy is indicated.

Therefore, clinically, the Committee proposes categorization of sexual dysfunctions in 3 types (Table7) according to their predominant aetiology.

g) Differentiating Organic and Psychogenic Etiologies

An essential point in clinical formulation of sexual
dysfunction in men and women is that organic and psychogenic factors coexist in many cases, particularly in those individuals or couples with longstanding or chronic sexual dysfunction. Key aspects of the history may be used to identify the potential role of specific organic and psychogenic causes or etiologies. The following table provides an overview of specific aspects of the patient’s history that may be useful in differentiating organic from psychogenic sexual dysfunction (Table 8) [43]. It should be emphasized however that psychogenic and organic etiologies co-exist in a large number of cases.

### Table 8: Characteristics of organic and psychogenic sexual dysfunction. Modified from [43].

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Organic</th>
<th>Psychogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumstances</td>
<td>gradual (except trauma or surgery)</td>
<td>acute</td>
</tr>
<tr>
<td>Symptom course</td>
<td>progressive</td>
<td>intermittent or selective</td>
</tr>
<tr>
<td>Organic risks</td>
<td>present</td>
<td>absent, variable</td>
</tr>
<tr>
<td>Partner problem</td>
<td>secondary</td>
<td>at onset</td>
</tr>
<tr>
<td>Anxiety</td>
<td>secondary</td>
<td>primary</td>
</tr>
</tbody>
</table>

### Table 7: ICSM classification system for Sexual Dysfunction

<table>
<thead>
<tr>
<th>TYPES</th>
<th>CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>I - psychogenic</td>
<td>Absence of biological findings</td>
</tr>
<tr>
<td>II - organic</td>
<td>Biological findings, NOT significant mental (cognitive) or emotional (affect) distress</td>
</tr>
<tr>
<td>III - mixed</td>
<td>Biological findings, significant mental (cognitive) or emotional (affect) distress</td>
</tr>
</tbody>
</table>

### Table 9: Questions to Initiate Discussions About Sexual Activity. Modified from [38].

<table>
<thead>
<tr>
<th>Type of Question</th>
<th>Example Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open-ended questions</td>
<td>“So, how are you doing with sex lately?”</td>
</tr>
<tr>
<td>Rating question</td>
<td>“Rate your recent sexual function on a scale of 1–10.”</td>
</tr>
<tr>
<td>Permission-giving questions</td>
<td>“Many of my patients your age have noticed some change in their sexual function. How about you?”</td>
</tr>
<tr>
<td>Asking the partner</td>
<td>“How has sex been lately?”</td>
</tr>
<tr>
<td>Asking men with chronic illnesses/medication</td>
<td>“How has your illness affected your sex life?”</td>
</tr>
<tr>
<td>Asking men with chronic illnesses/medication</td>
<td>Did your medication affect your sex life?</td>
</tr>
</tbody>
</table>

### Table 10: Quick review assessment (A-G). Adopted from [44].

<table>
<thead>
<tr>
<th>Quick Review Assessment (A-G)</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>About? What happens, feelings, thoughts</td>
</tr>
<tr>
<td>B</td>
<td>Both partners sex response</td>
</tr>
<tr>
<td>C</td>
<td>Context- relationship, environment, culture, why now?</td>
</tr>
<tr>
<td>D</td>
<td>Depression? – Mental health, including self-image</td>
</tr>
<tr>
<td>E</td>
<td>Experiences in the past</td>
</tr>
<tr>
<td>F</td>
<td>Feelings for partner</td>
</tr>
<tr>
<td>G</td>
<td>General Health</td>
</tr>
</tbody>
</table>

h) Initiating the discussion

A single question (e.g., “Do you have questions or concerns about your sexual functioning?”) may be sufficient in some circumstances, whereas a series of questions is indicated in others (Table 9) [38]. Sexual inquiry is most often conducted by face-to-face interview with the patient, although paper-and-pencil questionnaires or internet-based methods may be of value. Each of these methods has distinct advantages and limitations. The style or manner in which sexual inquiry is conducted is most important. This should reflect a high level of sensitivity and regard for each individual’s unique ethnic, cultural and personal background. TABLE 10 offers a simple way to ask the critical initial questions in order to achieve a quick review of the case [44].

Sexual history taking should be aimed at ascertaining the severity, onset and duration of the problem, as well as presence of concomitant medical or psychosocial factors. It is necessary to determine whether the presenting complaint, (e.g. erectile dysfunction, anorgasmia) is the primary or major sexual problem, or if some other aspect of the sexual response cycle (desire, ejaculation, orgasm) is involved. Other sexual problems may exist as concomitant disorders (e.g. hypoactive sexual desire), or as secondary to the primary sexual complaint [29,32,33]. The medical and sexual history is the most essential, and frequently the most revealing aspects of the assessment process.

A comprehensive sexual history is essential in confirming the patient’s diagnosis, as well as in the evaluation of the patient’s overall sexual function. Sample topics or questions for inclusion in the sexual history are illustrated in TABLE 11 below. These questions apply specifically to the evaluation of male arousal, desire and orgasm/ejaculation difficulties. In principle, these questions may be addressed to all patients presenting with sexual difficulties.

2. MEDICAL HISTORY

Although not always definitive, a detailed medical history may provide suggestive evidence for or
against the role of specific organic or psychogenic factors and should be obtained in all cases of sexual dysfunction. The goals of medical history-taking are:

(i) to evaluate the potential role of underlying or comorbid medical conditions. Sexual dysfunction may be symptomatic of an underlying medical disorder, such as atherosclerosis or diabetes. It is also a common presenting problem of depression in both men and women.

(ii) to differentiate between potential organic and psychogenic causes in the etiology of a patient’s sexual problem.

(iii) to assess the use of concomitant medications. Some of these medications can either cause or contribute to the patient’s sexual difficulties, and a change in medication may result in improvement in sexual function. Additionally, the use of certain medications may be important contraindications for the use of specific treatments.

Medical history may include all medical conditions that may interfere with sexual function [45-52]. TABLE 12 includes a list such conditions.

3. PSYCHOSOCIAL HISTORY

Potential etiologies for sexual dysfunction include a wide range of organic/medical factors, but also multiple psychological or interpersonal factors (e.g. anxiety, depression, relationship distress) [30, 36, 40-45, 48]. A detailed psychosocial assessment is essential in every case of sexual dysfunction. Given the interpersonal context of sexual problems in men and women, the physician should carefully assess past and present partner relationships. Sexual dysfunction may affect the patient’s self-esteem and coping ability, as well as his or her social relationships and occupational performance. These aspects should be assessed in each case. The physician should not assume that every patient is involved in a monogamous, heterosexual relationship. For this reason, it is advisable to begin the history with a broad question, such as: “Are you sexually active at the moment”, or “Do you have a regular sex partner?” and then to ask a follow-up question, such as “Is this a same-sex or opposite-sex relationship?” The early stages in the development of a problem are often of crucial significance to assessment and treatment. Were there particular times of change in the sexual relationship? If so, what events occurred in the patient’s life at those times? In addition, questions should be asked about other relevant aspects of the patient’s life, including interpersonal relationships, occupational status, financial security, family life and social support.

4. PHYSICAL EXAMINATION

The etiology or causal factors for sexual dysfunction may or may not be apparent from the patient’s history alone. In specific sexual dysfunctions, e.g.
anatomic problems or erectile dysfunction, further investigation by means of a physical examination and selected laboratory testing may be of value in confirming or disconfirming specific etiologies or comorbidities. In most cases, the physical examination will not identify the specific etiology or cause of sexual dysfunction, however a focused physical examination is highly recommended [14, 27]. The physical examination should include a general screening for medical risk factors or comorbidities that are associated with sexual dysfunction, such as body habitus (secondary sexual characteristics), assessment of the cardiovascular, neurological and genital system, with particular focus on the genitilia and secondary sex characteristics (TABLE 13). The physical examination may corroborate aspects of the medical history and can sometimes reveal unsuspected physical findings (e.g. decreased peripheral pulses, vaginal atrophy, atrophic testes, penile plaque). In addition to identifying specific etiologies or comorbidities, the physical examination may provide an opportunity to inform the patient about aspects of their sexual anatomy or physiology, as well as providing reassurance about body appearance and function. However, it should be recognized that the physical examination can also be a source of shame, embarrassment or discomfort for many patients. Every effort should be made to ensure the patient’s privacy, confidentiality and personal comfort while conducting the physical examination.

The physician should always review the major findings of the examination and should address any questions or concerns of the patient regarding their physical appearance or normality. In some settings, it may be advisable for the physician to perform the physical examination in the presence of a nurse or chaperone.

Specific considerations in conducting physical examinations in women with sexual dysfunction.

In some instances, a physical examination may be desirable, although not strictly essential. Possible examples include: a) situational problems; b) generalized dissatisfaction with sexual activity in the absence of specific sexual dysfunction; c) mood disturbances; or d) generalized dysfunction secondary to a change in socioeconomic status or a recent adverse life event. In these instances, a detailed history may provide adequate evidence for the diagnosis and evaluation of the problem. However, even in such cases, the physical examination may uncover occult organic or physical factors, as well as providing opportunity for reassurance and education of the patients. It may also be valuable in assessing the patient’s overall health status in potentially uncovering the presence of important comorbidities, such as cardiovascular disease or diabetes [46, 48-49].

5. LABORATORY TESTING

Recommended laboratory tests for men and women with sexual problems typically include fasting glucose, cholesterol, lipids and hormonal profile (TABLE 14) [14]. As with the physical examination, these tests are performed primarily to identify or confirm specific etiologies (e.g. hypogonadism), or to assess the role of potential medical comorbidities or concomitant illnesses (e.g. diabetes, hyperlipidemia). A detailed discussion of the role of hormonal assessment and treatment of sexual problems in men is reviewed in other Chapters. Additional laboratory tests (e.g., thyroid function) may be performed at the discretion of the physician, based on the medical history and clinician’s judgment.

### Table 13: Key Elements in the Physical Examination.

<table>
<thead>
<tr>
<th>Physical Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Complete genital exam (in men digital rectal)</td>
</tr>
<tr>
<td>2. Secondary sexual characteristics</td>
</tr>
<tr>
<td>3. BP, heart rate, peripheral pulses, edema</td>
</tr>
<tr>
<td>4. Lower body vibratory sensation</td>
</tr>
<tr>
<td>5. Lower extremity strength and coordination</td>
</tr>
</tbody>
</table>

### Table 14: Optional laboratory tests.

<table>
<thead>
<tr>
<th>Laboratory tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fasting glucose</td>
</tr>
<tr>
<td>2. Lipids</td>
</tr>
<tr>
<td>3. Hormones (sex hormones, gonadotropins, TSH)</td>
</tr>
</tbody>
</table>

**STEP 2: REVIEW OF FINDINGS**

Results of the initial evaluation should be reviewed with the patient and patient’s partner whenever possible, prior to initiating therapy. This review should be used as an opportunity to educate patients on the anatomy and physiology of sexual function, and to provide appropriate understanding of the pathophysiology (“what is wrong”). Potentially modifiable risk factors, such as cigarette smoking or alcohol abuse, should be addressed at this stage in the process. The potential role of prescription or nonprescription drugs, including psychotropic agents (e.g., SSRIs), cardiovascular drugs or other iatrogenic causes of sexual dysfunction, should also be addressed. Patients with specific endocrine deficiencies, such as hypogonadism, should be placed on hormone replacement therapy (in the absence of medical contraindications, such as prostate or breast cancer) prior to initiation of direct therapies for sexual dysfunction. A specialist referral is generally indicated in these cases. Additionally, sexual problems in the partner such as a lack of lubrication, hypoactive sexual desire or dyspareunia (painful intercourse) should be addressed whenever possible.

If psychological issues are evident at this time,
referral should be considered to a suitable sex therapist or mental health professional. Patients and partners should be fully informed about the range of treatment options available and the risks and benefits associated with each should be addressed.

1. REFFERALS

Physicians currently manage the majority of cases of male sexual dysfunction. This is largely true for women also, although the number of women seeking help from mental health or gynecologically-trained practitioners varies from one region or country to another. Only in a minority of patients, is referral for specialized consultation or testing absolutely necessary. However, either the patient or physician may wish to obtain further diagnostic evaluation for several reasons [31, 36, 41]. TABLE 15 indicates reasons for referral either for further consultation or for a specialized test.

2. SPECIALIZED TESTS

As shown, further diagnostic evaluation may be conducted at the patient’s request, in cases of lifelong or primary sexual dysfunction, in the presence of specific anatomic or endocrine factors, or in cases of complicated psychiatric or interpersonal problems [14]. Additionally, specialized diagnostic assessment may be indicated following failure of initial therapy. When referring patients for specialized testing or consultation, patients should be fully informed of the reasons for the referral and the possible implications for treatment discussed. In accordance with the principles of patient-centered medicine, patients (and partners where possible) should be included in the decision-making process regarding the need for specialized or additional diagnostic evaluation. Patients should be fully informed of the cost and potential risks of these procedures, as well as potential benefits and evidence-base in support of their use.

a) Specialized tests for women

Specialized diagnostic procedures for women are less advanced and less widely used than in men. In particular, a variety of measures have been used in laboratory studies to measure vaginal blood flow or vasocongestion during sexual stimulation. However, all of these methods suffer from methodological limitations and have not been found to be generally useful in the diagnostic assessment of female sexual dysfunction. All of the existing measures have important shortcomings and disadvantages and none are adequately validated. Moreover, there has been an inability to correlate most physiologic measures with subjective measures of sexual arousal [53, 54]. Given the complex nature of the sexual response in women, specialized diagnostic or physiologic measures should be considered in context of other data, including the history, physical examination, and validated questionnaires. Nonetheless, the existence of appropriate physiologic measures is vital to our understanding of female sexual function and dysfunction. TABLE 16 presents the level of evidence of specialized tests for women; detailed information regarding physiological measures and specialized tests for women are given in other chapters.

b) Specialized tests for men

A broad array of specialized diagnostic tests and procedures are available, particularly for assessing ED [14, 55]. Erectile dysfunction diagnostic tests have been extensively studied in the literature, and despite certain limitations, some of these tests are widely used in the everyday clinical practice, and are supported to varying degrees by published data. These tests may be used to separate organically based from purely psychogenic cases (e.g. nocturnal penile tumescence and rigidity testing), or to tailor specific vascular surgery in patients with arterial disease or veno-occlusive dysfunction. In the
majority of patients, however, the specialized diagnostic evaluation has little impact on the selection of therapeutic options. Diagnostic categorization is particularly indicated for those patients in whom a reversible form of ED is suspected (e.g. hypogonadism, Peyronie’s disease). Diagnostic procedures for ED are extensively discussed in a specific section of the chapter.

Following completion of the diagnostic evaluation, patients (and partners where possible), should be given a detailed description of the findings with specific explanations of the causes and the underlying pathophysiology. Furthermore, physicians should consider carefully the potential role of unrecognized comorbidities – or refer the patient for further diagnostic assessment - and afterwards offer the available treatment options. These should include both medical and non-medical options, whenever indicated.

Although certain options may be preferred by the majority of individuals with some sexual dysfunctions (e.g. PDE5 inhibitors for men with ED), all patients should be informed about the availability of other treatment options, including psychological treatment options. Similarly, patients should be informed about availability of treatment options for other male or female dysfunctions. This is in accordance with an essential principle of patient-centered medicine; viz., shared decision-making [24, 25]. Some patients may prefer “watchful waiting” or further consideration prior to selection of a specific treatment option. Additionally, some patients may wish to consult with their partner or other health-care provider before selecting a specific management approach. In each case, these options should be respected and encouraged, if appropriate. It is important for the clinician not to assume an authoritarian or patriarchal role in the selection (or rejection) of specific treatment options. Instead, the clinician should aim to educate the patient as fully as possible, making full use of evidence-based literature and guidelines wherever possible, regarding the risks and benefits of each treatment. The clinician should also provide a supportive and empathic environment for shared decision-making. Treatment of sexual dysfunction should not be delayed or postponed as most patients desire immediate treatment.

2. DEVELOPING A FOLLOW-UP STRATEGY: “FAST”

Follow-up is the final essential element in ensuring adequate management of common sexual problems. Sexual dysfunction should be managed in a similar way to other chronic medical or psychological conditions, including scheduling of regular follow-up visits. Follow-up visits are also essential to improve physician-patient communication, and to ensure the best treatment outcome. Monitoring of adverse events, assessing satisfaction or outcome associated with a given treatment, determining whether the partner may also suffer from a sexual dysfunction, and assessing overall health and psychosocial function, are important aspects of follow-up. Consideration should also be given as to whether an alteration in dose or treatment might be of value. Referral for specialist care with a urologist, gynecologist, endocrinologist, psychosocial therapist, or other appropriate specialist is important considerations in the follow up visit, especially in difficult-to-treat populations. The following “FAST” acronym (FIGURE 5) is a useful reminder of the key aspects of follow-up for ED, as well as sexual dysfunction generally [56]:

- FOLLOW-UP OF PATIENTS
Follow up to address treatment issues or problems that may have occurred (e.g., treatment administration, efficacy, adverse effects, partner’s acceptance), to identify changes in sexual function status or new medical conditions, and to offer continuing education and support to patients and their partners.

- ADJUSTMENT OF DOSING
Careful attention to prescribing instructions is necessary. Also, in patients who have more gradual or limited treatment response, such as those who are re-establishing sexual intimacy after a period of abstinence, repeated attempts or dosing may be necessary.

- SEXUAL STIMULATION
Currently available medical treatment, such as PDE5 inhibitors, enhances the physiologic response; therefore, sexual stimulation is essential and needs to be given at appropriate times following dosing. It may be also necessary to consider educating the patient and partner on suitable methods of stimulation.
3. EVALUATION OF SEXUAL WELL BEING

Treatment outcomes can be considered as having three major components; a) relief of symptoms and/or restoration of sexual function, b) tolerability and safety; and c) patient/partner adherence to treatment. In cases of positive outcomes, patient and partner satisfaction are expected, leading to relationship improvement and overall quality of life. The consequences of effective treatment should also involve diminished or abolished distress due to the resolution of the sexual problem, improvement of quality of life, increased life satisfaction and better perceived well-being (subjective well-being): i.e., better overall health and life satisfaction.

Figure 5: The “FAST” strategy. Modified from [56].

SUMMARY AND RECOMMENDATIONS IN EVALUATION

1. Sexual health is an integral part of overall health.

2. Health care providers should seek, receive and impart information related to sexuality. Individuals have the right to receive the highest attainable standard of sexual health, including access to sexual and reproductive health care services as a fundamental sexual right.

3. Sexual dysfunctions may have major impact on quality of life and psychosocial and emotional well-being. (Grade A)

4. The three principles for clinical evaluation and management of sexual dysfunctions are: a) adoption of a patient-centered framework, with emphasis on cultural competence in medical practice; b) application of evidence-based medicine in diagnostic and treatment planning; c) use of a unified management approach in evaluating and treating sexual problems in both men and women. (Grade C)

5. Sexual dysfunctions are essentially self-reported conditions. Therefore, diagnostic tests or procedures should not be recommended without controlled clinical data or research evidence supporting their use. (Grade C)

6. The ICSM-5 is a step-wise diagnostic and treatment algorithm for sexual dysfunctions in men and women. The main goal of ICSM-5 is to unmask the underlying aetiology and/or indicate appropriate treatment options according to men/women’s individual needs (patient-centered medicine), using the best available data from population-based research (evidence-based medicine). (Grade C)

7. Ignorance and knowledge gaps about sexual function and dysfunction are commonplace. Misinformation or myths may lead to uninformed sexual decisions with serious consequences. During the initial phase of assessment, physicians need to discriminate between sexual concerns, difficulties, dysfunctions and disorders. (Grade C)

8. For clinical purposes, sexual dysfunctions are categorized into 3 types according to their aetiology; type I: psychogenic, type II: organic, type III: mixed. Type II and III differ by the absence or presence of significant mental (cognitive) or emotional (affect) distress; in type II, resolution of the main symptom will adequately diminish mental and/or emotional distress, while in type III complementary psychotherapy is indicated. (Grade C)

9. Sexual, medical, and psychosocial history is mandatory in every case. (Grade B)

10. Physical exam and laboratory test are highly recommended, but not always necessary. (Grade C)

11. Specialized diagnostic procedures for women
are less advanced and less widely used than in men. Diagnostic procedures with the highest level of evidence should be used, when appropriate. (Grade B)

12. Improved management of sexual dysfunction depends on physicians’ inclination and ability to educate patients about their sexual function and dysfunction (Grade B)

B. OVERVIEW OF DIAGNOSTIC TESTS FOR ERECTILE DYSFUNCTION

The following section offers detailed guidelines for the clinical evaluation of erectile dysfunction (ED). Further guidelines for clinical evaluation of male orgasmic disorders, including early or delayed ejaculation, retrograde ejaculation and male anorgasmia are provided in other Chapters.

In the past decade, the scope of specialized evaluation of men with ED has shifted enormously [57]. Formerly, the primary purpose of testing was to define a treatment plan. To date, with the advent of effective pharmacological treatment modalities [58] and the knowledge that ED may be a predictor of cardiovascular dysfunction and a precursor of clinical cardiovascular disease in the majority of men consulting with ED, the focus of testing has moved towards the assessment of coronary risk [59-60]. The basic concept is that ED is an early symptom of urogenital ageing which is accelerated by a combination of multi (cardiovascular) co-morbidity and psychosocial factors. Endothelial dysfunction and autonomic hyperactivity are the basic pathological elements [61-65]. Current indications for specialized tests for ED patients are given in TABLE 17.

The frequent association of sexual and medical problems, especially in the aged population, make counselling, adjustment of lifestyle, and modification of risk factors, such as medication, overweight, smoking, alcohol consumption, and lack of exercise, the primary steps in a holistic approach toward the treatment of ED. It is especially important to educate these men to remain physically and sexually as active as possible for as long as possible. The phrase “use it or lose it” is particularly appropriate for the genitalia [63,67].

Table 17: Indications for specialized evaluation specialized tests for ED.

<table>
<thead>
<tr>
<th>Indications for ED patients’ referrals</th>
<th>VASCULAR FUNCTIONAL TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ED in the absence of cardiovascular co-morbidity or other factors. (ED may be the first presenting symptom of cardiovascular disease requiring treatment)</td>
<td>Color Duplex Doppler Penile Ultrasound</td>
</tr>
<tr>
<td>2 Peyronie’s disease and concomitant ED in whom surgery is considered</td>
<td>DICC (dynamic infusion cavernosometry and cavernosography)</td>
</tr>
<tr>
<td>3 Young men with a recent history of pelvic / perineal trauma in whom vascular surgery is considered</td>
<td>ICI (intracavernous injection pharmacotesting)</td>
</tr>
<tr>
<td>4 Primary ED in whom a congenital veno-occlusive dysfunction or arterial anomaly is suspected</td>
<td>Independent or jointly with vascular testing</td>
</tr>
<tr>
<td>5 Medicolegal cases</td>
<td>With or without: pharmacologic stimulation (oral, ICI)</td>
</tr>
<tr>
<td>6 Treatment failure</td>
<td>NPT (nocturnal penile tumescence and rigidity)</td>
</tr>
<tr>
<td></td>
<td>Erectiometer/ Rigidometer</td>
</tr>
<tr>
<td></td>
<td>NEUROPHYSIOLOGIC</td>
</tr>
<tr>
<td></td>
<td>Bulbocavernous Reflex Latency</td>
</tr>
<tr>
<td></td>
<td>Biothesiometry (vibratory thresholds)</td>
</tr>
<tr>
<td></td>
<td>Dorsal Nerve Conduction Velocity</td>
</tr>
<tr>
<td></td>
<td>CC-EMG (corpus cavernosum electromyography)</td>
</tr>
<tr>
<td></td>
<td>Plethysmography/ Electrobiome impedance</td>
</tr>
</tbody>
</table>

Table 18: Level of evidence for specialized evaluation specialized tests for ED.

<table>
<thead>
<tr>
<th>DIAGNOSTIC PROCEDURE</th>
<th>LEVEL OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>VASCULAR FUNCTIONAL TESTS</td>
<td></td>
</tr>
<tr>
<td>Color Duplex Doppler Penile Ultrasound</td>
<td>2B</td>
</tr>
<tr>
<td>DICC (dynamic infusion cavernosometry and cavernosography)</td>
<td>2B</td>
</tr>
<tr>
<td>ICI (intracavernous injection pharmacotesting)</td>
<td>2B</td>
</tr>
<tr>
<td>IMAGING TECHNIQUES</td>
<td></td>
</tr>
<tr>
<td>Selective Arteriography</td>
<td>2C</td>
</tr>
<tr>
<td>CT Angiography</td>
<td>4D</td>
</tr>
<tr>
<td>MRI</td>
<td>4D</td>
</tr>
<tr>
<td>Infrared Spectrophotometry</td>
<td>4D</td>
</tr>
<tr>
<td>Radioisotope Penography</td>
<td>5D</td>
</tr>
<tr>
<td>PET scanning of brain (during AVSS)</td>
<td>5D</td>
</tr>
<tr>
<td>VES: audio-visual sexual stimulation</td>
<td></td>
</tr>
<tr>
<td>Independent or jointly with vascular testing</td>
<td>3C</td>
</tr>
<tr>
<td>With or without: pharmacologic stimulation (oral, ICI)</td>
<td>3C</td>
</tr>
<tr>
<td>PENILE RIGIDITY TESTING</td>
<td></td>
</tr>
<tr>
<td>NPT (nocturnal penile tumescence and rigidity)</td>
<td>2B</td>
</tr>
<tr>
<td>Erectiometer/ Rigidometer</td>
<td>4D</td>
</tr>
</tbody>
</table>

TABLE 18 presents the level of evidence of specialized tests for ED. However, with the change of scope came a change of tools, in part because the classical specialized tests – with the exception of pharmacodenile duplex ultrasound (PPDU) and measurements of nocturnal penile tumescence (NPT) or sleep related erections – are not equipped to specifically and accurately assess cavernosal neuro-endothel-
lial function. On the contrary, these tests frequently do not add to data already available from the clinical history and assessments based on patient self-report, including self-administered questionnaires, event logs, and patient diaries [68], physical examination and laboratory testing, but typically at best confirm an already expected diagnosis [27,69,70]. Moreover, they are expensive, time-consuming, invasive, complication-prone (prolonged erections), and rarely conclusive except in experienced hands. Thus, the focus of has shifted to use of tests with demonstrated reliability in other medical fields, such as measurements of brachial artery flow mediated vasodilatation, dynamic contrast enhanced Magnetic Resonance Imaging (MRI), laser Doppler flowmetry and measurement of carotid intima media thickness. Recently, molecular technology entered the field as Foresta et al have shown that the amount of circulating endothelial progenitor cells may be used as a measure of cavernosal vascular damage [71].

I. PENILE VASCULAR EVALUATION

Since their introduction in the early 1980’s, penile selective angiography, the intracavernous injection test (ICI), penile duplex pharmaco-ultrasoundography (PPDU) and dynamic cavernosometry/gyphography (DICC) have become the most commonly used clinical tests to assess the vascular status of patients with erectile dysfunction [72]. These tests are aimed at the functional and anatomical evaluation of the cavernosal arterial inflow tract and veno-occlusive mechanism.

1. ICI-TEST

To date, the utilization of ICI testing as a vascular diagnostic test has become largely obsolete for several reasons: if penile rigidity is suboptimal, the diagnosis may be: arterial insufficiency, structural venous leakage or venous leakage due to situational high anxiety or too low a pharmacological challenge [73-75]. If rigidity is adequate, cavernous arterial insufficiency cannot be excluded. (ICI may be normal in as many as 20% of patients with borderline arterial inflow) [76].

2. PPDU AND DICC

Although the methodology of PPDU is widely used and well accepted to assess the arterial inflow tract, a lack of agreement about stimulation protocols and interpretation of the blood flow velocity waveforms still exists. For example, for peak systolic velocity (PSV), which is a common parameter to estimate arterial response, variation of cut-off values between 22 and 35 cm./sec has been reported. Moreover, PSV in young men may be falsely low [77]. Probably the unavailability of a valid reference methodology is responsible for this situation. Nevertheless, when vascular evaluation is indicated, PPDU provides the least invasive and accurate option to assess the penile arterial inflow tract [78]. The parameters used to infer the integrity of the penile inflow tract are cavernous arterial diameters, direction of bloodflow in the cavernosal artery [79], peak systolic flow velocity (PSV) and acceleration time (AT) (measured in ms from the start of systole to PSV) in the first 5 minutes following ICI. PSV < 25 cm/s has a 100% and 95% specificity in selecting patients with abnormal penile angiography. A PSV > 35 cm/sec is associated with normal angiography and defines normal cavernous arterial inflow. Speel et al have shown that AT has more power than PSV to diagnose atherosclerotic ED [80]. The cut-off point for acceleration time to discriminate between atherosclerotic and non-atherosclerotic erectile dysfunction was determined at acceleration time 100 ms or greater. Sensitivity was 66% and specificity was 71% [80]. There is recently some evidence that PSV measurements in the flaccid state may have value in predicting cavernosal arterial insufficiency silent coronary disease and the clinical response to ICI) [81,82]. However, Chatterjee et al showed that penile arterial inflow in renal transplant recipients could only be reliably detected following pharmacological stimulation with a PDE-5 inhibitor [83].

With PPDU the cavernous veno-occlusive mechanism can be evaluated in the late post injection phase (over 5 minutes following ICI). End-diastolic flow velocity (EDV) and resistance index (RI) may be used to estimate the degree of veno-occlusive function. Thus, persisting diastolic blood flow or a low RI, 5 minutes or more following ICI reflects persistent high flow rates due to impaired veno-occlusion. It is noteworthy, that in a series of normal controls, 30% had veno-occlusive dysfunction, indicating the inability of PPDU to differentiate between a pathological and a functional (anxiety induced incomplete smooth muscle relaxation) cause of veno-occlusive dysfunction [84]. In cases of doubt, DICC under the controlled condition of complete smooth muscle relaxation may be utilized to differentiate between these two entities [85].

DICC under the controlled condition of complete smooth relaxation is the primary modality available for quantifying and mapping of pathological veno-occlusive dysfunction. Since Newman introduced infusion cavernosometry in 1964 [86], various techniques have been described. Cavernous veno-occlusive function is assessed by determining the relationship between the intracavernous flow rate of a saline infusion required to sustain an intracavernosal pressure that equals the mean arterial systemic blood pressure under conditions of complete cavernous smooth muscle relaxation. A roller pump is typically utilized to regulate the infusion flow rates. Puech Leao introduced an alternative technique that requires less complicated technology and is less expensive: gravity cavernosometry. Instead of utilizing a roller pump to regulate the infusion flow rate, an infusion set is used to generate a steady infusion pressure above mean arterial systemic pressure. The closer intracav-
taneous pressure equals infusion pressure, the better the status of the veno-occlusive mechanism [87]. For accurate testing, a condition of complete smooth muscle relaxation is mandatory [88]. This can be induced with repeated administrations of vasoactive agents (redosing) and demonstrated by a linear relationship between infusion rate and intracavernous pressure and that the resistance to venous outflow is constant and independent of intracavernous pressure [89]. Cavernosography may be utilized to identify the location of the venous leak, although this may prove difficult in men with low grade veno-occlusive dysfunction [90]. Kayigil et al postulated that the percent decrease in the amplitudes of the electrical activity of CC as assessed with ccEMG may be utilized as a measure of the degree of relaxation of the cavernous smooth muscle [91]. Because of its invasiveness, DICC is reserved for the rare patient who might have a site-specific venous leak, e.g. Peyronie’s disease with poor rigidity, history of penile fracture, perineal / pelvic trauma history and is only performed when surgery is considered a treatment option [92, 93].

3. SELECTIVE INTERNAL PUDENDAL ANGIOGRAPHY

Selective internal pudendal angiography is primarily reserved for imaging and subsequent embolization of arterio-cavernous fistula causing high-flow priapism [94, 95]. Moreover, the test may be of value in the few cases of young men with ED who have a history of pelvic / perineal trauma who may be candidates for operative revascularization [96, 97].

4. NEAR INFRARED SPECTROPHOTOMETRY

In 2000 Burnett et al described near infrared spectrophotometry of the penis as a possibility for non-invasive continuous monitoring of the hemodynamic events of erection in the human penis [98].

5. DYNAMIC CONTRAST ENHANCED MRI

Penile Magnetic Resonance Imaging (MRI) is a diagnostic technique with great opportunities of application in the field of sexual medicine. It allows a better definition of anatomical details and a better knowledge of penile micro-circulation [99]. The signal intensity is dependent on the rate of blood flow within the cavernous spaces that constitute the corporal bodies. Also visible are the layers of fibrous tissue that envelop the corporal bodies, the deep arteries and veins, subcutaneous connective tissue, tunica Darts, epidermis, and urethra. MR imaging may be used to detect and stage arterial insufficiency, assessment and visualisation of veno-occlusive dysfunction [100], identify penile fractures, evaluate penile prostheses, and identify plaques of Peyronie’s disease [101]. Departing from the idea that pelvic ischemia can manifest as vascular mediated ED and lower urinary tract symptoms (LUTS) and is associated with cardiac ischemia, Hou et al demonstrated that pelvic perfusion assessed with dynamic contrast-enhanced MRI correlates with validated measures of ED and LUTS [102].

6. MEASUREMENT OF INTIMA MEDIA THICKNESS (IMT)

High-resolution ultrasonography has been used to obtain measurements of the thickness of the intima and media of the carotid arteries. Previous studies have shown cross-sectional associations between common-carotid-artery intima–media thickness and cardiovascular risk factors[103], the prevalence of cardiovascular disease [104], an increased risk of myocardial infarction and stroke in older adults without a history of cardiovascular disease[105] and the involvement of other arterial beds with atherosclerosis [106]. Changes in common-carotid-artery intima–media thickness have also been adopted as a surrogate end point for determining the success of interventions that lower the levels of low-density lipoprotein cholesterol [107]. IMT measurements, in hypertensive men have shown that the presence of vasculogenic erectile dysfunction is associated with subclinical atherosclerosis[108]. Measuring IMT at the carotid and femoral artery, Foresta et al demonstrated that femoral IMT was significantly higher than carotid IMT in men with ED, suggesting that in ED patients atherosclerosis develops predominantly in the pelvic area [109].

7. ENDOTHELIAL-DEPENDENT FLOW-MEDIATED VASODILATION OF THE BRACHIAL ARTERY

Endothelial dysfunction is an important factor in the pathogenesis of ED. In the 1990s, high-frequency ultrasonographic imaging of the brachial artery to assess endothelium-dependent flow-mediated vasodilation (FMD) was developed. The technique provokes the release of nitric oxide, resulting in vasodilation that can be quantitated as an index of vasomotor function. The noninvasive nature of the technique allows repeated measurements over time to study the effectiveness of various interventions that may affect vascular health[110]. To what extend FMD of the brachial artery predicts FDM of the cavernosal artery remains a subject for further research [111]. The combined use of brachial FMD and carotid IMT may predict vasculogenic ED with 80% accuracy [112].

8. LASER DOPPLER FLOWMETRY (LDF)

Laser Doppler flowmetry (LDF) is a relatively novel way to explore the mechanisms of vasoregulation. By use of LDF at the glans penis, genital vasoregulation can be semi-quantitatively assessed. For example, sympathetic nervous system activity provides one of the fundamental mechanisms for the control of cutaneous microcirculation. Sympathetic nerves are continuously active. They
rhythmically discharge so that all innervated blood vessels are under some degree of continuous contraction and relaxation. Their control of the blood distribution to the end cells or organs is exerted in several frequency bands, including rhythms related to the cardiac and respiratory cycles [113].

Translation of this knowledge into a methodology to study penile hemodynamics is still experimental. One can hypothesize that vasodilatation in the early stage of sexual arousal is a parameter of the function of the parasympathetic innervation. Therefore, assessment of the oscillation of the vascular tone at the glans penis before and after visual erotic stimulation may be a method to monitor the process of neuronally induced vasodilatation. With the aid of LDF, Rubin et al demonstrated that post reactive hyperemia in patients with cavernosal vascular insufficiency is reduced and patient with neurogenic ED have signs of sympathetic denervation and decreased respiratory response [114].

II. PSYCHOPHYSIOLOGICAL EVALUATION

One of the questions in the differential diagnosis of ED is whether the neurovascular axis is intact. For this purpose psychophysiological evaluation may be utilized. It entails the direct observation of penile responses.

1. NOCTURNAL PENILE TUMESCENCE (NPT)

A sleep related erection or NPT is a recurring cyclic phenomenon associated with rapid eye movements during sleep [115]. Evaluation of NPT has the main advantage that it is relatively free from psychologically mediated effects. Therefore, it is useful for separating psychological and organic cases. Moreover, it appears to correlate well with corporeal smooth muscle content which is the key structure of erection [116-119]. The documented presence of a full erection indicates that the neurovascular axis is functionally intact and that the cause of the ED is most likely psychogenic. To measure not only tumescence but also rigidity a Rigiscan® device may be used [120]. The instrument has two loops, one to be placed around the base of the penis and the other towards the tip, that tighten every fifteen or thirty seconds to measure radial compression force. Disadvantages of NPT evaluation are that the equipment is costly and it is time consuming as accurate assessment of sleep-associated penile erection requires in nearly 50% of men at least 2 consecutive nightly recordings that are ideally done in a specially equipped sleep centre to exclude sleep disturbances as possible cause of disturbance of NPT [121]. Moreover, it has been questioned whether the methodology of measuring radial compression force as a parameter a penile rigidity yields a valid reflexion of real life ax-

All in all the diagnostic accuracy of NPT evaluations has been estimated to be at best about 80%. Factors such as depression, negative dream content, sleep disorders and smoking can produce false-negative NPT readings. False-positive NPT responses can be elicited in patients with pelvic steal syndrome and in certain cases of peripheral neuropathy [124].

To date, NPT evaluation is mainly used in clinical studies to quantify the erectogenic effect of oral agents and the potentially antierectogenic effects of environmental agents [125-135].

2. VISUAL EROTIC STIMULATION

Another methodology to evaluate the penile neurovascular axis is measuring erection in response to visual erotic stimulation (VES). A full erectile response makes a somatic cause of ED unlikely [136]. However, unlike NPT, response to VES, although possibly closest to normal sexual response, is strongly susceptible to psychological factors, such as erotic excitement inhibition, and can be normal in states of endocrine abnormality [137]. Moreover, the response to VES is negatively correlated with age, limiting its value in older men. To date, the most important application of VES is to investigate the erectogenic or anti-erectogenic effect of drugs in clinical pharmacological studies.

III. NEUROLOGICAL EVALUATION

Neurological testing is only recommended in specific research protocols or medico-legal investigations, including cases of trauma or surgical complications. Based on the available evidence, these tests lack adequate sensitivity and reliability for routine clinical use [138,139].

Penile erection is elicited by two different neurophysiologic mechanisms and mediated by somatic and autonomic pathways. Psychogenic erections, initiated in supraspinal centres in response to auditory, visual, olfactory, and imaginative stimuli, are mediated by sympathetic pathways. Reflexogenic erections, elicited by tactile stimulation at the genital level, are mediated by a spinal reflex arc consisting of afferent somatic and efferent parasympathetic nerve fibers [140]. The ideal neurophysiological assessment objectively and quantitatively evaluates the functional status of all parts of this neurological network; no one test alone achieves this [141].

In the last two decades, a series of tests has been developed, each of which reflects a specific part of the network. The medical history and physical examination provide the basis for these tests [142,143]. Tests can be classified as those detecting somatic efferent (motor) pathways, afferent (sensory) path-
ways, reflexes and autonomic responses [143]. The somatic nerves are evaluated by testing nerve conduction velocities and evoked potentials. These tests have well-known reproducibility, validity and range of confounding factors. Autonomic function tests are less reliable, because they simultaneously measure a chain of events or reactions involving receptors, small fibers, and target organs. Confounding factors such as medication, caffeine, temperature, hypovolemic, mental mood, and receptor or target organ dysfunction may influence each individual component. Additionally, the complex interaction between central and peripheral sympathetic and parasympathetic nerve systems, as in the pelvic plexus, makes autonomic testing difficult. Moreover, efferent autonomic function tests involve the evaluation of vasomotor and sudomotor fibers and target organs, which may not be equally affected by neuropathy. Toxic metabolic events, especially cause length-dependent neuropathy, because long fibers are more prone to metabolic damage than short fibers. Finally, current autonomic tests are not well standardised, therefore reproducibility, validity and comparability of test results between laboratories are difficult. Thus, autonomic testing is difficult and must be tailored to the specific small fibers or target organ to be tested, with elimination or standardisation of confounding factors. If these conditions are fulfilled, a normal test result rules out neuropathy, while an abnormal test result does not necessarily imply neuropathy.

A well known and extensively used test is the bulbo cavernous EMG, that can identify damage to the sacral motor roots and the pudendal efferents. It samples large myelinated fibers. It is relevant in ED associated with lesions to the low backbone, with nerve root damage. Clinical indications are lumbar disc disorders, pelvic anatomical lesions, pelvic surgery etc [144]. Dorsal nerve conduction velocity is a test for the large myelinated dorsal penile sensory fibers, which can be valuable in the evaluation of neuropathy, for example in patients with diabetes mellitus. Sensitivity and specificity of this test have not been established yet [145, 146].

Latencies of SEPs are a measure for the conduction velocity along the sensory pathways from the genital region to the sensory cerebral cortex [147]. Thermal threshold measurements yield data on the conductance of small sensory nerve fibres and therefore may reflect indirectly the function of the penile efferent (motoric) nerve fibers. The rationale of performing this test is that evidence of impaired thermal sensation might suggest similar impairment of the autonomic motoric innervation of the cavernous body [148, 149].

Cardiovascular reflex tests assess variations in heart rate and blood pressure in response to various stimuli such as forced breathing, standing up or tilting, Valsalva’s manoeuvre, sustained isometric hand-grip, mental arrhythmic task, or cold pressure. Heart rate variations reflect parasympathetic function, while blood pressure variations reflect sympathetic function. Loss of variation is indicative for autonomic neuropathy, presuming absence of confounding factors such as cardiac arrhythmia, nicotine, or caffeine use before testing, medication (especially antihypertensives), hypo, or hypervolemic, and dysfunction of baroreceptors or target organs [150].

CcEMG is a relatively new technique, in which needle or surface electrodes record the electrical activity of the CC [151]. Basic questions regarding the signal recorded, and how to interpret it, are still unresolved. Thus, despite some clinical use this test must be regarded as experimental [152-159].

Functional MRI and PET-scanning may be used to assess brain centers that are involved in different phases of the sexual response cycle: simultaneous audiovisual erotic stimulation (AVES) is required [160]. Radioisotopic penography assesses the rate of washout of a radioisotope from the penis following pharmacostimulation or visual erotic stimulation. This test remains experimental [161].

**SUMMARY AND RECOMMENDATIONS ON SPECIALIZED TESTING FOR ERECTILE DYSFUNCTION**

Multiple diagnostic tests and procedures have been reported in the literature for medical or urological evaluation of ED. The principal diagnostic methods described in this section and in Table 18, including first and foremost the Color Duplex Doppler Penile Ultrasound (CDDPU) test. This widely used and accepted test in urology was given a rating of 2B on the evidence available, and was ranked equally with the Intracavernous Injection Pharmacotesting (ICI) procedure, rated as 2B also, along with Dynamic Infusion Cavernosometry and Cavernosography (DICC), similarly rated as 2B on the evidence available. In the same evidence-based category (2B), the Nocturnal Penile Tumescence and Rigidity (NPTR) procedure was ranked by the committee. It should be noted that these four widely used tests can be performed alone, or in combination over several visits. Improvements in diagnostic accuracy or reliability with combined testing has not been systematically investigated overall, and accordingly was not reviewed by this committee.

Other diagnostic procedures for ED reviewed by the committee ranged from moderately highly recommended (2C) for selective penile or pudendal arteriography (PPA), followed by audiovisual sexual stimulation (VSS) which was ranked, with or without pharmacostimulation, as 3C based on the evidence. Other forms of CT angiography or
C. SYMPTOM SCALES AND QUESTIONNAIRES

I. INTRODUCTION

The use of symptom scales and questionnaires in sexual medicine is accepted into everyday practice, as sexual problems have the essential characteristic of being self-reported conditions, with potentially major impact on psychosocial and emotional well-being, while in many cases there may be no biological findings [162]. Therefore the use of self-administered symptom scales has become essential in clinical research in sexual medicine, and has been applied extensively in everyday clinical practice in many settings.

Sexual dysfunction, according to recent definitions, exists when satisfaction arising from the integrated components of sexual function, are reduced or absent [14]. Therefore, outcomes assessment questionnaires are essential in sexual medicine not only to determine reduction of distress or resolution of symptoms, but also to assess the overall well-being – sexual or otherwise - of the individual. This section of the chapter outlines the principles of scales and questionnaires and afterwards presents the most widely accepted questionnaires reporting on sexual function. Finally, recommendations are given based on the level of evidence.

II. STANDARDS OF SCALES AND QUESTIONNAIRES

A questionnaire, sexual function scale or quality of life measure has to meet several standards [163] : (1) The scale should be developed and validated according to currently accepted standards of psychometric evaluation, including both quantitative and qualitative methods. (2) The scale should be acceptable to clinicians, who will be using it in everyday clinical situations; and (3) The scale should be acceptable to scientific reviewers and journal editors and others involved in everyday use or interpretation of these scales. The scale should have at minimum an evidence-based rating of Grade B or C for consideration in clinical or research settings. Several of the scales and questionnaires the committee reviewed are able to meet this standard.

Most importantly, although valuable in recognizing and identifying sexual dysfunction, screening tools and questionnaires should not be substituted for a thorough sexual, medical, and psychosocial history [162]. For patients with multiple sexual dysfunction symptoms (e.g., ED and low libido), further evaluation of these symptoms is always recommended prior to initiating sexual medicine therapy.

Whenever possible, the temporal association or causal relationship between the symptoms should be assessed.

III. PROCESS OF SCALE DEVELOPMENT

The process of scale development and evaluation consists of three phases, including the development of: (i) a conceptual model based on the most recent evidence in the field; (ii) domains and a draft item pool derived from qualitative interviews with well-selected patients – either individual or focus-group based; and (iii) psychometric validation studies in both patient and non-patient groups [164]. Typically, at least two quantitative validation studies are required to establish discriminant validity (patient with a diagnosis (i.e., cases) versus healthy individuals (i.e., non-cases)) and treatment sensitivity or responsiveness – i.e., if the scale is being evaluated for use as an endpoint measure [165]. For questionnaires which are designed to serve as diagnostic
screeners only, this latter type of validation (treatment sensitivity) may not be necessary or required.

1. DEVELOPMENT AND ROLE OF SELF-ADMINISTERED SCALES OR QUESTIONNAIRES (SAQ’S)

The primary format for evaluation of sexual function or sexual symptoms is the self-administered questionnaire (SAQ). In common with all psychometric scales or instruments, the two fundamental and necessary psychometric requirements for such instruments are reliability and validity [163]. Reliability refers to the consistency or replicability of data, with reliability «coefficients» serving as formal indicators of measurement consistency. These need to be reported with every scale or questionnaire, and should include both test-retest and inter-item reliabilities. Each of these aspects of reliability can be determined using standard psychometric measures (e.g., Cronbach’s alpha).

In contrast to consistency of measurement, validity addresses the essence of what is being measured; it reflects the degree to which an instrument measures what it purports to measure. Unlike reliability, which is established through a specific, rigorously prescribed series of statistical exercises, the validation of a measuring instrument is iterative in nature. Validation is much more of an enduring process, which accumulates evidence from numerous studies and trials; it is an ongoing process, at least theoretically, and serves to test and extend the generalizability of the validation statement. Nunnally [163] has likened the validation process to «...an expanding network of circumstantial evidence» supporting the validity of the measuring instrument.

The two essential indicators of validity for measures of sexual function are, sensitivity to functional versus dysfunctional status (discriminant validity), and sensitivity to therapeutically induced change (treatment responsiveness) [164,165]. The former refers to an instrument’s capacity to discriminate sexually dysfunctional individuals from those persons who are sexually healthy (its sensitivity and specificity in epidemiological terms, or discriminant validity in psychometric terms), while the latter refers to an instrument’s capacity to register treatment-induced change (longitudinal validity in psychometric terms).

Both are essential features of instruments designed to serve as diagnostic and/or efficacy measures in both clinical settings and in clinical research. In evaluating the treatment sensitivity or responsiveness to change (another term for this concept), it is important to assess the specific scale or instrument in the context of a clinical trial or other intervention study associated with significant change over the measurement period. The finding of the intervention study can be used to demonstrate the responsiveness of the scale to change, and most importantly, to develop mathematically from the study data a cut-point or criterion of clinically meaningful change.

2. SEXUAL SATISFACTION, TREATMENT SATISFACTION AND SEXUAL QUALITY OF LIFE MEASURES

An important distinction should be made between self-report measures of sexual function (e.g., IIEF) and validated, self-report measures of sexual satisfaction or quality of life (e.g., SEAR, SQLL). Some of these measures (e.g., EDITS) address treatment satisfaction and others are directed at psychosocial outcomes of treatment (e.g., SEAR, PAIRS). It is important to make distinctions between the conceptual focus or theoretical rationale for each of these outcome measures, in addition to the psychometric strengths and weaknesses of each scale. These measures differ also in the degree to which they are couples-oriented or more directed at the individual male or female patient. Substantial progress has been made in recent years in the development and validation of several excellent tools in this area, which can be reviewed according to pre-set criteria. Specific measures in the field can be reviewed in terms of: (i) the conceptual focus of the measure; (ii) qualitative and quantitative psychometrics; (iii) extent of clinical use; (iv) overall recommendations.

SUMMARY AND RECOMMENDATIONS

Self-administered questionnaires and symptom scales are valuable tools in the assessment of sexual function in both research and clinical settings. Recent guidelines have emphasized the need for these measures to be based on: (i) qualitative interviews with patients (and partners) whenever possible for content validity assessment; (ii) psychometric validation studies to establish the reliability and discriminant validity of the measure; and (iii) treatment sensitivity studies to establish the responsiveness to changes and minimally important change (MIC) of the measure. Development of any new measure of sexual function should include all three of these components of scale development and validation. In addition to questionnaire measures of sexual function in men and women, various questionnaires have been developed for monitoring sexual satisfaction and quality of life. These are valuable adjunctive measures for use in either research or clinical settings.

IV. RECOMMENDED QUESTIONNAIRES IN SEXUAL PROBLEM ASSESSMENT

The following review, along with the detailed information contained in Tables 19-20, characterizes 16 contemporary instruments designed to measure the status of an individual or couple’s sexual function. With the exception of two, all of these instruments
have been developed during the past decade, with the majority having been published during the past few years. Although not all of these measures were designed specifically for use in clinical trials, most have been designed as outcomes measures that are suitable for use in clinical trials. Most of these instruments are relatively early in their validation programs; however, all have performed well against established psychometric criteria and have demonstrated sound early-stage empirical evidence of reliability and validity. The instruments described in Table 1 meet minimal criteria; the instruments described in Table 2 meet more extensive criteria and are recommended for use in assessing sexual function status in the indicated populations. These latter instruments are presented in greater detail in the next section. The order of presentation is alphabetical.

1. RECOMMENDED QUESTIONNAIRES FOR USE IN BOTH MEN AND WOMEN

A small number of questionnaires have been developed and validated for use in both men and women (i.e., the same questionnaire can be administered to men or women). Specific questions within each of these questionnaire are designed for men and some for women to answer. This varies from questionnaire to questionnaire as follows.

a) Changes in Sexual Functioning Questionnaire (CSFQ)

1) DESCRIPTION

The CSFQ was developed by Clayton et al (1997 [166]). The women's version is a 34 item instrument designed to be a global measure of women's current sexual function, and differentiates between those who have poor lifelong psychosexual adjustment and those who have acquired sexual dysfunction after prior normal functioning. It was designed to detect changes in sexual function due to illness (e.g. depression) or the administration of medication (e.g. SSRIs). A 36-item version was designed for men. Fourteen core sexual functioning items are rated on a five point Likert style scale. The CSFQ is comprised of 5 factor-analytically determined dimensions, labeled sexual desire-interest, sexual desire-frequency, sexual pleasure, sexual arousal/excitement, and orgasm/completion. In addition, a Total CSFQ score representing overall sexual function may also be derived. Higher scores on total score and each of the subscales indicate better sexual function. A 14-item short-form has been developed and validated [167] and is scored into three scales: desire, arousal and orgasm.

2) ADMINISTRATION TIME

The CSFQ interview requires approximately 15 minutes. The 14-item self report scale can be completed in about 5 minutes.

3) TARGET POPULATION

The CSFQ is designed to be appropriate for heterosexual and homosexual respondents.

4) RELIABILITY AND VALIDITY

Reliability for the dimensions of the CSFQ has been demonstrated in the acceptable range (r's = .64 to .80). Concurrent validity has been established by comparisons with analogous measures from the Derogatis Interview for Sexual Functioning (DISF), with r's ranging from .66 to .68 [8]. Discriminative validity of a specific type was demonstrated by its ability to discriminate between a clinical sample (depressed patients) and a non-clinical sample [168]. The instrument was also able to demonstrate differential rates of sexual dysfunction associated with specific antidepressant medications [169].

5) NORMS – CUT-OFF VALUES

Norms are available for the CSFQ based on the medical student/resident sample, and medical outpatients.

6) LANGUAGES

Validated in English and Spanish [170], with linguistic validation in 50 other languages. It is available on request from Dr. Anita Clayton, University of Virginia Medical Center.

7) RATING ON AVAILABLE EVIDENCE : GRADE B AND LEVEL 3

b) Derogatis Interview for Sexual Functioning (DISF/DISF-SR)

1) DESCRIPTION

The DISF has been developed by Derogatis (1997) [171]. The DISF is a semi-structured interview comprised of 25 items and reflects quality of sexual functioning in a multi-domain format. The DISF-SR is a matching self-report inventory designed to accomplish the same goal in a patient self-report mode. There are gender specific male and female versions of both the DISF and the DISF-SR. The instruments in the DISF series are designed to be interpreted at three distinct levels: discrete items, functional domains, and aggregate summary (Total) score. DISF items are arranged into five primary conceptual domains of sexual functioning: sexual cognition/fantasy, sexual arousal, sexual behavior/experience, orgasm, and sexual drive/relationship. The primary conceptual domains have been empirically confirmed through factor analysis [172]. An aggregate DISF Total Score summarizes quality of sexual functioning across the five primary DISF domains.
<table>
<thead>
<tr>
<th>Inventory Name</th>
<th>Modality**/Gender</th>
<th>No. of Items</th>
<th>Admin. Time</th>
<th>Domains</th>
<th>Reliability</th>
<th>Discriminative Validity</th>
<th>Sens./ Spec.</th>
<th>Published Norms</th>
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<tbody>
<tr>
<td>Changes in Sexual Functioning Questionnaire (CSFQ)</td>
<td>CI and SR Male and Female</td>
<td>35/14</td>
<td>&lt;20 min/ &lt;5 min</td>
<td>Desire/frequency, desire/ interest, pleasure, arousal, orgasm, total</td>
<td>0.64-0.80</td>
<td>0.66-0.88</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Derogatis Interview for Sexual Functioning (DISF-SR)</td>
<td>CI and SR Male and Female</td>
<td>25</td>
<td>&lt;15 min</td>
<td>Cognition, arousal, behavior, orgasm, drive/ relationship, total score</td>
<td>0.74-0.80</td>
<td>0.80-0.90</td>
<td>YES</td>
<td>YES 0.89/0.75</td>
</tr>
<tr>
<td>Female Sexual Function Index (FSFI)</td>
<td>SR Female only</td>
<td>19</td>
<td>&lt;15 min</td>
<td>Desire, arousal, lubrication, orgasm, satisfaction, pain</td>
<td>0.82</td>
<td>0.79-0.86</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Golombok-Rust Inventory of Sexual Satisfaction (GRISS)</td>
<td>SR Male and Female</td>
<td>28</td>
<td>&lt;15 min</td>
<td>5 male domains, 2 male and female domains, total score</td>
<td>≥ 0.70</td>
<td>0.47-0.82</td>
<td>N/A</td>
<td>0.86/0.76-M 0.75/0.59 - F YES</td>
</tr>
<tr>
<td>International Index of Erectile Function (IIEF)</td>
<td>SR Male only</td>
<td>15</td>
<td>&lt;15 min</td>
<td>Erectile function, orgasm, desire, intercourse/satisfaction, overall</td>
<td>0.73-0.95</td>
<td>0.64-0.84</td>
<td>N/A</td>
<td>YES 0.97/0.88</td>
</tr>
<tr>
<td>Sexual Function Questionnaire (SFQ)</td>
<td>SR Female only</td>
<td>26</td>
<td>&lt;15 min</td>
<td>Desire, arousal-sensation, arousal-lubrication, enjoyment, orgasm, dyspareunia, partner, total</td>
<td>0.79-0.91</td>
<td>0.42-0.78</td>
<td>N/A</td>
<td>YES 0.90/0.98</td>
</tr>
</tbody>
</table>

SR = Self Report, CI = Clinical Interview

**Table 19: Psychometric Properties of Highly Recommended Scales**

IC (α)  TRT (r)  IRR  Funct/Dys.  Therap.Chg.  Sens./ Spec.  Published Norms
<table>
<thead>
<tr>
<th>Inventory Name</th>
<th>Modality**/Gender</th>
<th>No. of Items</th>
<th>Admin. Time</th>
<th>Domains</th>
<th>Reliability</th>
<th>Discriminative Validity</th>
<th>Sens./Spec.</th>
<th>Published Norms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derogatis Sexual Functioning Inventory6 (DISF-SR)</td>
<td>SR Men and Women</td>
<td>254</td>
<td>40 min</td>
<td>Information, experience, drive, attitudes, symptoms, affects, gender role def., fantasies, body image, satisfaction</td>
<td>0.71-0.97</td>
<td>N/A</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Decreased Sexual Desire Screener (DSDS)</td>
<td>SR + CI Women only</td>
<td>5</td>
<td>15-30 min</td>
<td>Sexual desire</td>
<td>N/A</td>
<td>N/A</td>
<td>YES</td>
<td>N/A</td>
</tr>
<tr>
<td>Female Sexual Distress Scale (FSDS)</td>
<td>SR Women only</td>
<td>13</td>
<td>&lt;15 min</td>
<td>Sexual distress</td>
<td>0.86-0.87</td>
<td>.80-.92</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Hypoactive Sexual Desire Disorder Screener (HSDD Screener)</td>
<td>SR Women only</td>
<td>4</td>
<td>2-3 min</td>
<td>Overall total score</td>
<td>0.79</td>
<td>0.94</td>
<td>N/A</td>
<td>YES</td>
</tr>
<tr>
<td>Index of Premature Ejaculation (IPE)</td>
<td>SR Men only</td>
<td>10</td>
<td>10-15 min</td>
<td>Ejaculation, control, distress</td>
<td>0.82-0.91</td>
<td>0.74-0.82</td>
<td>N/A</td>
<td>YES</td>
</tr>
<tr>
<td>Monash Women’s Health Program Female Sexual Satisfaction Questionnaire (MFSSQ)</td>
<td>SR Women only</td>
<td>12</td>
<td>5 min</td>
<td>Receptivity, arousal, lubrication, orgasm, sexual pleasure, sexual satisfaction</td>
<td>–</td>
<td>0.52-0.78</td>
<td>N/A</td>
<td>YES</td>
</tr>
<tr>
<td>Male Sexual Health Questionnaire (MSHQ)</td>
<td>SR Men only</td>
<td>25</td>
<td>20-30 min</td>
<td>Ejaculation, erection, satisfaction</td>
<td>0.81-0.90</td>
<td>0.86-0.88</td>
<td>N/A</td>
<td>NO</td>
</tr>
<tr>
<td>Premature Ejaculation Diagnostic Tool (PEDT)</td>
<td>SR Men only</td>
<td>5</td>
<td>&lt;5 min</td>
<td>Ejaculation, control, distress</td>
<td>0.71</td>
<td>N/A</td>
<td>0.73</td>
<td>YES</td>
</tr>
<tr>
<td>Premature Ejaculation Profile (PEP)</td>
<td>SR Men only</td>
<td>4</td>
<td>&lt;5 min</td>
<td>Ejaculation, satisfaction</td>
<td>N/A</td>
<td>N/A</td>
<td>0.66-0.80</td>
<td>YES</td>
</tr>
<tr>
<td>Sexual Interest and Desire Inventory – Female (SIDI-F)</td>
<td>CI Women only</td>
<td>13</td>
<td>&lt;15 min</td>
<td>Overall total score</td>
<td>0.90</td>
<td>-</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

**SR = Self Report, CI = Clinical Interview**
2) **Administration Time**

Both the DISF and the DISF-SR take approximately 12 to 15 minutes to administer.

3) **Target Population**

Both male and female versions of the DISF/DISF-SR are designed to measure quality of sexual functioning in community and medical populations.

4) **Reliability and Validity**

Internal consistency reliabilities for measures of the DISF-SR are within acceptable ranges (.74 to .80), as are test-retest coefficients (.80 to .90). Inter-rater reliability estimates for the DISF interview were in the range .84 to .92. The DISF/DISF-SR series has demonstrated good discriminative validity and sensitivity to treatment-induced changes in both general clinical research and in clinical trials.

5) **Norms**

Gender-keyed actuarial norms (in terms of area T-scores) are available for all versions of the test.

6) **Languages**

The DISF/DISF-SR are currently available in 10 languages. It is available from www.Derogatis-tests.com, or Clinical Psychometric Research (410-321-6165).

7) **Rating on available evidence: Grade B and Level 3 evidence.**

c) **Golombok Rust Inventory of Sexual Satisfaction (GRISS)**

1) **Description.**

The GRISS was developed by Rust and Golombok [173]. The GRISS is a 56-item questionnaire (28 items for women and 28 items for men) self-report instrument, designed to assess the existence and severity of sexual problems in the context of sexually active individuals and heterosexual couples. It is designed to assess each individual partner’s function and the overall relationship. For assessment of individuals the men’s and women’s items can be presented as two separate forms. The GRISS is comprised of 12 domain scores, 5 for women, 5 for men and 2 scores common to both. An aggregate total score for each respondent is also used to summarise the quality of relationship and sexual functioning in the couple. Domains pertaining to men include premature ejaculation (4 items), impotence (4 items), avoidance (4 items), nonsensuality (4 items) and dissatisfaction (4 items). Equivalent domains pertaining to women include anorgasmia (4 items), vaginismus (4 items), avoidance (4 items), nonsensuality (4 items) and dissatisfaction (4 items). The 2 domains common to both women and men are frequency of sexual contact (4 items) and non-communication (4 items). This instrument was designed for use with sex therapy clients and was originally standardized using 44 heterosexual couples (88 individuals) seeking marital or sex therapy [173]. A transformation key allows couples to see their scores plotted on a profile provided for the couple as part of therapy.

2) **Administration Time**

Approximately 15 minutes

3) **Target Population**

The GRISS was designed for use with heterosexual sex therapy clients.

4) **Reliability and Validity**

Internal consistency of the subscales was acceptably high and ranged from .61 to .83. Test-retest assessment involved a comparison of scores from both pre and post therapy for 41 of the couples. Test-retest calculations for women ranged from .47 to .82. Women in therapy showed higher rates of dysfunction across subscales compared to the control sample of general practitioner patients. A Dutch translated version of GRISS showed a similar factor structure to that of the English version, and demonstrated reasonably high internal consistency for the each of the subscales. The GRISS has demonstrated utility in establishing lowered sexual functioning among women with obsessive compulsive disorder and psychiatric comorbidity among women identified as having FSD using scales from the GRISS.

5) **Norms**

Norms are available from the development sample of therapy clients as well as for a comparison nonclinical sample of 59 general practitioner patients.

6) **Languages**

Dutch and English language versions are available on request from the authors.

7) **Rating on available evidence: Grade B and Level 3 evidence.**

II. **MEASURES OF FEMALE SEXUAL FUNCTION**

The following questionnaire measures have been validated and developed for use specifically for use in women. The FSFI (below) is currently the most widely used measure in research and clinical settings. It is available from MAPI Institute (see website link below).

a) **Female Sexual Function Index (FSFI)**

1) **Description**

The FSFI was developed by Rosen et al., [174]. It is similar to the IIEF questionnaire used in men, but was developed separately for use in women [175,176].
Qualitative interviews were used to complement other sources of item construction. The FSFI scale is a 19-item self-report questionnaire which assesses sexual function in 6 partially overlapping domains of sexual function, including sexual pain [174]. Respondents were asked to base their responses on a period of recall of the “past 4 weeks”. Factor analysis was used to identify six components of sexual functioning; Desire, Arousal, Lubrication, Orgasm, Satisfaction and Pain. A total score is computed by summation of all 19 items and is used to represent overall sexual function. The FSFI refers to this total score as the Full Scale score. Higher scores on total scale and each of the subscales indicate better sexual function.

2) Administration Time

10 to 15 minutes

3) Target Population

Clinical trial and community populations. This instrument was designed for use among heterosexual and homosexual respondents.

4) Reliability and Validity.

The female validation sample included 131 healthy controls (age 21 to 69) and 128 women diagnosed with FSAD (age 21 to 69). Alpha coefficients for the five subscales were all above .82. Test-retest data over a 2 to 4 week period was relatively high for all the subscales (r=.79 to .86) and total score (r=.88). Women diagnosed with FSFI had significantly lower scores on all subscales of the FSFI than healthy women, demonstrating discriminant validity. Divergent validity was successfully established using the Locke-Wallace Marital Adjustment Test [177]. Correlations showed acceptably modest magnitude across subscales. As would be expected, the Locke-Wallace Marital Adjustment score correlation (r=.57) was highest with the FSFI Satisfaction (with partner) subscale. Other correlations with the Locke-Wallace ranged from r = .41 for FSFI Full Scale score to r = .19 for FSFI Desire. These correlations indicate an expected level of association between the theoretically related constructs of Marital Adjustment and Sexual Function. This finding provides support for the construct validity of the FSFI.

In a second validation study [175], the FSFI was shown to discriminate well between women without sexual dysfunction and women who met criteria for female orgasmic disorder (FOD) or hypoactive sexual desire disorder (HSDD). Highly significant discriminant validity was shown on all domains, as well as the total FSFI score between sexually dysfunctional and non-dysfunctional samples in both studies. Overall, the FSFI shows strong reliability and discriminant validity, although treatment sensitivity data has not been demonstrated to date. In a subsequent study, a cut-point for the total score was shown to be optimal for diagnostic classification across dysfunctions: a score of < 26 indicates sexual dysfunction [176].

Most recently, Sand et al (2009) [178] reviewed a total of 212 separate intervention or diagnostic publications in which the FSFI was featured. This broad array of studies included psychometric studies (n=8), studies in which FSFI was used as a comparator in the development of new diagnostic tools (n=3), studies of models of female sexual function (n=2), psychophysiological studies (n=6), studies assessing sexual function and/or the prevalence of FSD in specific geographical populations, or populations of women with particular diseases or conditions (n=111), and clinical trials and studies assessing the efficacy of different types of therapies for FSD (n=82). Overall, the reviewers of this systematic review concluded that the FSFI has been widely accepted and utilized by researchers worldwide, becoming in the process the “gold standard” measure of female sexual dysfunction for outcome and diagnostic studies in FSD [178]. The measure is available on-line without charge and has been translated into multiple languages.

5) Norms

Norms are available for both pre- and post-menopausal women and women with medical and sexual disorders [178].

6) Languages

The FSFI is available in multiple languages. Validation studies have been performed in multiple languages. The FSFI is available from the MAPI Institute at: www.mapi-institute.com

7) Rating on available evidence:

Grade A, Level 1

b) Monash Female Sexual Satisfaction Questionnaire (MFSSQ)

1) Description

The MFSSQ (Monash Questionnaire) was developed by Davison et al. [179]. It was developed to assess the broad aspects of female sexual experience and specifically to assess acute therapeutic effects. The 12-item measure was developed from ten interviews with women and the scoring of items was based on structures of similar female sexual dysfunction measures, which led to domains of receptivity, arousal, lubrication, sexual pleasure, sexual satisfaction and orgasm.

2) Administration Time

Approximately 5 minutes.

3) Target Population

For use in pre and post-menopausal women who are dissatisfied with their sexual function.
4) **Reliability and validity**

Strong correlations were demonstrated for the MFSSQ with similar domains on the Sexual Self-Self Rating Scale (orgasm (0.60), pleasure (0.72) and satisfaction (0.71)). Known-groups validity was shown with women who were dissatisfied with their sexual function having significantly lower scores than women who were satisfied with their sexual function. Reliability of the measure was, in the main, demonstrated (ICC > 0.70) (receptivity and orgasm domains showing poorer reliability, ICC = 0.52).

5) **Norms**

Norms are available.

6) **Languages**

English. Available on request from the senior author.

7) **Rating on Available Evidence:**

*Grade A, Level 3*

c) **Sexual Function Questionnaire (SFQ)**

The initial version of the Sexual Function Questionnaire (SFQ-V1) was developed by Quirk et al. [180]. The SFQ was developed as a patient-centered multidimensional measure of sexual function in women. Systematic pilot interviews and semi-structured interviews were used to focus the instrument. Women from seven countries (UK, U.S., Australia, the Netherlands, Denmark, France and Italy) reviewed key terms in sexual function to assess the appropriateness of the wording used. Those subjects with FSD diagnoses were asked to discuss feelings associated with their experience of FSD. Key phrases obtained in this way were incorporated into the questionnaire. Factor analysis was used to obtain seven domains. The SFQ can be reliably employed in three forms; a 34 item version which includes all 8 domains (Desire, Arousal-sensation, Arousal-lubrication, Arousal-cognitive, Orgasm, Enjoyment, Pain and Partner) and additional items; a 26 item version which includes the 7 domains only and a short 15 item version (Abbreviated SFQ) which includes 4 of the 7 domains (Desire, Arousal-sensation, Arousal-lubrication and Orgasm). It has been validated also as a screening tool for female sexual dysfunction [181].

1) **Administration Time**

10 to 15 minutes

2) **Target Population**

Women in a sexual relationship or having taken part in sexual activity within the previous month.

3) **Reliability and Validity**

The initial validation sample included 982 women, which incorporated women with a diagnosis of FSD and a normal aged-matched comparison group. Women were aged between 19 and 65 years. Internal consistency of the subscales was acceptably high and ranged from .65 to .91. Test-retest correlations, based on a four-week re-administration of the SFQ, ranged from .42 to .78. The SFQ was successful – for all of the domains – in discriminating between women with FSD and those without. In addition, women who by the end of the study indicated an improvement in sexual functioning had significantly higher SFQ scores compared to women who did not report an improvement in sexual functioning by the end of the study. Construct validity has been demonstrated in correlations between the SFQ domains, the DISF-R, the Life Satisfaction Checklist and the Hospital Anxiety and Depression Scale. Cut-scores for each domain have been developed to indicate likelihood of a given sub-type of FSD e.g. a score between 5 & 16 on the desire domain suggests a high probability of desire disorder [181].

5) **Languages**

The SFQ is available in twenty-one language versions and has been independently validated in Japanese [182]. Requests for use can be made at www.prolutssh.com

6) **Rating on Available Evidence:**

*Grade B and Level 3 evidence.*

d) **Female Sexual Distress Scale (FSDS)**

1) **Description**

The FSDS questionnaire was developed by Derogatis et al [183]. The FSDS is a brief 12-item self-report inventory designed specifically to measure sexually related personal distress in women – a necessary feature of HSDD and other sexual dysfunctions in women. The impetus for the development of the FSDS grew from a contemporary awareness of the importance of personal distress in defining women’s sexual dysfunctions accompanied by an equally compelling awareness that no operational measures of sexually-related personal distress existed [183]. The FSDS is unidimensional and serves as a valid and effective quantitative definition of personal distress.

1) **Administration Time**

The FSDS can be completed in 5 minutes.

2) **Target Population**

Women presenting for an evaluation concerning sexual dysfunction.

3) **Reliability and Validity**

Reliability estimates for the FSDS are available from
3 distinct trials. Coefficients $\alpha$ range from a low of .86 to a high of .97, while test-retest reliability coefficients ranged from .80 to .92. In a discriminative validity trial with samples of both natural and surgically menopausal women with sexual dysfunction compared to healthy controls, the FSDS demonstrated both sensitivity and specificity of .93, and a positive predictive value of approximately .90. In another of the trials the scale showed a high sensitivity to treatment induced change. There is also good evidence of convergent validity with other measures of distress, and ROC analysis produced an AUC of .95.

More recently, a 13-item revised version of the FSDS (the FSDS-R) was validated, designed to be more sensitive to distress arising from low sexual desire problems [183]. Consistent with the original FSDS, the FSDS-R showed very good internal consistency and test-retest reliabilities. The FSDS-R also demonstrated high discriminant validity, successfully identifying 92.7% of patients diagnosed independently with HSDD.

4) NORMS

Provisional cut-off score of 15 for distress level is currently recommended.

5) LANGUAGES

The FSDS is currently available in 14 languages and may be obtained from Dr. Leonard R. Derogatis (Lderogatis@sheppardpratt.org.)

6) RATING ON AVAILABLE EVIDENCE:

Grade B, Level 3 evidence.

e) Sexual Interest and Desire Inventory – Female (SIDI-F)

1) DESCRIPTION

The Sexual Interest and Desire Inventory (SIDI) was developed by Sills et al, [184]. It is a brief, clinician-administered rating scale focused on measuring severity and change in response to treatment of HSDD in premenopausal women. The SIDI was developed and tested for appropriateness in patients and then Item Response Theory analysis was used to elicit the most pertinent items, resulting in a 13-item measure [184]. The SIDI has a unique measurement format in that items address both intensity and frequency of events.

2) ADMINISTRATION TIME

The SIDI-F can be completed in 5-10 minutes.

3) TARGET POPULATION

Premenopausal women with low desire.

4) RELIABILITY AND VALIDITY

The SIDI has high internal consistency ($\alpha=0.90$), and has demonstrated discriminant validity [185]. Convergent validity was tested with the FSFI and CSFQ. The SIDI was highly correlated with the arousal, desire and satisfaction domains of the FSFI (all correlations >0.8) and the arousal, desire/frequency, desire/interest, and pleasure domains of the CSFQ (all correlations >0.7).

NORMS

Norms are available for women with no sexual dysfunction.

LANGUAGES

Linguistically validated in 12 languages. Available on request from the senior author.

RATING ON AVAILABLE EVIDENCE:

Grade C, Level 4

f) Hypoactive Sexual Desire Disorder Screener

1) DESCRIPTION

The HSDD Screener is a diagnostic screening tool developed by Leiblum et al. [186] for use in screening or evaluating women for HSDD. It is a simple 4-item screening tool for use in post-menopausal women. It was developed by an internationally recognized group of experts in female sexuality and then optimized based on feedback from groups of patients and physicians in Europe (Italy, the Netherlands, United Kingdom) and the United States. Both a validation study and subsequent convergent validity study against expert clinician have demonstrated this to be a valid and simple tool to aid in screening post-menopausal women for low sexual desire [186].

1) ADMINISTRATION TIME

The HSDD screener is brief (approximately 2 minutes) and simple to complete.

2) TARGET POPULATION

For use in post-menopausal women to determine sexual desire level.

3) RELIABILITY AND VALIDITY

The HSDD Screener is scored as a total score, as confirmed by principal component analysis. It showed good internal consistency ($\alpha=0.79$) and excellent test-retest reliability (intraclass correlation coefficient = 0.94). To determine the cut-score, sensitivity, specificity, positive predictive value and negative predictive value were calculated; a score of 7 or less suggests HSDD. Additionally, the Screener was tested for accuracy in determining presence/absence of HSDD in a group of post-menopausal women when compared against Clinician diagnosis. There was 83% agreement between the Clinician and
Screener, the associated Kappa statistic was 0.67 (95% CI, 0.5-0.78) indicating substantial agreement.

4) **NORMS**

Norms have been reported.

5) **LANGUAGES**

Available in US and Canadian English and, Canadian French. Requests for use can be made at www.prolutssh.com

6) **RATING ON AVAILABLE EVIDENCE**

Grade C and Level 4.

g) **Decreased Sexual Desire Screener (DSDS)**

1) **DESCRIPTION**

The DSDS is a diagnostic screener developed by Clayton et al. [187] for use in diagnosing acquired, generalized hypoactive sexual desire disorder (HSDD) in pre- or post-menopausal women. It is a 5-item screener, which includes both self-report questions (Items 1-4) and clinician-based differential diagnosis (Item 5). It was developed as a guide to diagnosis of acquired, generalized HSDD in women with or without other sexual disorders. Results of a recent validation study [187] showed excellent diagnostic accuracy of the DSDS when compared with expert, in-person diagnostic evaluation of women with and without HSDD.

2) **ADMINISTRATION TIME**

Approximately 15-20 minutes

3) **TARGET POPULATION**

The DSDS was developed for use in pre- or post-menopausal women with HSDD, with or without other sexual disorders.

4) **RELIABILITY AND VALIDITY**

Diagnostic assessment by means of the DSDS compared to standard diagnostic assessment by an expert sexual medicine clinician, were in in 85.2% of cases, with the sensitivity and specificity of the DSDS as 83.6% and 87.8% respectively. Content validity was also demonstrated by means of cognitive debriefing interviews

5) **NORMS**

Norms have not been reported.

6) **LANGUAGES**

Available in multiple languages. The DSDS is in the public domain [187].

7) **RATING ON AVAILABLE EVIDENCE**

Grade C and Level 4.

### III. MALE SEXUAL FUNCTION SCALES

a) **International Index of Erectile Function (IIEF)**

1) **DESCRIPTION**

The IIEF is a widely-used, 15-item self-report inventory developed by Rosen and colleagues [188] to provide a brief, standardized measure of erectile function and capacity. It measures 5 domains of sexual function in men. The IIEF was developed in conjunction with the clinical trial program for sildenafil (Viagra), and has since served as a major endpoint in over 50 clinical trials [188]. The principal domains of the IIEF were identified through literature search, review of existing instruments, and interviews with patients suffering from erectile dysfunction. The IIEF represents quality of male sexual function in terms of 5 domain scores: erectile function, orgasmic function, sexual desire, sexual satisfaction, and overall satisfaction. The IIEF does not yield a total score.

2) **ADMINISTRATION TIME**

The IIEF takes approximately 10 to 15 minutes to complete.

3) **TARGET POPULATION**

Men from the community and medical populations.

4) **RELIABILITY AND VALIDITY**

Both internal consistency (.73 to .95) and test-retest reliabilities (.64 to .84) are superior for the scale, and there is factor analytic confirmation of the principal domains. Sensitivity and specificity are very good, and concurrent validation against other comparable measures has been demonstrated. Discriminative validity has been well established in comparisons of functional versus dysfunctional samples, and sensitivity to therapeutic change has been consistently shown within the context of clinical trials of sildenafil and other treatments for ED. More recently, a 5-item brief form of the IIEF termed the Sexual Health Inventory for Men (SHIM) has been developed and validated, along with a diagnostic classification and an ED severity scale [189]. A recent systematic review of more than 60 studies found the IIEF scale to be highly robust in different ethnic and geographic populations, as well as sensitive to treatment effects across a variety of treatment agents [188].

5) **NORMS**

Numerous normative cut-off scores have been published for the IIEF.

6) **LANGUAGES**

The IIEF has been linguistically validated in 32 languages. Requests for use can be made at www.prolutssh.com. It is also available from the MAPI Institute at: www.mapi-institute.com
7) RATING ON AVAILABLE EVIDENCE:
Grade A and Level 1 evidence

2. PREMATURE EJACULATION MEASURES

Several premature ejaculation measures have been described in the literature [190-192], although only a small number couple have undergone extensive psychometric testing and validation. Currently, there are two questionnaires that meet most of the criteria for test development and validation: The Premature Ejaculation Profile (PEP) and the Index of Premature Ejaculation (IPE). A third brief diagnostic measure (PEDT) has also been developed, and is available for clinical use [191,192].

a) Premature Ejaculation Profile (PEP)

1) DESCRIPTION

A four-item, self-report measure of premature ejaculation have been described by Patrick et al [192]. The PEP is comprised of single-item constructs of: (1) perceived control over ejaculation; (2) satisfaction with sexual intercourse; (3) personal distress related to ejaculation, and (4) interpersonal difficulty related to ejaculation. Each of the four individual items is assessed on a 5-point scale, which are averaged to provide an index PE score. The measure has been used in observational studies and clinical trials of premature ejaculation [193]. It has also been recommended for clinical use in evaluating the subjective components of the disorder. Validation studies have been performed in comparison to stop-watch measures of intravaginal latency and other PRO measures of sexual function and distress [192].

2) ADMINISTRATION TIME

The four-item PEP scale takes less than 5 minutes to complete.

3) TARGET POPULATION

Men aged 21 and older with premature ejaculation.

4) RELIABILITY AND VALIDITY

Psychometric evaluation was conducted in both large-scale observational studies and clinical trials conducted for dapoxetine (a centrally acting agent for treatment of PE). Test retest reliability was reported as Intra Class Correlations (ICC), which ranged from 0.66 for perceived control to 0.80 for the overall PE index score in the US observational study. The measure showed adequate known groups validity in comparing men with PE to non-PE controls. As predicted, men with IELT of 0-2 mins showed significantly poorer scale scores than men above 2 mins (p < .001). Sensitivity to change analyses were also conducted.

5) NORMS

Norms have not been established for the measure.

6) LANGUAGES

Official translations are not available. Available on request.

7) RATING ON AVAILABLE EVIDENCE:
Grade C, Level 3 evidence

b) Index of Premature Ejaculation (IPE)

1) DESCRIPTION

The Index of Premature Ejaculation (IPE) was developed by Althof et al [190]. It is a 10 item self-administered questionnaire designed to evaluate sexual satisfaction, control and distress in men with premature ejaculation. It was developed using four stages: item pool development, initial psychometric analyses, patient interviews, and final psychometric analyses. It is currently being used in Phase III clinical trials.

2) ADMINISTRATION TIME

Five minutes

3) TARGET POPULATION

Heterosexual men from the community.

4) RELIABILITY AND VALIDITY

The IPE contains three factor analytically derived domains: control, sexual satisfaction and distress. All three domains have shown excellent internal consistency and reliability, as well as showing good known groups validity between men with and without PE. Convergent validity against IELT was also strong for all three domains (control (r=0.75); sexual satisfaction (r=0.60) and distress (r=0.68)). Treatment sensitivity has yet to be determined.

5) NORMS

Initial understanding of normative scoring is available.

6) LANGUAGES

It has been linguistically translated into several other languages and can be requested at the following web-site: www.prolutssh.com.

7) RATING ON AVAILABLE EVIDENCE:
Grade C and Level 4 evidence.

c) Premature Ejaculation Diagnostic Tool (PEDT).

1) DESCRIPTION

The previous two measures (PEP, IPE) are available for use as treatment change or outcome measures of PE treatment. The PEDT was developed and is available only in the form of a screening questionnaire
This questionnaire is a brief, 5-item measure used to screen men for potential presence of PE based on DSM-IV-TR criteria of lack of control, frequency, minimal stimulation, distress and interpersonal difficulty.

2) **Adminstration Time**

1 minute

3) **Target Population**

Heterosexual men from the community.

4) **Reliability and Validity**

Internal consistency (cronbach alpha = 0.71) and reliability (ICC = 0.73) were good. Importantly known-groups validity was strong when comparing men with time-defined PE (IELTs <2 minutes in 70% of coital attempts) and those with self-reported no PE. A score of >11 would suggest presence of PE and men scoring 9 or 10 are likely to have PE and are recommended for further assessment. This scoring system has shown good convergent validity with clinical expert diagnosis of PE (k-statistic=0.80).

5) **Norms**

Norms are available

6) **Languages**

The PEDT has been linguistically translated into several other languages and has additionally been psychometrically tested in Turkish [194]. Language versions can be requested at the following web-address: www.prolutssh.com

7) **Rating on Available Evidence:**

Grade C and Level 4.

5. DELAYED EJACULATION SCALES

a) **Male Sexual Health Questionnaire (MSHQ).**

1) **Description**

The MSHQ was developed by Rosen et al. [195]. It is a 25-item validated questionnaire to measure specific aspects of ejaculation in older men. The MSHQ, which includes independent domains for ejaculation (7 items), erection (3 items), and sexual satisfaction (6 items), provides a more in-depth assessment of ejaculatory function and sexual satisfaction than the IIEF. The ejaculation domain of the MSHQ assesses loss of ejaculation, delayed ejaculation, the force of the ejaculation, the amount of semen ejaculated, pleasure associated with ejaculation, pain/discomfort during ejaculation, and the bother associated with ejaculation. A 4-item MSHQ-EjD Short Form, with 3 ejaculatory function items and 1 bother item, has also been psychometrically validated for the assessment of EjD in clinical and research settings [196].

2) **Adminstration Time**

The 25-item MSHQ takes approximately 20 to 30 minutes to complete. The 4-item MSHQ-EjD Short Form takes approximately 5 minutes to complete.

3) **Target Population**

Older men from the community and medical populations

4) **Reliability and Validity**

In psychometric validation studies, the 3 domains of the 25-item MSHQ demonstrated a high degree of internal consistency (.81 to .90), rest-retest reliability (.86 to .88), and construct validity, together with the ability to differentiate between men with LUTS and sexual dysfunction and healthy men [195]. The 3 ejaculatory function items of the MSHQ-EjD Short Form maintain reliability and construct validity for assessing EjD in heterosexual, bisexual, and gay men [196].

5) **Norms**

Analyses to establish normative cut-off scores for the MSHQ are on-going.

6) **Languages**

The MSHQ has been linguistically validated in 16 languages and is available from the MAPI Institute at: www.mapi-institute.com

7) **Rating on Available Evidence:**

Grade B and Level 3 evidence

6. OUTCOME MEASURES AND QUALITY OF LIFE-RELATED SCALES (SEE TABLE 21)

a) **Treatment Satisfaction Scale (TSS)**

1) **Description of Measure**

The Treatment Satisfaction Scale (TSS) is a sexual quality of life measure developed by Kubin et al. [197]. The scale provides a comprehensive assessment of sexual satisfaction of men with ED, and their partners and to assess sequential measurements over time to evaluate satisfaction with treatment [197, 198]. It is a multi-faceted measure of patients' and partners' satisfaction with their sexual life relating to erectile dysfunction and intended for prospective use.

The TSS has 4 modules: unmedicated patient (12 items), medicated patient (19 items), unmedicated partner (12 items), and medicated partner (18 items). All TSS modules have these domains: spontaneity, quality of erection, quality of ejaculation, quality of orgasm, sexual pleasure, and confidence. The medicated patient and partner modules have these domains: reliability of treatment, convenience, treatment efficacy, conformity to treatment expectations, overall satisfaction and intentions for continued use of the particular drug.
Table 21: Psychometric Properties of Treatment Satisfaction and HQL Scales

<table>
<thead>
<tr>
<th>Inventory Name</th>
<th>Modality**/ Gender</th>
<th>No. of Items</th>
<th>Admin. Time</th>
<th>Domains</th>
<th>Reliability</th>
<th>Discriminative Validity</th>
<th>Sens./ Spec.</th>
<th>Published Norms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>Self-Esteem and Relationship (SEAR)</td>
<td>SR</td>
<td>Men and Women</td>
<td>14</td>
<td>50 mins</td>
<td>Sexual relationship, Confidence (self-esteem, overall relationship)</td>
<td>0.76-0.93</td>
<td>0.57-0.73</td>
<td>YES</td>
</tr>
<tr>
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<tr>
<td>Psychological and Interpersonal Relationship Scale (PAIRS)</td>
<td>SR</td>
<td>Men and Women</td>
<td>12</td>
<td>50 mins</td>
<td>Sexual self-confidence, Spontaneity, Time concerns</td>
<td>0.73-0.97</td>
<td>0.63-0.77</td>
<td>YES</td>
</tr>
<tr>
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<tr>
<td>Sexual Quality of Life – Male (SQQL-M)</td>
<td>SR</td>
<td>Men only</td>
<td>11</td>
<td>50 mins</td>
<td>Total score</td>
<td>0.87-0.93</td>
<td>0.77-0.82</td>
<td>YES</td>
</tr>
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</tr>
<tr>
<td>Sexual Quality of Life – Female (SQQL-F)</td>
<td>SR</td>
<td>Women only</td>
<td>18</td>
<td>50 mins</td>
<td>Total score</td>
<td>0.95</td>
<td>0.85</td>
<td>YES</td>
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<tr>
<td>Treatment Satisfaction Scale (TSS)</td>
<td>SR</td>
<td>Men and Women</td>
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<tr>
<td>Sexual Life Quality Questionnaire (SLOQ)</td>
<td>SR</td>
<td>Men and Women</td>
<td>12</td>
<td>8-10 mins</td>
<td>Sexual QOL Treatment satisfaction</td>
<td>0.96</td>
<td>Overall &gt;0.70</td>
<td>YES</td>
</tr>
<tr>
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</tr>
<tr>
<td>Erectile Dysfunction Inventory for Treatment and Satisfaction (EDITS)</td>
<td>SR</td>
<td>Men and Women</td>
<td>25</td>
<td>5 mins</td>
<td>EDITS index</td>
<td>0.91</td>
<td>0.98</td>
<td>YES</td>
</tr>
</tbody>
</table>

**SR = Self Report**
In all the modules, respondents answer the questions considering the previous 4 weeks. Item responses are scored on a 5-point scale, ranging from 1 "not at all" over "a little", "somewhat", and "very" to 5 "extremely". Some items have a sixth response "not relevant". The TSS scale scores are computed by taking the mean of each scale's item responses and converting the result to a 0-100 scale, with 0 being the worst possible score and 100 being the best. Higher score indicates greater satisfaction [198].

2) Administration Time
The TSS patient module takes approximately 13 minutes on average to complete, whereas the partners' module takes approximately 7 minutes on average to complete. It is a brief questionnaire and practical to use.

3) Target Population
Men with erectile dysfunction and their partners.

4) Reliability and Validity
The TSS baseline "unmedicated" and "medicated" modules have 63% item-congruence. The medicated patient and partner modules of the TSS comprise 95% identical items and the unmedicated patient and partner modules comprise 100% identical items. This multidimensional scale has good internal consistency, reliability and concurrent validity with the IIEF [197]. Specifically, all multi-item scales (satisfaction with erectile function, sexual confidence and satisfaction with medication) had Cronbach alphas above 0.70 at baseline and follow-up. Furthermore, all patient TSS domains were significantly correlated with three domains of the IIEF (erectile function, intercourse satisfaction and overall satisfaction) and there was a significant correlation between men's IIEF -erectile function results and the six partner TSS domains [198]. The TSS scales were able to discriminate between four ED severity groups, and between responders and non-responders to treatment; all patient and partner TSS scales were responsive (sensitive to change) for the respondents [197].

5) norms
Norms are available.

6) Languages
The TSS was linguistically validated in 20 languages. The TSS is available from the MAPI Institute at: www.mapi-institute.com

7) Rating on Available Evidence:
Grade B and Level 3 evidence

b) Sexual Life Quality Questionnaire (SLQQ)

1) Description of Measure
The Sexual Life Quality Questionnaire (SLQQ) was developed by Woodward et al. [199]. It is a validated, multi-dimensional questionnaire that consists of two domains: (i) sexual quality of life (SQoL) (10 items) and (ii) treatment satisfaction (6 items). The SQoL domain compares the current sexual experience of the subjects or his partner with their individual experience prior to the onset of the subject's erectile dysfunction [199]. Scores on each item can range from -4 to 4, with 0 indicating no change from before the onset of erectile dysfunction, negative numbers denoting worse outcomes, and positive scores indicating better outcome.

2) Administration Time
The SLQQ is easy to administer and takes about 8-10 minutes to complete.

3) Target Population
Men with erectile dysfunction

4) Reliability and Validity
The SLQQ is a good measure of treatment satisfaction as shown by a high correlation with response to a question asking about their likelihood of continuing the treatment (r= 0.89). The SLQQ is also responsive and able to detect changes in sexual quality of life [199]. For the quality of life domain, Cronbach alpha was 0.97 for patients and 0.98 for partners. For the treatment satisfaction domain, Cronbach alpha was 0.85 for patients and 0.87 for partners respectively [199].

5) Norms
Norms are available.

6) Languages
There are at least 7 languages available. The SLQQ is available from the MAPI Institute at: www.mapi-institute.com

7) Rating on Available Evidence:
Grade C and Level 4 evidence

c) Erectile Dysfunction Inventory for Treatment and Satisfaction (EDITS)

1) Description of Measure
The EDITS scale was developed by Althof et al [200]. It is a multi-dimensional scale to assess male treatment satisfaction following ED therapy, and which explores the impact of patient and partner's satisfaction on treatment continuation [200, 201]. The Patient EDITS version consists of 11 items, scored from 0 (no satisfaction or dissatisfaction) to 4 (high satisfaction) and measuring overall satisfaction, degree to which treatment met expectations, likelihood of treatment continuation, ease of use, satisfaction with onset of action, satisfaction with duration of action, impact of treatment on sexual confidence, partner satisfaction with treatment, how the partner felt about
the patient’s continuing with treatment by patient self-report), naturalness of erections and naturalness of erection hardness. The Partner version of the EDITS consists of 5 items assessing overall satisfaction, degree to which treatment met expectations, how treatment affected the partner’s sense of sexual desirability, partner satisfaction with duration of action, and how the partner feels about the patient’s continuing to use the treatment. The EDITS score is calculated by multiplying the mean EDITS score by 25 resulting in a treatment satisfaction range of 0- extremely dissatisfied to 100- extremely satisfied.

2) Administration Time
The questionnaire takes about 5 minutes on the average to administer.

3) Target Population
Men with erectile dysfunction and their partner.

4) Reliability and Validity
Scores on the Patient EDITS and the Partner EDITS were normally distributed with internal consistencies of 0.90 and 0.76 respectively [4]. The Patient EDITS has an internal consistency of 0.90 and a test-retest reliability of 0.98. The Partner EDITS has an internal constancy of 0.76 and a test-retest reliability of 0.83. The EDITS has shown sensitivity to change [201].

5) Norms
Norms are available.

6) Languages
The SEAR is available in 27 languages, which can be requested from www.prolutssh.com

7) Rating on available evidence:
Grade A, Level 2

e) Psychological and Interpersonal Relationship Scale (PAIRS)

1) Description of Measure
The PAIRS scale was developed by Swindle et al [205] to assess broad psychosocial outcomes associated with erectile dysfunction and its treatment. Items were generated based on literature review, focus groups, interviews with patients and partners, market research and consultation with clinicians. Of the 47-items initially developed, 23 were retained to form 3 domains: Sexual Self-Confidence (6-items), Spontaneity (9-items) and Time Concerns (8-items).

2) Administration Time
Approximately 5-10 minutes

3) Target Population
Men with erectile dysfunction

4) Reliability and Validity
Four studies were completed to psychometrically validate the PAIRS [205]. Factor analysis elicited the 3-domain structure and, convergent and divergent
Discriminant validity was also demonstrated with scores across all three domains being statistically significantly different between men with ED and those with no ED. Reliability was assessed using Pearson’s correlation coefficient and showed adequate results: Time concerns (r=0.63); Spontaneity (r=0.66); and Sexual Self-confidence (r=0.77). Additionally, strong internal consistency across the studies and domains was shown (α: 0.73-0.97). Responsiveness of the measure to treatment effect was also shown.

5) Norms
These are reported.

6) Languages
U.S. English only. Available on request from the first author.

7) Rating on available evidence:
Grade B and Level 3

f) Sexual Quality of Life – Male (SQOL-M)

1) Description of Measure
The Sexual Quality of Life measure for Men (SQOL-M) was developed by Abraham et al [206, 207] for or use in men with either premature ejaculation or erectile dysfunction to assess impact of these conditions on men’s self-esteem, relationship and emotional well-being. The item pool was taken from the Sexual Quality of Life measure for Females (SQOL-F – see below) after confirmation from experts, a review of the literature and interviews with men with either ED or PE that the items were applicable to men. Factor analysis and item-total correlations showed that 11-items, as a total score, of the 18-items were most pertinent to men [206].

2) Administration Time
Approximately 5 minutes.

3) Target Population
Men with sexual dysfunction (current validation in PE and ED cohorts).

4) Reliability and Validity
The reliability and validity of the SQOL-M was confirmed in both men with ED and PE. Internal consistency ranged from 0.87-0.93 and test-retest reliability ranged from 0.77-0.79. Convergent validity with the IIEF-Overall satisfaction domain for men with ED and IPE-satisfaction and distress domains for men with PE was confirmed. Highly significant differences were shown between men without sexual dysfunction compared to those with ED or PE, or as a combined sexual dysfunction group.

5) Norms
Norms are reported.

6) Languages
20 language versions are available and can be requested at the following web-site: www.prolutssh.com

7) Rating on available evidence:
Grade B and Level 3

g) Sexual Quality of Life – Female (SQOL-F)

1) Description of Measure
The SQOL-F was developed by Symonds et al [208] to assess the impact of female sexual dysfunction on women’s sexual quality of life, specifically self-esteem, emotional well-being and relationship. Items were developed through interviews with 82 women from 7 countries (United Kingdom, United States, Australia, France, Denmark, Netherlands, Italy). From these interviews 24-items were developed, which were then reduced down to 19-items by a multi-disciplinary clinical panel due to lack of clinical relevance, conceptual relevance, and face validity. Psychometric validation reduced it further to 18-items and confirmed the items formed one domain addressing the overall concept of sexual quality of life [207].

2) Administration Time
Approximately 5 minutes.

3) Target Population
Women with female sexual dysfunction.

4) Reliability and Validity
The reliability and validity of the SQOL-F was conducted in three separate studies (UK study, US Study, and Test-retest reliability study). Results across these three studies demonstrated the SQOL-Fs strong psychometric properties. Internal consistency was very high (α: 0.95), as was test-retest reliability (0.85). Convergent validity was good against both a sexual satisfaction measure and sexual function measures. Additionally, the SQOL-F can distinguish between women with FSD and those without FSD.

5) Norms
Norms are reported.

6) Languages
The SQOL-F is available in 23 languages and can be requested at the following web-site: www.prolutssh.com

7) Rating on available evidence:
Grade C, Level 4
SUMMARY AND RECOMMENDATIONS ON SYMPTOM AND SCALES

This section represents an overview from a clinical perspective of the scales and questionnaires currently available to measure and quantify the status of an individual’s or couple’s sexual functioning. The instruments covered in this section are for the most part, contemporary measures that have been recently developed. The design of these measures tends to emphasize brevity and the self-report modality, which articulate well with the majority of the primary formats for clinical trials. The measurement constructs these inventories and interviews are designed to operationalize tend to be consistent with the acknowledged elements of the sexual response cycle and consequences of problems, and are referenced under the general headings of desire, arousal, orgasm, pain and satisfaction.

It is evident that multiple, validated questionnaires and scales are currently available and recommended for use in practice settings and clinical trials:

1. The field of sexual psychometrics has progressed dramatically during the past decade from one in which there were only a handful of measures available to a field of measurement in which a great deal of activity and new development is taking place.

2. Instrument development is currently an area of high activity with new measures being developed rapidly and previous measures being revised to reflect new knowledge. Consequently the reviews and recommendations incorporated can only reflect the current state of the art.

Despite major advantages of these measures in efficiency and quantification of measurement, several disadvantages should also be noted:

1. First, these measures provide information only on current level of sexual function and cannot substitute for a detailed sexual or medical history. Furthermore, the questionnaires do not provide information regarding specific etiology or comorbid medical or psychiatric conditions.

2. Additionally, some patients experience discomfort or embarrassment while completing questionnaires or symptom scales, or may experience language or comprehension difficulties. Steps should be taken to ensure privacy and confidentiality and to assist the patient with comprehension when indicated.

3. Finally, the use of questionnaires or symptom scales should not be used as an alternative or substitute for direct inquiry or face-to-face clinical interaction with the patient.

As the field continues to evolve and development, new questionnaires will undoubtedly be developed and disseminated. It is incumbent on clinicians and researchers to be aware of these developments in the future.
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113. Soderstrom T, Stefanovska A, Veber M, Svensson H. In- -
114. Bots ML, Breslau PJ, Briet E, et al. Cardiovascular deterior- -


178. Sand M.


**APPENDIX 1.**

**BRIEF SEXUAL SYMPTOM CHECKLIST FOR MEN (BSSC-M)**

Please answer the following questions about your overall sexual function.

1. *Are you satisfied with your sexual function?*
   - □ Yes □ No

   If No, please continue.

2. *How long have you been dissatisfied with your sexual function?*
   ...............................................................................................................................................

3a. *The problems with your sexual function is: (mark one or more)*
   1. Problems with little or no interest in sex
   2. Problems with erection
   3. Problems ejaculating too early during sexual activity
   4. Problems taking too long, or not being able to ejaculate or have orgasm
   5. Problems with pain during sex
   6. Problems with penile curvature during erection
   7. Other: ................................................................................................................................

3b. *Which problem is most bothersome (circle)* 1 2 3 4 5

4. *Would you like to talk about it with your doctor?*
   - □ Yes □ No
APPENDIX 2.

BRIEF SEXUAL SYMPTOM CHECKLIST
FOR WOMEN (BSSC-W)

Please answer the following questions about your overall sexual function

1. Are you satisfied with your sexual function?
   - Yes □ No □

   If No, please continue.

2. How long have you been dissatisfied with your sexual function?
   ............................................................................................................................................

3a. The problems with your sexual function is: (mark one or more)
   1 Problems with little or no interest in sex
   2 Problems with decreased genital sensation (feeling)
   3 Problems with decreased vaginal lubrication (dryness)
   4 Problems reaching orgasm
   5 Problems with pain during sex
   6 Other : ................................................................................................................................

   ................................................................................................................................

3b. Which problem is most bothersome (circle) 1 2 3 4 5

4. Would you like to talk about it with your doctor?
   - Yes □ No □
APPENDIX 3.
SEXUAL COMPLAINTS SCREENER
FOR MEN (SCS-M)

This screener is a series of questions concerning your sexual experiences during the last 6 months. Each question can be answered by circling the condition that best characterizes your personal experience.

**Sexual activity** includes any kind of activity aimed at experiencing sexual satisfaction and enjoyment. The term sexual activity does not necessarily include sexual intercourse (vaginal or anal penetration).

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1a) Some men experience lack of or low sexual interest/desire in sex.</strong></td>
<td><strong>Has this happened to you during the last 6 months?</strong></td>
</tr>
<tr>
<td></td>
<td>0. Never/almost never</td>
</tr>
<tr>
<td></td>
<td>1. Rarely</td>
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<td>2. Sometimes</td>
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<td></td>
<td>3. Often</td>
</tr>
<tr>
<td></td>
<td>4. Almost all the time/Almost always</td>
</tr>
<tr>
<td><strong>1b) Has this been a personal problem for you?</strong></td>
<td>0. Not at all a problem</td>
</tr>
<tr>
<td></td>
<td>1. A very small problem</td>
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<tr>
<td></td>
<td>2. Some problem</td>
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<tr>
<td></td>
<td>3. A considerable problem</td>
</tr>
<tr>
<td></td>
<td>4. A very great problem</td>
</tr>
<tr>
<td><strong>2a) Some men find that they need much more sexual stimulation to achieve an erection than they needed in the past.</strong></td>
<td><strong>Has this happened to you during the last 6 months?</strong></td>
</tr>
<tr>
<td></td>
<td>0. No sexual activity</td>
</tr>
<tr>
<td></td>
<td>0. Never/almost never</td>
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<tr>
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<td>1. Rarely</td>
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<td>2. Sometimes</td>
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<td></td>
<td>3. Often</td>
</tr>
<tr>
<td></td>
<td>4. Almost all the time/Almost always</td>
</tr>
<tr>
<td><strong>2b) Has this been a personal problem for you?</strong></td>
<td>0. Not at all a problem</td>
</tr>
<tr>
<td></td>
<td>1. A very small problem</td>
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<tr>
<td></td>
<td>2. Some problem</td>
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<td></td>
<td>3. A considerable problem</td>
</tr>
<tr>
<td></td>
<td>4. A very great problem</td>
</tr>
<tr>
<td><strong>3a) Some men have difficulties in obtaining and/or maintaining hard erections lasting long enough for sexual activity.</strong></td>
<td><strong>Has this happened to you during the last 6 months?</strong></td>
</tr>
<tr>
<td></td>
<td>0. No sexual activity</td>
</tr>
<tr>
<td></td>
<td>0. Never/almost never</td>
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<td></td>
<td>1. Rarely</td>
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<td>2. Sometimes</td>
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<td>3. Often</td>
</tr>
<tr>
<td></td>
<td>4. Almost all the time/Almost always</td>
</tr>
<tr>
<td><strong>3b) Has this been a personal problem for you?</strong></td>
<td>0. Not at all a problem</td>
</tr>
<tr>
<td></td>
<td>1. A very small problem</td>
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<td></td>
<td>2. Some problem</td>
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<td></td>
<td>3. A considerable problem</td>
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<tr>
<td></td>
<td>4. A very great problem</td>
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</tbody>
</table>
**APPENDIX 3.  SEXUAL COMPLAINTS SCREENER FOR MEN (SCS-M)**

(Continued)

<table>
<thead>
<tr>
<th>4a) Some men cannot control their sexual excitement so that they cum (ejaculate) before or shortly (within approximately 2 minutes) after penetration.</th>
<th>4b) Has this been a personal problem for you?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Has this happened to you during the last 6 months?</strong></td>
<td><strong>Has this been a personal problem for you?</strong></td>
</tr>
<tr>
<td>0. No sexual activity</td>
<td>0. Not at all a problem</td>
</tr>
<tr>
<td>1. Rarely</td>
<td>1. A very small problem</td>
</tr>
<tr>
<td>2. Sometimes</td>
<td>2. Some problem</td>
</tr>
<tr>
<td>3. Often</td>
<td>3. A considerable problem</td>
</tr>
<tr>
<td>4. Almost all the time/Almost always</td>
<td>4. A very great problem</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5a) Some men have difficulty ejaculating or reaching orgasm with sexual activity.</th>
<th>5b) Has this been a personal problem for you?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Has this happened to you during the last 6 months?</strong></td>
<td><strong>Has this been a personal problem for you?</strong></td>
</tr>
<tr>
<td>0. No sexual activity</td>
<td>0. Not at all a problem</td>
</tr>
<tr>
<td>1. Rarely</td>
<td>1. A very small problem</td>
</tr>
<tr>
<td>2. Sometimes</td>
<td>2. Some problem</td>
</tr>
<tr>
<td>3. Often</td>
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<td>4. Almost all the time/Almost always</td>
<td>4. A very great problem</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6a) Some men are concerned about the size and/or shape of their penis.</th>
<th>6b) Has this been a personal problem for you?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Has this happened to you?</strong></td>
<td><strong>Has this been a personal problem for you?</strong></td>
</tr>
<tr>
<td>0. Never/almost never</td>
<td>0. Not at all a problem</td>
</tr>
<tr>
<td>1. Rarely</td>
<td>1. A very small problem</td>
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<td>3. A considerable problem</td>
</tr>
<tr>
<td>4. Almost all the time/Almost always</td>
<td>4. A very great problem</td>
</tr>
</tbody>
</table>
### 7a) Some men experience pain during or shortly after sexual activity.

**Has this happened to you during the last 6 months?**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>O</strong></td>
<td><strong>No sexual activity</strong></td>
</tr>
<tr>
<td>0.</td>
<td>Never/almost never</td>
</tr>
<tr>
<td>1.</td>
<td>Rarely</td>
</tr>
<tr>
<td>2.</td>
<td>Sometimes</td>
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<tr>
<td>3.</td>
<td>Often</td>
</tr>
<tr>
<td>4.</td>
<td>Almost all the time/Almost always</td>
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</table>

### 7b) Has this been a personal problem for you?

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<thead>
<tr>
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<th></th>
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<tbody>
<tr>
<td>0.</td>
<td>Not at all a problem</td>
</tr>
<tr>
<td>1.</td>
<td>A very small problem</td>
</tr>
<tr>
<td>2.</td>
<td>Some problem</td>
</tr>
<tr>
<td>3.</td>
<td>A considerable problem</td>
</tr>
<tr>
<td>4.</td>
<td>A very great problem</td>
</tr>
</tbody>
</table>

### 8) During the last 6 months, my sexual life has been:

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>0.</td>
<td>Very unsatisfying</td>
</tr>
<tr>
<td>1.</td>
<td>Unsatisfying</td>
</tr>
<tr>
<td>2.</td>
<td>Rather unsatisfying</td>
</tr>
<tr>
<td>3.</td>
<td>Rather satisfying</td>
</tr>
<tr>
<td>4.</td>
<td>Satisfying</td>
</tr>
<tr>
<td>5.</td>
<td>Very satisfying</td>
</tr>
</tbody>
</table>

### 9) Is there anything else you would like to tell us with respect to your sexual life?

*For those who have not been sexually active during the last 6 months please explain why you have been sexually inactive.*

### 10) Would you want your physician (counselor) to further explore sexual difficulties and/or problems with you?

<p>| | |</p>
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<tr>
<th></th>
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<tbody>
<tr>
<td>0.</td>
<td>No</td>
</tr>
<tr>
<td>1.</td>
<td>Not now</td>
</tr>
<tr>
<td>2.</td>
<td>Yes</td>
</tr>
</tbody>
</table>
This screener is a series of questions concerning your sexual experiences during the last 6 months. Each question can be answered by circling the condition that best characterizes your personal experience.

*Sexual activity* includes any activity aimed at experiencing sexual satisfaction and enjoyment. The term sexual activity does not necessarily include sexual intercourse (vaginal or anal penetration).

<table>
<thead>
<tr>
<th>1a)</th>
<th>Some women experience lack of or low sexual interest/desire in sex.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Has this happened to you during the last 6 months?</em></td>
</tr>
<tr>
<td>0</td>
<td>Never/Almost never</td>
</tr>
<tr>
<td>1</td>
<td>Rarely</td>
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<tr>
<td>2</td>
<td>Sometimes</td>
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<tr>
<td>3</td>
<td>Often</td>
</tr>
<tr>
<td>4</td>
<td>Almost all the time/Almost always</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1b)</th>
<th>Has this been a personal problem for you?</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not at all a problem</td>
</tr>
<tr>
<td>1</td>
<td>A very small problem</td>
</tr>
<tr>
<td>2</td>
<td>Some problem</td>
</tr>
<tr>
<td>3</td>
<td>A considerable problem</td>
</tr>
<tr>
<td>4</td>
<td>A very great problem</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2a)</th>
<th>Some women do not experience physical sexual excitement (e.g., genital swelling, vaginal wetness, tingling sensation) during sexual stimulation and/or sexual activity. Has this happened to you during the last 6 months?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Has this happened to you during the last 6 months?</em></td>
</tr>
<tr>
<td><strong>O</strong></td>
<td>No sexual activity</td>
</tr>
<tr>
<td>0</td>
<td>Never/Almost never</td>
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<tr>
<td>2</td>
<td>Sometimes</td>
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<td>3</td>
<td>Often</td>
</tr>
<tr>
<td>4</td>
<td>Almost all the time/Almost always</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2b)</th>
<th>Has this been a personal problem for you?</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not at all a problem</td>
</tr>
<tr>
<td>1</td>
<td>A very small problem</td>
</tr>
<tr>
<td>2</td>
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<td>4</td>
<td>A very great problem</td>
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</tbody>
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<table>
<thead>
<tr>
<th>3a)</th>
<th>Some women do not feel sexually turned on or do not have pleasurable sexual feelings when engaging in sexual activity.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Has this happened to you during the last 6 months?</em></td>
</tr>
<tr>
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<table>
<thead>
<tr>
<th>3b)</th>
<th>Has this been a personal problem for you?</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<tr>
<td>1</td>
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</tr>
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<td>2</td>
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<td>A considerable problem</td>
</tr>
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<td>4</td>
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</tr>
</tbody>
</table>
### APPENDIX 4.

#### SEXUAL COMPLAINTS SCREENER FOR WOMEN (SCS-W)

(Continued)

<table>
<thead>
<tr>
<th>4a) Some women experience difficulties reaching orgasm during sexual activities despite feeling sexually excited.</th>
<th>4b) Has this been a personal problem for you?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Has this happened to you during the last 6 months?</strong></td>
<td><strong>Has this been a personal problem for you?</strong></td>
</tr>
<tr>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>5a) Some women experience genital pain during or shortly after sexual activity.</th>
<th>5b) Has this been a personal problem for you?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Has this happened to you during the last 6 months?</strong></td>
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<tr>
<td>O No sexual activity</td>
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<td>3. Often</td>
<td>4. A very great problem</td>
</tr>
<tr>
<td>4. Almost all the time/Almost always</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6a) Some women experience difficulties allowing vaginal penetration despite their wish to do so.</th>
<th>6b) Has this been a personal problem for you?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Has this happened to you?</strong></td>
<td><strong>Has this been a personal problem for you?</strong></td>
</tr>
<tr>
<td>0. Never/almost never</td>
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<td>4. A very great problem</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7a) Some women experience persistent and unwanted genital arousal (tingling, throbbing, pulsating) in the absence of any sexual interest.</th>
<th>7b) Has this been a personal problem for you?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Has this happened to you during the last 6 months?</strong></td>
<td><strong>Has this been a personal problem for you?</strong></td>
</tr>
<tr>
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</table>
8) During the last 6 months, my sexual life has been:
0. Very unsatisfying
1. Unsatisfying
2. Rather unsatisfying
3. Rather satisfying
4. Satisfying
5. Very satisfying

9) Is there anything else you would like to tell us with respect to your sexual life?
For those who have not been sexually active during the last 6 months please explain why you have been sexually inactive.

10) Would you want your physician (counselor) to further explore sexual difficulties and/or problems with you?
0. No
1. Not now
2. Yes
Committee 7

Experimental Models for the Study of Female and Male Sexual Function

Chairpersons
FRANCOIS GIULIANO
JIM PFAUS

Members
PETTER HEDLUND
SHIN-ICHI HISASUE
LESLEY MARSON
BALASUBRAMANIAN SRILATHA
KIM WALLEN
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<td>V. REFERENCES</td>
<td>G. RECOMMENDATIONS</td>
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Kim Wallen, Ph.D.Dobbs Professor of Psychology and Behavioral Neuroendocrinology Department of Psychology and Yerkes National Primate Research Center Emory University Atlanta, GA 30322, USA
Understanding human sexual behavior requires balancing the simplicity of DSM-like definitions of normal and abnormal arousal, desire, performance, and orgasm, with the bewildering array of exceptions to those definitions that characterize sexual function and dysfunction in real people. Scientific blinders limit the nature of the questions we ask, the approaches we take, and research is normally constrained by research review committees pressured to enforce “community standards”. There is much that we simply cannot study in humans, either because of ethical concerns, impracticality, or the lack of sufficient technology. These constraints are most obvious when we ask questions about the neurobiology of sexual behavior. Although studies have viewed human brain activation in sexual circumstances and have monitored the sexual responses of individuals following drug treatments, there are significant limitations on what can be studies experimentally in humans. Most people will not knowingly allow themselves to be rendered sexually dysfunctional by some experimental manipulation, and few would allow monitoring of their copulatory behavior firsthand, even if review boards would allow such research. Lastly, there is the problem of self-selection of human subjects where those willing to allow detailed recording of their sexual interests and responses may represent a very special subset of people and may well not represent the general population.

Despite these constraints, we have made real progress in the past decade in elucidating neuroanatomical and neurochemical mechanisms of erection, ejaculation, and other sexual responses, and in the design of rational pharmacological treatments for certain sexual dysfunctions. We have begun to examine the mechanisms that underlie sexual desire, and how sexual stimulation and reward influence attractiveness and mate choice. Progress in these areas could not have been made without the help of animal models. However, appreciation of the importance of animal models is more limited than it needs to be for basic animal research to speed the advance of treatments for human sexual dysfunction.

Although studies of animal sexuality predate empirical studies of human sexuality we arrived at a place by the end of the 20th Century where sexuality research was divided into to camps, clinicians who studied people, and behavioral neuroendocrinologists who studied animals. These camps rarely shared common insights at scientific meetings. After all, human copulatory behavior doesn’t really resemble copulatory behavior in animals. In laboratory animals commonly used to study sexual behavior, such as rodents, gonadal hormones serve two primary functions: to make it physically possible for a male or female to engage in sex, and to motivate them to engage in sex (Wallen, 1990). By contrast, in humans and other anthropoid primates, only the latter function of hormones remains, with hormonal influences on the capability to mate having largely disappeared for evolutionary reasons which are still unclear. Thus unlike in laboratory rodents, there is no human equivalent of the lordosis, which is under tight hormonal regulation and whose execution is necessary for a male to get an intromission with a female. Similarly, although erection is necessary for mating in both rodent and human males, in men erectile capacity is no longer under the control of testicular hormones with castrated or hypogonadal men as responsive to sexual stimuli as are males with fully functioning testes. As Miller (1931) pointed out more than 75 years ago, humans can mate at any time and under any hormonal condition. Although he believed that this continual capacity to engage in sex was unique to humans, we now know that this is a proclivity that we share with most, if not all of our primate cousins, and something which distinguishes us from the laboratory rodents from which we have derived so much of our understanding of the neuro-
chemical and endocrine mechanisms that underlie sexual responding.

At another level of analysis, however, commonalities in sexual responding could be conceived of between animals and humans (Pfaus, 1999). The links started forming around the study of sexual pharmacology. For example, the dopamine receptor agonist apomorphine induces erection in rats and men (Lal et al., 1987; Melis, Argiolas, & Gessa, 1987) whereas the dopamine antagonist haloperidol reduces sexual arousal and desire in rats and men (Petrie, 1985; Pfaus & Phillips, 1991). Such results allowed researchers to make a predictive link between the sexual responses of male rats and men (e.g., Barfield, 1993; Everitt & Bancroft, 1991; Pfaus, 1996), and gave rise to an important theoretical implication that certain brain systems had been conserved in evolution to subserve similar or identical functions among species. This has led to a new understanding of how animal models can help elucidate mechanisms of sexual behavior in humans – provided that researchers can translate human clinical questions into experimental situations appropriate for animals.

1. WHAT MAKES A GOOD ANIMAL MODEL?

Animal models must relate in some predictive way to the human condition. At the simplest level of analysis, it is prudent to recognize that all organisms that engage in sexual behavior share common processes. We must be able to respond to hormonal and neurochemical changes that signal our own sexual desire and arousal. This capacity underlies our moment-to-moment level of sexual arousability (as conceived by Whalen, 1966), and defines a large part of the internal state that is commonly referred to as “sex drive”. The rest requires a complex mix of instinct, learning, and feedback; a neural organization that allows us to interact with external sexual incentives and predict their reactions along with our own responses to those reactions. We must be able to identify external stimuli that predict where potential sex partners can be found, to seek out, solicit, court, or otherwise work to obtain sex partners, distinguish external cues and behavioral patterns of willing sex partners from individuals who are not sexually receptive, and to pursue and execute sexual behavior once sexual contact has been made. Neural mechanisms exist that allow sexual responding to become habitual or automated with practice, and such processes may underlie the ability of sexually experienced animals to be less affected by treatments that disrupt sexual responding in sexually naive animals (e.g., Pfaus & Wilkins, 1995). Similarly, neural mechanisms exist that allow the stimulation received during sexual contact to be perceived as rewarding. Such reward alters subsequent behavior, for example, by contributing to the formation of preferences for salient stimuli associated with positive sexual reinforcement (Pfaus, Kippin, & Coria-Avila, 2003). These aspects of sexual responding go well beyond the traditional focus in animal studies on copulation or penile reflexes and make them particularly applicable to human sexual behavior. Although some appetitive and preparatory responses that animals make prior to copulation are not specific to sexual behavior, they can be considered “sexual” if they are conditioned using sexual reward as the positive reinforcer. This is as true for bar pressing in male rats (e.g., Everitt et al., 1987) as it is for giving flowers and remembering birthdays in men.

For all animals, sexual behavior occurs as a sequence or “cascade” of behavioral events. Beach (1956) recognized the heuristic value of separating sexual behavior into appetitive and consummatory phases. Essentially, this scheme followed from the work of early ethologists like Craig (1918) and experimental psychologists like Woodworth (1918), who defined appetitive (or “preparatory”) behaviors as those which bring an animal from distal to proximal and into contact with goal objects or incentives. In contrast, consummatory behaviors are performed once an animal is in direct contact with the incentive (i.e., to “consummate” the goal). Consummatory sexual behaviors tend to be species-specific, sexually differentiated, and stereotyped, whereas appetitive behaviors are more flexible. Indeed, survival often depends on an animal’s ability to learn a variety of strategies to obtain goals in different appetitive circumstances. We have found it useful heuristically to conceive of appetitive and consummatory behaviors as two overlapping Venn diagrams (e.g., Pfaus, 1996; 1999) in which the behavioral stream moves from appetitive to consummatory incentive sequences (Figure 1). The intersection of the diagrams defines precopulatory behaviors made once animals come into contact with potential sex partners. The diagrams are overlapping, rather than discontinuous, because the division between the two phases is rarely fixed. Some responses, such as solicitation, can be placed into both phases, especially if sexual interaction comes in bouts. We would therefore define solicitation as a precopulatory behavior that acts as a transition from appetitive to consummatory. It is also essential to place the behaviors into a comparative context: are they homologous or analogous to human sexual responses?

a) Homologies versus analogies

Homologies are typically defined in biology as tissues that correspond in evolutionary origin, structure, and function; for example, the flippers of a seal and the arms of a human being. However, homologies come in degrees. We may regard brain dopamine systems among different mammals as homologous because cell bodies originate and axons terminate in similar brain regions (e.g., ventral tegmental area to
nucleus accumbens). In addition, drugs that activate dopamine receptors (e.g., apomorphine) or block the reuptake of dopamine (e.g., amphetamine or cocaine) produce psychomotor stimulation in many mammalian species, thus we may regard the function of this neurochemical system as homologous at that level of analysis. We may also define tissues with different function, such as the labia and scrotum, as homologous structures because they differentiate from the same primordial anlage. Regarding behavior, homologies are usually easy to define because they have the same endpoints and are typically controlled by similar neural systems. Erections in rats and men are a good example: A large number of drugs, situations, and brain lesions, alter the latency to obtain an erection and the duration of erection similarly across species.

Analogies are less straightforward and require a degree of creativity in interpretation, inference, and design. What distinguishes analogies from homologies is the idea that things or events are dissimilar in form, yet may serve the same endpoint. In biology, this is usually taken to mean that the organ or structure is similar in function, but not necessarily in evolutionary origin. For example, the gills of a fish

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**Figure 1:** Incentive sequences for human and rat sexual behavior (modified from Pfaus, 1996, 1999, and Pfaus et al., 2003). The behavioral stream moves from left to right, through appetitive, precopulatory, and consummatory phases of behavior. This conforms to the movement of animals from distal to proximal to interactive with respect to the sexual incentive. Sexual excitement can manifest itself in learned or unlearned behaviors, whereas preparatory behaviors are learned responses that animals must make in order to acquire the incentive (e.g., operant behaviors, pursuit, preference etc.). Recognizing which responses occupy which parts of the behavioral stream allows researchers to compare behaviors that appear different among different species, but that accomplish a similar motivational endpoint. Such behaviors in one species (e.g., rat) may then serve as models of analogous behaviors in humans. The predictive validity of such models is enhanced when drugs or other treatments modify the behavior of both species the same way, suggesting that a common neural system for those behaviors has been conserved.
and the lungs of a mammal both remove oxygen from water or air, but cannot remove it from both media. However, analogous tissues may have similar neural control. With regard to behavior, something done by an animal may not appear similar to its human counterpart, despite serving a similar endpoint and being dependent on identical neural systems. Solicitation in female rats is a good example. During copulation, female rats control the initiation and pacing of copulation by soliciting mounts from males. Females make a headwise orientation to the male and then run away, forcing the male to chase them if they are interested in sex (e.g., McClintock, 1985). If the male is sluggish or nonresponsive, the female may increase the strength of her solicitations, to the point of kicking the male in the head before the runaway or even mounting the male if he does not respond to previous enticements (Afonso & Pfaus, 2006; Beach, 1969).

Nonhuman primates show a remarkably similar pattern of sexual initiation with female rhesus monkeys doggedly maintaining close contact with males they are sexual interested in until the male is finally induced to engage in sex (Wallen, et al., 1984; Wallen 1990). Male rhesus monkeys manipulate this propensity of female to pursue them by walking away from females who initiate close contact, one supposes, to see whether the female will follow. Indeed rhesus monkey females at peak fertility pursue males through several of these arrivals and departures, whereas females further from peak fertility typically will not initiate contact with the male, or if they do, will not pursue the male if he leaves. Similar approaching and leaving behavior would be seen as sexual solicitation in most human cultures, but the specific form that it would take would be highly culturally defined. Thus a woman walking across a crowded room at a party to stand near a specific man could be an expression of sexual interest, whereas standing the same distance from that man on a crowded subway may not express the same sexual intent. High levels of solicitation in females, or analogous courtship behaviors in males, suggest that the individuals are highly motivated to engage in sex. Whether the solicitations result in sex reflects an increasingly complicated social calculus that takes into account the social context, the specific individuals involved, and their social history and experience. While some components of this social calculus are evident in rodents, it is much more complicated in humans and has a much stronger influence on the likelihood that sex will occur.

At a strictly behavioral level of analysis, it does not matter whether the motivation to sexually initiate is driven by a primary desire for sexual gratification, offspring, conflict resolution, or other social rewards. Contrast solicitation behavior with the lordosis posture, the arching of the back characteristic of sexual receptivity in many mammalian females which elevates and rotates the female’s pelvis making it possible for the male to intromit with the female. As mentioned above, there is no human counterpart to this, as postural control of access to a woman’s genitals in not a spinal reflex as is lordosis and such access is under the woman’s voluntary control, except in cases of forced copulation, something that cannot occur in a nonreceptive female rat. Thus it is solicitation in rats, and not lordosis, which is the “analogous rat model” of behavior expressing sexual desire, such as sexual initiation in women.

b) Three features of a good animal model

Predictive validity: As mentioned previously, the most important requisite of an appropriate animal model is predictive validity. In addition to this, animal models should be simple and practical enough to have “high throughput”, meaning the ability to have experiments conducted relatively quickly. Issues of sample size and ease of testing and analysis are key. For example, testing the sexual effects of alcohol in male dogs may reveal processes similar to those in men (e.g., the ability of low doses of alcohol to increase the ejaculation latency in male dogs that led to the suggestion by Gantt (1952) that a couple of glasses of wine could be used as a quick remedy against premature ejaculation), but such experiments are cumbersome from an experimental testing and animal housing standpoint, and indeed might have a difficult time passing an animal ethics review by today’s standards.

Throughput in numbers: Because testing large animals is simply not practical except in field studies, many researchers utilize smaller animals, such as rats, rabbits, ferrets, gerbils, hamsters, voles, mice, snakes, lizards, or birds, to examine the neural and hormonal control of sexual behavior. These animals can be tested in large numbers at the same time, and do not present a challenge for animal housing in a colony room. Although some, like certain transgenic mice, require constant monitoring, this is not an overriding obstacle to their use as research subjects.

Optimal testing environments: Testing small animals means that suitable chambers and testing environments need to be constructed. Attention has to be paid to the ecological validity of those testing environments. Some animals, like rats, are very social and will copulate under a variety of circumstances regardless of the presence of a human experiment-er (Calhoun, 1962). The testing environment also needs to be optimized for each animal. For example, female rats like to pace the rate of copulation. Providing them with chambers that allow such behavior to occur (e.g., the preference chambers described by Emery, 1986; the pacing chambers described by Erskine, 1989 and Paredes & Alonso, 1987; or the biveral chambers described by Mendelson & Pfaus, 1989, Pfaus, Mendelson, & Phillips, 1990, and Pfaus, Smith & Coopersmith, 1999; shown in Figures 3 and 4), gives researchers the ability to de-
tect certain appetitive behaviors in both female and male rats in an unambiguous manner. Likewise, if the experimenter wishes to study appetitive responses made to acquire a sex partner, then the testing environment should contain some kind of operant apparatus upon which the animal must work to obtain sexual reinforcement (e.g., as described in Everitt et al., 1987). Each experimental question dictates the proper treatments and testing environment, so the rate-limiting factor in generating the appropriate animal model is really the inspired intuition of the experimenter (see Ågmo & Ellingsen, 2003).

A. BEHAVIORAL MODELS

Behavioral models comprise both copulatory and precopulatory responses, in addition to models of hypofunctionality that can be achieved either by hormonal manipulation or learned inhibition. Both copulatory and precopulatory behaviors in animals can be viewed in laboratory circumstances under different conditions. Virtually all animals will learn to copulate in a variety of testing chambers, although such chambers typically alter the acquired baseline behavior of the animals (e.g., the different number of intromissions or ejaculation latencies of male rats trained to copulate in unilevel versus bilevel pacing chambers: Ismail et al., 2008; Figure 2, 3). Likewise, female rats show different patterns of solicitation in unilevel or bilevel pacing chambers (Ismail et al., 2008; Pfau et al., 1999). Once learned, such automated patterns are difficult to retrain, even with extensive experience in different chambers.

It is useful to pattern the discussion of behavioral models after the phases of sexual behavior denoted in the DSM. Thus, animal models exist for sexual arousal, desire, and reward, which reflect analogies and homologies of sexual arousal, desire, and orgasm in humans. Recent work has also been aimed at models of sexual inhibition in animals that can inform both the etiology and treatment of sexual arousal, desire, and orgasm disorders in humans, or the ability of “prosexual” drugs to induce states of sexual disinhibition (e.g., alcohol, cocaine).

I. MODELS OF SEXUAL AROUSAL

Physiological sexual arousal in both humans and other animals can be defined as increased autonomic activation that prepares the body for sexual activity. This includes both parasympathetic blood flow to genital and erectile tissues, in particular the clitoris, labia, vaginal epithelium, and penis, and...
sympathetic blood flow from the heart to striated and smooth muscle that participate in sexual responses. Sexual arousal also includes a central component that increases neural “tone” or preparedness to respond to sexual incentives. This latter concept was defined as “arousability” by Whalen (1966), and may form around an intricate interaction of hormone priming and noradrenergic activity in different regions of the brain. Both peripheral and central arousal may be detected as part of the perception of subjective sexual arousal, and both clearly lead to changes in responsiveness in genital tissues and control certain copulatory responses, such as the latency to orgasm or ejaculation (with shorter latencies indicating an increase in arousal). There is a considerable degree of similarity between male rats and men in terms of the neuroanatomical, neuroendocrine, and neurochemical regulation of penile erection and ejaculation (see Andersson & Wagner, 1995; Meisel & Sachs, 1994; Rosen & Sachs, 2000, for comprehensive reviews). Penile erections in men can be either be “physiological” or “psychogenic” in response to parasympathetic arousal. They can be studied using mercury-in-rubber strain gauges either during the night (to gain an unbiased measure of physiological erectile capability), or in response to different types of erotic or somatosensory stimuli (to measure psychogenic arousal). Latency to erection (tumescence), percentage of full erection, and duration of erection can be studied following the administration of drugs that either enhance or delay parasympathetic arousal. Such studies are important diagnostically in distinguishing psychological from physiological erectile dysfunction, or in determining spared erectile capability in men with spinal cord injury. Ejaculation has been more difficult to study objectively in men, and has thus been the subject of far fewer studies. Typically, subjects masturbate in the presence of different types of erotic stimulation following an experimental treatment. Ejaculation latencies are recorded along with physiological measurements of ejaculate volume, sperm motility, or psychological measurements of orgasm intensity (e.g., Mah & Binik, 2002; Rowland, Strassberg, de Gouveia Brazao, & Slob, 2000). Subjective sexual arousal, or the ability of people to describe or monitor their own sexual arousal, is difficult if not impossible to determine in animals. We must use components of sexual desire, specifically behavioral excitation in response to changes in genital blood flow, to make inferences about subjective arousal in animals.

1. PENILE ERECTIONS

In rats, penile erections can be studied in isolation to obtain measures of physiological arousal (summarized in Meisel & Sachs, 1994) or in response to different types of sexually arousing stimuli (e.g., noncontact erections in response to estrous odors) to obtain measures of psychogenic arousal (Sachs et al., 1994; Sachs, 1995).

2. PENILE REFLEXES

In typical penile reflex tests, male rats are placed supine in a tube with their penile sheaths held back and the penis retracted. The penis then shows a characteristic pattern of tumescence and detumescence accompanied by “quick flips” (quivers following full erection) and “cups” (a flaring of the glans penis thought to be analogous to ejaculation). Latency to erection and the frequency of these different reflexes are counted following an experimental treatment, (e.g., systemic or central drug administration, brain lesions, or lesions of different nerves that innervate the pelvic ganglia). Many treatments that enhance penile erection in men (e.g., sildenafil, apomorphine, prostaglandin E1, oxytocin, α2-adrenergic receptor antagonists like yohimbine, idazoxan and imiloxan, and vasodilators that act through nitric oxide substrates, such as nitroglycerine, sodium nitroprusside, and lindsomine) enhance penile erection in rats (reviewed in McKenna 1999; Meisel & Sachs, 1994). Erectile responses to these drugs are also studied by monitoring intracavernosal pressure with electrodes (e.g., Andersson et al., 1999; Bernabe et al., 1999). Conversely, drugs that reduce sexual arousal in men, e.g., dopamine antagonists such as haloperidol (Crenshaw & Goldberg, 1996), also reduce penile reflexes in rats (Pehek et al., 1988). However, selective activation of different dopamine receptors in the mediopontic area alters autonomic arousal differently, with selective agonist actions on D1 receptors facilitating erections and inhibiting seminal emissions in male rats, and selective actions on D2 receptors having the opposite effect (Hull et al., 1989). This suggests that the erectogenic actions of apomorphine in rats occur through its binding to D2 receptors in this or other brain regions.

3. “PSYCHOGENIC” ERECTIONS

Noncontact erections in rats are studied in the presence of an inaccessible receptive female behind a mesh screen, or behind a series of walls with an air circulation system that brings the estrous odors to the male’s compartment. Erections in response to these salient sexual cues are viewed as a model of psychogenic erection because they do not require direct somatosensory stimulation to be induced. The neurochemical and hormonal mechanisms that control their expression have been studied in detail (e.g., nitric oxide release in the paraventricular hypothalamus, Melis et al., 2000; dopamine in the medial preoptic area, Adachi et al., 2003; peripheral and central actions of androgens, Manzo et al., 1999). Drugs that enhance noncontact erections also induce a “penile erection and yawning syndrome” in rats in the absence of sexual stimulation (Bertolini, Gessa, & Ferrari, 1975; Doherty & Wisler, 1994; Melis & Argiolas, 2002). It remains to be studied whether this “syndrome” is related neurochemically to psychogenic erection in rats, or whether it stems
from a more general activation of the autonomic nervous system. On the other hand, general autonomic activation by drugs or environmental circumstances may be translated into sexual arousal in the presence of a sexual incentive. This is reminiscent of the idea put forth by the ancient Roman poet Ovid, in Ars Amatoria (2 CE/1930; www.sacredtexts.com/cla/ovid/ibook/) that, under the right circumstances and occasion setting, high levels of general arousal can be manipulated into sexual arousal (see below).

Such an effect is also consistent with the notion by Meston and colleagues (Meston, 2000; Meston & Gorzalka, 1996), that sympathetic arousal provides a necessary background for the perception of sexual arousal.

4. COPULATORY RESPONSES IN MALES THAT INDICATE AROUSAL

Ejaculations in rats can be studied much the same way they are studied in humans, with the latency from first mount or intromission to ejaculation being the key variables. Male rats typically ejaculate following several penile intromissions, and can ejaculate several times before becoming sexually exhausted, in which the male no longer responds to estrous odors or female solicitations (Beach & Jordan, 1956). During successive ejaculatory series, the refractory period or postejaculatory interval between each ejaculation and the subsequent resumption of copulation increases progressively (Larsson, 1956). Penile intromission requires erection, and ejaculation typically requires sensory feedback from the penis that accumulates with multiple intromissions. The number of intromissions before ejaculation, the number of ejaculations achieved in a timed test, and the length of the postejaculatory interval, are all dependent on autonomic arousal and can be enhanced or disrupted by drugs that have similar effects on copulatory performance in men (see Bitran & Hull, 1987; Doman & Malsbury, 1989; Meisel & Sachs, 1994; Pfaus & Gorzalka, 1987, for selective reviews). For example, drugs that delay or abolish orgasm in men (e.g., selective serotonin reuptake inhibitors such as fluoxetine), increase the ejaculation latencies and reduce the total number of ejaculations in rats (Frank, Hendricks, & Olson, 2000; Yells et al., 1994). As in men, the reduced ability to ejaculate is more pronounced in rats following long-term daily administration (Cantor, Binik, & Pfaus, 1999). Acute alcohol intoxication also delays ejaculation in men (Malatesta et al., 1979) and in rats (Dewsbury, 1967; Pfaus & Pinel, 1989). Although tolerance to this effect appears to accrue contingently in rats (Pinel, Pfaus, & Christensen, 1991), it is not yet known if contingent or conditional tolerance occurs in humans to alcohol's sexual effects with long-term use.

A short ejaculation latency in rats, ejaculation with fewer than normal preejaculatory intromissions, or an increased number of ejaculations in a timed test or before sexual exhaustion sets in, suggests an enhancement of sympathetic arousal. Although at first glance, faster ejaculation and/or ejaculation with fewer intromissions suggest that the male may be a more "proficient" copulator, such behavior in the wild would be less likely to get a female rat pregnant (e.g., Adler, 1969), and should be considered a disruption of normal copulatory responding. Such behavior is more reminiscent of premature ejaculation in humans, and can be induced by drugs that stimulate sympathetic arousal (e.g., cocaine; Ferrari & Giuliani, 1997) or by experiential conditions that increase sympathetic arousal in sexual circumstances. For example, Larsson (1956) observed that male rats would ejaculate faster, and with fewer intromissions, if the stimulus female was removed from the test chamber for periods up to one minute between successive intromissions. Although Larsson's "Enforced Interval Effect" could constitute a rat analogue model of premature ejaculation, it remains to be seen whether drugs that can counteract premature ejaculation in men, such as alcohol or fluoxetine, can increase the latency of male rats to ejaculate in this condition.

Classically conditioned stimuli are also capable of increasing sexual arousal as reflected by copulatory rate measures. Zamble and his colleagues (Zamble, Hadad, Mitchell, and Cutmore, 1985; Zamble, Mitchell, and Findlay, 1986) used placement of male rats in a holding cage as a conditioned stimulus to signal non-copulatory exposure to a receptive female behind a wire-mesh screen on several training trials. On test trials, they found that placing the males into the holding cage prior to unrestricted copulation resulted in significantly shorter latencies to intromit and ejaculate than if the conditioned stimulus was omitted. Subsequent studies found that second-order conditioned stimuli (e.g., a plastic toy fish found in the holding cage) were effective in enhancing the same measures of arousal (Zamble et al., 1985), and such conditioning in sexually naive or sluggish males could increase the proportion of males that copulate on a subsequent test (Cutmore & Zamble, 1985). Hollis, Cadieux, and Colbert (1985) demonstrated that repeatedly pairing a light with non-contact exposure to a receptive female resulted in conditioning of sexual behavior in male gouramies, a type of Labyrinth fish. They found that males receiving the conditioning treatment displayed significantly lower latencies to initiate copulation and lower levels of aggression towards females when the conditioned stimulus was presented before access to a female. Similar results have been demonstrated Domjan and colleagues in birds, notably Japanese quail. Male quail that received repeated exposure to females following the presentation of a conditioned stimulus light displayed significantly shorter latencies to initiate copulation when the stimulus was present compared to when it was absent (e.g., Domjan, O>Vary, and Greene, 1989). Pfaus, Talianakis,
and Kippin (in preparation) recently found evidence that somatosensory stimuli can be used to condition sexual arousal in male rats. Males that received prior sexual experience with receptive females while wearing a rodent harness jacket displayed slower intromission and ejaculation latencies if tested without the jacket than with it on. A rat model of conditioned sexual arousal would be useful as an analogy of psychogenic copulatory sexual arousal, or perhaps even the development of certain fetishes. However, the ability of conditioned stimuli to “prime” sexual arousal may depend on the association of neutral stimuli with sexual reward in addition to arousal (see below). In fact, pairing stimuli with sexual arousal per se, without sexual reward, may result in counterconditioning, in which males show lower levels of arousal in the presence of such stimuli.

5. FEMALE SEXUAL AROUSAL

Physiological sexual arousal in women has not received nearly the same experimental attention as in men, in part because genital blood flow in women has been assumed to follow the same physiological and psychological rules as in men (Barlow, 1986). Certainly, drugs or stressful circumstances that block erections in men also block vaginal and possibly clitoral blood volume in women. However, clinical results with sildenafil in women with sexual arousal disorders have been inconclusive (Basson et al., 2002; Berman et al., 2001; Rosen, 2000). There may be real differences between men and women in patterns of sexual arousal and in the types of psychogenic stimuli that elicit genital blood flow (e.g., Palace & Gorzalka, 1990; Rosen & Beck, 1988). For example, women are reported to experience cyclic fluctuations in arousability and desire, with peak incidents of female-initiated sexual activity coinciding with ovulation (Wallen, 1995). Indeed, event related potentials (ERPs) that correspond to attention and stimulus processing for working memory (e.g., the P3 amplitude) increase following the presentation of sexually arousing pictures, but not pictures of babies or body care products, to women during the ovulatory phase (Krug, Pihal, Fehm, & Borh, 2000). The same pictures do not activate those ERP components during other phases of the menstrual cycle, or in women taking oral contraceptives (Krug, Pietrowsky, Fehm, & Borh, 1994). Timing may thus be extremely important when studying sexual arousal in women relative to men. Such a relationship has been established for rats and other species. Female rats display sexual “heat” only during the periovulatory period of their estrous cycle, a state that can be induced in ovariectomized rats by sequential administration of estrogens and progesterone (Bolling & Blandau, 1939).

In vivo experimental models of genital arousal in female New Zealand White rabbits have been developed by Traish, Goldstein, and their colleagues (e.g., Kim et al., 2003; Min et al., 2003; Munarriz, et al., 2003; Park et al., 1997; Traish et al., 2002a,b). In these models, electrical stimulation of the pelvic nerve is applied that mimics the type of stimulation normally received by females during vaginal intromission and results in increased vaginal blood flow, vaginal wall pressure, vaginal length, clitoral intra-cavernosal pressure and blood flow, and decreased vaginal luminal pressure. Similar effects have been reported following pelvic nerve stimulation in female rats (Giuliano et al., 2001; Vachon, Simonner, Zahran, & Carrier, 2000). In addition to vaginal and clitoral blood flow responses, vaginal smooth muscle preparations have been developed to examine the ability of different neurotransmitters to induce muscle contraction and relaxation. These studies have shown that ovariectomy diminishes vaginal blood flow, lubrication, and epithelial cell morphology, and that treatment with estradiol restores these measures of vaginal response. Moreover, the nitric oxide-cyclic GMP pathway appears to be critical for vaginal blood flow, as it is for penile blood flow. Treatment with androgens facilitates vaginal nitric oxide synthase activity, along with vaginal smooth muscle relaxation. Although it is not yet known how these vaginal responses are integrated with behavioral responses, Whalen and Lauber (1986) hypothesized that cyclic GMP was a common target for drugs that substitute for progesterone in the facilitation of lordosis in rats. Inhibition of the ability of nitric oxide to stimulate cyclic GMP in the rat brain results in a profound disruption of lordosis (Chu & Etgen, 1997) suggesting that the brain is an important target for nitric oxide/GMP stimulated activation of lordosis. However, it remains an intriguing possibility that increased vaginal blood flow could be perceived by females and help stimulate behavioral measures of sexual arousal. Such a relationship could be examined following inhibition of peripheral nitric oxide-cyclic GMP.

II. MODELS OF SEXUAL DESIRE

Sexual desire seems a straightforward concept, yet there is no agreed-upon definition of what it is or how it manifests itself. In the DSM-IV-TR, the diagnosis of Hypoactive Sexual Desire Disorder (HSDD) is given when “desire for and fantasy about sexual activity are chronically or recurrently deficient or absent.” By converse logic, then, sexual desire is the presence of desire for, and fantasy about, sexual activity. This definition while coherent is circular and provides no objective way in which to identify sexual desire. Many clinicians view desire as distinct from arousal in both animals and humans. This is apparent in the DSM’s categorization of arousal disorders as distinct from desire disorders, a distinction that generally reflects blood flow to the genitals and erectile tissues versus a “psychological” sexual interest in which individuals “want” sex (as defined by Robinson & Berridge, 1992). In practice, however, desire may well be informed or even confirmed by the presence
of autonomic and central responses that define arousal, and there is growing evidence that people regard desire and arousal as parts of one another, despite being given distinct definitions. When an individual expresses sexual desire behaviorally, it follows that attention and behavior focus on obtaining some form of positive sexual reinforcement. This can occur alone in fantasies or together with others in goal-directed social and sexual behaviors. Thus, in addition to subjective appraisals of desire, the concept encompasses the effort, including risk, which individuals engage in to obtain sexual rewards, the excitement displayed in anticipation of such rewards, and the strength of the incentive value ascribed to a particular sexual stimulus.

1. HORMONAL INFLUENCES.

Although the vast majority of studies of hormonal influences on sexual motivation have utilized rodents, their relevance to understanding human sexual desire is more limited than is generally credited. In females, both the behavioral endpoints used and the hormones underlying sexual motivation are markedly different than those thought to operate in primates, including humans. Lordosis has been the primary behavioral evidence of female sexual motivation in rats and is one of the most completely understood behavioral systems in behavioral neuroendocrinology (Pfaff, 1980; Pfaff et al., 1994).

However, as previously described, there is no behavioral equivalent in humans. In addition, although estradiol can induce some expression of lordosis, full expression in rodents requires sequential exposure to estradiol followed by progesterone separated by at least 24 hours. While no study has specifically ruled out the possibility of progesterone synergism with estradiol to produce full sexual receptivity, there is no evidence for a role for progesterone in stimulating sexual behavior in primates. Thus the elegant understanding we have of the hormonal and neural modulation of lordosis is likely to be of little use as an animal model with reference to human sexual desire. Instead, female initiation and pacing (Erskine, Pfau) are analogues much more likely to be valuable. It is the use of female initiation, for example, which produced convincing evidence that bremelanotide, a melanocortin receptor agonist (previously referred to as PT-141), specifically influenced sexual motivation and not the capacity of females to respond to the male’s sexual initiation (Pfaus, et al, 2004). The parallels between rodent female sexual solicitation and that seen in monkeys (McClintock reference; Wallen, et al, 1984) are striking and ovarian estrogens capacity to induce female sexual solicitation is similar in both rodents and primates. However the specific role that progesterone plays in female rat sexual solicitation is unclear. Full sexual receptivity in female rats requires progesterone after a period of estrogen exposure. Though estradiol alone increases the female rats attraction to males, the largest increase in time spent with male rats occurs after a sequential estradiol and progesterone treatment (Pfeiffe and Edwards, 1984) In monkeys in naturalistic social groups, the time females spend near males is strikingly correlated with estradiol levels, increasing as estradiol increases, declining as estradiol declines, and inversely correlated with progesterone levels, declining rapidly as luteal progesterone increases during the ovarian cycle (Wallen, et al., 1984). In naturalistic social groups of monkeys, females initiate more than 90% of all copulatory episodes during the fertile portion of their cycle (Wallen, et al., 1984). They typically initiate sex by approaching and sitting near males where if the male is not responsive they may stimulate him be staccato movements such a suddenly standing up, or slapping the ground to solicit copulation (Wallen, et al, 1984). As shown in Figure 4, the pattern of sexual initiation seen in female rhesus monkeys across the ovarian cycle is strikingly similar to the menstrual cycle variation seen in increased sexual desire reported by women (Stanislaw & Rice, 1988). Additionally, estradiol in ovariectomized female rhesus monkeys reinstates female sexual initiation, even when males are not sexually responsive, strongly supporting that this behavior reflects female sexual desire (Zehr, Maestripieri, and Wallen, 1988).

![Figure 4 Top: The number of women reporting sexual desire for the first time in their ovarian cycle in relation to ovulation (data from Stanislaw and Rice, 1988). Bottom: Mean frequency of female macaque approach (closed circles) and sexual solicitation (open circles) of males in relation to the female’s mid-cycle estradiol peak (data from Wallen et al., 1995).](image-url)
While data in monkeys strongly support the role of estradiol in female sexual motivation, and so far provide no evidence for a facilitating role for progesterone, it is the precursor of estradiol, testosterone, which has gotten the greatest attention in women. Studies from the 1930's and '40s reported that testosterone treatment increased libido (Salmon and Geist, 1943) However, these treatments used massive doses of testosterone resulting in deepening of the women's voices and clitoromegally. While this was seen as a therapeutic treatment, there was no known source for such levels of T in women. This changed in 1959 when Waxenberg Drellich and Sutherland reported that adrenalectomized and ovariectomized women reported significantly less sexual intercourse than did women ovariectomized only and concluded that ovarian hormones were unimportant and that adrenocortical androgens were the source of libido in women. Leaving aside that this study was done in women with terminal cancer, who received adrenocortical androgens were the source of libido in women. When reported changes in sexual desire. When reported changes in sexual desire instead of sexual intercourse were compared, this study actually provided the first evidence for the importance of ovarian hormones in women's sexual desire. When reported changes in sexual desire instead of sexual intercourse were compared, they were significantly reduced following ovariectomy, whereas intercourse frequency was not. This likely reflects the capacity of women to engage in sex whether or not they desire sex, something which is not possible in rats and other laboratory species. Although there was evidence in this study that ovarian hormones influenced female desire, this was unrecognized until Sherwin's landmark studies which definitively demonstrated that ovariectomy dramatically reduces or eliminates female sexual desire (Sherwin, Gelfand, and Brender, 1985; Sherwin and Gelfand, 1987). These studies also seemed to show that testosterone combined with estradiol reinstated women's sexual desire, whereas estradiol alone did not. The notion that in women, T is the libidinal hormone has become well entrenched, leading several pharmaceutical companies to develop potential T therapies for HSDD, though none have received approval for treatment in the US.

A recent survey of all random double blind studies of hormonal therapy in surgically or naturally menopausal women found that T combined with low levels of E was successful in reinstating sexual desire in women, but that E alone was effective in two of the three studies in which women were not hypoestrogenic (Alexander et al., 2004). Because of concerns about the long term consequences of estrogen therapy, few human studies use estradiol levels that would not be considered hypoestrogenic. Thus it is not possible to tell whether the effectiveness of combined estrogen and androgen therapies reflects an aromatization of the testosterone or some sort of synergism. In female rats, testosterone is capable of synergizing with estradiol to induce a full state of female sexual desire and receptivity (Jones et al., in press). This is true in ovariectomized female rats and gonadally intact females over the age of 15 months, after their ovarian steroid output has become acyclic. The exact physiological role of this synergism is still not known.

2. ANTICIPATORY MOTOR RESPONSES.

Male rats in bilevel chambers (Figure 3) display an increase in level changing in anticipation of the arrival of a sexually receptive female (Pfaus, Mendelson, & Phillips, 1990; van Furth & van Ree, 1996a,b). Typically, males are placed into the testing chamber for a 5-min adaptation period prior to the placement of a receptive female. The anticipatory behaviors develop naturally over a few trials but do not develop if the chamber is baited with an ovariectomized (nonreceptive) female or another male. Dopamine receptor antagonists decrease the number of anticipatory level changes displayed by male rats in bilevel chambers at doses that do not alter copulatory responses once receptive females are placed into the chamber (Pfaus & Phillips, 1991). Interestingly, a loss of desire and interest in sex is a common complaint among patients taking these drugs as major tranquilizers (Crenshaw & Goldberg, 1996). Long-term use of the stimulant drug cocaine is also reported to decrease sexual desire in men (MacDonald et al., 1988; Siegel, 1982; Washton & Gold, 1984). We have recently found that long-term administration of cocaine to sexually active male rats decreases conditioned level changes progressively over time (Pfaus et al., in preparation).

III. INSTRUMENTAL RESPONDING FOR PRIMARY OR SECONDARY SEXUAL INCENTIVES

All animals will work to obtain sexual rewards, and such behavior can be viewed as analogous to desire. Sexual rewards may come in the form of primary reinforcers (e.g., orgasm in humans; ejaculation in male rats or pacing in female rats), or secondary reinforcers, such as stimuli associated with sexual gratification (e.g., certain facial features, clothes, or smells in humans; certain odors or place cues in rats). In male rats, those behaviors have included performance in obstruction boxes (Jenkins, 1928; Moss, 1924; Stone, Barker & Tomlin, 1935; Warner 1927), straight-alley running (Beach & Jordan, 1956a; Sheffield, Wulff, & Backer, 1951; Ware, 1968), maze learning (Drewett, 1973; Eliasson & Meyerson, 1975; Hetta & Meyerson, 1978; Kagan, 1955; Meyerson & Lindstrom, 1973; Warner et al., 1991; Whalen, 1961), crossing of electrified grids (Moss, 1924), nose-pokes, and other attempts to “get to” a potential sex partner behind a wire-mesh screen (Damsma et al., 1992; Pfaus et al., 1995; Pfaus et
Some appetitive instrumental sexual responses are expressed easily, without much prior experience (e.g., nose-pokes, digging, obstruction box performance, crossing electrified grids), whereas others require some degree of training (maze learning, bar pressing). Those behaviors can be reduced following castration, indicating that gonadal steroid actions in the brain are necessary for their development and/or maintenance, or following lesions of certain steroid-concentrating brain regions, e.g., basolateral amygdala (Everitt et al., 1987; Nissen 1929). They can also be reduced after a devaluation of the reward offered by the incentive the male is working for (e.g., switching from receptive female to no female, an extinction procedure), or following infusions of dopamine antagonists to the nucleus accumbens (Everitt, 1990; Mendelson & Pfaus, 1989). Restoration of bar pressing in male rats with lesions of the basolateral amygdala can be made following infusions of amphetamine to the nucleus accumbens, indicating that mesolimbic dopamine release is critical for the expression of that behavior, and suggesting that the extensive glutamate projections from basolateral amygdala to the nucleus accumbens modulate dopamine release (Everitt, 1990). Dopamine antagonists administered systemically to male rats reduce running speed in a runway that leads to a goal box containing a sexually receptive female (López & Ettenberg, 2001). Antagonists infused to the medial preoptic area of the hypothalamus disrupt maze learning for sexual reinforcement in male rats (Warner et al., 1991). It is likely that different dopamine terminal regions play a role in different types of unconditioned and conditioned sexual activity. Although many of these paradigms have been in the literature for over 50 years, they have not been mined extensively by sex researchers to study the effects of drugs that activate or inhibit other neurotransmitter systems. Likewise, they have been applied sparingly to females. Bermant (1961) and Bermant and Westbrook, (1966) reported that female rats would bar-press for access to gonadally-intact, sexually active males. More recently, Matthews et al. (1997) reported that access to intromissions from a male that were made contingent on poking a lever with the nose increased the incidents of nose-poking in sexually receptive female rats. Contingent access to male bedding or emulsified preputial gland did not support increases in behavior, indicating that the copulatory stimulation was rewarding. The paradigm used by Matthews et al. ensured that females could control or “pace” the rate of copulation, a characteristic of copulatory interaction that female rats find rewarding (see below). Becker and colleagues (Becker, Rudick, & Jenkins, 2001; Jenkins & Becker, 2003; Mermelstein & Becker, 1995) found increased dopamine release in the striatum and nucleus accumbens of females that had to press a lever to gain access to a male, or run back and forth from behind an opaque barrier, relative to females that did not. Indeed, lesions of the striatum reduced the efficiency of females to pace the copulatory interactions, whereas lesions of the nucleus accumbens resulted in females that avoided sexual contact (Jenkins & Becker, 2001).

1. SEXUAL PREFERENCE PARADIGMS.

Sexual desire can be inferred from the strength of preference made toward particular features of a person or conspecific, or toward a place in which potential sex partners have been found in the past. As with other instrumental responses, preferences are typically displayed prior to sexual interaction so that animals and people can focus their forward trajectories toward sexual incentives. In humans, preferences exist for gender, and within gender for certain individually-defined physical features that people find attractive (shape of face, smile, eye or hair color, body type, etc). Preferences also exist for scents, for certain types of clothing, even for fetish objects. There are likely as many combinations of these as there are people, and the role of such preferences is to focus the attention of individuals on other individuals so that sexual interactions can occur. Some preferences are determined by particular cultures or epochs within a culture, whereas others are learned during a critical period of sexual behavior development, especially during an individual’s first sexual experiences. Some may be genetic. However, what is clear is that the association of particular features with sexual gratification entices people to seek out those features in future sexual interactions, even if those interactions are made at a distance or are part of a rich fantasy life. We would never deny that preferences exist in humans that are conditioned by experience; yet arguments continue to be made that the sexual preferences of animals (and even humans) are hard-wired for ultimate reproductive success and fitness, rather than more proximate rewards, such as sexual pleasure (e.g., Buss, 1994; Symons, 1979). Is this true? Certainly animals do not exist within a social organization that approximates human culture, and therefore are not subject to moral restrictions or the whims of advertising executives. However, recent evidence indicates that animals do show preferences for specific fea-
tures, many of which are learned during experience with sexual reward, rather than driven instinctually to maximize reproductive fitness. This latter dimension represents an exciting new foray into a level of animal behavior that approximates our own.

Some preferences seem instinctual and hard-wired by hormonal influences on the brain. For example, numerous studies have shown that male rats spend more time near sexually receptive compared to nonreceptive females (Edwards & Einhorn, 1986; Hetta & Meyerson, 1978; Merkx, 1984). Likewise, sexually receptive females spend more time near gonadally intact, sexually active males versus castrated, sexually inactive males (Gilman & Westbrook, 1978). Male rats also show unconditioned preferences for the odors of sexually receptive versus nonreceptive females (Bakker, van Ophemert, & Slob, 1996; Carr, Wylie, & Loeb, 1970; Stern 1970). These studies have been conducted in Y-mazes, T-mazes, radial-arm mazes, or open fields, that contain goal boxes baited with feathered receptive versus nonreceptive conspecifics (e.g., Gilman & Westbrook, 1978), different conspecifics behind wire-mesh screens (e.g., Ågmo, 2003a,b; Bakker, van Ophemert, & Slob, 1996), or in which different anesthetized stimulus animals are contained at opposite ends (e.g., Landauer, Wiese, & Carr, 1977). Castration of male rats abolishes their preference to remain near a sexually receptive female, whereas replacement with testosterone restores the preference (Ågmo, 2003a). Moreover, intact, sexually experienced males display significant preferences for sexually receptive females versus nonreceptive females and for sexually receptive females versus males, but not for sexually nonreceptive females versus males. Those data suggest that amount of time spent near the receptive female is based on the intensity of her olfactory cues. Indeed, Ågmo reported that the intensity of preference for a live receptive female could be generated by bedding that contained estrous odors, suggesting that olfactory cues are important sensory determinants of incentive value in the rat. Estrous odors are known to induce dopamine release unconditionally in the nucleus accumbens of intact, sexually inexperienced male rats (Mitchell & Gratton, 1991, 1992; Wenkstern, Pfaus, & Fibiger, 1993), and such odors increase neural activation in several key brain regions known from lesion studies to be critical for male sexual behavior, including the medial preoptic area, bed nucleus of the stria terminalis, medial amygdala, nucleus accumbens, and ventral tegmental area (Bialy & Kaczmarek, 1996; Bressler & Baum, 1996; Kippin, Cain & Pfaus, 2003; Newman et al., 1997; Pfaus & Heeb, 1997, Swann & Fiber, 1997; Veening & Coolen, 1998).

The studies of Mitchell and Gratton (1991, 1992) are of particular interest because they suggest that endogenous opioid release in the ventral tegmental area occurs in response to estrous odor cues, and this release in turn disinhibits ascending mesolimbic dopamine neurons. However, systemic treatment with a dopamine agonist or antagonist (amphetamine, cis-flupenthixol) or opioid agonist or antagonist (morphine, naloxone) did not alter the amount of time sexually experienced males spent near a sexually receptive versus nonreceptive female in an open field, except at higher doses that induced motor deficits (Ågmo, 2003a). Although Ågmo’s data suggest that dopamine and opioid systems are not necessary for the processing of unconditioned incentive cues, infusions of the dopamine antagonist cis-flupenthixol to the ventral tegmental area of male rats decreases the percentage of time spent near a sexually receptive female in an X-maze (Warner et al., 1991), and infusions of the dopamine antagonist haloperidol to the nucleus accumbens or medial preoptic area decreases conditioned level changing in bilevel chambers (Pfaus & Phillips, 1991). It is also known that sexually experienced males are relative resistant to many treatments that disrupt sexual behavior in inexperienced males, including castration, pentile anesthesia, novelty of a testing chamber, olfactory deprivation, and age (Gray, Smith, Dorsa, & Davidson, 1981; Lisk & Heiman, 1980; Lodder, 1975; Pfaus, Kippin, & Centeno, 2001; Pfaus & Wilkins, 1995; Thor & Flannelly, 1977). It is not clear whether experience may have buffered Ågmo’s males from the effects of dopaminergic or opioid drugs.

The kinds of studies outlined above are considered “pure” measures of preference because they are not confounded with copulation. However, that fact leads to the question of what is actually being studied. Meisel and Sachs (1994) note that, in the absence of the opportunity to engage in sexual behavior, the choice to spend time near one conspecific over another could reflect sexual preference, but could also be measuring social affiliation, opportunity to engage in aggression, curiosity, or a reaction to other incentive aspects of the stimulus animal that have nothing to do with sexual behavior. This concern was partially addressed in the study mentioned above by Ågmo (2003a): Sexually experienced males displayed selective preferences for sexually receptive females, but had no preference when the choice was between sexually nonreceptive females and other males. Indeed, although these kind of preferences are displayed by sexually naive males, they are not as strong as those displayed by sexually experienced males (Carr, Loeb & Wylie, 1969), indicating that sexual experience increases the incentive value of sex-related odors in the rat. Repeated exposure to estrous odors are known to sensitize mesolimbic dopamine release (Mitchell & Gratton, 1992), and intermittent exposure to amphetamine, which also sensitizes mesolimbic dopamine release, facilitates copulatory behavior in sexually naive male rats (Fiorino & Phillips, 1999).

Some preferences are not instinctual, in the sense
of being hard-wired, but rather reflect a process of Pavlovian conditioning in which neutral stimuli associated with sexual reward become conditioned sexual incentives. Such conditioned preferences can be assessed along with copulation in sequence. For example, studies by Domjan and colleagues have examined conditioned preferences in the seasonally-monogamous Japanese quail. Male Japanese quail respond differentially to females based on the presence of stimuli previously paired with copulation. Nash and Domjan (1991) allowed male quail to copulate with females of two strains of quail that have different plumage color (brown versus blond). Subsequently, males chose to spend more time in the proximity of females whose color was the same as that of females with whom they had copulated previously. Similarly, males allowed to copulate with females that were adorned with bright orange feathers subsequently spent more time near, and engaged in more sexual activity with, females similarly adorned compared to unadorned females. Moreover, males trained with adorned females attempted to copulate with a taxidermic model of a female quail, but only when it was adorned with the same color feathers (Domjan, O’Vary, & Greene, 1988). Domjan and Hall (1986) also demonstrated that males would stay in the vicinity of a window in their home cage through which they could see a sexually receptive female during a precopulatory period. However, this behavior developed only if the males had the opportunity to copulate with the female after the precopulatory period. A variant of this procedure, similar to that used to study anticipatory motor responding in rats, was used by Balthazart and colleagues to study the role of hormones and brain dopamine systems in conditioned sexual behavior in quail. Male quail were placed into a chamber that contained a window and sliding door at one end through which the male could see a sexually receptive female. After a 10-min period, the sliding door opened, and the animals could interact freely (Balthazart et al., 1995). As in Domjan and Hall (1986) and Mendelson and Pfaus (1989), only males that copulated with the females during this period developed the behavior, in this case, a preference to stay close to the window in the precopulatory period of subsequent tests. Castrated males did not develop this conditioned proximity behavior, nor did males that did not copulate. Castration also reduced the time spent near the window males trained prior to castration, and subsequent replacement with testosterone or estradiol restored the behavior. Subsequently, Castagna, Ball, & Balthazart (1997) reported that nomifensine, a dopamine reuptake inhibitor, decreased the appetitive social proximity response, but increased the frequency of mount attempts. In contrast, amfonelic acid, a compound that enhances dopaminergic tone, increased aspects of both appetitive and consummatory sexual behaviors. Thus, brain dopamine systems in birds and mammals seem to have analogous functions in the control of appetitive or conditioned sexual behaviors.

We have developed a model to examine the role of associative learning on sexual partner preferences in male and female rats during sexual interaction. Kippin et al. (1998) trained male rats to associate a neutral odor (almond or lemon extract) with copulation to ejaculation in either unilevel or bilevel pacing chambers (Figure 2, 3). The odor was dabbed around the back of the female’s neck and anogenital area, two regions that the male reliably places his nose during copulation. Males in several control groups were either not exposed to the odor or had the odor randomly paired with sexually receptive and nonreceptive females. On a final test, each male was presented with two receptive females in a large open field (Figure 5, top).

![Figure 5: Open field partner preference paradigm.](image)

Top: Males are placed into the open field for 5 min, after which two receptive females, one bearing a conditioned cue (e.g., odor) and one without the conditioned cue are presented at opposite corners. Latency and frequency measures for mounts, intromissions, and ejaculations are then calculated for each female during a 30-min test. Choice of female for first mount, intromission, or ejaculation, and the distribution of these measures across the test, are then determined for each male.

Bottom: The same preference test for females. Females are placed into the open field that already contains two sexually vigorous males, one bearing the conditioned cue and one without the cue. Because males tested in pairs with a single female will crawl over one another, they must wear rodent jackets that are tethered to opposite corners of the open field by a spring. Females can then “sample” both males, or display a preference for a single male by staying in his vicinity. Latency and frequency measures for mounts, intromissions, and ejaculations are calculated for each male, along with appetitive measures of solicitation and hops and darts, and defensive responses. Choice of male for first mount, intromission, or ejaculation, and the distribution of these measures across the test, are then determined for each female.
One female was scented with the odor, whereas the other was left unscented. The males were allowed to copulate freely with both females for 30 min. Males in the control groups did not show a preference for either female for first mount, intromission, or ejaculation, or for the total number of mounts, intromissions, or ejaculations displayed throughout the test. In contrast, although males in the paired group did not show a preference of female for mounts or intromissions, they chose the scented female for their first ejaculation, and displayed significantly more ejaculations overall with that female compared to the unscented female.

Thus, a simple odor-conditioning paradigm reversed what is typically considered a hard-wired biological predisposition in the polygamous male rat to prefer a novel partner over a familiar partner (Symons, 1979).

Subsequent studies identified the postejaculatory interval, rather than ejaculation per se, as the critical unconditioned stimulus for the development of this preference (Kippin & Pfau, 2001a). Significant conditioning also occurred after the male’s very first ejaculation, although it was considerably stronger if the males had multiejaculatory trials with the scented female (Kippin et al., 2001). Males were found to become “choosy” during their last few mounts before ejaculation (Kippin & Pfau, 2001b), and males in the paired group were more likely to attempt to mount sexually nonreceptive females scented with the conditioned odor, indicating that the odor acquired conditioned excitatory properties. When presented alone, the conditioned odor activated regions of the brain associated with olfactory processing and reward, including the main olfactory bulb, main olfactory (piriform) cortex, basolateral amygdala, and core of the nucleus accumbens (Kippin, Cain, & Pfau, 2003). Those findings suggest that estrous odors and sexually-conditioned odors are processed by distinct pathways that may converge in the ventral striatum. Finally, males showed greater conditioning in unilevel pacing chambers bisected by 1-hole versus 4-hole dividers (Ismail et al., 2009). Given that males take longer to ejaculate in 1-hole chambers, and require more intromissions prior to ejaculation, those data suggest that sexual reward is greater when it rides on a higher level of arousal.

We have found similar results in female rats (Coria-Avila et al., 2006, 2007). In those studies, the odor was paired with a different unconditioned stimulus: The ability of females to pace the copulatory contact. This was done using a unilevel pacing chamber bisected by a 4-hole divider. During training, females in the paired group received sequential access to scented males on one side of the divider or unscented males with no divider, on alternate testing days. Females in the explicitly unpaired group received the opposite order of experience. On the final test, each female was placed into an open field with two intact, sexually experienced males, both tethered to opposite sides of the open field (Figure 4, bottom). One male was scented and the other was not. Females in both groups were significantly more likely to solicit and receive their first intromissions from the male paired with pacing. However, only females in the paired group showed a significant preference to stay with that male for their first ejaculation; females in the unpaired group did not show a conditioned partner preference. The selective copulation and mating behavior on the part of females in the paired group would be expected to assure paternity (Coria-Avila, et al., 2005). The development of conditioned partner and ejaculatory preferences is disrupted by treatment with the opioid antagonist naloxone during training in both male and female rats (Coria-Avila et al., 2008a; Ismail et al., 2009). In contrast, treatment with the dopamine antagonist flupenthixol disrupts conditioning in females, but not males (Coria Avila et al., 2008b; Ismail et al., 2009).

2. DESIRE IN COPULATORY MEASURES.

Sexual desire can also be inferred from certain unconditioned copulatory measures. For example, the rate at which female rats will solicit and pace their copulatory contact with males, and the willingness of males to chase females, can be considered analogues of desire (and possibly arousal). These measures can be recorded unambiguously in bilevel chambers, pacing chambers, mazes, or choice boxes (e.g., Ågmo, 2003). Solicitations by the female usually result in mounts and intromissions by the male. Following intromission, the female runs away in order to “pace” the rate of copulation. In an open field or in bilevel chambers, the male typically chases her until she stops again and holds a lordosis crouch, allowing him to mount. If the male stops chasing, then she will have to solicit to initiate another bout of copulation. Essentially, pacing refers to the amount of temporal distance the female keeps from the male between bouts of copulatory activity. This measure is inversely related to her degree of sexual interest; for example the timing between intromissions increases with successive intromissions, and increases dramatically following several ejaculations (Pfaus, Smith, & Coopersmith, 1999). Rates of pacing are also much larger in ovariectomized female rats primed with estrogen but no progesterone, relative to females primed with both hormones. To the extent that solicitation and pacing reflect inversely a general desire for sexual contact, then experimental treatments that increase solicitations and/or keep pacing durations low, may increase desire in women. For example, ovariectomized female rats primed with estrogen and progesterone, or estrogen alone, and administered the melanocortin agonist bremetanotide, display a dramatic and selective increase in solicitations (Pfaus et al., 2004). This drug increased vaginal arousal in women viewing a female-centric...
erotic film, and increased the ability of women with lifelong HSDD to initiate sex with their partners (Diamond et al., 2006). This finding was a landmark in that solicitations in female rats had predictive validity as a model of sexual desire in women.

Another feminine copulatory behavior that is taken as a measure of the willingness to have sex is lordosis, the arching of the back displayed by female rats (and other species) that indicates their sexual “receptivity” (Beach, 1976). More is known about the hormonal, neurochemical, and neuroanatomical control of lordosis than any other mammalian sexual behavior (Pfaff, 1980; Pfaff et al., 1994). This reflex is dependent on estrogen, although treating ovariectomized females with estrogen alone produces only a moderate activation of the reflex in response to flank stimulation by the male. Full receptivity depends on additional activation by progesterone. Indeed, so does the full expression of proceptive behaviors like solicitation, and the normally low expression of pacing (Beach 1976; Pfaus, Smith, & Coopersmith, 1999). Drugs that bind to D1 dopamine receptors, α1 adrenergic receptors, oxytocin receptors, 5 opioid receptors, or GABA receptors in certain hypothalamic brain regions can increase lordosis in ovariectomized rats primed with estrogen alone, e.g., (see Kow, Mobbs, & Pfaff, 1994; Pfaff, 2000; for reviews). These substances may work on neurochemical substrates normally activated by progesterone, or could work via cell-signalling cascades that activate progesterone receptors (e.g., as has been described by Mani et al., 1994, for dopamine in the ventromedial hypothalamus). If these drugs also enhance solicitations and delay the increase in pacing normally observed at the beginning of estrus termination, they might stand as suitable candidates for the treatment of HSDD.

In males, the willingness to mount, intromit, and pursue females, can be used as analogues of male desire. Several drugs are known to decrease mount and intromission latencies in sexually naive or sluggish male rats, including the opioid receptor antagonist naloxone, (Gessa et al., 1979; McIntosh et al., 1980; Pfaus & Gorzalka, 1987). Although chasing behavior displayed by male rats in open fields or bivel-level chambers has not been studied in detail, it was noted that dopamine antagonists reduced this behavior in bivel-level chambers at doses that did not alter the initiation of copulation (Pfaus & Phillips, 1991).

IV. MODELS OF SEXUAL REWARD

How do we infer sexual reward in animals? There are at least three ways. The first involves assessments of operant or instrumental responding for a particular sexual reinforcer. Anything an animal must do to get closer to, or obtain, the reward can be assessed in this manner. In rats, this would include behaviors like nose-poking through a wire-mesh screen, navigating obstruction boxes or complex mazes, or bar-pressing for first- or second-order reinforcers. The inference here is simple (albeit circular): if the animal will work for it, it must be reinforcing. But Meisel and Sachs’ caveat for understanding preference without copulation also applies here: without knowing what animals will actually do with the reinforcer once they obtain it, it is difficult to know exactly what the motivation was behind the responding and hence difficult to specify what was rewarding about the stimulus in the first place. Consider male rats with bilateral lesions of the medial preoptic area. Those rats display normal or even elevated rates of anogenital investigation of a receptive female, and will pursue females if solicited (Heimer & Larsson, 1967; Everitt et al., 1987). They will even bar-press at high rates to obtain second-order sexual reinforcers (Everitt & Stacey, 1987). However, they cannot translate that arousal and desire into copulation. The female is clearly a reinforcer, but the males cannot do the one thing required to “prove” that it is sexual.

1. REWARD IN COPULATORY MEASURES.

The second way to infer sexual reward is based on copulatory activity. Indeed, solicitation and pacing in female rats, and courting, chasing, or other copulatory rate measures in male rats, can all be construed as indices of the reward value of the stimulus animal. These behaviors are also operants in the sense that animals must perform them in order to achieve the goal of copulatory interaction/sexual stimulation. Beach (1956) originally proposed that two separate but interactive sexual mechanisms existed in male rats, an Arousal Mechanism (AM) and Copulatory Mechanism (CM). The AM integrated distal olfactory, auditory, and visual cues from receptive females. When the cue strength became sufficiently intense, the AM activated the CM to initiate copulatory responding (mounts and intromissions). The CM then integrated somatosensory stimulation from the penis with each vaginal intromission, leading eventually to ejaculation. Given the fact that sexually naive males can show preferences for receptive females, and that they are responsive to sex odors from receptive females, the first unconditioned reinforcer in the cascade of sexual reinforcers would be sex odors. The goal would be getting to them. In Beach’s terms, this would be the primary function of the AM. But what about copulation? Whalen (1961) asked what the necessary stimulation must be for the development of copulatory behavior. The answer was penile stimulation. Whalen varied whether males achieved mounts without intromission, intromissions without ejaculation, or intromissions with ejaculation, with sexually receptive females. On a final test, males were allowed to copulate to ejaculation with receptive females. Many rats that achieved only mounts during their sexual experience trials did not copulate, whereas rats that achieved intromissions with or without ejaculation were able to copulate to ejaculation normally. Thus, exposure to sex odors alone was not...
sufficient to crystallize patterns of copulation; sensory feedback from penile stimulation was necessary. This makes penile stimulation a second goal or reinforcer in the cascade (and the first of the CM).

Related to penile stimulation is the fact that the male is chasing a moving target: A soliciting and pacing female generates much excitement for the male during copulation. As mentioned above, the female often directs the behavior of the male by forcing him to chase her. Pacing behavior in bilevel chambers typically increases dramatically as the male approaches ejaculation, in a natural expression of Larsson’s “Enforced Interval Effect” (Pfaus, Smith, & Coopersmith, 1999). This increased pacing almost always results in the male ejaculating. Everitt (1990) reported that sexually vigorous male rats given subthreshold neurochemical lesions of the mesolimbic dopamine system initiated copulation normally with sexually receptive and proceptive females. However, if the females were treated with the dopamine receptor antagonist flupenthixol (which has the effect of prolonging the time spent in lordosis and eliminating proceptive solicitation and pacing), the males took significantly longer to initiate copulation.

The next copulatory goal or reinforcer is ejaculation. López, Olster, and Ettenberg (1999) asked whether sexually naive rats would show decreased run times in a straight-arm runway if their prior copulatory experience was intromissions with or without ejaculation. Only rats that achieved ejaculation showed decreased run times. Thus, it would seem that a cascade of reinforcing events, from perception of sex odors to chasing receptive females to penile stimulation during mounting to ejaculation, is necessary for the normal display of appetitive and consummatory sexual responses. However, ejaculation itself may not be the final endpoint in the cascade of copulatory reinforcers for male rats. In the odor-conditioning studies mentioned above, the postejaculatory refractory period was identified as the necessary unconditioned stimulus for the development of the preference in the paired groups (Kippin & Pfaus, 2001a). Ejaculatory preferences developed only if males were allowed to be in close proximity of the odor during the postejaculatory period. If the females were removed immediately after ejaculation, no preference developed. Moreover, if males were allowed to achieve only 5 intromissions without ejaculation prior to the removal of the scented female, they displayed the opposite preference in the final choice test and ejaculated preferentially with the unscented female (despite having never had access to an unscented receptive female before). Finally, a small but significant ejaculatory preference developed if males copulated with an unscented female but had her replaced with a scented female during the postejaculatory refractory period. Thus, ejaculation induces a powerful reward state that occurs during the postejaculatory interval.

Experience with an ejaculatory sexual reward can also alter the incentive properties of an unconditionally aversive odor (cadaverine) applied to the neck and anogenital region of female rats (Pfaus, Kippin & Centeno, 2001). During conditioning trials, male rats copulated with cadaverine-scented females. Subsequently, when males were given a final open-field test with two receptive females, one scented with cadaverine and one unscented, males in the paired group did not show any preference for either female. In contrast, males in the unpaired group copulated exclusively with the unscented female, despite aggressive solicitations and interceptions by the scented female. Indeed, in a final test, males in the paired group would approach and chew on a wooden dowel scented with cadaverine, whereas males in the unpaired group, or in a cadaverine-alone preexposure group, would avoid contact with the dowel, or would bury the dowel in bedding. Pairing an aversive stimulus with drug reward has been shown previously to induce taste preferences for initially nonpreferred flavors (e.g., a bitter taste paired with the consequences of morphine in rats; Zellner et al., 1983). The same basic phenomenon, pairing sexual reward with a highly arousing circumstance -- whether aversive or appetitive, painful or pleasurable -- may underlie human sex behavior preferences or fetishes (see Krafft-Ebbing, 1928).

Conditioned partner and place preference. Contextual factors such as settings are important components of positive sexual experiences for both men and women (e.g., Basson, 2001; Hoon, 1984; Kinsey, Pomeroy, & Martin, 1948; Kinsey, Pomeroy, Martin, & Gebhard, 1953; McCarthy, 1977). Salient cues in the environment or on partners may be associated with sexual reward in such a way that they increase arousal or desire directly in their presence. Accordingly, the third way to infer sexual reward is to examine responses made toward contextual or partner-related cues paired with sexual reward. With animals, this can be done using the conditioned partner or ejaculatory preference or place preference (CPP) paradigms. Animals often display a preference to remain in a context that has been paired consistently with access to a reward (e.g., drugs of abuse, highly palatable foods, a mate) over a context that has not. This type of CPP is typically demonstrated in an apparatus with two distinctive compartments that are connected to either side of a third neutral compartment. During training, the compartments are paired differentially with unconditional stimuli, (e.g., one side is paired with a sex partner, food, or a rewarding drug, and the other side is paired with either nothing or a control manipulation). On the final test, the subject is placed into the neutral compartment with the two doors on either side opened to allow free access to either compartment (Figure 6).

In male rats, sexual CPPs have been established...
The compartment paired with copulation is preferred over the other compartment (e.g., Ågmo & Berenfeld, 1988). A CPP induced by this procedure is referred to as a “postejaculatory CPP”. Demonstrations of postejaculatory CPPs might appear puzzling at first glance because the conditioned stimulus (i.e., the distinctive environment) is presented after the unconditioned stimulus (copulation to ejaculation), in what learning theorists call “backward conditioning” (that would not be expected to yield conditional responding to the environment). However, if the neural reward state induced by ejaculation is the unconditional stimulus, then the pairing of environmental cues with it is simultaneous. Thus postejaculatory CPP can be accounted for by the rules of Pavlovian conditioning.

CPPs have also been demonstrated in female rats and hamsters. Oldenburger et al. (1992) found that when copulation occurred within one of the distinctive compartments of a CPP apparatus, female rats showed only a weak CPP. Conversely, Paredes and Alonso (1997) and Paredes and Vazquez (1999) demonstrated a robust CPP in female rats that depended on whether the females were able to pace the rate of copulation without having to employ defensive behaviors. This was accomplished using unilevel pacing chambers, in a Plexiglas divider bisects the chamber (e.g., Figure 3). The divider contains one or more holes that only the female can pass through. This allows her to pace the rate of copulation by moving freely from side to side. Like males, females acquired a strong preference for a distinctive environment only if they were placed into the CPP box immediately after paced copulation. No preference was found if the copulation was unpaced prior to placement in the CPP box (meaning that it had occurred in the same pacing chamber but without the divider). Thus, for a female rat, CPP develops only if she has been able to control the initiation and rate of copulation freely without having to use defensive behaviors. Although a sexually vigorous male rat is a clear unconditioned stimulus for approach and solicitation in female rats (e.g., Ågmo, 1999), contextual cues associated with pacing elicited a conditioned sexual reward state in those females. However, these results may also indicate the presence of an unconditional aversive state during unpaced copulation. To examine this possibility, Afonso, Woehrling, and Pfaus (2003) allowed female rats to copulate in two paced conditions using Plexiglas dividers that had either 4 holes or 1 hole. This was done to eliminate the possibility of an “aversive” state resulting from unpaced copulation. Trials were conducted sequentially at 4-day intervals, and each pacing condition was paired with one of the distinctive sides of a CPP apparatus, in a counterbalanced fashion. Control groups contrasted the 4-hole condition with no divider, or the 1-hole condition with no divider (as was done by Paredes and colleagues).
Control females developed significant CPP for either the 1-hole or 4-hole condition, relative to unpaced copulation with no divider. Those control data replicate the findings of Paredes and colleagues, and indicate that both the 4-hole and 1-hole condition are rewarding relative to the unpaced (no divider) condition. However, they do not rule out the possibility that the real distinction being made is between an aversive condition (unpaced copulation) and a rewarding condition (paced copulation). This was addressed in the group allowed to contrast the 4-hole versus 1-hole condition. In this group, females developed significant CPP for the 4-hole condition, relative to the 1-hole condition, suggesting strongly that copulatory CPP reflects a true sexual reward state in females. Similarly, Jenkins and Becker (2003) found that female rats developed significant CPP for paced relative to unpaced mating, but also for unpaced mating in which the experimenter removed the male for a period that approximated the female’s imposed inter-intromission interval, relative to unpaced mating in which male removal did not occur. Thus, female rats develop CPP for sex at their own preferred intervals. Taken together with the results of Matthews et al. (1997), these data suggest that reward comes from the sexual stimulation that females receive, namely mounts with intromission, so long as that stimulation occurs at the desired time intervals. Accordingly, artificial stimulation of the vagina and cervix (Meerts and Clark, 2009) or clitoris (Parada et al., 2009) that is distributed in time to approximate a desired or paced interval can also induce a significant CPP in rats.

What about males? Martinez and Paredes (2001) found that males developed significant CPP if they had unrestricted access to females (as occurs in pacing chambers without a barrier). This was the opposite preference to the one developed by females in their studies. Although both copulatory and postejaculatory CPP procedures produce effects of similar magnitude in male rats, there are differences in the underlying neurobiology. The opioid receptor antagonist naloxone disrupts both copulatory and postejaculatory CPPs, but in different ways. Ågmo and Berenfeld (1988) found that the development of postejaculatory CPP was blocked by injections of naloxone prior to each training session. Conversely, the development of a copulatory CPP was unaffected by naloxone prior to each training session (Meharra & Baum, 1990). However, once a copulatory CPP had developed, its expression was blocked by naloxone injections prior to the final test (Hughes et al., 1990; Meharra & Baum, 1990). There is also evidence that the site of action of naloxone is different for these effects. Ågmo and Gomez (1993) found that naloxone’s disruption of the development of postejaculatory CPP occurred following infusions into the medial preoptic area, whereas infusions of naloxone into this brain region did not disrupt the expression of a copulatory CPP (Hughes et al., 1990). In females, naloxone blocked the acquisition of a pacing-related CPP, suggesting that common opioid systems in the brain of male and female rats is activated by sex-related cues (Paredes & Martinez, 2001). As with approach behaviors toward sex-related odors, castration disrupts the expression of a copulatory CPP on the first postoperative test in male rats (Miller & Baum, 1987; Hughes et al., 1990), and acquisition of a copulatory CPP was blocked by naloxone in castrated, but not gonadally-intact, male rats (Meharra & Baum, 1990). Endocrine responses have also been detected in male rats following exposure to contextual stimuli associated with copulation. Kamel et al. (1975) reported that serum testosterone, luteinizing hormone, and prolactin levels were elevated after 45 min of exposure to an arena in which prior copulation occurred. Interestingly, a wintergreen odor paired with copulation to ejaculation was able to elevate serum testosterone and luteinizing hormone levels relative to the same odor not paired with sexual reward (Graham & Desjardins, 1980). Dopamine antagonists have not been reported to alter the development or expression of copulatory CPPs in either male or female rats, or postejaculatory CPPs in male rats (Ågmo & Berenfeld, 1988; Portillo et al., 2001). In contrast, Meisel, Joppa, and Rowe (1996) found that the development of a copulatory CPP in female hamsters was blocked by injections of the D2-receptor antagonists sulpiride or raclopride prior to each training session. To summarize, sexual reward appears to involve the activation of brain opioid systems. In some cases, odor or contextual stimuli associated with sexual reward activate mesolimbic dopamine pathways (either to increase attention or drive goal-directed behaviors). Likewise, stimuli associated with sexual reward also activate pituitary and gonadal hormone release in male rats.

V. MODELS OF SEXUAL INHIBITION

All behaviors have a beginning, middle, and end. The end typically comes with the attainment of reward large enough to activate mechanisms of satiety. In any motivational system, reward is a dynamic function with an inverted U-shaped relationship to ongoing behavior: Low rewards do not generally sustain behavior, moderate to ideal rewards do, and high rewards induce the inhibitory feedback that characterizes satiety (Toates, 1992). With regard to sexual behavior, rewards that sustain sexual arousal and desire might be considered low-to-moderate, whereas high rewards like orgasm might be those that induce a period of sexual refractoriness. Although sexual satiety decreases sexual responding in the short term, the reward associated with it in male and female rats is necessary for the conditioning of sexual preferences in the long term.

The notion of separate (but interactive) neural systems for behavioral excitation and inhibition goes
back to the work of early neuropsychologists like Sechenov, Sherrington, and Pavlov, and more modern psychologists like Jeffrey Gray. It has important implications for motivation in general because it posits that behavior can commence either due to direct excitation or through a process of disinhibition. A “Dual Control Model” of sexual function has been advanced by researchers (Bancroft and Janssen, 2000; Perelman, 2006; Pfau, 2009) that posits excitatory and inhibitory mechanisms in the brain that interact to produce a level of sexual responsivity in all individuals during all phases of the sexual response cycle. This model stresses the adaptive nature of both excitatory and inhibitory processes. For example, the adaptive nature of sexual excitement would drive individuals to seek out sex partners for reproductive or reward purposes. The adaptive nature of sexual inhibition would guard against situations that threaten the individual, including chronically stressful life events. However, too little activation of the excitatory mechanisms, as might occur in hypogonadal individuals, or too much activation of the inhibitory mechanisms, would be expected to lead to decreased sexual motivation. The study of sexual inhibition is also critical if we are to understand how certain events or “prosexual” drugs (e.g., alcohol, cocaine) induce sexual disinhibition.

Sexual inhibition is most likely to occur in the presence of an obvious threat or a conditioned cultural proscription against the activity (complete with the possibility of getting caught). However, this raises some interesting issues regarding the arousing nature of inhibition. As mentioned above, central excitation and inhibition both activate the autonomic nervous system. A small degree of stress or threat (i.e., something “naughty” or even painful) can be arousing, especially for individuals with low levels of arousability. Translated to a sexual situation, such arousal could be “transferred” directed into sexual activity, perhaps to the point in some individuals that it becomes a necessary antecedent. Anger, fear, or even short-lived terror, can be preludes to sex because they “stir passion” or arousal. The stimuli that evoke excitation and inhibition may be different for different individuals and what inhibits one person may actually excite another.

1. PUNISHMENT AND STRESS

Although punishment with shock can suppress a variety of appetitive and consummatory behaviors in rats (Mackintosh, 1974), such punishment has never been reported to induce sexual inhibition in males (Beach & Fowler, 1959; Beach et al., 1956b; Hayward, 1957; Zimbardo, 1958). In fact, shock, short-term pain (e.g., tail-pinches), or neutral stimuli paired with them, actually stimulate mounting in sexually sluggish or inactive male rats (Barfield & Sachs, 1968; Caggiula, 1972; Crowley, Poplaw, & Ward, 1973), and reduce the number of intromissions required for ejaculation in sexually active males (Beach & Fowler, 1959; Sachs & Barfield, 1976). As mentioned above, both male and female rats will readily cross electrified grids to gain access to sexually receptive partners (Moss, 1924). Thus, punishment with shock or pain is not workable. Indeed, arousal is a necessary antecedent to sexual activity in both male and female rats. Drugs that decrease the activity of the sympathetic nervous system (e.g., α2 adrenergic receptor agonists like clonidine) decrease sexual responding in both male and female rats (Clark, Smith & Davidson, 1985; Meston, Moe, & Gorzalka, 1996).

More reliable methods of punishment have been used. Rodents live in a predominantly olfactory world, and pairing estrous odors with gastrointestinal distress (induced by contingent injections of lithium chloride that make animals sick) induces a conditioned odor aversion in males rats and hamsters that translates to avoidance of female vaginal secretions (Zahorik & Johnson, 1976), increased mount and intromission latencies (Johnson et al., 1978), decreased proportion of males that ejaculate (Peters, 1983), or avoidance of copulation altogether (Peters, 1983; however see Lawrence & Keifer, 1987). This effect occurs if conditioning took place when the males were juveniles (Koch & Peters, 1987), and conditioned males utter distress vocalizations in the presence of vaginal secretions (Peters et al., 1988). Lawrence and Keifer (1987) demonstrated robust conditioned odor aversions using a second-order pairing of almond odor with lithium chloride injections. This conditioning paradigm led males to avoid copulation with almond-scented receptive females. That this conditioning was specific to the neutral odor was demonstrated by Ågmo (2002). Conditioned males in that study were allowed to copulate with females scented with capelin oil (a “fishy” smelling oil extracted from capelin, a fatty fish found off the coast of Iceland) to 1 ejaculation, after which they were injected with lithium chloride. Subsequently, those males avoided copulating with capelin-scented females, although they continued to copulate normally with unscented females. Moreover, in subsequent partner preference tests conditioned males avoided being near capelin oil-scented receptive females, indicating that their approach behavior was inhibited. Taken together with the results of our studies on appetitive odor conditioning, these results indicate that neutral odors can become “good” or “bad” depending on their consequences.

When are animals in the wild exposed to circumstances in which they must inhibit their sexual responses? Interestingly, adult male rats in the wild are rarely observed to attempt copulation with sexually nonreceptive females (Calhoun, 1962; Barnett, 1962). This is in marked contrast to most laboratory settings in which males will attempt to copulate with nonreceptive females placed into chambers in which
the males have copulated previously with sexually receptive females. We have shown that training sexually active male rats to differentiate between sexually receptive and nonreceptive females on alternating test trials leads quickly to a substantial reduction in the proportion of males that attempt to copulate with nonreceptive females (Pfaus & Pinel, 1989). The aversive stimuli provided by the nonreceptive females include a thwarting of attempted copulations due to the female’s lack of receptivity, along with aggressive and defensive behaviors (e.g., boxing, biting, kicking) when the male attempts to mount. By virtue of the females being nonreceptive, these behaviors are paired with a lack of estrous odors. Males learn quickly to differentiate the presence of estrous odors with proceptive and receptive behaviors, and the lack of estrous odors with thwarted sexual advances and female aggression (which can be severe). In the wild, such conditioning may occur normally during adolescence. As juveniles, male and female rats mount almost anything, including one another. As the expression of this behavior transitions into adult forms, males likely attempt to mount adult females that are not in heat. Of course, those females teach the males not to try it again.

We have shown that low-to-moderate doses of alcohol can release sexual behavior from inhibition induced by pairing males with sexually nonreceptive females (Pfaus & Pinel, 1989). After learning to suppress their copulatory advances toward sexually nonreceptive females, males were treated with low to moderate doses of alcohol. Low doses of alcohol that increase the mount, intromission, and ejaculation latencies when males are paired with sexually receptive females, increased the proportion of males that attempted to mount the nonreceptive females. Moreover, many of those males ejaculated, despite never gaining vaginal penetration. However, if the alcohol dose was high enough to induce motor disruption, the males did not attempt any copulation with the nonreceptive females. These findings are of interest for several reasons, most notably because alcohol intoxication figures in high-risk sexual activity (Castilla et al., 1999; Lowry et al., 1994; McCusker et al., 1990; Steele & Josephs, 1990; Woody et al., 1999) and is one of the strongest antecedent predictors of men actually carrying out a rape (Rada, 1975; Ranieri-Collins, 1995; Ullman & Brecklin, 2000; Wild, Graham, & Rehm, 1998). In contrast, cocaine intoxication did not release sexual behavior from primary inhibition (Pfaus, Benibgui, & Wilkins, in preparation).

We have also shown that neutral odors can be paired with access to sexually nonreceptive females, or with sexual activity restricted to intromission without ejaculation, can inhibit male choice in male rats (Kippin et al., 1998; Kippin & Pfaus, 2001). Although those conditions were used as controls in our previous studies of appetitive odor conditioning, in both cases males chose to ejaculate preferentially with the unscented, rather than scented, females during the final choice test. This indicates that, despite the presence of estrous odors and vigorous proceptive behaviors of both females during the final choice test, the neutral odor had acquired sufficient aversive properties to deter the male from ejaculating with a receptive female bearing it. We have recently found that alcohol does not alter the expression of this aversive conditioning, but a low dose of cocaine can eliminate the preference for the unscented female (Pfaus, Benibgui, & Wilkins, in preparation). Given the fact that cocaine use is also implicated in uninhibited or risky sexual behavior, these data suggest that alcohol and cocaine disrupt different types of sexual inhibition.

Finally, situational stressors can be used as models of sexual inhibition in male rats. Sexually naive males are extremely sensitive to novel environments, and a high proportion of naive males will not copulate in a novel environment, despite intense proceptive behaviors displayed by receptive females (Pfaus & Wilkins, 1995). In fact, many of these males never copulate, and in the past have been discarded as research subjects by many laboratories. However, in our study, the effect of novelty was attenuated by systemic administration of the opioid receptor antagonist naloxone, or by preexposure of males to the sex chamber. Novel environments are stressors that induce naloxone-reversible analgesia (Izquierdo & McGaugh, 1987). In turn, naloxone-reversible analgesia is taken to indicate the release of endogenous opioids. Thus, the release of endogenous opioids in response to being placed into a novel environment disrupts copulation in sexually naive male rats, as if they had been administered morphine exogenously. Like treatment with naloxone, preexposure to the chamber lessened the novelty effect naturally, allowing males to copulate. However, sexual approach and copulatory behaviors were not disrupted in sexually experienced male rats placed into a novel environment, indicating that the males had acquired sufficient knowledge of the female as an appetitive sexual incentive to offset the induction of opioid release. This paradigm could be used as a model of situational anxiety in sexually naive males.

Refractoriness and sexual satiety: If male rats are allowed to copulate to sexual exhaustion, they display reduced responsiveness to female solicitations and many will not copulate to ejaculation for 24 to 48 hrs (Beach & Jordan, 1956; Larsson, 1956). This inhibition is due to neurochemical events that underlie sexual satiety, and can be partly or fully reversed with several drugs, notably the α2-adrenergic receptor antagonist yohimbine (which increases noradrenergic tone), the 5-HT1A agonist 8-OH-DPAT (which decreases serotonin release), and the opioid receptor antagonists naloxone or naltrexone (which block the binding of endogenous opioids) (Rodriguez-Manzo & Fernandez-Guasti, 1994; 1995a,b). This suggests
that increased release of serotonin and endogenous opioids, and decreased release of noradrenaline, somewhere in the brain underlies the neurochemical state of sexual satiety. Interestingly, the generation of sexual satiety can be delayed by changing the stimulus female for every ejaculatory series (i.e., by inducing a “Coolidge effect”; Rodriguez-Manzo, 1999). As with men, sexual inhibition in women can occur as a result of stress, lack of intimacy, sexual nonreward, or in the refractory state after orgasm that denotes satiety. Sexual inhibition in female rats has been explored rudimentarily in paradigms of estrus termination (in which sexual behavior is inhibited by a large amount of vaginocervical stimulation prior to testing), after subthreshold administration of ovarian hormones to ovariectomized rats (which stimulates a low level of lordosis but no appetitive behaviors), and following sexual nonreward (induced as noted above by naloxone treatment during the females’ early sexual experience). Appetitive sexual behaviors like solicitation are the most sensitive to those treatments. As the intensity of the inhibition progresses, females display increases in pacing and defensive behaviors and a decrease in high-intensity lordosis.

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B. PHYSIOLOGICAL PARAMETERS CHARACTERIZING SEXUAL RESPONSES

I. FUNCTIONAL ASSESSMENT OF PENILE ERECTION IN PRECLINICAL RESEARCH

1. INTRODUCTION

Basic research on penile erection using an animal model was started at least in the latter half of the 19th century by Eckhard, who reported the relevant involvement of the pelvic nerve in erection in dogs.[1] Langley introduced the wording “autonomic nervous system” and also coined the term “parasympathetic” in accordance with his insights into the selective stimulatory action on fibers contained in the cranial and sacral outflows.[2] In the 20th century, the discipline of pelvic neuroanatomy investigation had evolved to a consensus of thought regarding the primarily important nerve plexus of the pelvis.[3] In 1968, historical advances enabled the measurement of intracavernous pressure (ICP), which was performed in bulls by Lewis.[4]

Later, to investigate erectile function, several animal models, including the use of monkeys, dogs and rabbits, were developed. In the 1980s Sjöstrand used plethysmography to quantify penile erection in rabbits.[5] and Lue’s and Goldstein’s groups conducted experiments in monkeys, dogs and rabbits to show the hemodynamic events in the penis and the crucial role of cavernosal smooth muscle.[6-8] Epoch-making experiments using commercially available small animals, rats and mice, were conducted in the last decade. Walsh is known as the pioneer of nerve-sparing radical prostatectomy in humans, and his group reported the historical first study on penile erection using rats, which enabled researchers to conduct erectile function studies easily, resulting in significant progress in this research field.[9] More recently, the first experiments that used mice were reported by Burnett’s group.[10] The use of transgenic mice has widened the physiological and pharmacological understanding of erection.[11, 12] The neuroanatomy and physiology of the penis in rats and mice was also gradually elucidated, and contemporary knowledge and techniques on animal experiments have progressed.[13]

Evaluation of erectile response in anesthetized animals

Erection is a hemodynamic event in the penis. It is the consequence of relaxation of the smooth muscle that involves both the central nervous system and local factors. The current basic concepts of erectile physiology were obtained greatly from in vivo and in vitro experiments, mostly with animals.[14, 15] In the flaccid state, the cavernous tissues are contracted by dominant sympathetic control of the arterioles and the cavernous smooth muscles.[14] Following sexual stimulation, parasympathetic nerve activity induces a blood flow increase through the cavernous artery via relaxation of smooth muscle of cavernous tissue. The inflow of a huge amount of blood induces a rapid increase in ICP. In this phase, the reflexogenic contraction of the ischiocavernous and bulbocavernous muscles also enhances the peak pressure, which rises to well above the arterial blood pressure and gives the maximal rigidity to the penis. Simultaneously, the blood outflow from the cavernous system is decreased via passive compression of veins due to sinusoid expansion (venous occlusion).[16]

The gold standard for quantitative measurement of penile erection during experiments conducted in anesthetized and conscious animals is the recording of intracavernous pressure (ICP).[17] ICP can be recorded in freely moving rats by a miniaturized telemetric device (a catheter implanted in the corpus cavernosum that is connected to a pressure transducer located subcutaneously).[18] In anesthetized animals, we have to apply some stimulation to induce erection because direct somatosensory stimulation such as estrous odor is not applicable. The most common technique to induce erection is electrical field stimulation of specific sites in the nervous system responsible for erection. As well as electrical stimulation, chemical stimulation or drug administration in the periphery or within the central nervous system, including the brain and spinal cord, is feasible in anesthetized animals to study their effects on penile erection.[17] When investigating the prorerecile effect of pharmacologic compounds in animals, certain aspects must always be taken into account. These include the dose used, route of administration, pharmacokinetics, half-life, metabolism of the studied compounds, etc.

2. INTRACAVEROUS PRESSURE MONITORING IN RATS

ICP measurement represents a direct investigation of erectile function (Fig.1). It makes the objective evaluation of even subtle erectile responses possible, but also facilitates the physiologic approach and has resulted in a new understanding of penile erection. The most common animal used to evaluate ICP is the rat.[17] The benefit of using the rat as an experimental model is the simple anatomy of the peripheral nervous system. It is easy to identify the cavernous nerve and the major pelvic ganglion (MPG), which is the origin of the cavernous nerve and the center of the pelvic nervous system. The unilateral MPG of rats consists “one ganglion.” In rats, it is not a “plexus” or a “complex of several ganglia”, which are common in other mammals.[19] Moreover, behavioral studies and the other neurophysiological
studies are possible in the same study group,[20] and many pathophysiological erectile dysfunction models are easy to make with rats such as a diabetic model, aging model, castrated model cavernous nerve injured model and so on.[21-24] The analogy of the anatomy and neurophysiology of penile erection between rats and humans is moderate compared with the reproductive organ responsible for ejaculation. Recently, the cavernous nerve distribution in humans was reported to be broad around the prostate rather than the neurovascular bundle,[25] and the importance of the ancillary nerve as well as the main cavernous nerve in rats was also reported,[26] which is one of the analogies between them.

3. SURGICAL PROCEDURE FOR MONITORING ICP IN RATS

One of the basic methods in rats is described below,[27] and the procedure for mice is basically similar to that for rats;[28] however, those in mice are generally difficult because of its size (especially in the part of carotid artery cannulation). Either rats or mice are weighed and lightly anesthetized with intraperitoneal sodium pentobarbital 30-50-mg/kg so that they breathe spontaneously during the experiment.[9, 29] It should be noted that pentobarbital is a relatively poor analgesic and leads to a decrease in blood pressure in animals with significant tachycardia compared with a mixture of ketamine and xylazine.[30]

For continuous systemic blood pressure measurements, a heparinized polyethylene catheter is introduced into the left carotid artery.[29, 31-33] Mills et al. were the first to evaluate the effect of the blood pressure (BP) or maximal arterial pressure (MAP) on ICP.[34] Since BP sometimes fluctuates during cavernous nerve stimulation due to autonomic responses. The change of BP affects the ICP via the change of blood inflow into the cavernosum; high BP leads to high ICP and low BP leads to low ICP. BP is also influenced by the degree of anesthesia. Therefore it is important to monitor the BP simultaneously and ICP should be corrected by BP and represented as normalized ICP/BP or normalized ICP/MAP (mean arterial pressure). Peripheral nerves, such as pelvic nerve, MPG and cavernous nerve stimulation possibly increased BP due to activation of pelvic nerve afferents to induce pressor responses such as that known as the vesico-vascular reflex.[35]

Figure 1 Original recording of intracavernous and arterial blood pressures when stimulating cavernous nerve. 1: flaccid state; 2: latent phase; 3: tumescence phase; 4: maximal tumescence of the corpora cavernosa; 5: detumescence phase. ICP and BP were mean values of intracavernous and arterial blood pressures during full phase. Filling rate of corpora cavernosa is slope of increase of intracavernous pressure during tumescence phase. Slope of dramatic drop of intracavernous pressure after end of stimulation represents corpora cavernosa emptying rate (Giuliano et al).
The bilateral MPG and pelvic nerves are exposed and the incision is extended to the skin around the penis. A needle connected to a polyethylene tube filled with heparinized saline is inserted into the left penile crus through the tunica albuginea and ICP is registered by means of a pressure transducer. Electrostimulation (20 Hz, pulse width 0.5 ms, 10 V) of the pelvic nerve is applied with a bipolar hook electrode and changes of ICP are measured.

4. SITE FOR ELECTRICAL STIMULATION

For in vivo evaluation of erectile function in rats, most researchers employ either an apomorphine-induced erectile response or neural electrical stimulation with or without pharmacologically induced ICP changes. Apomorphine-induced erectile function bioassay involves systemic administration of apomorphine 80 mg/kg, followed by recording of erectile responses in male rats.[36] Every site in the neural system responsible for erection can be used for electrical stimulation, from the central nervous system to the peripheral nervous system, including the medial preoptic area (MPOA) in the hypothalamus, the pelvic nerve, the major pelvic ganglion or the cavernous nerve.[37] Electrical stimulation of the MPOA was first presented by Giuliano.[38] The erection elicited by MPOA stimulation is thought to be the most physiological erection because the MPOA is the most central component for penile erection.[37] This procedure, however, is the most invasive, and requires considerable skill and experience. The basic procedure consists of fixation of a rat to a stereotaxic head holder in the flat skull position and electrode placement in the MPOA. Stereotaxic coordinates for the electrode tip are 0.1 to 0.25 mm posterior, 0.4 to 0.6 mm lateral (right) and 8.6 to 8.8 mm ventral.[39]

The erection elicited by cavernous nerve stimulation was first introduced by Quinlan.[9] The cavernous nerve is the terminal point on the neural pathway of penile erection, and just before the target organ = corpus cavernosum. Cavernous nerves in rats originate from the bilateral MPG and mainly from the posterolateral surface of the prostate toward the corpus cavernosum (Fig. 2). In the radical prostatectomy nerve-injury model, electrical stimulation of the cavernous nerve itself following cavernous nerve injury is technically difficult because it is necessary to stimulate proximal to the injured site. Thus, as stimulation sites, the pelvic ganglia and pelvic nerve located superior to the pelvic ganglia are available.[40]

The normalized ICP/BP in control or sham operated rats are listed in Table 1. Those via several stimulation sites which were done unilaterally seemed to show similar results. The mean ± SD value in peripheral nerve stimulation is 0.632 ± 0.087. Therefore, ideally normalized ICP/BP should be 0.545 at least. If the ICP/BP is far below from this in the normal control model, one should consider some problems in the procedure.

5. CAVERNOUS NERVE (CN) INJURY MODEL

Clinically, nerve-sparing technique in radical prostatectomy dramatically improves the recovery of erectile function; however, it is not sufficient to achieve the full recovery.[41] Thus, the preclinical research in this field still plays an important role.[24]

Various types of CN injury have been done in rodent animal models, especially in rats. These models were stratified by the extent of the injury, which includes crush, freezing, transection, and excision (from less severe to more severe). Table 2 shows the CN injury models, in which functional assessment by ICP was done. The least severe model is considered to be the crush model. Interestingly, however, the only exposure of CN affected the erectile function as well as the crush models.[31] The crush model and the freezing model as the nerve-sparing radical prostatectomy or the cryoablation model, does not disrupt the nerve continuity preserving the nerve sheath. As more severe CN injury models, transection/excision models were used as the non-nerve sparing or nerve construction model with a nerve graft technique.

The timing of the assessment following CN injury seems to be important for the standardization of the CN injury experiment. The time frames were different among the experiments (Table 2). Some of the transection/excision models were used to investigate the immediate effect of the CN injury, but most of these models were used for the cavernous nerve construction with a graft or a conduit. Therefore, it needed relatively longer period (around 3 months). In adulthood, each rat month is roughly equivalent to 2.5 human years, 42 thus, 3 months in adult rats roughly equivalent to 7.5 years in human. For less
severe technique which used as a nerve-sparing model, a relatively less time frame is administered. In the crush model, even animals without proerectile treatment could recover from erectile dysfunction in a long term period over 2 months, thus postoperative assessment within 1 month is generally accepted. One month in rat estimated to be 2.5 years in human. Therefore, it is a reasonable time frame for the nerve-sparing technique assessment.[43]

6. STUDY OF ERECTION IN CONSCIOUS ANIMALS

In conscious rats, penile erections can be studied in isolation to obtain measures of physiologic arousal or in response to different types of sexual arousal stimuli (e.g., noncontact erections in response to estrous odors) to obtain measures of psychogenic arousal. Ex copula reflex erections are thus elicited after 5 to 10 minutes. Ex copula reflex erections are generated by spinal reflex mechanisms and modulated by supraspinal control. These erections are divided into 2 components, lengthening of the penile body and glans erection. The dorsiflexions of the penile body are called “flips” and the intense glans erections with flaring of the glans extremity are called “cups”. [44]

Table 1: Normalized ICP/BP in control rats MPOA: medial preoptic area, PN: pelvic nerve, MPG: major pelvic ganglion, CN: cavernous nerve.

<table>
<thead>
<tr>
<th>Author</th>
<th>Electrical stimulation site</th>
<th>Frequency, pulse width, voltage or amp</th>
<th>ICP/BP in control or sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giuliano et al. 1997 37</td>
<td>MPOA</td>
<td>30Hz, 2ms, 7V</td>
<td>0.58-0.70</td>
</tr>
<tr>
<td>Sato et al. 2001 2636</td>
<td>MPOA</td>
<td>30Hz, 2ms, 150μA</td>
<td>0.78</td>
</tr>
<tr>
<td>Hisasue et al. 2005 39</td>
<td>MPOA</td>
<td>30Hz, 2ms, 100μA</td>
<td>0.52, 0.67</td>
</tr>
<tr>
<td>Suzuki et al. 2007 23</td>
<td>MPOA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kato et al. 2007 40</td>
<td>PN</td>
<td>20Hz, 0.5 ms, 10V</td>
<td>0.64</td>
</tr>
<tr>
<td>Mills et al. 1994 34</td>
<td>MPG</td>
<td>12Hz, 5ms, 6V</td>
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<td>Hurt et al. 2002 46</td>
<td>CN</td>
<td>16Hz, 1-5ms, 4-6V</td>
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<tr>
<td>Burnett et al. 2004 29</td>
<td>CN</td>
<td>16Hz, 1-5ms, 6V</td>
<td>0.78</td>
</tr>
<tr>
<td>Mullerad et al. 2006 31</td>
<td>CN</td>
<td>20Hz, 5ms, 7.5V</td>
<td>0.70, 0.70</td>
</tr>
<tr>
<td>Muller et al. 2008 47</td>
<td>CN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mulhall et al. 2008 48</td>
<td>CN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lagoda et al. 2007 49</td>
<td>CN</td>
<td>16Hz, 5ms, 2-8V</td>
<td>0.59</td>
</tr>
<tr>
<td>Fibbi et al. 2008 50</td>
<td>CN</td>
<td>16Hz, 5 ms, 2.5 V</td>
<td>0.55</td>
</tr>
<tr>
<td>Pu et al. 2008 51</td>
<td>CN</td>
<td>15 Hz, 1ms, 5V</td>
<td>0.72</td>
</tr>
<tr>
<td>Bal et al. 2009 52</td>
<td>CN</td>
<td>20 Hz, 1.0ms, 5V</td>
<td>0.56</td>
</tr>
<tr>
<td>Canguven et al. 2009 53</td>
<td>CN</td>
<td>16Hz 5ms 4V</td>
<td>0.50</td>
</tr>
</tbody>
</table>

A model of noncontact erections in rats is studied in the presence of an inaccessible receptive female behind a mesh screen, or behind a series of walls with an air circulation system that brings the estrous odors to the male’s compartment.[45] Erections in response to these salient sexual cues are viewed as a model of psychogenic erection because they do not require direct somatosensory stimulation to be induced, which is different from ex copula reflex erections. The oral drug efficacy test should be conducted in the conscious state; thus a noncontact erection model is ideal for this purpose.

7. CONCLUSIONS

Experimental research assessing penile erection quantitatively via ICP has been very productive regarding the physiology, pathophysiology and pharmacology of penile erection. The technique makes it possible to evaluate even subtle erectile responses. The development of the new models using small commercially available animals such as rats and mice has facilitated in vivo investigation. The study of ICP in transgenic animals has opened a new door to research on the mechanism of penile erection from higher neural control down to molecular events within the erectile tissue.
Table 2: Cavernous nerve injury models analyzed by ICP.

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of injury</th>
<th>Side</th>
<th>Time frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mullerad et al. 2006</td>
<td>Exposure, Crush, Transection</td>
<td>Bilateral</td>
<td>3, 10, 28 days</td>
</tr>
<tr>
<td>Sezen et al. 2001</td>
<td>Crush</td>
<td>Unilateral, Bilateral</td>
<td>1, 3, 7 days</td>
</tr>
<tr>
<td>Lagoda et al. 2007</td>
<td>Crush</td>
<td>Unilateral, Bilateral</td>
<td>14 days</td>
</tr>
<tr>
<td>Mulhall et al. 2008</td>
<td>Crush</td>
<td>Bilateral</td>
<td>28 days</td>
</tr>
<tr>
<td>Muller et al. 2008</td>
<td>Crush</td>
<td>Bilateral</td>
<td>10 days</td>
</tr>
<tr>
<td>Cangven et al. 2009</td>
<td>Crush</td>
<td>Bilateral</td>
<td>7 days</td>
</tr>
<tr>
<td>El-sakka et al. 1998</td>
<td>Freezing</td>
<td>Unilateral</td>
<td>1,3 months</td>
</tr>
<tr>
<td>Paick and Lee 1994</td>
<td>Transection</td>
<td>Bilateral</td>
<td>0 days</td>
</tr>
<tr>
<td>Giuliano et al. 1997</td>
<td>Transection</td>
<td>Unilateral CN and Lumber sympathetic chain</td>
<td>0 days</td>
</tr>
<tr>
<td>Sato et al. 2001</td>
<td>Transection</td>
<td>Unilateral, Bilateral, main CN and Ancillary penile nerve</td>
<td>0 days</td>
</tr>
<tr>
<td>Quinlan et al. 1989</td>
<td>Transection, Excision</td>
<td>Bilateral</td>
<td>0.7, 30 days</td>
</tr>
<tr>
<td>Ball et al. 1992</td>
<td>Excision</td>
<td>Bilateral</td>
<td>2,4 months</td>
</tr>
<tr>
<td>Jung et al. 1998</td>
<td>Excision</td>
<td>Unilateral</td>
<td>1,3 months</td>
</tr>
<tr>
<td>Burnett and Becker 2004</td>
<td>Transection, Excision</td>
<td>Bilateral</td>
<td>28 days</td>
</tr>
<tr>
<td>Allaf et al. 2005</td>
<td>Transection, Excision</td>
<td>Unilateral</td>
<td>14 days</td>
</tr>
<tr>
<td>Syme et al. 2007</td>
<td>Excision</td>
<td>Bilateral</td>
<td>3 months</td>
</tr>
<tr>
<td>Connolly et al. 2008</td>
<td>Excision</td>
<td>Bilateral</td>
<td>1,3 months</td>
</tr>
<tr>
<td>Hisasue et al. 2005</td>
<td>Transection, Excision</td>
<td>Bilateral</td>
<td>1,3 months</td>
</tr>
</tbody>
</table>

REFERENCES

2. Langley JN. On the reaction of cells and of nerve-endings to certain poisons, chiefly as regards the reaction of striated muscle to nicotine and to curari. J Physiol 1906;33:374–413.


II. PHYSIOLOGICAL INVESTIGATION OF EJACULATION

1. INTRODUCTION

Ejaculation consists in the succession of distinct physiological events that form two distinct although intimately connected phases: emission and expulsion. Closure of the bladder neck, to prevent the flow of semen backward in the bladder, precedes and goes with the emission phase, i.e. secretion of the various components of sperm by seminal vesicles, prostate and ampullary vasa deferentia contents into the prostatic urethra (Bohlen et al., 2000; Gil-Vernet et al., 1994). Forceful expulsion of sperm to the urethral meatus is then caused by rhythmic contractions of pelvic and perineal striated muscles, with a primary role for the bulbospongious muscles (Master and Turek, 2001; Gerstenberg et al., 1990).

Occurrence of ejaculation necessitates the process of somato-sensory and visceral sensory information from the reproductive organs to the spinal cord and the brain. Both sympathetic and parasympathetic tones act in a synergistic fashion to initiate seminal emission by activating respectively smooth muscle contraction and epithelial secretion throughout the seminal tract. The expulsion phase of ejaculation is under the sole control of the somatic nervous system that activates perineal muscles and smooth muscles of the urethra. High coordination of autonomic and somatic systems is required for normal antegrade ejaculation.

From a neural perspective, the ejaculatory process requires somato-sensory afferents and sympathetic, parasympathetic, and somatic systems as efferent pathways. Afferent nerve impulses are driven to the spinal cord via pudendal nerves for the most part (Johnson and Halata, 1991), but also through hypogastric nerve continued by paravertebral sympathetic chain (Baron and Janig, 1991). The sympathetic fibres relay in the paravertebral sympathetic chain and, in the majority of mammalian species, the fibres then proceed whether directly via the splanchnic nerve or after relaying in the coeliac superior mesenteric ganglia via the intermesenteric nerve to the inferior mesenteric ganglia (Owman and Stjernquist, 1988). Emanating from the inferior mesenteric ganglia is the hypogastric nerve that forms, after joining the parasympathetic pelvic nerve, the pelvic plexus from which arise fibres innervating the anatomical structures involved in ejaculation. The parasympathetic fibres travel in the pelvic nerve to reach the pelvic plexus. Efferents of somatic motoneurons proceed via the motor branch of the pudendal nerve to the pelvic floor striated muscles, including bulbospongiousus and ischiocavernous muscles (Schroder, 1985).

Both autonomic and somatic tones are under the influence of sensory genital and/or cerebral erotic stimuli integrated and processed at the spinal cord level. The thoracolumbar sympathetic, lumbosacral parasympathetic, and sacral somatic neurons are the components of the spinal centres of ejaculation. These spinal centres play a pivotal role in ejaculation as they integrate peripheral and cerebral signals and sends outputs to pelvic organs. The conversion of sensory and cerebral information into secretory and motor outputs involves spinal interneurons which have been recently characterized in rats (Truitt and Coolen, 2002). These cells (named lumbar spinothalamic (LST) cells), located in laminae X and VII of the spinal lumbar segments 3 and 4, have been demonstrated as playing a pivotal role in the command of ejaculation and are therefore regarded as a spinal generator of ejaculation. As a centrally integrated and highly coordinated process, ejaculation involves cerebral sensory areas and motor centres which are tightly interconnected, forming a network specifically dedicated to the control of the ejaculatory process (Giuliano and Clement, 2005).

Researches into the physiology and pharmacology of ejaculation have been mostly led using behavioural paradigms. Such a behavioural approach is necessary for studying the ejaculatory process in a 'natural' context and in relation with other components of the male sexual behaviour such as sexual motivation, copulatory activity, and sex-related rewarding. However, the use of ejaculatory models in anaesthetised animals, in addition to accelerate the pace of research, permits to provide deep insight into mechanisms of ejaculation and drugs mode of action. In those models, measures of organs activity regarded as physiological markers can be reliably and readily monitored for the different phases of ejaculation.

2. PHYSIOLOGICAL PARAMETERS OF EJACULATION

As described above, two phases can be distinguished for ejaculation: emission and expulsion phases. Organs and anatomical structures participate specifically to one of those phases, rendering
possible differential investigation of both phases of ejaculation.

a) Emission phase

Organs responsible for the emission phase of ejaculation include accessory sex glands (seminal vesicles, prostate, and bulbo-urethral glands), which manufacture and secrete almost all the volume of the seminal fluid, and testicles, which produce spermatozoa conducted to the urethra via vasa deferentia. All of these entities receive a dual innervation from parasympathetic and sympathetic systems. It is widely accepted that parasympathetic tone controls the glandular epithelium and that sympathetic tone commands the contraction of smooth muscle cells. Epithelial secretory cells are responsible for synthesis of the seminal secretions that are expressed into the ducts of the glands. Smooth muscle cell contractions promote the discharge of gland secretions into the urethra where mixing of the different components of the seminal fluid occurs. In anaesthetised rats, contractile activity of smooth muscle cells can be monitored by recording variations of the pressure into ejaculatory hollow viscera. Interestingly, pressure measurement into seminal vesicle and vas deferens can readily be done in various experimental paradigms in anaesthetised rats.

1) Seminal vesicle pressure

Seminal vesicles are a pair of tubular glands which stroma is composed of smooth muscle layers. They are responsible for the secretion of 50-80% of the entire ejaculatory volume.

Figure 1: Samples of seminal vesicle pressure (SVP) measurement obtained in anaesthetised rats. A; SVP is monitored in rat i.v. injected with the dopamine D2/D3 receptors agonist 7-OH-DPAT. Phasic multi-peaks increases (inset) in SVP are observed in response to 7-OH-DPAT delivery that correspond to seminal vesicle contractions. B; Phasic SVP increase are also observed following systemic administration of the amphetamine derivative p-chloroamphetamine (left trace). Bilateral section of the hypogastric nerves, which drive sympathetic tone to seminal vesicles, results in inhibition of amphetamine-induced seminal vesicle contractions (right trace).
Pressure in one seminal vesicle can be measured using a polyethylene catheter (0.58 mm inner diameter) filled with mineral oil to prevent coagulation and backflow of gland secretions into the catheter. The catheter, with a bevelled tip, is inserted into one seminal vesicle through the apex with no prior incision and slowly advanced into the gland over 0.5-0.8 mm. Catheter is carefully tied on the seminal vesicle to prevent leakage without pressing the tubing. The opposite free end of the catheter is connected to a pressure transducer coupled with an amplifier (gain x1000). An analog-to-digital converter transforms (5 kHz sampling rate) the amplified output signal to numeric data on a computer where the signal can be visualised in real-time and recorded (figure 1). Measurement of seminal vesicle pressure can be performed in several models of ejaculation (Cf pages 40, 41, and 42).

2. Vas deferens pressure

The vas (or ductus) deferens arises from the tail of the epididymis and terminates in the urethra posteriorly to the prostate. The terminal part of the vas is dilated and tortuous, forming the ampulla where spermatozoa can be stored. The vas has a thick wall of outer longitudinal and inner circular smooth muscle that are responsible for intense peristaltic movement carrying out transport of spermatozoa.

To measure intra-luminal vas deferens pressure, the vas is incised before it reaches the prostate and a catheter (0.58 mm inner diameter) is advanced into the lumen over ~1cm in direction to the urethra. Catheter is carefully tied on the vas and basal vas deferens intra-luminal pressure is kept at 15-20 mmHg through continuous isotonic salt perfusion, preventing catheter tip obstruction. Measurement, amplification, and conversion of the pressure changes are performed as described in the previous section (see figure 2 for illustration). Measurement of vas deferens intra-luminal pressure can be performed in several models of ejaculation (Cf pages 40, 41, 42).

b) Expulsion phase

Pelvic floor striated muscles, including ischiocavernosus, levator ani and more particularly bulbospongiosus muscles, have a preponderant role in the expulsion phase of ejaculation by promoting ejection of semen from the urethra. An important role for bladder neck and urethra, more particularly the external urethral sphincter, during expulsion is also reported. The latter structures receive a dual innervation from sympathetic and parasympathetic systems whereas perineal striated muscles are under the sole control of somatic motoneurons. Contractile activity of the perineal muscles during expulsion is characterized by synchronous activation of ischiocavernosus, bulbospongiosus and levator ani muscles, anal and external urethral sphincters that propel semen within the urethra. In addition, energetic contractions of the bladder neck occur that prevent semen reflux into the bladder. In different experimental models in anaesthetised rats, contractile activity of bulbospongiosus muscle and external urethral sphincter can be visualised by recording electromyogram using thin electrodes placed within the tissue of interest.

1. Bulbospongiosus muscle

The bulbospongiosus muscle, a superficial muscle of the perineum, consists of two symmetrical parts that cover the bulb (or base) of the penis. It serves to empty the canal of the urethra but also contributes to erection and feelings of orgasm in male individuals.

Figure 2: Sample of intra-luminal vas deferens pressure (VDP) measurement obtained in anaesthetised rats. VDP is recorded in rat receiving electric stimulation at the level of the spinal generator of ejaculation (SGE). A short lasting single peak increase in VDP is observed immediately after stimulation.
Bulbospongious muscle is exposed via a perineal incision and electromyogram can be monitored by passing a Teflon insulated stainless–steel wire (diameter, 230 µm) laterally throughout the muscles with two 1-2 mm pieces (separated by 1-2 mm) of insulation stripped off. At one end of the wire, a spherical fishing sinker is attached to avoid electrode displacement caused by intense contractions of the muscle. The other end of the wire is connected to an amplifier (gain x1000) where the incoming signal is filtered (low pass 1 KHz; high pass 10 Hz). An analog-to-digital converter transforms the amplified output signal to numeric data on a computer where the signal can be visualised in real-time and recorded (figure 3). Measurement of bulbospongious muscle electromyogram can be performed in several models of ejaculation (Cf pages 40, 41, 42).

2. **EXTERNAL URETHRAL SPHINCTER**

The external urethral sphincter is a striated muscle that envelopes the membranous part of the urethra extending from the prostate to the meatus. Its contractions, commanded by somatic motoneurons, constrict the urethra. In rats, external urethral sphincter is activated during ejaculation contrary to human where it relaxes. The role of these potent rhythmic contractions is unclear but they could contribute to the build up of a pressure chamber facilitating the expulsion of semen which is in the form of a viscous plug in rats.

Perineal incision is performed to reach the part of the external urethral sphincter where the electromyogram is measured. The same recording electrode as described in the previous section is inserted into the muscle of the middle urethra, ~6 mm from the blad-

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**Figure 3**: Sample of bulbospongious muscle electromyogram obtained in anaesthetised rats. Electromyogram is recorded in rat injected with the dopamine D2/D3 receptors agonist 7-OH-DPAT into the cerebral ventricle (i.c.v.). Several clusters of intense burst of contraction of the bulbospongious muscle are observed following drug delivery. Rhythmic organisation of the bursts is detailed in the inset.

**Figure 4**: Sample of external urethral sphincter electromyogram obtained in anaesthetised rats. Electromyogram is recorded in rat injected with the dopamine D2/D3 receptors agonist 7-OH-DPAT into the cerebral ventricle (i.c.v.). Several clusters of intense burst of contraction of the external urethral sphincter are observed following drug delivery. Rhythmic organisation of the bursts is detailed in the inset.
nder neck. The electric signal from the external urethral sphincter is amplified, filtered, and converted as described in the previous section (see figure 4 for illustration). Measurement of external urethral sphincter electromyogram can be performed in several models of ejaculation ( Cf pages 40, 41, 42).

It is implicit that several physiological parameters can be monitored in the same animal during the same experimental session ( figure 5). This renders possible the investigation of both phases of ejaculation as well as the synchronisation between them, which is important for a normal anterograde ejaculation, in the same experimental conditions.

3. EXPERIMENTAL MODELS OF EJACULATION

The available experimental paradigms to investigate ejaculation in anaesthetised male rats are briefly described.

a) Ejaculation induced by electrical stimulation of the intermesenteric nerves in anaesthetised rat

OBJECTIVE:

To induce a complete ejaculatory response in anaesthetised rat. In this model, physiological markers of the emission and expulsion phases of ejaculation induced by electrical stimulation of the intermesenteric nerves (IMN), which contains both pelviperineal afferents and efferents, can be measured. Contractions of the seminal vesicle and the bulbospongious muscle are regarded as physiological markers of, respectively, emission and expulsion phases of ejaculation ( figure 6).

SUMMARIZED METHODOLOGY:

Rats are anaesthetised with isoflurane and seminal vesicle pressure (SVP) as well as bulbospongious muscle (BS) electrical activity (BS EMG) are monitored. A stimulating electrode is placed on the IMN and electrical stimulation is applied consisting of 5 square wave pulses (1 ms duration, 6 V, 60 Hz) during 30 s.

ENDPOINTS:

Number and latency of ejaculations (corresponding to the expulsion of a seminal plug)

Number, latency, amplitude, duration and area under the curve of SVP increases

Number, latency, frequency and duration of BS contractions


Figure 5: Sample of recording of seminal vesicle pressure (SVP), bulbospongiosus muscle electromyogram (BS EMG), and external urethral sphincter electromyogram (EUS EMG) obtained in anaesthetised rats after i.c.v. delivery of 7-OH-DPAT (10 µg). A magnification of the tracing is displayed to show the temporal organisation. Typically, SVP rise was followed, after 1.0 ± 0.2 s, by EUS rhythmic contractions, then, after 6.8 ± 0.8 s, by BS rhythmic contractions. SVP responses were characterised by multi-peak (2-4) increases lasting 18.0 ± 0.6 s and reaching maximal amplitude of 3.5 ± 0.3 mmHg. BS and EUS responses occurred in the form of intense and rhythmic bursts of contraction lasting 35.7 ± 1.4 and 28.0 ± 1.0 s respectively, and with burst frequency of 0.40 ± 0.01 and 1.71 ± 0.07 s⁻¹ respectively. (from Clement et al., 2009)

Figure 6: Example of seminal vesicle pressure and bulbospongiosus muscle electromyogram (EMG) responses following electrical stimulation (ES) of the intermesenteric nerves.
b) Para-chloroamphetamine-induced ejaculation in anaesthetised rat

OBJECTIVE:
To induce a complete ejaculatory response in anaesthetised rat. In this model, physiological markers of the emission and expulsion phases of ejaculation induced by the amphetamine derivative para-chloroamphetamine (PCA) can be measured. Contractions of the seminal vesicle and the bulbospongiosus muscle are regarded as physiological markers of, respectively, emission and expulsion phases of ejaculation (figure 7).

SUMMARIZED METHODOLOGY:
Under anaesthesia (isoflurane, urethane or pentobarbital), the carotid artery and the right seminal vesicle are catheterized to measure concomitantly arterial pressure (AP) and seminal vesicle pressure (SVP). Electrical activity of the bulbospongious muscle (BS EMG) is also recorded. Physiological markers are monitored before and over 30 min after PCA systemic injection (i.v. or i.p.). Computerized analysis of the recordings is then performed a posteriori using custom-written analysis programs (Sadoc, CNRS, Gif-sur-Yvette, France).

ENDPOINTS:
Number and latency of ejaculations (corresponding to the expulsion of a seminal plug)
Number, latency, amplitude, duration and area under the curve of SVP increases
Number, latency, frequency and duration of BS contractions
Time interval between SVP increase and BS contractions

REMARKS:
PCA triggers ejaculation by releasing serotonin and noradrenalin at the spinal level. Therefore, this model is suitable for studying peripheral and spinal modulations of the ejaculatory process and not recommended for investigating supra-spinal modulation.


c) 7-hydroxy-2-(di-N-propylamino)tetralin-induced ejaculation in anaesthetised rat

OBJECTIVE:
To induce a complete ejaculatory response in anaesthetised rat. In this model, physiological markers of the emission and expulsion phases of ejaculation induced by the dopamine D3 preferring agonist 7-hydroxy-2-(di-N-propylamino)tetralin (7-OH-DPAT) can be measured. Contractions of the seminal vesicle and the bulbospongious muscle are regarded as physiological markers of, respectively, emission and expulsion phases of ejaculation (figure 8).

Figure 7: Example of recording of seminal vesicle pressure (SV-P) and bulbospongious muscle electromyogram (BS-EMG) during ejaculation induced by i.p. p-chloroamphetamine (PCA). On the left panel are illustrated the successive SVP and BS-EMG peaks that occur over the 30 min-period following PCA injection (5 mg/kg). Right panel: a sample response from the left panel shows the time shift (T) between the beginning of the SVP rise and the first consistent BS contraction (Pelvipharm internal data).
SUMMARIZED METHODOLOGY:

Under anaesthesia (isoflurane, urethane or pentobarbital), the carotid artery and the right seminal vesicle are catheterized to measure concomitantly arterial pressure (AP) and seminal vesicle pressure (SVP). Electrical activity of the bulbospongiosus muscle (BS EMG) is also recorded. Physiological markers are monitored before and over 30 min after PCA systemic injection (i.v. or i.p.). Computerized analysis of the recordings is then performed a posteriori using custom-written analysis programs.

ENDPOINTS:

Number and latency of ejaculations (corresponding to the expulsion of a seminal plug)
Number, latency, amplitude, duration and area under the curve of SVP increases
Number, latency, frequency and duration of BS contractions
Time interval between SVP increase and BS contractions

REMARKS:

7-OH-DPAT triggers ejaculation by stimulating dopamine D2/D3 receptors at the brain level. Therefore, this model is suitable for studying peripheral and spinal modulations of the ejaculatory process but also supraspinal modulations that involve dopaminergic system.


d) Ejaculation induced by electrical stimulation of the lumbar spinothalamic cells in anaesthetised rat

OBJECTIVE:

To induce a complete ejaculatory response in the anaesthetised rat. In this model, physiological markers of the emission and expulsion phases of ejaculation induced by electrical microstimulation of the lumbar spinothalamic cells (LSt), the key component of the spinal generator for ejaculation, can be measured. Contractions of the vas deferens and the bulbospongiosus muscle are regarded as physiological markers of, respectively, emission and expulsion phases of ejaculation.

SUMMARIZED METHODOLOGY:

Rats are anaesthetised with urethane or pentobarbital and intraluminal vas deferens (VD) pressure as well as bulbospongiosus muscle (BS) electrical activity...
(BS EMG) are monitored. For LSt microstimulation, an electrode is positioned in laminae VII-X (figure 9). Electrical stimulation protocol is adapted to the aim of the experimental investigation. Analysis of the recordings is performed a posteriori using custom-written routines in Elphy software (Sadoc, CNRS, Gif-sur-Yvette, France).

**ENDPOINTS:**
Latency, amplitude, duration and area under the curve of VD increases
Latency, frequency, duration and area under the curve of BS contractions

Figure 9: The spinal location where microstimulation evokes ejaculation related events corresponds to the LSt neuron area. (a) Strong current injections through the stimulation electrode at the end of the experiment marked the spinal location from which ejaculation and ejaculation related events could be evoked (spinal cord section at L4, cc = central canal). (b) Left: Dp(SV) response (red) in a single rat for various electrode depths, ie vertical distance from the dorsal surface of the spinal cord at L4 level. Green line indicates stimulation period, red numbers stimulation sequence. Middle: corresponding maximal amplitude of Dp(SV) (red dots) vs. electrode depth (vertical axis). The Gaussian function (black) used for data fitting peaks at t1540 mm from the spinal cord’s dorsal surface. Right: summary data for the maximal amplitude of Dp(SV) and electrode depth (n = 9, red) with mean Gaussian fit (black). For each animal, data was normalized by the Dp(SV) maximal amplitude and the peak position of the Gaussian. Microstimulation applied at L2 and L4 evoked the highest maximal amplitude of Dp(SV) (c) and BSM-rEMG (d). Animal numbers indicated for spinal levels. (e) When placing two electrodes spaced 500 mm laterally at L4, significantly larger maximal amplitudes of Dp(SV) (red) and BSM-rEMG (black) were evoked near the spinal cord midline.
III. UROGENITAL REFLEX

Neurophysiologic recordings in both men and women have shown that rhythmic contractions of the genital organs, anal sphincter and pelvic floor muscles occur concomitant with ejaculation and the sensation of orgasm/climax [4,5,16,17,32]. In men, orgasm is closely associated with ejaculation and can be defined as the expulsion of fluids from the urethra, which is facilitated by rhythmic perineal muscle contractions. Therefore, strictly speaking both emission (secretion of seminal fluids) and ejaculatory reflexes (rhythmic perineal muscle contractions) are required for the full ejaculatory pattern in men. However, there is little conclusive evidence that women ejaculate during orgasm [3,22]. In women, pelvic floor, vaginal, uterine and anal sphincter contractions have been reported to be associated with the sensation of orgasm and climax. Therefore, similar physiological responses occur during orgasm in men and women.

The urogenital (UG) reflex is a model developed on the rat that mimics the expulsion phase of ejaculation and the genital changes seen during orgasmic responses in both men and women [7,18,45,57]. Use of this model has provided important information on the physiological, pharmacological and neuroanatomical control of ejaculation. The UG reflex comprises rhythmic contractions of the perineal muscles, (ischio cavernousus and bulbospongious muscles), penile erections and expulsion of the urethral contents [21,45]. The clonic contractions of the perineal muscles seen during the UG reflex strongly resemble that seen during sexual climax in humans. Examination of the UG reflex in female rats demonstrated rhythmic contractions of the pudendal motor nerve, vagina, anal sphincter and uterus which could be elicited by brief urethral distension or pudendal sensory nerve stimulation [7,45,62]. These physiological responses also occur during orgasm in women.

The UG reflex is generated by a spinal pattern generator which involves multiple spinal segments that coordinate somatic, sympathetic and parasympathetic efferents innervating the sexual organs [35,38,45,46,59]. Distension of the urethra or stimulation of the pudendal sensory nerve triggers the UG reflex in the spinally transected, anesthetized rat. The responses are difficult to evoke in the intact fully anesthetized preparation, but can be induced pharmacologically, suggesting a tonic supraspinal inhibition [6,9,21,55,57].

Peripheral nerves relaying the afferent (sensory) and efferent (motor) information during the UG reflex are the pelvic and pudendal nerves, and damage to these nerves during pelvic surgery (e.g. prostatectomy, hysterectomy) can result in orgasmic dysfunction. The pudendal (somatic) nerve relays sensory stimuli from the perineum, penis, clitoris, urethra and the pelvic floor musculature. These sensory signals are essential for activation of the UG reflex 7,45. The pudendal nerve afferents enter the spinal cord through the superficial dorsal horn of segments L6-S1 (human - S2-S4) and travel through the medial dorsal horn to the dorsal gray commissure, which is located in the medial cord [13,46,52,58,61]. Autonomic afferents may also contribute to sensory inputs from the genital organs. Pelvic afferents terminate primarily in spinal segments L6-S1 (sacral cord in humans). The fibers course through the lateral dorsal horn and extend toward the intermediolateral cell column [2,14,48-50]. The efferent fibers of the pudendal nerve provide innervation of the pelvic floor and anal and urethral sphincters which contract rhythmically during the UG reflex. The pudendal motoneurons are located in the ventral horn of the lumbar spinal cord in Onuf’s nucleus, which in the rat is divided anatomically into the dorsomedial and dorsolateral nuclei [46]. Therefore, spinal pathways regulating the UG reflex are located in the lower lumbar-sacral spinal cord. However, there is some evidence that the sensation of orgasm in women may be perceived through higher spinal (hypogastric pathways) and brain (vaginal) circuits [29-31]. A spinal pattern generator for the UG reflex has been proposed and evidence from several sources suggests it includes...
neurons in the medial gray of spinal segments L3-L4 [6,45,59]. Some of these neurons have been identified (LSt cells) which project to the thalamus and contain galanin and NK1 receptors; these neurons are activated with ejaculatory behavior and with the UG reflex in males but not in females [35,38,59,60]. Further elucidation of the spinal generator mediating female genital responses is required.

Neuroanatomical tract tracing studies using the neurotrophic virus, pseudorabies virus (PRV), have been used to identify the spinal and brain neurons innervating the pelvic organs that contribute to the UG reflex [33,36,43,44,63]. Injection of PRV into the pelvic organs (penis, clitoris and perineal muscles) resulted in labeling of postganglionic neurons in the major pelvic ganglia (penis and clitoris) and pudendal motor neurons (perineal muscles). Sympathetic and parasympathetic preganglionic neurons of the hypogastric and pelvic nerve, respectively, were also labeled. Spinal interneurons were located in and around the intermediolateral cell column and in the medial gray forming a column of neurons through segments T13-S1. These studies suggest that spinal interneurons involved in the UG reflex course through the lower thoracic lumbosacral cord in the lateral and medial gray. These cells may be important in the integration of multiple pelvic responses seen during sexual behavior.

Activation of c-fos, an immediate early gene, has been used to identify spinal neurons that are activated during the UG reflex [35,38]. Activation of the UG reflex resulted in increased c-fos expression in lower thoracic-lumbosacral spinal segments. The spinal circuits involve an afferent arc via the pudendal nerve and efferent outputs via the parasympathetic and sympathetic nerves (pelvic and hypogastric). In addition, c-fos positive nuclei were found in the dorsal horn suggesting that the dorsal horn neurons form connections within the superficial laminae and these cells may be important in coordinating intraspinal and supraspinal information. Spinal interneurons in the lateral, intermediate and medial gray were also activated with the UG reflex; these cells include components of the spinal pattern generator that regulates the UG reflex.

The brain exerts an inhibitory and facilitatory influence on the lumbosacral pathways involved in the UG reflex. Physiological and pharmacological studies demonstrated that the UG reflex was tonically inhibited by neurons in the ventral medullary reticular formation (the nucleus paragigantocellularis, nPGi) [40,41]. Further studies confirmed that lesions of this region facilitated ex copula sexual reflexes in males and improved ejaculatory performance [39,64]. Neuroanatomical tract tracing studies confirmed that the nPGi projects to and receives inputs from the penis, clitoris, perineal muscles and pelvic efferent neurons and interneurons in the lumbosacral spinal cord that modulate pelvic reflexes. Excitatory and inhibitory neurons in the nPGi respond to genital stimulation in the female rat and to manipulations of the pelvic, pudendal nerves and dorsal nerve of the penis in the male [23-25,27,28]. These studies provide evidence that the nPGi tonically inhibits somato-motor output that is associated with the UG reflex and receives sensory information related to sexual function. It is well established that the medial preoptic area (MPOA) plays an important role in sexual behavior [15,20,26,42,51]. Stimulation of the MPOA induces rhythmic contractions of the pudendal motor nerve.

![Responses to urethral distension in the spinalized, anesthetized female rat (38)](image_url)
and the bulbospongiosus muscle [42]. The MPOA does not directly innervate spinal circuits involved in sexual reflexes and physiological and neuroanatomical studies have shown that the midbrain peri-aqueductal gray (PAG) and the ventrolateral medulla (VLM) are important relay sites for these mediated by the MPOA responses [34,37,53,54].

Research efforts continue to examine the pharmacological control of the UG reflex. Currently a number of neurotransmitters acting on specific receptors have been shown to activate or inhibit the UG reflex [1,8,10-12,19,21,41,56,57,67,68]. Briefly, compounds that inhibit the UG reflex include serotonin and opioid agonists, while muscarinic agonists and dopamine activate/ facilitate the UG reflex. Adrenergic systems are also involved [47,65,66,68]. In addition, to specific neurotransmitters, universal compounds that can activate general excitatory receptors (glutamate) or inhibitory receptors (GABA) are involved.

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**IV. PARAMETERS OF PERIPHERAL FEMALE SEXUAL RESPONSE**

Physiological responses that are associated with female sexual behavior, as well as animal models, are not as clear as those that mimic male sexual behavior. One difficulty in developing animal models of female sexual responses has been the historical lack of studies in women and the lack of sensitive equipment to measure women’s sexual responses. However, over the past 20 yrs developments have been made allowing further understanding of women’s sexual responses [1-10]. Female sexual behavior and the integrity of the female genital organs are dependent on gonadal steroid hormones (estrogen and progesterone) [11-14]. However, sexual behavior can occur in conditions of suboptimal or very low...
levels of these hormones, suggesting that sexual behavior/responses can be triggered with adequate stimulation from the genitals or from the brain.

Sexual responses in women include desire, arousal and orgasm, while these sensory responses are perceived by the brain, there are associated peripheral autonomic and somatic changes that occur in the genital organs that are indicative of female sexual responses. Genital arousal responses include vasocongestion and neuromuscular changes of the clitoris and vagina and vaginal lubrication [7,15-19]. Phasic contractions of the striated and smooth muscles of the pelvic floor, perivaginal muscles, vagina and uterus occur during sexual excitement and often during orgasm [2,8,20-23]. The peripheral models of female sexual responses involve monitoring changes in vaginal and clitoral blood flow and temperature and vaginal secretions as well as monitoring smooth and striated muscle contractions of the vagina, uterus, anal sphincter and pelvic floor muscles. Examination of tissue responses (in vitro studies) also provides information of the neural and local neurotransmitters involved.

1. NEURAL PATHWAYS

The genitalia and pelvic floor muscles are regulated by the sympathetic and parasympathetic nervous system (pelvic nerves, hypogastric nerve, paravertebral sympathetic chains) and by somatic nerves (pudendal nerve). Evidence has also been published suggesting a role for the vagus nerve in genital sexual responses. The peripheral innervation of the pelvic organs has been reviewed by several authors [24-26]. These nerves convey impulses from the brain and spinal cord to control motor, secretory and vascular functions, or mediate pleasurable or painful sensations [24,27-31]. The autonomic nerves regulate blood flow and the involuntary smooth muscle contractions that may accompany arousal while the somatic nerves control the voluntary or striated muscle responses that often occur during climax / orgasm. In addition, there is some evidence that clitoral erection is mediated by local mechanisms that are similar to that of penile erection [32-34]. Sensory inputs from the genitalia or brain can facilitate arousal and climactic responses and are mediated by both the somatic and autonomic systems.

2. VAGINAL RESPONSES

Genital arousal in females is associated with increased blood flow to the vagina and clitoris which results in clitoral erection, vaginal engorgement, changes in vaginal luminal diameter and vaginal lubrication. Studies have been published investigating the physiological changes that occur in the vagina and clitoris [15,32-39], and these studies provide a working model for genital arousal in females. The first studies examining female genital function were focused on the estrous cycle and its relationship to pregnancy [40-43]. Techniques developed during

Effect of repeated electrical stimulations (6V, 10Hz, 1 ms) of the pelvic nerve on vaginal parameters including blood flow in anesthetized female rat (15).
these studies included monitoring vaginal blood flow and temperature in multiple species and provided the tools that were translated to monitoring changes of the genital organs during sexual responses.

The majority of these studies have used stimulation of the pelvic nerve in the anesthetized model and monitored changes in vaginal and/or clitoral blood flow [15,32,34,35,38,39,44,45]. Stimulation of the pelvic nerve in the rabbit resulted in increases in vaginal length, pressure and blood flow, and clitoral blood flow. Similar changes in vaginal and clitoral hemodynamics were elicited by pelvic nerve stimulation in the rat and dog (i.e. increases in vaginal blood flow, increases in vaginal wall tension and stimulation of the dorsal clitoral nerve elicited increased clitoral blood flow).

A more recent study reported that stimulation of the somatosensory afferents could also elicit increases in vaginal blood flow [38]. Stimulus intensities required to increase vaginal blood flow were significantly lower than those evoking rhythmic firing of the pudendal motor nerve or contraction of the vaginal smooth muscle. The increase in vaginal blood flow induced by activation of pudendal nerve afferents was abolished by pelvic nerve cuts, suggesting that sensory stimulation can increase vaginal blood flow (genital arousal) through spinal pathways that activate parasympathetic (pelvic nerve) efferent output.

The effects of gonadal steroid hormones on genital blood flow have been examined and they confirm that ovariectomy changes vaginal tissue morphology and reduces blood flow response to pelvic nerve stimulation [32,36,46]. However, other studies showed consistent pelvic nerve induced increases in blood flow to the vagina and clitoris, although evidence for larger responses was reported with the addition of estradiol [15,35,45,46]. A number of studies have shown that the hypogastric and pelvic nerves are sensitive to the levels of circulating gonadal steroid hormones and this altered sensitivity changes vaginal arousal [28,47,48]. Further studies are required to understand the role of gonadal steroid hormones in sexual responses as well as changes that occur with and post menopause.

More research is also required to understand the pharmacological control of genital arousal responses. Only a few studies have been published. Intravenous administration of low doses of apomorphine caused an increase in pelvic nerve stimulation-induced peak clitoral intracavernosal and vaginal wall blood flow in rabbits [49]. In rats, atropine failed to affect the pelvic nerve induced increase in vaginal blood flow, but did block the vaginal contraction, suggesting acetylcholine may not play a major role in vaginal engorgement during sexual arousal [15]. Several studies have documented that nitric oxide mechanisms are involved in mediating increases in vaginal blood flow and lubrication [34,39,50]. Local administration of papaverine hydrochloride and phentolamine increased vaginal wall pressure and vaginal blood flow in rabbits [32]. Further studies are required to understand the role of these neurotransmitters as well as examining the role of specific adrenergic receptors and neuropeptides in the regulation of genital arousal.

Other models of genital arousal include monitoring the appearance of external genitalia in conscious rats after apomorphine treatment in which engorgement of the tissue surrounding the vagina and increased introitus diameter occurred (lasted 2-3sec) [19]. However, these response are very infrequent (1-4 every 30min) and thus studies confirming these usefulness of this model are required [19]. Changes in vaginal temperature have been monitored in animal models; however, the reproducibility of detecting temperature changes in small animals is questionable.

Little research has been conducted on the brain mechanism regulating female genital arousal responses; however one study demonstrated an increase in vaginal blood flow upon electrical stimulation of the medial preoptic area [15].

3. ORGASMIC-LIKE RESPONSES

Contractions of the pelvic muscles, anal sphincter and vagina frequently occur during orgasm or climax in women and these responses have been used as a model to further understand the CNS control of orgasmic responses in females [38,51,52]. Some of the physiological components are neurologically similar to those that occur during ejaculation/ orgasm in men (see urethrogenital (UG) reflex section). Rhythmic contractions of the pudendal motor nerve, vagina, anal sphincter and uterus were elicited by brief urethral distension or pudendal sensory nerve stimulation [38,51,52].

Brain and spinal pathways regulating the UG reflex in female rats appear similar to that reported in male rats. However, the spinal pattern generator thought to mediate ejaculatory reflexes in males does not appear to be activated during the UG reflex in females [52,53]. Further elucidation of the spinal generator mediating female genital responses is required.

V. REFERENCES

Cardiovascular disease, hypertension or related risk-factors that cause endothelial dysfunction and progressive vascular structural changes are linked to male and female sexual dysfunctions (Kirby et al 2005, Esposito et al 2008, Shabsigh et al 2008, Veronelli et al 2009). The microcirculation is proposed to be of particular interest and at risk for functional and structural alterations during the development of cardiovascular and metabolic diseases (Gates et al 2009). Sexual symptoms are reported often to proceed the onset of signs of coronary artery disease and undiagnosed hyperglycemia in men with erectile dysfunction and it has been proposed that the small-diameter penile resistance arteries due to a smaller diameter / wall ratio less favourably tolerate lumen narrowing and vascular wall remodelling and plaque formation (Montorsi et al 2005, Grover et al 2006). Altered clitoral or vaginal hemodynamics have been described in preclinical female models for vascular disease but although some postmenopausal patients with genital arousal disorder are reported to exhibit lower vaginal vasocongestive responses to erotic stimuli, the relations to cardiovascular disease, human genital vascular dysfunction and peripheral arousal disorder are unclear (Min et al 2002, Park et al 2002, Basson and Brotto 2003, Kim et al 2006). Furthermore, clitoral and vulvar swelling and lubrication has been proposed to rather be an automatic reflex that may not well correlate to the subjective arousal in women which in turn reflects a need for well defined endpoints and interpretations of results in relation to sexual function or health risk factors in studies of female genital vascular responses in animal models (Basson 2008).

Below follows an overview of findings on the male and female genital responses in models for lifespan parameters (ageing, hormones), disease processes (hypertension, diabetes), or lifestyle factors (diet, smoking, recreational drugs). When convenient, molecular biological information, functional activities of isolated tissues, and in vivo genital responses are described for various mammals in relation to findings in humans.

II. MODELS FOR LIFESPAN FACTORS

1. AGEING

The structure and function of arteries change throughout a lifetime. In general, changes in arterial function and structure with increasing age are similar across species (human, monkey, rodents) with respect to many parameters such as e.g. stiffness (decreased elastin; increased collagen), endothelial dysfunction, intimal thickening and medial dysfunction, increased levels of inflammatory chemokines, reduced availability of nitric oxide (NO) and vascular endothelial growth factor, and increased activity of

C. VASCULAR ASPECTS & MODELS OF DISEASE

I. BACKGROUND

Improved understanding of the pathophysiological mechanisms and significance of peripheral vascular disease in sexual dysfunctions are of interest not only to identify novel therapeutic approaches in sexual medicine but also to define relations to common health risk factors and to at earlier stages detect and prevent progression of systemic metabolic and vascular diseases.

transforming growth factor-β1 and the Angiotensin II–signaling cascade (Najar et al 2005).


Reduction in the smooth muscle content of clitoral erectile tissue from human cadavers have been described correlated with increase in age and that presence of cardiovascular mortality increased progression of fibrosis (Tarcan et al 1999). Little information is available on structural or functional changes of female genital responses in preclinical models of aging. One study investigated the affect of aging on apomorphine-induced genital vasocongestive arousal (GVA) recorded by visual inspection and defined as significant engorgement of tissue surrounding the vagina as well as an increase in the dimensions of the introitus that lasted for 2–3 seconds. Compared to young rats (225 – 250 gr), only 40% of 18-month old female rats responded to apomorphine and exhibited an approximately 50% reduction of the number GVA responses during a 30-minute observation period. In comparison in a small study of 48 women, when analyzed by age, older women (ages 55 - 67 y) had significantly lower basal clitoral, labial, urethral and vaginal blood velocities than younger women (ages 25 - 54 y), whereas following sexual stimulation using a erotic video, no differences in genital blood velocities were recorded (Berman et al 1999).

2. SEX HORMONES


Contrasting results on the effects of testosterone on female genital vascular responses in ovariecetomized animals have been reported. In a castrate rat model, testosterone-treatment (5.5-55 microgram/day; 2 weeks) was described to increase vaginal blood-flow recorded with laser Doppler flowmetry (Traish et al 2007). In contrast, testosterone (100 microg/day) failed to improve genital blood-flow (laser oximeter recordings) or vaginal lubrication in ovariecetomized rabbits (Min et al 2002). Further studies are necessary to understand if these findings reflect differences between species or in methodological approach.

The effects of antiandrogens or estrogens on erectile responses have received little attention. One study describe that a single dose of flutamide, a clinically available androgen receptor antagonist, significantly decreased apomorphine-induced erections to less than 50% over 12 hours with recovery of erectile response within 48 hours. In comparison, a single dose of p,p-DDE, a DDT-metabolite and environmental pollutant acting as an androgen receptor antagonist, decreased apomorphine-induced erections for at least two weeks (Brien et al 2000). A phytoestrogen,
daidzen (100 mg/kg daily), was shown to decrease apomorphine-induced erections from the 30th day of treatment without differences compared with a synthetic estrogen (Pan et al 2007). In isolated corpus cavernosum tissue, chronic treatment with estradiol or daidzein decreased smooth muscle cell and elastic fiber content of the erectile tissue, reduced relaxant responses to acetylcholine, nitroglycerin, or activation of nerves and potentiated noradrenaline-induced contraction (Srilatha and Adaikan 2004, Huang et al 2008).


### III. MODELS FOR DISEASE PROCESSES

#### 1. HYPERTENSION

Several investigations have shown that hypertensive animals exhibit altered structure and function of the erectile tissue. Specifically, corporal tissue from SHR exhibit smooth muscle remodelling and increased fibrosis, reduced elastin content, subcellular alterations to mitochondria, endoplasmic reticulum and Schwann cells, reduced levels of endothelial NOS, reduced relaxant responses to acetylcholine or activation of nerves, reduced cGMP levels, increased superoxide dismutase activity, and increased Rho-kinase associated protein activity (Toblli et al 2000, 2007a, Chitaley et al 2001, Ushiyama et al 2004, Jiang et al 2005, Mazza et al 2006, Fibbi et al 2008). These findings correspond well to reduced erectile responses in vivo to activation of the cavernous nerve or after administration of apomorphine in SHR and compared to controls (Dorrance et al 2002, Bhr-Roussel et al 2003, Mayoux et al 2004, Hannan et al 2006). Interestingly, in a longitudinal study by Bhr-Roussel et al (2005), the onset of erectile dysfunction was detectable before the onset of hypertension in the SHR. Decreased erectile responses upon electrical stimulation of the major pelvic ganglion has also been recorded in doxycorticosterone-salt and stroke prone-spontaneously hypertensive rats (Chitaley et al 2001). Numerous studies have also evaluated pharmacotherapy for erectile dysfunction or hypertension on erectile function or structure and function of the erectile tissue in hypertensive rat models (Dorrance et al 2002, Tong 2000, Hale et al 2002, Toblli et al 2004ab, 2006ab, 2007a, Bhr-Roussel et al 2005, Mazza et al 2006, Hannan et al 2006, Shamloul and Wang 2006, Ushiyama et al 2006, 2008, Fibbi et al 2008).

Hypertensive models have not been extensively used to study female genital structure and function. Spontaneously hypertensive rats have been described to exhibit smooth muscle proliferation and increased levels of TGF-β1 in clitoral vasculature, higher arterial wall/lumen ratio and increased interstitial fibrosis in both the vagina and clitoris (Bechara et al 2003). Treatment with ramipril was reported to counteract these changes and to increase the expression of clitoral endothelial NOS in comparison to untreated SHR (Toblli et al 2007b). To our knowledge, functional in vivo data on female genital blood flow in hypertensive models is lacking.

#### 2. DIABETES


In animal models for diabetes, insulin-treatment is reported to improve erectile function (Abdelbaky et al 1998, Rehman et al 1997, Escrig A et al 2002, Pu et al 2007). The majority of studies of diabetic erectile dysfunction have been conducted in animals with type 1 diabetes mellitus induced by streptozotocin or alloxan and describe reduced erectile responses recorded as intracavernous pressures to stimulation of the cavernous nerve, intracorporal administration of vasoactive drugs or systemic administration of...
apomorphine (Italiano et al 1993, Yamaguchi and Kobayashi 1994, Rehman et al 1997, Yildirim et al 1999, Bivalacqua et al 2004b, Zhang et al 2006, Morelli et al 2009, Shukla et al 2009). Rats that spontaneously develop type 1 diabetes (BB / WOR) which is proposed to parallel findings in the human insulin-dependent disease have been shown to exhibit reduced NOS activity of the erectile tissue and diminished erectile reflex responses but no change in nerve-induced intracavernous pressure profiles (Murray et al 1992, Vernet et al 1995, Garban et al 1997, Whalen et al 2001). Information is scarce on the impact of type 2 diabetes on erectile function in preclinical models. Penile reflexes are reported reduced in the BBZ/WORdp rat, and recently, intracavernous pressure responses to activation of the cavernous nerve were shown to be significantly reduced in obese-diabetic Zucker rat, a strain which may provide a valuable animal model for studying type 2 diabetes because of an impaired glucose tolerance associated with obesity (Vernet et al 1995, Wingard et al 2007). Interestingly, erectile tissue from the Zucker obese rat exhibited also changes in the activities of PKC and Rho-kinase, enhanced vasoconstrictive responses, and reduced relaxations to a NO-donor, whereas no changes in NOS activities were observed (Wingard et al 2007).

For the study of female genital tissue structure and function, only animals with type 1 diabetes have been used. In these investigations, histological and functional studies of isolated vaginal and clitoral tissues in diabetic rats, rabbits and mice have reported reduced epithelial thickness and atrophy of the muscularis layer, fibrosis and increased amounts of TGF-β1, reduced vaginal levels of eNOS and arginine, reduced neuronal NOS-activity, elevated levels of PKG, signs of oxidative stress, reduction in estrogen receptor activities, and altered sensitivities to activation of angiotensin receptors (Giraldi et al 2001, Park et al 2001b, 2002, 2005, Kim et al 2006, Ferrini et al 2006, Cushman et al 2009). In vivo, the vaginal blood flow response to pelvic nerve stimulation was significantly reduced in diabetic rats and mean baseline flaccid and peak clitoral cavernous blood flow was significantly decreased in the diabetic rabbits compared with the control groups (Park et al 2002, Kim et al 2006). In comparison, premenopausal women with insulin-treated diabetes have been shown to exhibit lower baseline clitoral blood flow compared to controls (Caruso et al 2006).

### IV. MODELS FOR LIFE-STYLE FACTORS

#### 1. HYPERCHOLESTEROLEMIA AND ATHEROSCLEROSIS

Fat cell lesions, loss of intercellular connections, decreased levels of elastin, decreased content of smooth muscle and endothelial cells, reduced levels of vascular endothelial growth factor (VEGF), diminished endothelium-dependent relaxation and endothelial NOS levels, altered adrenergic tonus-generating capacity, and increased Rho-kinase activity are reported findings in isolated corpus cavernosum tissue from diet-induced hypercholesterolemic rats and rabbits (Junemann et al 1991, Srilatha et al 1999, Byrne et al 2001, Yesilli et al 2001, Xie et al 2005a, Ruy et al 2006a). Similar to findings in diabetic erectile tissue, varying responses to NO-donors have been described for isolated corpus cavernosum from hypercholesterolemic animals, but it is not clear if this is related to progression of disease (Azadzoi and Saenz de Tejada 1991, Byrne et al 2001, Firooz et al 2005). Studying temporal changes in the erectile tissue from rabbits with hypercholesterolemia, Xie et al (2005b) reported that alterations in corporeal VEGF levels occurred before abnormalities in vasoreactivity. A study by Behr-Roussel et al (2002) showed that the atherosclerotic changes related to erectile dysfunction were distinct from ageing-related processes in cholesterol-fed rabbits.

Angiographically verified luminal narrowing and atherosclerotic lesions of pelvic arteries of hypercholesterolemic rabbits may be considered to correspond to findings using angiography or duplex ultrasonography in men with erectile dysfunction due to peripheral arterial disease and vascular riskfactors (Gray 1982, Vicari et al 2006).

In vivo, erectile responses to activation of the cavernous nerve or to intracorporeal administration of vasoactive agents have been shown to be reduced in rats, rabbits or monkeys with diet-induced hypercholesterolemia (Azadzoi et al 1996, Behr-Roussel et al 2002, Park et al 2006, Christ et al 2009). In the hypercholesterolemic atherosclerotic apolipoprotein E knock-out mouse, erectile responses to cavernous nerve stimulation have also been described to be reduced (Behr-Roussel et al 2006).

Various pharmacotherapies, protein therapies or gene transfer procedures have been investigated in diet-induced arterial disease of rats, rabbits, and monkeys to overcome erectile dysfunction (Byrne et al 2001, Firooz et al 2005, Kang et al 2006, Ruy et al 2006b, Christ et al 2009).

No information is available on the effects of a high cholesterol diet alone on female genital vascular responses. In a rabbit model combining a cholesterol
diet and ballon-injury of the aorto-iliac arteries, vaginal and clitoral hemodynamic insufficiency in response to pelvic nerve stimulation have been described (Park et al 1997). Histological examination of the clitoris and vagina in these animals revealed atherosclerotic changes of pelvic and clitoral arteries, reduced smooth muscle content and fibrosis (Park et al 1997, 2000).

Kim et al (2002) reported significantly increased plasma cholesterol levels, increased levels of LDL and reduced endothelium-dependent relaxations of clitoral cavernosal tissue from ovariectomised rabbits and proposed chronic estrogen deficiency-induced hypercholesterolemia as a risk factor for female endothelial dysfunction.

2. RECREATIONAL SUBSTANCES

Epidemiological data link cigarette smoking and erectile dysfunction and it is shown that tobacco smoke in general has negative effects on endothelial cells, decreased eNOS activity, impair endothelium-dependent vasorelaxation, impair regulation of thrombosis and reduce responses to VEGF (Gocmen et al 2005, Tostes et al 2008). In preclinical investigations, the effect of smoking on peripheral genital responses has only been studied in models for erectile function and dysfunction. In rats, irrespective of age, daily passive smoking for 8 wks (enclosed cage, 1 hour, 5 days per week) reduced penile neuronal NOS activity, whereas no reduction in the amount of endothelial NOS was observed (Xie et al 1997). In vivo, the authors did not find reduced erectile functions in response to activation of the cavernous nerve in smoke exposed rats compared to controls (Xie et al 1997). In contrast, Bivalacqua et al (2009) reported reduced erectile responses in vivo to cavernous nerve stimulation in mice exposed to 3 weeks of secondhand smoke (enclosed cage, 5 hours, 5 days per week). Mice that were exposed to smoke also exhibited impaired endothelium dependent erectile responses to Ach and the erectile tissue from these animals showed increased superoxide anion activity, decreased constitutive nitric oxide synthase activity, and increased inducible nitric oxide synthase activity, reactive oxygen species generation and nitrotyrosine formation (Bivalacqua et al 2009).

No studies are available that have investigated the effect of alcohol on cavernous nerve-induced erectile responses or endothelium-dependent erectile function in vivo. Dose-dependent negative effects of acute administration of ethanol on apomorphine-induced rat erections have been reported (Heaton and Varrin 1991). In isolated corpus cavernosum tissue, acute exposure to ethanol or its main metabolite decreased nerve-mediated and bethanecol-induced relaxations in isolated precontracted corpus cavernosum from rabbits (Saito et al 1994a, Kim et al 2000). Surprisingly, after chronic ethanol consumption (5% in drinking water for 6 weeks) corpus cavernosum tissue from rabbits exhibited increased relaxations induced by field stimulation or bethanecol, whereas relaxations to sodium nitroprusside were not changed (Saito et al 1994ab). In contrast, in a more recent investigation using continuous ethanol vapor by inhalation for 14 days, isolated corpus cavernosum exhibited abolished endothelium-dependent relaxations whereas the relaxation to EFS and NO were unaltered (Aydinoglu et al 2008). In support of a role for ethanol under the current experimental condition as a risk factor for penile corpus cavernosum endothelial damage, electron microscopy of the erectile tissue from the above mice described nuclear endothelial cell alterations such as reorganisation of heterochromatin, appearance of deep nuclear indentations and a decrease in the number of pinocytic vesicles (Aydinoglu et al 2008).

Central effect of cocaine on sexual behavior and erectile function has been documented (Chang et al 2000). Chronic cocaine abuse is associated with serious cardiovascular complications, including endothelial dysfunction, and atherosclerosis, and recently peripheral mechanisms of erectile function in a rat model of triple-binge cocaine administration were evaluated (Kendrici et al 2007). Decreased erectile responses as measured by intracavernous pressure changes in vivo were observed after cocaine-treatment. Animals exhibited increased plasma levels of big-endothelin-1, and the erectile tissue was shown to contain increased expression of endothelin-A receptors and myeloperoxidase, decreased eNOS expression and NO production, and also to exhibit reduced endothelium-dependent relaxant responses and nerve-induced relaxations (Kendrici et al 2007).

V. CONCLUDING REMARKS

Overall, good evidence of the role for ageing, hypertension, testosterone, type 1 diabetes or hypercholesterolemia / atherosclerosis on erectile function is available in several strains or species, and contain information from molecular biological analyses, functional responses of isolated tissue and in vivo models. Additional studies in models for type 2 diabetes and models for the use of recreational drugs seem important for penile erection and erectile dysfunction.

Information on the role for estrogens, type 1 diabetes or hypercholesterolemia / atherosclerosis on the female genital vascular responses is found in at least one strain or species, and contain data from in vivo models and from molecular biological or functional investigations of isolated tissues. Information of vascular aspects of the female genital response is scarce or absent in the other currently reported models of disease.
Human cardiovascular disease is of multifactorial origin and even if preclinical models to evaluate the impact of vascular risk factors on sexual dysfunction may not depend upon simultaneous presence of known and unknown causative components, these models are important steps to evaluate mechanisms and targets of disease (Faxon et al 2004). Analyses at genetic and molecular biological levels, in isolated tissues and in vivo systems, as well as comparative investigations in human tissues and clinical trials are important to evidence and identify common pathophysiological pathways and putative novel targets of therapy. In extended studies, models that consider combinations of lifespan parameters, disease processes, or lifestyle factors probably serve the purpose better as they mimic the actual clinical condition (Singh et al 2009).

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D. CELLULAR AND MOLECULAR STUDIES IN SEXUAL MEDICINE

Over the years, three-dimensional cultures of tissues or dispersed cells have been developed under well-maintained physiological conditions with the purpose of elucidating the intracellular biochemical reactions, ion or signal transfer pathways and others. These in vitro systems do provide useful information on the in vivo interactions and modulations in the presence or absence of chemical, biological, vascular, neurologic, endocrine and genetic inputs. The limitations have included the possible changes in the tissue/cellular integrity due to stages of processing and some intricate differences attributable to the in vivo cellular responses in a physiological milieu. Technically too, there are needs for stringent levels of expertise and control in order to achieve the anticipated results. However, these methods do replace the need for elaborate functional studies or expensive animal models and also provide much useful information at the biochemical enzymatic levels. In the area of sexual medicine, researchers have grown animal and human corpus cavernosal smooth muscle (CCSM) cells as explant cultures in the pure form as characterized by their morphologic appearance and positive immunolucultures in the pure form as characterized by their cavernosal smooth muscle (CCSM) cells as explant research has grown animal and human corpus and genetic levels. In the area of sexual medicine, useful information at the biochemical enzymatic expensive animal models and also provide much replace the need for elaborate functional studies or other methods do not replace the need for elaborate functional studies or expensive animal models and also provide much useful information at the biochemical enzymatic levels. In the area of sexual medicine, researchers have grown animal and human corpus cavernosal smooth muscle (CCSM) cells as explant cultures in the pure form as characterized by their morphologic appearance and positive immunofluorescent staining. As such, the spindle-shaped CCSM cells can well grow into an overlapping confluence and immunostain positively for alpha-smooth muscle actin, which has known specificity for the smooth muscle and non-reactivity towards skeletal or cardiac muscles and fibroblasts (Kershen RT et al., 2002; Chen B et al., 2004). Meeting standards of structural and functional integrity, successfully cultured CCSM has been a useful tool for the understanding of the cellular mechanisms relating to the neurotransmitter- and neuromodulator-mediated responses in the normal erectile process and also provides for an understanding of the changes in ED. Furthermore, the in vitro culture systems can be used for the primary evaluation of newer drugs or agents for their therapeutic potentials in male and female sexual medicine.

In many respects, breakthrough information was provided by way of advanced cell culture techniques when Christ and others delineated the physiological signals in the inter- and intra-cellular erectile pathways (Christ & Brink, 1999; Serels S et al., 1998). Various ion channels, vasoactive agents and second messenger systems were also evaluated (Christ et al., 1999; Kim et al., 2000) in such in vitro physiological environments, albeit with finite life spans. In these studies, several enzymatic, morphological and immunochemical methods were superimposed to characterize the pathophysiological changes in the confluences of human and animal genital tissues (Sadeghi-Nejad H et al., 1998; Traish A et al., 1999; Munarri R et al., 2003). Of noteworthy mention to this evidence-based approach is the finding that the endothelium rather than the interstitium of the corpus cavernosum is more sensitive to the long term side-effects of the age-old intracavernous injection therapy (Pilatz et al., 2005). Presently, as part of our learning from the human cell constructs, there seems little doubt that a daily administration of PDE5 inhibitors is unlikely to upregulate PDE5 expression or decrease cGMP levels (Vernet D et al., 2006). These and other findings illustrate the usefulness of studies at the cellular and molecular level and their possible contribution to our ultimate objective of the restoration of erectile health (Burnett AL, 2008).

Over the decades, standard biochemical principles have been used in all branches of clinical sciences and sexual medicine research is no exception. Several time-tested methods have established that while androgen-priming upregulated nNOS, arginase, PDE5 gene and protein levels (Chamness S L et al., 1995; Traish AM et al., 2002; Morelli et al., 2004), estrogen downregulated both nNOS and eNOS expressions (Al-Hijji J et al., 2000; Yoon HN et al., 2001). Such in vitro experience also showed that exogenously administered testosterone can increase both androgen and estrogen receptor (AR and ER) proteins (Traish AM et al., 2007) and advantageously help to upregulate the responsiveness to PDE5 inhibitor(s) (Zhang XH et al., 2004). Towards a greater molecular understanding of the three types of NOS isoforms, some variation seems to exist in the genetic makeup of nNOS although biochemically, binding of the excitatory amino acids to the postsynaptic N-methyl-D-aspartate receptor triggered it to release NO (Magee T et al., 1996; Gonzalez-Cadavid NF et al., 2000). On the other hand, iNOS could be induced in response to bacterial lipopolysaccharide (Hung A et al., 1995) and the iNOS-cDNA may be able to mitigate age-related changes in erectile function (Garban H, 1997). With the current awareness of lifestyle modification, attempts at calorie restriction and exercise seemed to instigate molecular prevention, seen as limited interaction of eNOS with caveolin-1 (Musicki B et al., 2008).

What more can be said about the value of molecular and biochemical techniques? In diseased animal models, classical western blot studies were able to show that diabetes-related ED was associated with low levels of eNOS and arginase, reductions in ERalpha and AR and a downregulation of cGMP-dependent protein kinase-1 (cGKI) (Waldkirch E et al., 2008). On the other hand, there may be an iNOS induction and NO-ROS interaction indicative of the coexistent oxidative stress (Kim NN et al., 2006; Ferrini MG et al., 2006). Some groups have also reported down-regulation of mRNA transcript and alternative splicing of Slo gene (encoding the BK or Maxi-K
channel alpha-subunit) and a down-regulated variable coding sequence protein A1 (Vcsa1 - hSMR3A) in this organic ED (Autieri MV et al., 1996; Davies KP et al., 2007; Tong Y et al., 2007); the latter predicament has led to an experimental trial with gene transfer of plasmids expressing Vcsa1.

Over the decades, the unique structure of the CCSM has been recognized as a fundamental functional requirement and as described by DiSanto et al., its myosin isofrom is of an intermediate subtype between the vascular and visceral smooth muscles, made up of low (noninserted) and high (inserted) actin-mediated ATPase activities. This seems to also explain the state of "high resting tone but an inherent ability to relax instantly" (DiSanto ME et al., 1998). As for its toxicity, in addition to the well-known adrenergic system, mRNA transcripts for muscarinic acetylcholine receptor (mAChR) m1, m2, m3 and m4 subtypes have been identified in the past through RNase protection assays to account for their balancing role in the smooth muscle tone (Traish AM et al., 1995). Recent studies point to the effect of GTPase RhoA and Rho-kinase as additional factors leading to impaired erectile function with aging and specific co-morbid states. Incidentally, the increased RhoA/Rho-kinase signaling with Rho- guanine nucleotide exchange factors (GEFs) observed in these conditions indicates the prospect of selective GEF inhibitors as novel molecular targets for ED therapy (Linder AE et al., 2005; Jin L et al., 2006). Along these lines, intrinsic biochemical and molecular studies have also characterized some other modulators such as aquaporins (Gannon BJ et al., 2000), hydrogen sulphide (Srilatha B et al., 2007) and the kalikrein system (Wang T et al., 2005) in the male corpus cavernosum. It would be interesting to find out what the future holds for these moieties by way of translational application.

In the specific evaluation of ED therapy, an older binding assay found that the PGE1 receptor density was significantly lower in ED patients (Aboseif S et al., 1993) indicating thereby, the importance of being aware of the possibility of reduced therapeutic responsiveness to intracavernosal PGE1 in such situations. Pursuing the success of PDEIs, several groups showed that these drugs effectively inhibited cGMP hydrolysis in the presence of NO in the intact cells of the human penile and clitoral cavernosum (Kim NN et al., 2001; Park K et al., 1998) and as a proof of concept, new drug discovery is being based on the distribution pattern of the PDE isoenzymes (Qiu Y et al., 2000; Küthe A et al., 2000). It is interesting to note that PDE5A1 and A2 are expressed in a tissue-specific manner although the latter is more dominant (Lin CS et al., 2003). To exemplify the developments in ion channels, the ability of ATP sensitive K+ channel subtype to play a key role in cavernosal relaxation has opened avenues for specific modulators/openers as molecular targets (Venkateswarlu K et al., 2002). Even the purported aphrodisiac mechanism of action of some plant androgens are being tested with the help of these in vitro systems and true enough, Jiang and others found that icariin for instance, worked through increasing cGMP levels and advantageously inhibiting PDE5 mRNA expression (Jiang Z et al., 2006).

As potential markers for La Peyronie's, in depth molecular and biochemical studies using DNA-based chip arrays and ionization mass spectrometry detected 3 upregulated and 2 downregulated proteins and a higher expression level of monocyte chemotactrant protein 1 (MCP-1) and transforming growth factor beta (TGF-beta 1-3). In addition, mRNA transcripts for TGF alpha, insulin like growth factor (IGF) and nerve growth factor (NGF) were also expressed in the tested specimens (Dahiya R et al., 1999; Gonzalez-Cadavid NF et al., 2002; Qian A et al., 2004; Lin GT et al., 2005; Hassoba H et al., 2005). In an advancing pathology, the identified activity of osteogenic progenitor stem cells may explain the calcification of fibroed plaque (Vernet D et al., 2005) and timely attempts at gene transfer using plasmid-expressing INOS indicate that endogenous iNOS induction may be protective or even preventive (Davila HH et al., 2004). The other areas of clinical interest where some of the above mentioned and additional factors come into play include increases in apolipoprotein D (ApoD) and IGF-1, 3, and 5 binding proteins in ischemic (Lin CS et al., 2001) and TGF-beta1, hypoxia inducible factor-1 alpha (HIF-1alpha) and collagen III in neurogenic ED states (Leungwattanakij S et al., 2003). Furthermore, in this era of proteomics, researchers have identified defective expression of several important proteins in some cases of neurogenic ED (Liu, X et al., 2007). Although analysis and interpretation of such protein modifications still present formidable challenges, these advanced techniques do provide fundamental insights into some of the key dysfunctional changes.

Moving from the cell-based gene therapy with endothelial cells, adeno-myoblasts and others (Wessells H et al., 1999; Tirney S et al., 2001), the day is not far when skeletal muscle-derived stem cells, which eventually convert into smooth muscle cells when implanted in the cavernosum (Nolazco G et al., 2008), may provide yet another viable cellular option in the area of stem and molecular therapy. Although there may still be limitations, the already successful attempt of gene therapy using naked DNA as the vector with maxi-K gene / alpha subunit of the human Maxi-K channel (hSlo) for ED is continuing to be focused on providing a practically restorative approach with adequate assurance of clinical safety (Melman A et al., 2008). If this exciting modality answers queries and stands the test of time, it will quietly succeed and overtake the other forms of ED management as the primary option for the future generation.
Not lagging far behind, molecular genetic studies using female genital tissues have investigated the principles of woman's sexual functioning. Although the complexities are yet to be completely unraveled, there are surely a number of advancements. In the context of extrapolating the available oral pharmacotherapy to the female disorders, there were some disappointments in spite of the fact that PDEIs are very successful in men. The low expression states of PDE5 in the human clitoral, labial and vaginal tissue, as shown by Uckert's group might be an answer to this limitation (Uckert S et al., 2007a). However, since both PDE3 and PDE4 are also present in the clitoris (Oelke M et al., 2006) and there is a widespread distribution of several cAMP- and cGMP-PDE isoenzymes (PDE3, PDE4, PDE5, PDE10 and PDE11) in the labia minora (Uckert S et al., 2007b), there are more avenues for therapeutic developments for FSD. Similarly, since all three NOS subtypes viz., nNOS, eNOS and iNOS (Park JK et al., 2002) are also present in the female genital tract, more studies are needed to delineate their roles in the functional outcome regulation.

Looking at the neuromodulators, in addition to functional adrenergic alpha-1 and -2 receptor subtypes (Kim NN et al., 2002), molecular characterization has further identified the expressions of angiotensin I (AT1a and AT1b) and II receptor mRNA; the regulation of the smooth muscle tone is probably through cross-talks with NO (Park JK et al., 1997; 2000). Classical cell culture studies have confirmed the modulatory roles of VIP, NO, PGE1 and others in this context and in further studies, tissue oxygen and hemoglobin contents were mentioned as additional tools to aid in the hemodynamic evaluation of sexual functioning (Min K et al., 2001a; 2001b). There is no doubt that these advances bear significance to our continuing quest for efficient pharmacological treatment of female sexual disorders.

Anatomically, regional differences exist with particular reference to vagina. The higher expression of myosin heavy chain isoform in the proximal vagina may contribute to its phasic contractile characteristics compared to the tonic type in the distal vagina (Basha M et al., 2006). In times of estrogen deprivation, there is an enhanced NO activity in the proximal but not the distal region (Traish AM et al., 2003). The exact impact of such regional variations in the elicited female sexual response is not known at this stage. However, threat to structural integrity is also an important factor in the female. There may be a disproportionate increase in caldesmon relative to myosin in certain situations, with a resultant inhibition of the vaginal smooth muscle contractility (Boreham MK et al., 2001) and estrogen-mediated increase in cystatin C may be seen as a compensatory or protective mechanism. As identified by cDNA array, increased vaginal cystatin C expression in the fibroblasts and smooth muscle bundles can help to strengthen the vaginal wall (Slayden OD et al., 2004).

After all, genital tissue reconstruction is now a possibility both in the male and female. We are moving ahead with the successful engineering of three-dimensional male erectile tissue architecture, basically grown from human CCSM and endothelial cell seeds on acellular collagen matrices (Park HJ et al., 1999; Falke G et al., 2003). On the women’s front, similarly seeded polymer scaffolds have notably converted into vascularized vaginal tissue possessing the same phenotypic and functional properties as the normal tissue (De Filippo RE et al., 2003). The clinical advantage of having such transplantable autologous tissue is manifold.

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E. EXPERIMENTAL MODELS FOR THERAPEUTICAL DEVELOPMENT

It is clear that animal models exist that can be used to develop treatments for – or to understand the etiology of – various sexual disorders. What is key in this analysis is the baseline of the animal. It is fine to study normative sexual function in animals, but “ceil-ing effects” may well prevent the ability to observe a facilitation of sexual function. To have a model of dysfunction, one must use animals that are hypofunctional. For example, albino male rats do not readily show psychogenic erections, whereas pigmented males do. The serotonin synthesis inhibitor parachlorophenylalanine (PCPA) had no effect on the number of psychogenic erections in pigmented Long-Evans males, but facilitated erections in albino Wistar males. Likewise, the stimulation of spontaneous erections by bre melanotid was always observed consistently in albino Sprague-Dawley rats, but not consistently in pigmented rats (A. Shadiack, personal communication). Because of their unique physiology that may well suppress erection due to higher than normal serotonin turnover, albino rats provide a lower baseline of erection that allows for an easier treatment effect.

Determining the “right” hormone baseline has been an issue for a long time in the female literature, as most of the doses used to induce sexual receptivity in female rats are maximal. Even repeated administration of low doses of estradiol to female rats (e.g., at 4-day intervals) results in a progressive upward drift in the number of solicitations and high-intensity lordoses (Farrell et al., in preparation). It is instructive to understand that in the natural world, although female rats are capable of estrous cycles every 4 or 5 days, they rarely do because they are either pregnant or pseudopregnant, which results in a far longer period of sexual nonreceptivity and suppression of the estrous (cycling) hormonal profile. Indeed, the induction of estrus termination by high amounts of distributed vaginocervical stimulation is masked by estradiol priming at 4- or 7-day intervals, but not by 14- or 28-day intervals (Pfaus et al., 2000). This indicates that the timing and dose of hormone priming is critical in generating a reliably low baseline upon which facilitative effects of a drug or treatment can be observed. This is also true of males, and will depend critically on the level of sexual experience and the amount of time since castration has occurred.

For sexual arousal, both behavioral and vascular models exist to examine mechanisms of erection, ejaculation, and vaginal/clitoral blood flow. Those models can be employed to study drug effects or molecular interactions, and to examine how peripheral actions are integrated in the brain, both in terms of sensory awareness and descending influences. For example, behavioral models of premature ejaculation exist in rats (Chan et al., 2008; Pattij et al., 2005) and those animals can be used as models for treatment paradigms or studied with regard to the neurochemical and neurophysiological mechanisms that underlie their rapid ejaculation.

For sexual desire and reward, it is vitally important to use models that have predictive validity. In copulatory circumstances, solicitations perhaps the display of high-intensity lordoses, are augmented by drugs (dopamine or melanocortin agonists) or conditioned cues associated with sexual reward. Conversely, pacing and defensive behaviors are diminished by those pharmacological or sensory primes. Likewise, conditioned partner or place preferences can be used to infer reward states that feed back positively on desire. The lack of reward, induced by early sexual experience that is not accompanied by opioid transmission, diminishes the desire of female rats to initiate sexual activity, and abolishes conditioned place and partner preferences in both male and female rats. A similar effect is observed in long-term castrated rats given subthreshold hormone priming. In both male and female rats, precopulatory operant or anticipatory locomotor paradigms, or responses made to unconditioned sexual incentives (e.g., sexually active vs. castrated conspecifics) or conditioned cues paired with reward, are useful to elucidate the basic neurochemical systems associated with their display. Castration, nonreward, and satiety diminish the display of those responses, and thus those paradigms provide a means to examine treatments that might stimulate sexual desire directly.

Sexual inhibition paradigms, either unconditional (in which the animals are presented with sexually non-receptive or unresponsive partners), or conditional (in which the animals are presented with stimuli on sexually responsive partners that was paired previously with sexually nonresponsive partners, or with a lack of sexual reward induced by concurrent treatment with naloxone), are likely to increase in use. Many premenopausal women with HSDD do not possess low hormone levels, thus it is likely that experiential factors have played a role in the etiology of the disorder. The appropriate animal model for such a clinical situation may well be one of low desire induced by sexual nonreward. Again, the most important requirement of the preclinical model will be predictive validity.
F. CONCLUSION - PERSPECTIVES

Animals possess appetitive and consummatory aspects of sexual behavior that are homologous and analogous to our own and that are controlled by similar or identical neurochemical and hormonal systems. They experience sexual arousal, desire, reward, and inhibition. Males are excited by females that require some form of courtship or pursuit, and will work hard to obtain even small sexual rewards. Females like to control the initiation and rate of sexual contact. Sexual behavior in males is strengthened with experience, making them less vulnerable to treatments that disrupt sexual responding. The same may occur in females. From an evolutionary perspective, sexual behavior appears to have similar processes and endpoints for all mammalian species, and perhaps for all species that engage in it. This makes the study of sexual behavior in animals, and the use of animals as models of sexual dysfunction.

If the process and endpoints of sexual response are the same (even if the outward expression of appetitive behaviors or copulation is species-specific), then animals can indeed be used as models of human sexual response provided the homology or analogy is specified unambiguously, and that treatments or experiences have similar effects between the species, giving the animal model predictive validity. This requires that we understand the particular behaviors of both species as best we can, which in turn requires that we be careful and creative in how we ask our scientific questions. For example, it was once believed that male rats lack the cognitive capacity and sophisticated cultural conditioning for sexual inhibition, thereby making them unsuitable models for the disinhibitory effects of alcohol (e.g., Wilson, 1977). Yet they clearly learn not to attempt copulation with sexually nonreceptive females, and show disinhibition under the influence of low doses of alcohol. It was also believed that female rats didn’t “enjoy” copulation because it took them longer to return to a male following intromission or ejaculation, relative to precopulatory interaction or mounts without intromission. However, Paredes and colleagues provided an important glimpse of what female rats really like about sex: their ability to control its occurrence and rate. If they have control over the initiation and rate of sexual interaction, then female rats will develop copulatory CPPs; if not, then CPPs do not develop despite the fact that females still copulate and are sexually receptive. For male rats, the reward state induced by ejaculation and/or its aftermath is critical for the development of CPP and partner preference. Larsson (1956) reported that some enforced intervals between intromissions were optimal for ejaculation whereas others that were too long (e.g., greater than 5 min) led to an inhibition of sexual activity. It may be that male rats also require a form of "control" with regard to female accessibility (as suggested by Martinez and Paredes, 2001). This can be expressed naturally in chasing or pursuit, or in other behaviors that maximize the desired rate of genital contact and stimulation. Control is an important aspect of sexual function in both men and women, and problems with locus of control may form an important part of the etiology of different sexual disorders (McCullough & Fine, 1999). Female rats display preceptive and receptive sexual behaviors only during their periovulatory period, or if they are ovariectomized and given appropriate replacement with estrogen and progesterone. Although female primates, including humans, can have sex throughout their ovulatory cycles, they display increased female-initiated solicitation and sexual activity during their periovulatory periods (Wallen, 1982, 1995). Making the conceptual connection between animal and human sexual behaviors is the primary challenge for researchers. Subsequent testing of those connections is easier, but equally important.

We believe that animal models will continue to be indispensable for studies of the neurobiology of sexual behavior. We need the knowledge that lesion and drug studies, neurochemical and neuroanatomical analyses, and molecular approaches, provide in animals to guide our emerging work in the neuroanatomy of sexual responding in humans using functional magnetic resonance imaging or positron emission tomography. We need animal models to further understand the hormonal processes that lead to changes in sexual arousability (e.g., following hormone replacement therapy in postmenopausal or hypogonadal individuals). The kind of invasive and direct studies of brain or organ function in animals simply cannot be conducted in human subjects.

Although studies of human and animal sexual behavior have advanced independently, their convergence is long overdue. More and more animal models of human sexual response are being used productively by clinical sex researchers and neuroendocrinologists to study the neuroanatomy, neurochemistry, and pharmacology of sexual behavior. The cross-fertilization of these two fields can only lead to a greater understanding of sexual behavior in general, and provide more scientific sophistication to understand its unique -- and common -- expression in all species.
G. RECOMMENDATIONS FROM THE COMMITTEE FOR THE STUDY OF MALE AND FEMALE SEXUAL FUNCTION AND DYSFUNCTION

This committee notes the continuing development of animal models of behavioral, physiological, and pathophysiological conditions in humans. Although the committee recognizes that human sexual behavior and its disruption by organic or psychological conditions is best studied in humans, the committee notes the ethical and practical considerations that make it difficult—if not impossible—to do this on a wide scale. The committee also notes that animal studies provide crucial information from a basic science point of view that both informs treatment strategies and provides sexual medicine with the ability to identify mechanisms in the central nervous system and periphery that can be targets for physiological, pharmacological, behavioral and surgical interventions. It is difficult to make many specific recommendations, other than to strongly endorse the continuing creative development of ethologically-and clinically-relevant animal models.

1. WHAT MAKES A GOOD ANIMAL MODEL FOR THE STUDY OF THE SEXUAL FUNCTION?

Predictive validity is the most important requisite of an appropriate animal model. In addition to this, animal models should be simple and practical enough to have “high throughput”, meaning the ability to have experiments conducted relatively quickly. Issues of sample size and ease of testing and analysis are key factors. The validity of any homologous or analogous animal model can only be determined in situations that test whether a treatment that modifies behavior and/or sexual function in the animal does so in humans.

Rats continue to be the most frequently-used animals in the study of sexual functions and behavior. Rats resemble humans in many analogous and homologous ways.

2. PENILE ERECTION

From a physiological perspective, it appears that there is a close similarity between local mechanisms of penile erection between non-human mammals and humans except for the role of striated muscles which are less important in humans compared to various animal species.

Although care must always be taken before extrapolating quickly from experimental data to the clinical situation, there is a high degree of predictability from rat models to men. Nature appears to have conserved mechanisms of erection in mammalian males.

Behavioral paradigms that assess penile erection in rats include both spontaneous and noncontact erections. The latter is stimulated predominantly by olfactory stimuli (either unconditioned estrous odors from a female, or conditioned odors (e.g. almond) associated with ejaculation) and thus appears to analogous to “psychogenic” erection in men stimulated in response to erotic visual cues.

3. ERECTILE DYSFUNCTION

A non-exhaustive list of pathophysiological models of ED comprises hypertensive rats, atherosclerotic rabbits, diabetic type I and II rats and rabbits, rats with metabolic syndrome, aged rats, castrated rats, cavernous nerve-injured rats... The question of extrapolation to humans using of these various experimental conditions must always be asked before drawing conclusions regarding applicability. It is noteworthy that there is no established standard in this domain and no standardization paradigms between laboratories. Both are critical in particular for diabetes and cavernous nerve injury, therefore we propose that the endpoints must be analogous or homologous (e.g., the restoration of erectile capability sufficient for copulation). Overall there is a high degree of predictability from rat models to men.

Transgenic or knock-out mice have contributed to our understanding of the physiological mechanisms of erectile function as well as various pathophysiological processes occurring during ED.

Cellular and molecular investigation techniques are available including cavernosal smooth muscle cell culture, 2nd messenger pathway: cGMP, cAMP, qRTPCR ...

Tissue engineering and stem cell research is also well established using erectile tissue, pelvic plexus, cavernosal nerve.

4. GENE THERAPY

The apparent preclinical success of most, if not all, gene-based strategies for the treatment of erectile dysfunction is consistent with the multifactorial regulatory mechanisms governing the erectile process.

5. LAPEYRONIE’S DISEASE

An experimental model of transforming growth factor-beta 1 (TGF-β1) induced Lapeyronie’s like condition in the rat has been proposed.

6. PRIAPISM

A transgenic sickle-cell mouse model to study the pathophysiology of priapism has been recently established.
7. EJACULATION

In behavioral experiments, ejaculations in rats can be studied much the same way they are studied in humans, with the latency from first mount or intromission to ejaculation being the key variables. A variety of paradigms have been developed in anesthetized rats, most of them recently:

- Urethrogenital reflex in spinalized rat may be considered as mimicking an orgasm-like response.
- Electrical stimulation of the hypogastric nerve elicits a rise in seminal vesicle and bladder neck pressures partly mimicking emission.
- Pudendal motoneuron reflex discharge is thought to be an experimental model representing what occurs in human during sexual intercourse and that culminate with expulsion of sperm.
- Complete ejaculation can be elicited by electrical stimulation of intermesenteric nerves or more reliably by microstimulation of the lumbar spinothalamic neurons
- Pharmacologically-induced ejaculation can be elicited by para-chloroamphetamine, 8 or 7-OH DPAT.

8. MALE SEXUAL DESIRE

The willingness to mount, intromit, and pursue females, can be used as analogues of male desire. Desire can be also inferred from certain appetitive responses that occur during copulation such as chasing behavior in males. Appetitive responses that occur prior to sexual activity, especially conditioned appetitive responses, may have the most direct applicability to human sexual desire.

9. FEMALE SEXUAL RESPONSE

In anesthetized female rabbit or rat, peripheral neural electrical stimulation elicits vaginal and clitoral vascular response.

10. FEMALE ORGASM

The paradigm of the uro-genital reflex allows the investigation of a female orgasm-like response.

11. FEMALE SEXUAL DESIRE

Psychological arousal or desire in women is likely to be very close to appetitive and precopulatory behaviours, such as solicitations. Accordingly the study of appetitive behaviors and precopulatory behaviours is relevant to any preclinical investigation of potential of compounds for the treatment of female sexual disorders or dysfunctions.

12. SEXUAL REWARD MODELS

Several recent studies have linked the state induced by ejaculation in male rats and by paced mating in female rats with the induction of sexual reward. Paradigms include both conditioned place and partner preferences. Interestingly, the induction of behaviors indicative of sexual desire in both male and female rats are strongly related to the reward state that induce place and partner preferences. Therefore the committee recommends continued development of those paradigms and further basic research into the neuroanatomical and neurochemical support mechanisms that underlie those reward states.

13. MODELS OF SEXUAL INHIBITION

There is a need for the development of animal models of hypoactive sexual desire in both males and females. Such models may include hypogonadal conditions following removal of the gonads and replacement with sub-optimal hormone priming (e.g., estradiol-alone in females or subthreshold testosterone in males), sexual non reward paradigms in which the induction of reward is blunted pharmacologically (e.g., using the opioid receptor antagonist naloxone), or the induction of sexual satiety or estrus termination that leads to inhibition of sexual desire, arousal and copulation.

There is a need for the development of sexually-related pain models of both behavior and neurphysiology.
Committee 8

Cardiovascular Aspects of Sexual Medicine

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I. INTRODUCTION

1. SIZE OF THE PROBLEM

Erectile dysfunction (ED) is a common worldwide clinical problem[1]. It is estimated that 150 million men worldwide currently experience ED to a variable degree and by 2025 the prevalence is predicted to rise to over 300 million men[2]. In the Massachusetts Male Aging Study (MMAS), a large population-based random sample of 1290 healthy men aged 40 to 70 years, 52% and 70% of men aged 40–70 or >70 years of age, respectively had some degree of sexual dysfunction. ED was related to age, number of risk factors and concomitant heart diseases [3].

2. ROLE OF RISK FACTORS: “OVERLAP OF RISK FACTORS”

The risk factors for coronary artery disease (CAD) and ED leading to endothelial damage and vascular obstruction are similar, including age, dyslipidaemia, hypertension, diabetes, smoking, sedentary lifestyle, obesity and depression. As a consequence men with ED have a higher incidence of concomitant (silent or manifest) CAD or peripheral vascular disease than non-ED. In addition men with a common vascular disorder, mainly CAD, have an increased incidence of concomitant (not declared) ED or peripheral vascular disease than non-ED. In addition men with a common vascular disorder, mainly CAD, have an increased incidence of concomitant (not declared) ED. Most patients with ED are known to have at least one significant cardiovascular risk factor[4-8]. Seftel et al[9] found that in a general ED population the prevalence of 4 major risk factors - hypertension, diabetes, hyperlipidemia and depression - were 41.6%, 42%, 20% and 11%, respectively. Prevalence was age-related with at least one risk factor found in 85% over 75 years of age. Overall, ED men have a much higher prevalence of risk factors than non-ED men after adjusting for age[10]. In addition, the number of risk factors has been found to be correlated with the likelihood of having abnormal penile blood flow hemodynamics as assessed by penile duplex Doppler ultrasound [11,12]. Interestingly, in many patients with a first diagnosis of ED, underlying, undiagnosed cardiovascular co-morbidities can be detected. For example, both Seftel et al[9] and Sun et al[13] reported 40% undetected hypertension in ED patients. Any form of underlying glucose intolerance or true diabetes was found in up to 17% of ED subjects[14].

a) Hypertension

A significant number of hypertensive patients are likely to have ED. In the MMAS the age-adjusted probability of complete ED was 15% in treated hypertensives compared to 9.6% of the whole population[3]. In another study, ED was reported in 17% of men with untreated hypertension in comparison with 25% of men who were receiving current antihypertensive treatment; a finding which suggests that certain treatments can induce significant deleterious effect on erectile mechanisms. Furthermore, these data indicate that there needs to be careful assessment of the impact of antihypertensive medications in the analysis of hypertension-associated ED. Burkardt et al mailed the International Index of Erectile Function (IIEF) questionnaire to 476 male patients with hypertension[15]. One hundred and four patients (mean age 62.2 years) completed the questionnaire. of these, 68.3% had some degree of ED. ED was mild in 7.7%, moderate in 15.4% and severe in 45.2%. Compared to the general population of ED cases, patients with hypertension had more severe ED (45.2% in hypertensives versus ~10% in a general population as reported by the MMAS). The authors concluded that ED was more prevalent in patients with hypertension than in age-matched controls and that the degree of ED was more severe in patients with hypertension than the general male population. In a survey of 7689 patients (mean age 59 years) using the Sexual Health Inventory in Men (SHIM) questionnaire, Giuliano et al[16] reported an ED rate of 67% in 3906 men with isolated hypertension, 71% in 2377 men with isolated diabetes and 77% when the combination of hypertension and dia-
b) Smoking

In the original MMAS[1] smoking increased the age-adjusted probability of complete ED in men with treated heart disease. Moreover, it doubled the chance of developing ED over an eight-year follow-up period in those who were free from ED at study entry[3]. Smoking is well known as a risk factor for endothelial damage and vascular disease. Although cessation of smoking later in life may still be of some benefit to the 3-4 mm coronary arteries, it may be too late to reverse damage to the small (1-2 mm) penile arteries[17].

c) Lipid abnormalities

A study by Wei et al[18] followed-up for almost two years 3250 men with dyslipidemia and no ED. They showed that a cholesterol value >240 mg/dL (6.2 mmol/L) increased the risk of ED by 1.8 times compared to men with a <180 mg/dL (4.78 mmol/L) level. A high density lipoprotein level >60 mg/dL (1.55 mmol/L) was associated with a lower (0.3 times) risk of ED as compared to <30 mg/dL (0.78 mmol/L) level. Every 1 mmol/L increase in total cholesterol level was associated with a 1.32 times risk of ED whereas a similar increase in HDL-cholesterol was associated with a 0.38 decrease of ED. In contrast to what might be expected, lipid-lowering therapy may not benefit ED and in some cases can actually cause or exacerbate ED, possibly due to a central action secondary to blood-brain barrier penetration, though additional multiple risk factors may also be causative[19].

d) Diabetes

Diabetics suffer from both endothelial/vascular and neurological ED, with ED prevalence as high as 80% in those over 60 years of age[20]. As compared to non diabetics, ED occurs at an earlier age and is strongly influenced by the duration of the metabolic alteration. It is possible that early and vigorous glucose control might be preventative. In addition, the early use of statins and perhaps prophylactic PDE-5 inhibitors as daily therapy theoretically could preserve endothelial function[21].

e) Lifestyle issues

Recent epidemiologic studies have investigated in a longitudinal assessment the role of different risk factors on the development and progression of ED[22]. The long-term extension of the original MMAS study investigated whether cigarette smoking, heavy drinking, sedentary lifestyle, and obesity were associated with an increased risk of developing moderate-to-severe ED in a population of men who were initially potent or mildly impotent, and were followed for an average of 8 years. Results revealed a low risk of ED among men who maintained a physical activity level of at least 200 kcal per day. In addition, the ED risk was high among men who exhibited sedentary activity levels at both baseline and follow up. Most importantly, the risk of ED was significantly reduced among men who were sedentary at baseline and became physically active during the course of the study.

3. CARDIOVASCULAR RESPONSE TO SEXUAL ACTIVITIES

The cardiovascular response to sexual activity is the combination of mild-to-moderate physical activity and a state of arousal (so-called sexual arousal). Opposite to what is commonly thought, sexual arousal is the major determinant of the cardiovascular response to sex. The fundamental paper by Bohlen et al[23] evaluated the hemodynamic and metabolic response to sexual activity in 10 healthy men (mean age 33 yr). Four different types of sexual activity (self stimulation, partner stimulation, orgasm with men on top and with woman on top) were tested. The response was compared with that of a symptom-limited treadmill test. During sexual activity, the heart rate progressively increased with a peak value during orgasm greater with men on top than with woman on top (127±23 bpm vs. 110±24 bpm, p<0.02). During orgasm, the heart rate increase varied to 54-67% of the peak heart rate achieved during the treadmill, with little difference between the four types of sexual activity. Similar results were obtained for oxygen consumption (VO2), expressed as the metabolic equivalent of the task (MET) where 1 MET is equivalent to the VO2 consumption in a resting state, was calculated. During orgasm, the VO2 consumption varied by 11-22% of that obtained at peak treadmill test. The mean METs value was 3.3 for coitus with man on top. Thus, sexual activity poses little cost to the heart and is similar to ordinary daily activities and much less than maximal exercise. Sexual arousal more than exertion is the major determinant of VO2 consumption.

The cardiovascular responses during sexual activity in patients with CAD elicit qualitative changes similar to normals (Table 1). In a study of 30 men and 5 women with stable angina patients assessed by 24 hour ECG monitoring, the heart rate response averaged 122 beats/minute (range:102-137 beats/min) during intercourse compared to a maximum of 124 beats/minute during the rest of the day[24].

Some general considerations should be kept in mind. Firstly, the cost of intercourse is lower (3-4 METs) for couples in a long standing relationship than for extramarital intercourse with an unfamiliar partner. In this setting, the higher heart rate achieved during the sexual intercourse, mainly due to an high degree of sexual arousal, performance anxiety, ingestion of alcohol and food, social disapproval, accounts for the higher cardiac workload and the risk of an
acute cardiac event[25]. Secondly, younger couples may be more vigorous in their sexual activity than older ones expending up to 5-6 METs. Finally, the concomitant use of cardiovascular medication such as beta-blockers and/or calcium-antagonist, may lower sexual activity cost even in CAD patient with reduced coronary reserve, limiting the risk of effort-induced acute coronary events.

Thus, exercise stress test is the most indicated tool to check functional reserve before sex. Drory et al[26] assessed the cardiovascular response to sex by exercise testing and Holter monitoring in 88 CAD patients with stable angina when off-therapy. In the 34 patients with negative exercise testing none had ischemia with Holter monitoring whereas positive exercise testing was associated with ischemic changes by Holter monitoring during sex in 50% of patients. Thus, CAD patients should be always asked to perform an exercise stress test before initiating or resuming sexual activity. If they can exercise up to 3-6 METs without evidence of myocardial ischemia, they can generally engage in sexual activity without experiencing cardiac symptoms.

In an asymptomatic subject, tolerance to sexual activity may be assessed by simple everyday guidelines. If he/she can tolerate walking 1 mile (1.5km) briskly on the level in 20 minutes (3-4 METs) or climb two flights of stairs without limiting symptoms (6 METs), it is highly probable that sexual activity can be tolerated without cardiac symptoms. (Table 2)

However, because there may be a significant variation in the physiologic response to sexual activity, it is important to individualize the advice. If sexual activity leads to angina pectoris because of a disproportionate myocardial oxygen demand relative to the supply, the effect of exercise training can decrease the myocardial oxygen demand for the same amount of total body work and should decrease or obviate the occurrence of angina pectoris.

### Table 1: Cardiovascular response during sexual activity in normals and CAD.

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Mean peak heart rate (beats/minute)</th>
<th>METs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nemec (1964)</td>
<td>10</td>
<td>114</td>
<td>114</td>
</tr>
<tr>
<td>Larson (1980)</td>
<td>17</td>
<td>115</td>
<td>115</td>
</tr>
<tr>
<td>Masini (1981)</td>
<td>10</td>
<td>126 (M) – 137 (F)</td>
<td>126</td>
</tr>
<tr>
<td><strong>CAD patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hellertsein (1970)</td>
<td>14</td>
<td>117</td>
<td>117</td>
</tr>
<tr>
<td>Stein (1977)</td>
<td>16</td>
<td>127</td>
<td>127</td>
</tr>
<tr>
<td>Jackson (1981)</td>
<td>35</td>
<td>122</td>
<td>122</td>
</tr>
<tr>
<td>Garcia-Barreto (1986)</td>
<td>23</td>
<td>111 (M) – 104 (F)</td>
<td>111</td>
</tr>
<tr>
<td>Drory (1995)</td>
<td>88</td>
<td>118</td>
<td>118</td>
</tr>
</tbody>
</table>

M= male; F= female

### Table 2: Metabolic equivalent of task units (METs) as a guide to relating daily activity to sexual activity.

<table>
<thead>
<tr>
<th>Daily Activity</th>
<th>METs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual intercourse with established partner</td>
<td>2-3</td>
</tr>
<tr>
<td>Lower range (normal)</td>
<td>3-4</td>
</tr>
<tr>
<td>Lower range orgasm</td>
<td>5-6</td>
</tr>
<tr>
<td>Upper range (vigorous activity)</td>
<td></td>
</tr>
<tr>
<td>Lifting and carrying objects (9-20kg)</td>
<td>4-5</td>
</tr>
<tr>
<td>Walking 1.6km (1 mile) on the level in 20 minutes</td>
<td>3-4</td>
</tr>
<tr>
<td>Golf</td>
<td>4-5</td>
</tr>
<tr>
<td>Gardening (digging)</td>
<td>3-5</td>
</tr>
<tr>
<td>Do-It-Yourself, wallpapering, etc</td>
<td>4-5</td>
</tr>
<tr>
<td>Light housework; e.g. ironing, polishing</td>
<td>2-4</td>
</tr>
<tr>
<td>Heavy housework; e.g. making beds, scrubbing floors, cleaning windows</td>
<td>3-6</td>
</tr>
</tbody>
</table>
5. POST-MI SEXUAL DYSFUNCTION AND COITAL DEATH

At least half of the patients who have suffered a MI never regain their earlier frequency of sexual activity. In one of the earliest studies of post-MI sexual dysfunction, 39 men were evaluated one year after MI. One-third of them had intercourse only half as often, and another one-third, only one-quarter as frequently as they did before their MI[32].

There is considerable variation in the incidence of post-MI symptoms, which occur in 8 to 57% of patients, depending on the time after MI at which they are evaluated, how carefully they are questioned about their symptoms, and whether they participate in an exercise rehabilitation program[33]. The relative risk of triggering the onset of MI among patients with a history of prior angina or prior MI was not greater than that observed in those without prior cardiac disease.

Hence, it is safe for the recovering MI patient who is in stable condition and not suffering from congestive heart failure, unstable angina, or arrhythmia not responding to treatment, to resume sexual activity.

### Table 3: Relative risk of myocardial infarction during the 2 hours after sexual activity: physically fit equals sexually fit.

<table>
<thead>
<tr>
<th>Patient type</th>
<th>Relative risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>2.5 (1.7-3.7)</td>
</tr>
<tr>
<td>Men</td>
<td>2.7 (1.8-4.0)</td>
</tr>
<tr>
<td>Women</td>
<td>1.3 (0.3-5.2)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>2.9 (1.3-6.5)</td>
</tr>
<tr>
<td>Sedentary life</td>
<td>3.0 (2.0-4.5)</td>
</tr>
<tr>
<td>Physically active</td>
<td>1.2 (0.4-3.7)</td>
</tr>
</tbody>
</table>

4. SEXUAL ACTIVITY AS A RISK FACTOR

Overall, the risk of myocardial infarction during sexual activity is negligible[27]. Although maintaining sexual activity has been reported to have potential health benefits, it can trigger myocardial infarction (MI), arrhythmia or sudden death in a very small minority of patients[28,29]. The Myocardial Infarction Onset Study (MIoS) enrolled 1712 patients with a first episode of myocardial infarction (MI)[30]. Sexual activity was the potential trigger for myocardial infarction in 1.5% of cases. Among 858 sexually active in the year before MI, 70 (9%) reported sexual activity in the 24 hours preceding the acute coronary event, and 27 (3%) in the two hours preceding the onset of symptoms. The relative risk of MI was assessed by “case-crossover” methodology.

Table 3 shows the figures for different categories of patients developing MI during sexual activity. Overall, the relative risk of MI was increase by 2-3 times and was confined to the 2 hours after sexual activity. After correcting for chance occurrence, 0.9% of cases could be attributed to sexual activity within the 2-hour period before MI onset. Of paramount importance was the observation that the risk decreased to none if the subject engaged in regular physical activity (at least 3 times/week) at moderate workload (5-6 METs).

A more important concept is the absolute risk of MI during sex. In other words: “How much does sexual activity increase an individual’s risk of MI above their baseline risk?”. We know from the Framingham Heart Study that the baseline risk of MI for a 50-year-old non-smoking, non-diabetic man is 1% per year or 1 chance in a million per hour. As sexual activity increases the relative risk by 2-3 times, this subject will have a 1.01% per year (or 2-3 chances in a million, only for a 2-hour period). In patients who have had a previous MI, the baseline risk of reinfarction or death is: 10% per year or 10 chance in a million per hour increasing to 10.1% per year or 20 chance in a million for a 2-hour period after sexual activity. Once again, the risk decreased to <3% if the patient could exercise >7 METs.

Coital sudden death is very rare. In three large studies death related to sexual activity was 0.6% in Japan, 0.18% in Frankfurt, and 1.7% in Berlin[31]. Extramarital sex was responsible for 75%, 75% and 77% respectively, and the victims were men in 82%, 94% and 93% of cases respectively. The partnership of an older man with a younger woman was the most common setting. Excessive drinking and sex too close to a large meal were frequently associated.

The association between cardiovascular disease and ED may be related to increased catecholamine loading during sexual performance, especially in patients with ED. Factors such as fear of failure, performance anxiety, anger, shame, and embarrassment may lead to release of systemic norepinephrine. Catecholamine loading during sexual performance may also be related to physiologic and psychologically mediated sexual-related pain, such as Peyronie’s disease, prostatitis, epididymitis, or nongenital pain (e.g. headache). In addition, a physiologically induced catecholamine load may be related to sexual performance itself.
Studies of post-MI patients have shown that heart rate, blood pressure, and ST segment changes recorded during intercourse are within the limits of many other ordinary daily activities[34].

6. CAUSES OF POST-MI SEXUAL DYSFUNCTION

a) Psychological factors

Patients with angina are likely to experience a conflict between the desire for intercourse and the fear of anginal pain and its implication for the heart[35]. Psychogenic factors, rather than physical distress or medication side effects, are the most common cause of post-MI sexual dysfunction. Patients may react psychologically to the MI with fear, denial, manipulation or acceptance. Each of these reactions may affect their sexual function[36].

b) Physical distress

Patients may develop chest pain, palpitations, shortness of breath, or fatigue, which often creates fear and thereby affects the frequency and quality of sexual encounters[33]. Patients with CAD may report chest pain during sexual activity. A patient who had such symptoms before he developed acute coronary event is likely to be even more fearful and anxious upon resuming a normal sex life after recovery. When pain originates “in the heart” the individual feels especially vulnerable, since from childhood on, the heart is understood to be at the centre of life itself. Therefore, the individual who is subjected to attacks of angina tends to try to avoid any activity that could provoke an attack.

c) Drugs

Some cardiovascular drugs, such as diuretics, digoxis, beta-blockers, central-acting antihypertensives drugs, antiarrhythmics, lipid lowering agents, may affect patient’s sexuality. Psychotropic drugs may also have negative effects. All these drugs may affect libido, erection, ejaculation or orgasm (Table 4) [37].

d) Prior sexual problems

Prior abnormal sexual function such as, ED or ejaculatory disorders will continue or be exaggerated after a heart attack. Some patients use their illness as a source of power to manipulate or control those around them in order to obtain their desires. Such behaviors commonly include demands for or abstinence from sexual activity, especially in those relationships where sex has always been used to reward or punish[36].

e) Spouse fear and anxiety

Spouses are most often concerned that sex may be too stressful or unsafe for a cardiac patient. Such fears ultimately will affect their desire to resume sexual relations. Many wives of post-MI patients expressed concerns about risks of sexual activity and the negative effects of this situation on the couple’s emotional relationship[34].

7. ASSESSING THE RISK OF SEX IN ED PATIENTS: THE PRINCETON CONSensus CONFERENCE

The first Princeton Consensus Conference (Princeton I) in 1999 addressed the evidence linking sexual activity and cardiac risk and developed guidelines for safe management of cardiac patients regarding sexual activity and the treatment of ED. The second conference (Princeton II) updated the recommendations based on the expanding knowledge base and new treatments available[38,39].

Princeton I has proved to be a useful clinical guide to evaluating ED and sexual activity in cardiac patients and those at cardiac risk. The importance of ED as a risk marker in men with no cardiac symptoms is highlighted in Princeton II as is the value of lifestyle

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**Table 4: Medications that may cause ED.**

<table>
<thead>
<tr>
<th>Antihypertensives</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics (thiazides, spironolactone)</td>
<td>Calcium antagonists</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>Sympathomylitics</td>
</tr>
<tr>
<td>Sympathomylitics</td>
<td>Beta blockers</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychotropics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants (monoamine oxidase inhibitors, tricyclics, selective serotonin reuptake inhibitors)</td>
<td>Tranquilizers (phenothiazines, butyrophenones, thioxanthenes)</td>
</tr>
<tr>
<td>Tranquilizers</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Opiates</td>
</tr>
<tr>
<td>Opiates</td>
<td>Antipsychotics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hormonal/endocrine</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oestrogens</td>
<td>Anti-androgens</td>
</tr>
<tr>
<td>Anti-androgens</td>
<td>Gonadotropin agonists</td>
</tr>
<tr>
<td>Gonadotropin agonists</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Metoclopramide</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Fibric acid derivatives</td>
</tr>
<tr>
<td>Fibric acid derivatives</td>
<td>Statins</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory/allergy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Bronchodilators</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>Antihistamines (chlorpheniramine, diphenhydramine, chlortrimeton)</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Decongestants (especially pseudoephedrine)</td>
</tr>
</tbody>
</table>

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changes. The concept of “physically fit = sexually fit” is emphasized. The categories of low-, intermediate- or indeterminate-, and high-risk patients are maintained but updated (Table 5) and the algorithm changed to emphasize the importance of CAD and general vascular disease risk assessment (Figure 1).

The Second Princeton Consensus Conference recommendations addressed this topic more specifically in patients with sexual dysfunction and heart disease [39]. According to the number of conventional risk factors (if asymptomatic) or the presence

Table 5: Risk from sexual activity in cardiovascular diseases. Second Princeton Consensus Conference.

<table>
<thead>
<tr>
<th>Low risk: typically implied by the ability to perform exercise of modest intensity without symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic and ≤3 major risk factors (excluding gender)</td>
</tr>
<tr>
<td>Major cardiovascular disease risk factors include age, male gender, hypertension, diabetes mellitus, cigarette smoking, dyslipidaemia, sedentary lifestyle, and family history of premature CAD</td>
</tr>
<tr>
<td>Controlled hypertension</td>
</tr>
<tr>
<td>Beta-blockers and thiazide diuretics may predispose to ED</td>
</tr>
<tr>
<td>Mild, stable angina pectoris</td>
</tr>
<tr>
<td>Non-invasive evaluation recommended Antianginal drug regimen may require modification</td>
</tr>
<tr>
<td>Post-revascularisation and without significant residual ischaemia</td>
</tr>
<tr>
<td>ETT may be beneficial to assess risk</td>
</tr>
<tr>
<td>Post-myocardial infarction (MI) (6-8 weeks) but asymptomatic and without ETT-induced ischaemia, or post-revascularization</td>
</tr>
<tr>
<td>If post-revascularization or no ETT induced ischaemia, intercourse may be resumed 3-4 weeks post-MI</td>
</tr>
<tr>
<td>Mild valvular disease</td>
</tr>
<tr>
<td>May include select patients with mild aortic stenosis</td>
</tr>
<tr>
<td>LVD (NYHA class I)</td>
</tr>
<tr>
<td>Most patients are low risk</td>
</tr>
</tbody>
</table>

Intermediate or indeterminate risk: evaluate to reclassify as high/low risk

Asymptomatic and ≥3CAD risk factors (excluding gender)
Increased risk for acute MI and death ETT may be appropriate, particularly in sedentary patients

Moderate, stable angina pectoris
ETT may clarify risk

MI >2 weeks but < 6 weeks
Increased risk of ischaemia, reinfarction, reinfarction, and malignant arrhythmias ETT may clarify risk

LVD/congestive heart failure (CHF) (NYHA class II)
Moderate risk of increased symptoms Cardiovascular evaluation and rehabilitation may permit reclassification as low risk

Non-cardiac atherosclerotic sequelae (peripheral arterial disease, history of stroke or transient ischaemic attacks)
Increased risk of MI Cardiological evaluation should be considered

High risk: defer resumption of sexual activity until cardiological assessment and treatment

Unstable or refractory angina
Increased risk of MI

Uncontrolled hypertension
Increased risk of acute cardiac and vascular events (e.g. stroke)

CHF (NYHA class III, IV)
Increased risk of cardiac decompensation

Recent MI <2 weeks
Increased risk of reinfarction, cardiac rupture or arrhythmias, but impact of complete revascularization on risk is unknown

High risk arrhythmias
Rarely malignant arrhythmias during sexual activity may cause sudden death Risk is decreased by an implanted defibrillator or pacemaker

Obstructive hypertrophic cardiomyopathies
Cardiovascular risks of sexual activity are poorly defined Cardiological evaluation (ETT and echocardiography) may guide patient management

Moderate to severe valve disease
Use vasoactive drugs with caution

Adapted from Kostis et al [39]
CAD – coronary artery disease; CHF – congestive heart failure; CV – cardiovascular; CVA – cerebrovascular accident; ED – erectile dysfunction; ETT – exercise tolerance test; LVD – left ventricular dysfunction; MI – myocardial infarction; NYHA – New York Heart Association
and the severity of common heart diseases, subjects are divided into three risk categories: low, intermediate- or indeterminate and high risk. Low-risk patients should be reassured and retested in about 5 years. Medications for ED can be prescribed without need for additional tests. High risk patients, mainly those with severe heart diseases, should undergo further cardiologic assessment and should receive aggressive treatment of their risk factors. In this group of patients, treatment for ED should be deferred until a full cardiologic assessment is performed. Men at intermediate- or indeterminate risk, may benefit from additional non-invasive tests aimed to better define the presence and the extension of subclinical coronary atherosclerosis and be re-allocated patients into low or high categories[40,41].

8. ASSESSING THE RISK OF SEX IN ED PATIENTS AT INTERMEDIATE- OR INDETERMINATE RISK: ROLE OF NON-INVASIVE TESTING

An exercise treadmill stress test is performed for the detection of CAD and for assessment of cardiovascular efficacy during exercise and risk stratification of patients. Stress echocardiography, a feasible and accurate technique for the identification and localization of CAD[42], has been added to the investigation profile to increase the sensitivity for the detection of CAD. Men with ED who have a negative stress echocardiography study are at low risk for cardiac death for two years following the stress study[43]. If at least one of these tests was positive, the patients should be referred for coronary angiography for documentation and assessment of the severity of possible CAD.

Some tests address obstructive atherosclerosis by directly assessing coronary flow reserve (e.g. standard exercise stress test, rest/stress myocardial scintigraphy or echocardiography). Other tests are general measures of atherosclerosis burden (not necessarily obstructive) either in the coronary circulation (e.g. coronary calcium score by electron-beam computed tomography [EBCT]), or in extracoronary vessels (e.g. ankle brachial index [ABI], carotid intima-media thickness [IMT] by B-mode ultrasound) as surrogate markers of CAD[44-46]. Although a systematic use of these measures of non-obstructive atherosclerosis burden has not yet been recommended in the guidelines for coronary risk assessment, their use is progressively being extended from the research area to clinical practice[47].

Efforts to identify diagnostic tools that might improve the prediction of acute coronary events beyond the role of classical risk factors continue. These tools include measures of atherosclerosis burden and indexes of vascular function (endothelial dysfunction) or vascular inflammation (high-sensitivity C-reactive protein [hsCRP])[48].

Nineteen percent of patients with ED of vascular origin have angiographically documented silent CAD. According to these studies, the prevalence of CAD determined angiographically in coronary asymptomatic patients ranges from 1.34 to 4.5%[49,50]. Although an exercise ECG is advocated to identify patients at increased cardiovascular risk, this method will identify only those people with obstructive flow-limiting CAD. Wherever possible, intermediate and high-risk patients should be considered for elective computed tomography coronary angiography to identify the presence of non-flow limiting lipid plaques that are potentially vulnerable to rupture[51]. By implementing these measures, it should be possible to initiate early aggressive cardiovascular risk reduction in 'at-risk' patients, thereby taking advantage of
the 2-5 year window of opportunity between the development of symptomatic ED and CAD[52,53].

9. CONCLUSION

<table>
<thead>
<tr>
<th>ED and CAD share the same risk factors</th>
<th>LOE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual activity for couples in a stable relationship does not increase cardiac events</td>
<td>LOE 1</td>
</tr>
<tr>
<td>Sex is not an undue stress to the heart</td>
<td>LOE 1</td>
</tr>
<tr>
<td>Several medications can cause ED</td>
<td>LOE 1</td>
</tr>
</tbody>
</table>

10. RECOMMENDATIONS

<table>
<thead>
<tr>
<th>Men with ED should have their CAD risks assessed and treated</th>
<th>Grade A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual activity safety can be assessed using non-invasive stress testing</td>
<td>Grade A</td>
</tr>
<tr>
<td>Exercise stress testing and computed coronary angiography can be used to detect occult CAD</td>
<td>Grade A</td>
</tr>
</tbody>
</table>

II. VASCULOGENIC ERECTILE DYSFUNCTION

Vascular erectile dysfunction consists of arteriogenic ED (cavernosal artery insufficiency) and veno-occlusive ED (dysfunction of penile venous system)[54]. Although frequently discussed separately, in reality these two mechanisms often coexist in the same patient, and may reflect two stages of the same pathological process.

Erectile rigidity depends upon the rate and volume of blood flow into the corpora cavernosa of the penis via cavernosal arteries as well as passive veno-occlusion, which maintains rigidity[55]. It is estimated that 70% of all ED is the result of changes related to both the intrapenile and pre-penile vasculature either through diminished inflow or excessive outflow[56].

1. PATHOPHYSIOLOGY OF VASCULAR ERECTILE DYSFUNCTION

Vascular erectile dysfunction is the result of a combination of functional as well as structural changes of the penile vascular bed. In the presence of vascular risk factors functional vascular erectile dysfunction takes place, at least in part, due to endothelial dysfunction resulting from a reduced bioavailability of vasodilators. In particular, a deficit in nitric oxide

Figure 2: Development and progression of vascular erectile dysfunction.
(NO) action and the associated reduction in vasodilation of penile vessels is likely to be a key component of inadequate erectile responses because of the resultant decrease in arterial inflow and the attenuated cavernosal smooth muscle relaxation required for engaging sufficiently the veno-occlusive mechanism. This early stage of functional erectile dysfunction is characterized clinically by inability to maintain a rigid erection and the treatment of risk factors and vascular conditions associated with endothelial dysfunction (e.g., hypertension, hypercholesterolemia, obesity, physical inactivity) has been shown, in some studies, to improve erectile function[57, 58]. Over time, structural erectile dysfunction takes place in the form of atherosclerosis of penile blood vessels leading to arterial stenosis with reduced blood inflow and smooth muscle atrophy and fibrosis leading to increased blood out flow. This late stage of structural erectile dysfunction is currently considered to be irreversible (Figure 2).

Occlusive disease of the pudendal-cavernosal-helicine arterial tree is primarily caused by the development of atherosclerotic lesions leading to narrowing of the hypogastric-pudendal arterial bed and diminished arterial perfusion pressure which decreases arterial inflow to the lacunar spaces of the corpora cavernosa[59-61]. Arterial insufficiency also triggers a cascade of ischaemic/hypoxic cytotoxic events impairing the erectile tissue endothelium, smooth muscle, nerves, and microvessels[59, 62, 63].

2. ENDOTHELIAL DYSFUNCTION

The vascular endothelium of the penis has an important role in mediating vascular tone and blood flow into the penis in response to humoral, neural and mechanical stimuli[55, 64]. Endothelial cells lining the internal surface of penile arteries and sinusoids of the cavernosal tissue affect the tone of adjacent smooth muscle cells through the release of relaxing factors (such as nitric oxide, prostaglandin-E2 and C-type natriuretic peptide) and vasoconstrictive agents (such as endothelin-1 and angiotensin-II)[65-67]. In vasculogenic ED, the regulatory role of the endothelium is hindered, resulting in decreased bioavailability of and/or responsiveness to vasodilatory mediators; this may also be combined with increased levels and/or sensitivity to vasoconstricting agents[55]. Even a subtle alteration in the balance between the factors favoring corporal relaxation and contributing to contraction may result in ED[68].

The nitric oxide (NO) pathway is of critical importance in the normal induction and maintenance of erections[69, 70]. NO induces vasodilatation through increase in cGMP and counter balances RhoA/Rho-kinase-mediated vasoconstriction[71]. Apart from the neurally derived NO, the endothelial NO is also an important mediator of vascular responses in the penis[72, 73]. The neuronal NO synthase (nNOS) and the constitutive endothelial NO synthase (eNOS) isoforms are tightly regulated and produce physiologically relevant levels of NO in autonomic nerve endings and endothelial cells of the penis. In vasculogenic ED, dysfunctional endothelial cells lining the penile arterial system and the corpus cavernosum produce less NO. Hence, phosphodiesterase type 5 (PDE-5), abundant in perivascular smooth muscle cells, can rapidly degrade the reduced quantities of cyclic guanosine monophosphate (cGMP), thus limiting duration of vasodilation, an effect which will negatively impact on the ability to initiate and sustain an erection[69]. Impaired bioavailability of NO may result from impaired eNOS regulatory function through various mechanisms including asymmetric dimethyl arginine -mediated eNOS uncoupling[69, 71] and disturbance in systemic or local secretion or degradation of angiotensin II[65]. The angiotensin II component is not just a result of direct vasoconstrictor activity but also because of the increased tissue generation of reactive oxygen species that decreases NO activity[64].

Another important mechanism in endothelial cell dysfunction is the imbalance between endothelium-dependent relaxation due primarily to NO, and endothelium-dependent constriction due primarily to endothelin-1. Numerous conditions characterized by an impaired availability of NO have been found to be associated with enhanced synthesis of endothelin-1, and vice versa, suggesting that these two factors have a reciprocal regulation[74]. Experimental studies provided evidence that endothelin-1 may influence NO production and that NO can inhibit endothelin-1 synthesis[75].

3. EXCESSIVE SMOOTH MUSCLE CONTRACTION

Chronic ischaemia increases the contractile reactivity of the cavernosal smooth muscle. Ischaemia selectively enhances neurogenic contractile reactivity to electrical-field stimulation while having no effect on contraction to noradrenaline[76]. Indomethacin, a cyclooxygenase inhibitor, decreases neurogenic contraction of ischaemic tissues. These changes are associated with significant increases in the production of constrictor eicosanoids such as PGF-2α and thromboxane. Increased constrictor eicosanoids, in addition to direct interference with smooth muscle tone that favours contraction, also produce adverse effects on the inhibitory role of NO pathway in cavernosal tissue and indirectly augment contraction[76]. High levels of eicosanoids interfere with the expression of NOS proteins and down-regulate NOS expression[77].

4. SMOOTH MUSCLE ATROPHY AND FIBROSIS

Prolonged exposure to ischaemia results in loss of
smooth muscle and increased collagen fibers[60,78]. A close relationship between cavernosal smooth muscle degeneration and the development of corporal veno-occlusive dysfunction has often been reported[63]. Smooth muscle content, normally 42–50% of cavernosal tissue, can decrease to as low as 13% in some men with ED[78]. Thus degenerative changes in the cavernosal smooth muscle are associated with impaired veno-occlusive function. Another consistent finding in patients with ED seems to be a loss of elastic fibers, which is also associated with a pathological increase in collagen accumulation[63,78].

III. THE METABOLIC SYNDROME

1. INTRODUCTION

Metabolic syndrome (MS) refers to the clustering of several cardiometabolic risk factors, including abdominal obesity, hyperglycemia, dyslipidemia and elevated blood pressure, that are likely linked to insulin resistance[79]. The clinical relevance of MS is that it identifies people who are at increased long-term risk of cardiovascular disease and type 2 diabetes, thus providing an opportunity for preventive lifestyle interventions. Insulin resistance is also associated with a wide spectrum of clinical disorders, including polycystic ovary syndrome, non-alcoholic fatty liver disease, sleep-disordered breathing, chronic kidney disease and certain cancers[80]. In men, insulin resistance is associated with erectile dysfunction, with endothelial dysfunction likely to be one of the underlying mechanisms[81]. Increased visceral fat mass is also associated with hypogonadism[82].

2. ORIGIN OF THE SYNDROME

The association between hypertension, hyperglycemia and hyperuricemia was first reported over 80 years ago[83]. Subsequently, this cluster was expanded to include upper body ("android") adiposity[84] and dyslipidemia, and was observed to be linked to atherosclerosis. Hanefeld and Leonhardt in 1981 were the first to coin the term metabolic syndrome. Because that report was published in German and behind the "Iron Curtain," it remained unnoticed by many scientists and clinicians[85]. The authors stated that MS represented the common prevalence of obesity, hyperlipoproteinemia, dyslipoproteinemia, maturity onset diabetes (type 2), gout, and hypertension, associated with increased incidence of atherosclerotic vascular disease, fatty liver, and gallstones, that develops from genetic susceptibility combined with overnutrition and physical inactivity. In 1988, Reaven described a set of metabolic abnormalities (hypertension, hypertriglyceridemia, low high-density lipoprotein (HDL)-cholesterol level and hyperinsulinemia) associated with increased cardiovascular risk, which he termed “Syndrome X”, and postulated that impaired insulin action was the underlying pathophysiology[86].

3. CLINICAL DEFINITIONS

The first definition of MS was proposed by the World Health Organization[87], with hyperglycemia and/or insulin resistance as a central feature, associated with two or more related metabolic abnormalities (elevated blood pressure, dyslipidemia, central obesity or microalbuminuria).

The National Cholesterol Education Program (NCEP) definition requires three or more of the following features: abdominal obesity, elevated triglyceride levels, reduced HDL-cholesterol level, elevated blood pressure or elevated fasting glucose level[88].

In 2005, the International Diabetes Federation (IDF) proposed a definition of MS similar to that of the NCEP, but with increased waist circumference as a necessary requirement, emphasizing the central importance of abdominal obesity[89]. Ethnicity-specific cut-off points were proposed for waist measurements.

The definitions of MS (Table 6) provide clear criteria by which subjects can be evaluated by physicians; however, not all clinical studies have used the same definition, making comparisons among such studies difficult. The various definitions usually include the same core criteria of central obesity, hyperglycemia, dyslipidemia and high blood pressure, but differ in the cut-off points for individual criteria, in specific mandatory requirements (e.g. abdominal obesity or insulin resistance) and in the inclusion of additional factors (e.g. microalbuminuria). Hence, they identify broadly similar, but not identical, groups of individuals with MS.

4. PREVALENCE OF METABOLIC SYNDROME

The National Health and Nutrition Examination Survey 1999–2002 estimated the age-adjusted prevalence of MS in US adults aged 20 years and over to be between 34.6% (NCEP) and 39.1% (IDF)[90].

Approximately one-fourth of the adult European population has MS. Prevalence varies somewhat depending on the age group studied, geographic location, or characteristics of the population studied. With NCEP criteria, less than one-fifth of the studied population in Southeast Asia has MS. This lower prevalence, compared with North American and European populations, may be attributable in part to a younger population[91].

MS is more prevalent with increasing age, affecting half of adults aged 60 years and over[90]. It is more common in men when WHO or IDF criteria are used, but there is little difference between the sexes when
the NCEP definition is used[90,92]. Ethnicity also influences MS prevalence[90].

The prevalence of MS is increasing. Ford et al estimated that 50 million Americans had MS in 1990 and 64 million had the syndrome in 2000[93,94]. Two factors appear to account for this increase. One of these is obesity; in 1988 to 1994 the prevalence of obesity was 22.5%, and in 1999 to 2000, it had increased to 30.5%[95]. A second factor is aging of the population. For any level of BMI, the prevalence of MS in the US population rises with increasing age. This effect can be explained largely by age-related rises of blood pressure and glucose[96].

5. THE LINK BETWEEN METABOLIC SYNDROME AND ERECTILE DYSFUNCTION

Men with the metabolic syndrome have an increased prevalence of erectile dysfunction, and reduced endothelial function score. Erectile dysfunction prevalence increases as the number of components of the metabolic syndrome increases, with approximately 20%, 30%, and 35% of patients with ED having 3, 4, or 5 components of MS, respectively. By contrast, there is an inverse relationship between the number of components of the metabolic syndrome and the endothelial function score[97]. Corona et al re-
ported that among 236 patients diagnosed as having MS, 96.5% exhibited ED[98], and Bansal et al also reported that of 154 men with organic ED, 43% displayed MS (general population, 24%), 79.2% displayed insulin resistance (general population, 25%) and 90.9% displayed both insulin resistance and MS[81]. Clearly, ED represents a risk factor and may be a warning signal for MS and insulin resistance, both being clear risk factors of CVD. Interestingly, the largest jump in expression of MS occurred between men with moderate ED and men with severe ED (21.7%–70%). The authors also demonstrate the prevalence of elevated fasting blood sugar (>110 mg/dL: 5.6 mmol/L), a component of MS is associated with increased severity of ED[81].

Shabsigh et al assessed the relationship between the prevalence of comorbidities and ED severity in a cross-national survey on men’s health (ages 20–75). Hypertension and high cholesterol were the most prevalent comorbidities for each degree of ED severity. The authors also found that men between the ages of 70 and 75 were 14 times as likely to develop ED as compared with men between the ages of 20 and 29. This finding is consistent with the observation that as androgen levels decline with ageing, there is a concomitant increase in the prevalence of MS[99].

Zhody et al linked androgen deficiency with ED and MS by analyzing BMI and other factors in 158 obese men[100]. The authors found a significant association between increasing BMI and the following parameters: systolic blood pressure, low serum testosterone (T), penile duplex parameters, triglycerides, HDL, and LDL cholesterol. With increasing BMI, the frequency of hypogonadism and ED increased, whereas total serum T showed a strong negative correlation. To assess the effect of BMI on vasculogenic ED, the authors examined this relationship in the absence of other risk factors and found that for a BMI ≤25, 3 out of 13 men (23.1%) had vasculogenic ED, as compared with 32 out of 54 men (59.3%) with a BMI ≥25.

6. METABOLIC SYNDROME AND ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction is a particularly relevant finding in patients with ED, especially in the early phase of the disease. In a later phase, other factors, such as impaired arterial flow of hypogastric/pudendal arteries, cavernosal fibrosis, and hypoxia, come into play to cause and maintain sexual dysfunction[102] (Figure 3).

Esposito et al. evaluated endothelial function in erectile dysfunction patients with metabolic syndrome versus age- and BMI-matched controls. Compared with controls, patients with the metabolic syndrome had an increased prevalence of erectile dysfunction, reduced endothelial function, and higher circulating concentrations of C-reactive protein. Their results show the prevalence of erectile dysfunction increased linearly with C-reactive protein levels, with impairment of endothelial function, and as the number of components present of the metabolic syndrome increased[97].
7. THE LINK BETWEEN METABOLIC SYNDROME AND HYPOGONADISM

Hypotheses have been offered to explain the deleterious effect of adiposity on circulating testosterone[82,101]. There is high aromatase activity in adipocytes, an enzyme involved in the metabolism of testosterone to estradiol. That is, the greater the number and volume of adipose tissue, the greater is the breakdown of testosterone. Testosterone inhibits lipoprotein lipase, an enzyme on the outer surface of the fat cell that regulates the conversion of free fatty acids into triglyceride[103]. Thus, lower testosterone levels would enhance the enzyme activity, thereby promoting greater uptake of triglyceride into the adipocytes, increasing fat storage and also stimulating the formation of new fat cells from pre-adipocytes. In turn, this would exacerbate insulin resistance and further drive the cycle to lower testosterone levels. Furthermore, the hypothalamic-pituitary axis would detect the falling testosterone level and increase gonadotrophin secretion to stimulate the testis. This response is potentially inhibited by three different mechanisms: (i) estradiol mediated inhibitory action on LH production[104], (ii) the inhibitory actions of inflammatory adipokines, tumour necrosis factor a (TNF-a) and interleukin 6 (IL-6), on LH release and (iii) the development of leptin resistance of the hypothalamic-pituitary axis (normally leptin stimulates LH release and directly inhibits the action of gonadotrophins on the testis, but in human obesity the HP axis becomes leptin resistant)[105,106] (Figure 4).

Increasing abdominal obesity leads to increased activity of the enzyme aromatase, present in adipose tissue, which converts testosterone to estrogen. The resulting low testosterone level increases lipoprotein lipase enzyme activity and triglyceride uptake leading to increased obesity and insulin resistance. This in turn causes further androgen deficiency and visceral fat deposition. Estradiol inhibits gonadotrophin release from the pituitary. Furthermore, testosterone levels are also lowered as a result of leptin resistance at the hypothalamic-pituitary level and the inhibitory effect of leptin on the testicular axis. Proinflammatory adipocytokines such as tumour necrosis a (TNF-a) and interleukin 6 (IL-6) could also potentially inhibit the pituitary axis resulting in low testosterone levels[107].

8. NEGATIVE IMPACT OF METABOLIC SYNDROME ON THE RESPONSIVENESS TO PDE-5 INHIBITORS

Suetomi et al analyzed the impact of MS on the responsiveness to 50-mg sildenafil in Japanese patients with ED. They reported a lower response rate for patients with MS, compared to the overall efficacy in Japanese ED patients (40% versus 70.9% respectively)[101,108]. The IIEF-erectile function score and the response rate for sildenafil decreased as the number of MS components increased. Moreover, the presence of MS was a significant independent risk factor of nonresponse for sildenafil. The hazard ratio for the presence of MS in sildenafil non-responders was 3.30.
9. CONCLUSION

<table>
<thead>
<tr>
<th>Statement</th>
<th>LOE</th>
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</thead>
<tbody>
<tr>
<td>ED is primarily a vascular condition</td>
<td>1</td>
</tr>
<tr>
<td>ED is closely linked to the metabolic syndrome</td>
<td>1</td>
</tr>
<tr>
<td>The metabolic syndrome is associated with hypogonadism</td>
<td>1</td>
</tr>
<tr>
<td>The metabolic syndrome reduces the effectiveness of the PDE-5 inhibitors</td>
<td>1</td>
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</tbody>
</table>

10. RECOMMENDATIONS

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men with ED should undergo a comprehensive risk factor evaluation</td>
<td>A</td>
</tr>
<tr>
<td>Testosterone should be measured when the metabolic syndrome is present</td>
<td>A</td>
</tr>
</tbody>
</table>

IV. ERECTILE DYSFUNCTION AS A SILENT MARKER OF CORONARY ARTERY DISEASE

As cardiovascular disease and erectile dysfunction (ED) overlap in risk factors, prevalence and manifestation, they are thought to share both the etiology of and progression of the disease process. Pathological changes which link these conditions include endothelial dysfunction, inflammation, alterations in androgen levels and blood vessel size (Table 7).

1. ROLE OF ENDOTHELIAL DYSFUNCTION/INFLAMMATION

a) Endothelial dysfunction

Both cardiovascular disease and ED have been linked to endothelial dysfunction. As with conduit and small vessels of the limb, increased flow- and resultant increased shear stress-induced vasodilatation in the penile arteries appears to be mediated largely through nitric oxide (NO). The small diameter of the cavernosal arteries and the relatively high content of endothelium and smooth muscle on a per unit volume tissue basis compared to other organs suggests that the penile vascular bed may be a sensitive indicator of systemic vascular disease. Men with penile vascular dysfunction generally have endothelial dysfunction in other vascular beds as well. Despite differences in the clinical characteristics of the patient populations, including age, risk factors and type of ED, the results have consistently shown blunted endothelium-dependent vasodilation response in patients with ED as compared to controls. Interestingly, in a study of subjects with vasculogenic ED, endothelial dysfunction was found in the small resistance arteries of the forearm in spite of a negative extensive cardiologic work-up[119].

Table 7: Erectile dysfunction and coronary artery disease: a close relationship.

<table>
<thead>
<tr>
<th>Prevalence</th>
</tr>
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<tbody>
<tr>
<td>Prevalence of ED in CAD: 42%-75%[109,110]</td>
</tr>
<tr>
<td>Prevalence of CAD in ED patients with no overt heart disease: 8-56% have positive EST. Among those ED patient with positive EST who were submitted to coronary angiography or coronary CT-angiography, 31/33 (94%) and 11/20 (55%) have significant coronary stenosis, respectively[50,51,111]</td>
</tr>
</tbody>
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<tr>
<th>Prognosis</th>
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<tr>
<td>ED has a twofold increase in the risk for AMI; incident ED is associated with a hazard ratio of 1.25 for developing subsequent cardiovascular events, while the ratio is 1.45 for incident and prevalent ED; hazard ratio for diabetics: 1.6[112-116]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factors</th>
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<tbody>
<tr>
<td>Hypertension, diabetes, hyperlipidemia, smoking, obesity, sedentary lifestyle, depression</td>
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</table>

<table>
<thead>
<tr>
<th>Pathophysiologic mechanisms</th>
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<tbody>
<tr>
<td>Endothelial dysfunction; Inflammation; Oxidative stress; Low testosterone level</td>
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<table>
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<tr>
<th>Time Internal between ED &amp; CAD</th>
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<tbody>
<tr>
<td>In men with ED and CAD, erectile function abnormalities become evident prior to the clinical manifestation (or documentation) of CAD by a mean time interval of 2-3 years[50,109,117,118]</td>
</tr>
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</table>

<table>
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<tr>
<th>Severity</th>
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<tbody>
<tr>
<td>Significant association between severity of ED and extent of CAD[110,118]</td>
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<tr>
<th>LV function</th>
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<tbody>
<tr>
<td>LV dysfunction is an independent risk factor for ED</td>
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<tr>
<th>Cardiovascular drugs and ED</th>
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<tbody>
<tr>
<td>Improvement: ACE inhibitors/ARB, statins. Deterioration: beta-blockers, thiazide diuretics, digoxin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment of ED and CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE-5 inhibitors: favorable effect on LV function, coronary and peripheral vasculature; reduction of cardiovascular morbidity and mortality</td>
</tr>
</tbody>
</table>

ACE: angiotensin converting enzyme; AMI: acute myocardial infarction; ARB: angiotensin receptor blocker; CAD: coronary artery disease; ED: erectile dysfunction; EST: exercise stress test; LV: left ventricle; PDE-5: phosphodiesterase type-5
together with other evidence, this finding suggests that endothelial damage occurs differentially in various vascular beds and in a time-dependent manner such that dysfunction within the penile endothelium is likely to occur prior to its occurrence in other parts of the circulation.

An association between erectile and endothelial dysfunction has also been found for non-conventional biomarkers of disease. Specifically, increased plasma levels of endothelin-1 and asymmetric dimethylarginine (ADMA), and decreased levels circulating endothelial progenitor cells involved in repair and C-type natriuretic peptide may also mechanistically link ED and endothelial dysfunction.

In addition, circulating microparticles (e.g. membrane vesicle fragments shed from the surface of endothelial cells during activation and injury) have been found to increase in non-diabetic ED patients compared to the amounts found in men without ED[120-123].

**b) Inflammation**

Chronic low-grade inflammation contributes to all stages of atherosclerosis, from the initial phase of increased endothelial permeability to the formation of the mature atherosclerotic plaque and plaque rupture. Increased levels of inflammatory markers have been documented in various settings of CAD, especially in acute coronary syndromes, bearing a strong association with clinical outcome[124].

Endothelial function and inflammation are associated in a bidirectional mode. Normal vascular endothelium has anti-inflammatory properties; on the other hand, endothelial function is impaired in the presence of inflammatory conditions and increased oxidative stress. Several studies have shown that presence and extent of ED are associated with markers and mediators of subclinical inflammation and endothelial activation, such as hsCRP, fibrinogen, von Willebrand factor, interleukins (IL)-1β and 6 and adhesion molecules (ICAM and VCAM). Of those, fibrinogen and IL-6 and their combination appear to have the potential to aid ED diagnosis or exclusion. Recent data also suggest that ED and CAD are similar in terms of the prevalence of inflammatory and endothelial-prothrombotic activation, with ED patients having an incremental burden. (Figure 5)[48,125].

**Figure 5: Unfavorable endothelial and inflammatory state in erectile dysfunction patients with or without coronary artery disease.**

A and B. Box-and-whisker plots of levels of inflammatory and endothelial-prothrombotic markers/mediators according to erectile dysfunction and coronary artery disease. Erectile dysfunction and coronary artery disease appear to confer a similar unfavorable impact on the inflammatory and prothrombotic state, whereas erectile dysfunction adds an incremental activation on top of coronary artery disease. C. Simple biochemical substances such as fibrinogen or interleukin-6 appear to have the potential to aid erectile dysfunction diagnosis or exclusion. Charts showing the diagnostic performance of fibrinogen and interleukin-6 for erectile dysfunction at cut-off values associated with 95% sensitivity. CAD: coronary artery disease, ED: erectile dysfunction; hsCRP: high sensitivity C-reactive protein; IL-6: interleukin 6; PAI-1: plasminogen activator inhibitor-1. With permission from Vlachopoulos C, et al. [126]
Oxidative stress, particularly via reactive oxygen species, is associated with decreased erectile function mediated by increased oxidative catabolism of NO and activation of the proinflammatory nuclear factor kappa B, which in turn induces cellular inflammation and adhesion molecule production. Oxidative modifications of low-density lipoproteins are involved in development of the atherosclerotic lesions. Myeloperoxidase-modified low-density lipoprotein has been found both in atherosclerotic plaques and in the corpus cavernosum of patients with ED of vascular origin[126,127].

Interestingly, the vasculature of the penis may itself generate a pro-inflammatory milieu. The human corpus cavernosum produces in a paracrine fashion angiotensin II, a pro-oxidant and pro-inflammatory substance, and a deletion polymorphism in the gene encoding ACE (DD genotype) has been reported to be more common in men with a diagnosis of organic ED.

2. THE “ARTERY SIZE” HYPOTHESIS

In all tissues and organs, the lumen diameter of the main feeder artery is a key factor controlling the maximum capacity for blood flow. The arteries supplying the penile tissue are inherently limited by having a vessel diameter that is narrower than in other tissues. From this understanding, Montorsi et al.[117] generated the “artery size hypothesis”, a concept which proposed that the differential timing of the onset of signs and symptoms of ED and CVD is caused, at least in part, by the difference between larger vessels and smaller ones (e.g. penile artery) with regard to their ability to tolerate encroachment upon the lumen (Figure 6). Because of the smaller size of the penile vessels, the same level of plaque burden, vascular remodeling and/or endothelial dysfunction would have a greater effect on blood flow through the penile arteries than through the coronary, carotid and femoral arteries. Therefore, the clinical manifestations of penile endothelial dysfunction (ED) and encroachment on the vascular lumen may become evident much earlier than with coronary or peripheral vascular disease. That is, by the time the lumen of the larger arteries become significantly obstructed (>50%) the capacity for penile blood flow will already decreased considerably, a concept which explains why so many men newly diagnosed with CAD are found to already have ED (Figure 6).

Thus on the basis of this hypothesis and the fact that the endothelium is the same throughout the arterial tree, a malfunction in the penile arteries causing ED may be a predictor of silent, subclinical cardiovascular disease (CVD). Furthermore, because an acute coronary syndrome often arises as the result of rupture of an angiographically subcritical plaque, the presence of ED might be an early warning sign of both a “vulnerable” atherosclerotic burden potentially leading to acute coronary events as well as being a manifestation of advanced obstructive CAD leading to chronic inducible ischemia[109].

3. CLINICAL EVIDENCE OF CAD IN ED PATIENTS WITH NO CVD

Insufficiency of the penile vasculature causing ED may be a predictor of silent subclinical cardiovascular disease[51,53,111,128,129]. The rate of underlying CAD was addressed in patients with vasculogenic ED, either new onset or long-standing, who had no clinical evidence of CAD. These patients frequently had one or more traditional risk factors, including diabetes in about 20% of the cases. Coronary reserve was tested by means of standard exercise stress testing or by dobutamine stress echocardiography.
Coronary angiography was carried out in a part of those who have positive non-invasive results. The rate of positive exercise stress test averaged up to 22%, ranging from 8% to 56% (Table 8). As documented in a prospective angiographic study, almost one out of five men without symptoms for CAD, presenting with erectile function abnormalities of vascular origin as their only symptom, do actually have underlying significant coronary artery stenosis. This is a substantially higher proportion than the 4% found in the general population of comparable profile.[50]

<table>
<thead>
<tr>
<th>Patient (n)</th>
<th>Age (yrs)</th>
<th>ED duration (months)</th>
<th>≥2 RF/DM (%)</th>
<th>Positive EST/DSE (%)</th>
<th>Significant CAD by coronary or CT-angiography*</th>
</tr>
</thead>
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<tr>
<td>Pritzker MR.</td>
<td>50</td>
<td>40-60</td>
<td>NA</td>
<td>80/20</td>
<td>28 (56) 20/20</td>
</tr>
<tr>
<td>Kawanishi Y.</td>
<td>58</td>
<td>25-78</td>
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<td>NA</td>
<td>8 (14) NA</td>
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<tr>
<td>Kim SW</td>
<td>97</td>
<td>45-75</td>
<td>NA</td>
<td>41/31</td>
<td>8 (8) 2/3</td>
</tr>
<tr>
<td>Shamloul R</td>
<td>40</td>
<td>&gt;40</td>
<td>&gt;3</td>
<td>NA</td>
<td>12 (30) NA</td>
</tr>
<tr>
<td>Vlachopoulos C</td>
<td>50</td>
<td>41-74</td>
<td>25±21</td>
<td>78/20</td>
<td>12 (24) 9/10</td>
</tr>
<tr>
<td>Jackson G</td>
<td>20</td>
<td>39-69</td>
<td>9-36</td>
<td>40/ none</td>
<td>2 (10) 11/20</td>
</tr>
<tr>
<td>Mulhall J</td>
<td>49</td>
<td>28-56</td>
<td>30±24</td>
<td>72/ none</td>
<td>10 (20) NA</td>
</tr>
</tbody>
</table>

CAD=coronary artery disease; ED=erectile dysfunction; DM=diabetes mellitus; DSE=dobutamine stress echocardiography; EST=exercise stress test; NA=not available; NR=not representative; RF=risk factor.

* significant CAD defined as >50% lumen reduction and/or high calcium score assessed by coronary angiography and/or CT-angiography, respectively.

Modified from Vlachopoulos C et al[130]

Table 8: Obstructive, subclinical CAD in ED patients without heart disease.

<table>
<thead>
<tr>
<th>Patient (n)</th>
<th>Type of CAD</th>
<th>ED rate (%)</th>
<th>ED prior to CAD (%)</th>
<th>ED-CAD time interval months (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montorsi F 2003</td>
<td>Unselected</td>
<td>49</td>
<td>67</td>
<td>38.8 (1-168)</td>
</tr>
<tr>
<td>Montorsi P 2005(abs.)</td>
<td>1st ACS</td>
<td>41</td>
<td>100</td>
<td>28 (1-240)</td>
</tr>
<tr>
<td>Montorsi P J 2006</td>
<td>CCS</td>
<td>67</td>
<td>93</td>
<td>24 (12-36)</td>
</tr>
<tr>
<td>Hodges L 2007</td>
<td>Unselected</td>
<td>66</td>
<td>55</td>
<td>60±60</td>
</tr>
<tr>
<td>Shi H 2007</td>
<td>Unselected</td>
<td>48</td>
<td>49</td>
<td>33 (2-87)</td>
</tr>
<tr>
<td>Foroutan SK 2007</td>
<td>Unselected</td>
<td>46</td>
<td>42</td>
<td>23 (10-36)</td>
</tr>
<tr>
<td>Vlachopoulos C 2009 (abs.)</td>
<td>Unselected</td>
<td>100</td>
<td>78</td>
<td>36.4 (4-174)</td>
</tr>
</tbody>
</table>

Table 9: ED-CAD temporal relationship.

Coronary angiography was carried out in a part of those who have positive non-invasive results. The rate of positive exercise stress test averaged up to 22%, ranging from 8% to 56% (Table 8). As documented in a prospective angiographic study, almost one out of five men without symptoms for CAD, presenting with erectile function abnormalities of vascular origin as their only symptom, do actually have underlying significant coronary artery stenosis. This is a substantially higher proportion than the 4% found in the general population of comparable profile.[50]

4. ERECTILE DYSFUNCTION IN PATIENTS WITH ESTABLISHED CAD

The prevalence of ED in patients with angiographically proven CAD has been assessed in several studies and found to range between 42% and 75%[50,112,118,131-133]. This wide range may be the result of differences in population characteristics, definitions of ED and CAD, sensitivity and specificity of methods used to diagnose both diseases and concomitant effect of drugs that can interfere with sexual function. Nevertheless, age, common risk factors (mainly diabetes) and extent of CAD (assessed by specific score systems) were repeatedly found to be independent predictors of ED. Interestingly, ED symptoms frequently came before either symptoms or non-invasive detection of CAD, confirming the new concept of ED as an early marker of sub-clinical vascular disease (Table 9).

In the study of Montorsi F et al[109], 47/300 (49%) patients with angiographically proven CAD had ED according to the IIEF-EFD questionnaire. Among these patients, 97 (67%) reported ED symptoms...
prior to CAD symptoms by an average of 36 months. The clinical presentation of CAD was acute coronary event (mainly acute myocardial infarction) in 40% and chronic coronary syndrome in the remaining 60%.

In the subsequent Association Between eRectile dysfunction and coronary Artery disease (COBRA) trial, the same authors found that 93% of patients with chronic CAD reported ED symptoms prior to the onset of angina pectoris, with a mean interval of 24 (range 12-36) months[118] fueling the concept of a lead time of at least 2-5 years between the development of ED and symptomatic CAD. Interestingly, the time interval (range) for patient with one-, two-, and three-vessel disease were 12 (9.5-24), 24 (16.5-36) and 33 (21-47) months, respectively. There was a significant trend between the length of the time interval between ED and CAD and the number of the coronary vessel involved (p=0.0016). Moreover, ED rate was different according to the type of clinical presentation: acute vs. chronic coronary syndrome. Patient with AMI and 1-vessel disease – the common clinical presentation of AMI – had an ED rate (22%), similar to those with angiographically no CAD (24%) and significantly lower than patients with AMI and multi-vessel disease (55%) or chronic CAD (65%). The reason for the low ED rate in AMI with 1-vessel disease may be explained by the peculiar pathophysiological background of AMI. In fact, AMI is usually due to abrupt closure of a previous single, non-critical stenosis in an otherwise coronary tree without additional critical lesions (i.e. low atherosclerotic burden pattern). Since atherosclerosis is a systemic disorder, penile circulation might be poorly involved resulting in a low ED rate. (Figure 7).

It should be stressed that although the prevalence of ED in subjects with CAD is quite high, some patients with severe CAD still report normal erectile function as shown by the normal erectile function score and penile Doppler findings. Reasons for this finding are not fully elucidated. Potential mechanisms include age-related hormonal, metabolic and inflammatory changes[118].

Efforts have been put forth in cardiovascular research to identify diagnostic tools that might improve the prediction of acute coronary events beyond the role of classical risk factors. A normal exercise stress testing (ECG treadmill, stress echocardiography, scintigraphy) can be falsely reassuring as it may not detect non-low limiting, vulnerable, lesions that often patients harbor. Thus, diagnostic tools include both measures of atherosclerosis burden (coronary calcium score), measures of vascular damage influencing prognosis (carotid wall thickening or plaque, carotid-femoral pulse wave velocity, ankle-brachial pressure index) and indexes of endothelial activation, inflammation and thrombosis (ICAM-1, hSCR, fibrinogen, von Willebrand factor, IL-6 and IL-18) (Table 10). Studies support the association between ED and non-obstructive CAD, as demonstrated with the relationship between ED and coronary calcium deposition in the walls of the coronary arteries. Importantly, the latter is correlated in a dose-dependent fashion with future risk of cardiovascular events above and beyond that predicted by standard cardiovascular risk factors[51,125,132].

Figure 7: International index of erectile function-erectile function domain score and prevalence of erectile dysfunction according to clinical presentation.(With permission from reference 118)

ACS: acute coronary syndrome, CCS: chronic coronary syndrome.
5. CARDIOVASCULAR ASSESSMENT IN THE TYPICAL SUBJECT WITH ED AND NO CVD

As stated in the introduction, a diagnosis of ED should prompt an initial cardiovascular assessment based on the history and clinical examination in order to define the baseline risk according to (i) their likelihood of silent CAD or to the stage of clinically evident CAD; (ii) other cardiovascular conditions either unrelated, or related to ED (e.g. heart failure, peripheral arterial disease). The second Princeton Guidelines offer a comprehensive and practical way of stratifying risk especially for men with sexual dysfunction who already have heart or atherosclerotic disease [39]. Those at low risk can initiate or resume sexual activity, whereas for those at high risk, sexual activity must be deferred until the condition is treated or stabilized. Those belonging in the intermediate/indeterminate category would require additional cardiologic tests for further risk stratification.

Looking for silent obstructive CAD can involve multiple tests of varying degrees of complexity and expense. Evaluating the pretest likelihood of CAD according to the clinical presentation is of utmost importance in the selection of an appropriate diagnostic strategy and interpretation of diagnostic test results.

Table 10: Cardiovascular assessment in men with vascular ED.

<table>
<thead>
<tr>
<th>Exam</th>
<th>Evidence</th>
<th>Clinical Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treadmill stress test</td>
<td>The ability to perform exercise of modest intensity (e.g. &gt; 6 METS) without symptoms typically implies low risk</td>
<td>First line exam for identification of coronary flow reserve Evaluation of exercise tolerance</td>
</tr>
<tr>
<td>Stress echocardiography SPECT</td>
<td>They reveal myocardial ischemia in patients with low and intermediate risk Negative predictive value for long-term prognosis</td>
<td>Identification of regional ventricular abnormalities prior to the appearance of angina or ST wave changes (higher sensitivity) Assessment of the site of coronary stenosis</td>
</tr>
<tr>
<td>Invasive assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>Has determined that there is significant incidence of silent myocardial ischemia (~15-20%) Angiographic findings correlate with ED severity</td>
<td>Documentation of CAD and assessment of severity of coronary atherosclerotic lesions</td>
</tr>
<tr>
<td>Vascular function and atherosclerotic burden</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penile color Doppler</td>
<td>Low PSV (&lt;35 cm/s) in the cavernous artery is thought to be a useful predictive factor of CAD in ED patients</td>
<td>Measure of a nonspecific, endothelium-independent vascular impairment of penile circulation (high negative predictive value)</td>
</tr>
<tr>
<td>Aortic stiffness</td>
<td>Association with the presence and extent of ED as well as with penile vascular damage assessed by penile color Doppler</td>
<td>Determinant of cardiovascular system performance and independent predictor of cardiovascular risk</td>
</tr>
<tr>
<td>IMT (carotid+femoral)</td>
<td>Correlation between subclinical atherosclerosis and penile vascular damage</td>
<td>Marker of early atherosclerosis and independent predictor of cardiovascular events</td>
</tr>
<tr>
<td>ABI</td>
<td>Convincing data on the association between ED and ABI lacking</td>
<td>Marker of generalized atherosclerosis. Predictor of cardiovascular events</td>
</tr>
<tr>
<td>CTA</td>
<td>Detection of subclinical non-flow limiting CAD CAC is independently associated with the presence and severity of ED</td>
<td>Measure of atherosclerosis burden (not necessarily obstructive) in the coronary circulation. Implications for vulnerable plaques</td>
</tr>
<tr>
<td>Inflammatory and endothelial-prothrombotic activation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsCRP, IL-6, fibrinogen, PAI-1</td>
<td>Association with the presence and severity of ED Inflammatory equivalence between ED and CAD</td>
<td>Predictors of future cardiovascular outcomes, special implications for acute coronary syndromes</td>
</tr>
</tbody>
</table>

ABI: Ankle-brachial index; CAC: coronary artery calcification; CAD: coronary artery disease; CTA: computed tomography coronary angiography; hsCRP: high sensitivity C-reactive protein; ED: erectile dysfunction; IL-6: interleukin 6; IMT: intima media thickness; PAI-1: plasminogen activator inhibitor-1; PSV: peak systolic velocity

Depending on the initial clinical presentation, cardiac echocardiography may offer valuable information for left ventricular performance, wall-motion abnormalities and valvular function[133]

Subjects with ED and no overt heart disease – so called “normals” – are those physicians should concentrate on. Those at low risk need lifestyle advice, risk factors addressed and regular monitoring by their primary health care providers (e.g. family doctors). Those at high risk, apart from treatment of risk factors, should definitely undergo further cardiologic assessment. Once again, the intermediate/indeterminate category would require additional cardiologic tests for further risk stratification.
The resting ECG is usually normal, but if it is abnormal, entry into a higher risk category is automatic. As a next step, an exercise ECG is the simplest, most readily available, and least expensive evaluation and is recommended for all men at higher risk. When an exercise ECG is not interpretable (e.g., in the case of a left bundle branch block), or when it is inconclusive, or when it cannot be undertaken due to mobility problems, obtaining a scintigraphy perfusion scan or stress echocardiogram is advised. If the stress tests are abnormal and depending on their exact findings, the option for further evaluation with cardiac angiography emerges[47,133-135].

Ideally, evaluation of patients at increased risk should include determination not only of silent CAD but also of risk for developing future CAD events that may be related to the development of obstructive lesions, but also to the rupture of vulnerable, non-obstructive plaques. Techniques such as aortic stiffness, carotid ultrasound, ankle-brachial index, flow-mediated dilation of the brachial artery, penile Doppler, coronary calcium scoring and inflammatory markers/mediators show great potential and their future implementation is currently evaluated according to their individual predictive ability, easy of use, cost, and safety. At this stage, aortic stiffness, carotid ultrasound (for the determination of intima-media thickness [IMT] and carotid plaque) and ankle-brachial index, which are measures of arterial (target organ) damage, could be advocated as a recommended, where available, test, in the paradigm of the ESC/ESH guidelines for the treatment of arterial hypertension (Table 10)[136].

Special mention should be made for treatment of risk factors. All patients, independently of risk category, should have their risk factors properly addressed, which may seem obvious, but it is surprising how often they are not acted on. Specialist referral, such as a hypertension specialist or diabetologist, may be recommended. This is, first, to ensure effective address of risk factors, and, second, to adopt a more aggressive approach (that may include specific drug therapy), since the ED may be viewed as either a target organ damage or a parameter that re-stratifies the patient to a higher risk category.

Factors other than atherosclerosis and endothelial dysfunction that may cause ED in CAD patients include side-effects of drugs (beta-blockers, diuretics), and hypoperfusion in the setting of low cardiac output following myocardial infarction. Erectile function has been demonstrated to correlate with functional capacity (6-min walk test, Duke treadmill score) in patients with chronic heart failure[134].

Taken together, available data put forth the issue whether ED is a “CAD equivalent”. While accumulating evidence points towards this direction, further research in needed both at the pathophysiological and clinical level.

6. ED AS A PREDICTOR OF CV EVENT: CLINICAL EVIDENCE

ED appears to be associated with a future risk for cardiovascular events[113-115]. In a retrospective cohort study, ED was associated with a 2-fold increased risk for acute myocardial infarction after adjusting for a number of confounding risk factors[114]. Prospective studies have also offered solid information[112,113,115,116,137]. In the first such study, among men enrolled in the Prostate Cancer Prevention Trial (finasteride vs. placebo), 4247 subjects, 55 yr of age or older, had no ED at study entry and were followed up for 5 years. Onset of both ED and CV events was monitored. Over time, 57% of subjects developed ED. After adjusting for all covariates, incident ED was associated with a hazard ratio of 1.25 for developing subsequent cardiovascular events over the follow-up period, while for men with either incident or prevalent erectile dysfunction, the hazard ratio was 1.45[113]. In another interpretation of the findings of the same study, incident ED predicted subsequent acute CAD to a degree equal to or greater than that of cigarette smoking, hyperlipidemia or family history of acute myocardial infarction. Interestingly, in the Krimpen study, reduced and severely reduced erectile rigidity (assessed by a single question) were independent predictors for a combined cardiovascular outcome with hazard ratios of 1.6 and 2.6 respectively[115].

Attention has been directed to diabetic patients. In a cohort of 2,306 diabetic men with no clinical evidence of CAD (27% suffered from ED at baseline), over a median course of 4 years, ED was independent predictor of CAD with a hazard ratio of 1.58 after adjustment for confounding factors[116]. In a study that followed type 2 diabetes with angiographically detected silent CAD the presence of ED had an incremental effect on the already higher risk of major adverse CV events[112]. Interestingly, this study showed that treatment with statins and phosphodiesterase type-5 (PDE-5) inhibitors might reduce the occurrence of major adverse cardiovascular events among CAD diabetic patients with ED.

An issue that has important clinical implications is by how long the clinical manifestation of ED precedes the clinical manifestation of CAD. In men with ED and CAD, erectile function abnormalities became evident prior to the manifestation (or documentation) of CAD by a mean time interval of 2-5 years[52,118,133,13,8,139] (Table 9). This time window offers a unique opportunity for aggressive risk factor intervention and close follow-up of patients with a view of altering the progression of the diffuse vascular disease.

However, ED does not precede CAD in all patients. In the Prostate Cancer Prevention Trial, a quarter
of patients with incident ED, developed sexual dys-
function after CAD[137]. A potential explanation may
be that a patient with single vessel disease and an
acute coronary syndrome (due to the rupture of a
nonstenotic unstable plaque) who has no ED at the
time may progress over the time to diffuse arterial
disease including the penile and (the noninfarcted)
coronary arteries[118].

Given the frequent co-existence of sexual dysfunc-
tion and cardiovascular disease it has become very
clear there are common etiologies and mechanistic
linkages. An extension of this concept is that drugs
used to treat cardiovascular disease may also re-
verse or prevent the progression of underlying dis-
ease that is causally-linked to the progression of
sexual dysfunction. Although chronic therapeutic
approaches are used in conditions such as hyper-
tension and conventional medical management
of ED normally involves acute treatments that en-
hance penile vasodilatory mechanisms, neither one
is designed to particularly target the underlying pa-
thology. That is, while various therapies will lower
blood pressure in hypertensive patients and improve
erectile responses in ED sufferers they have not
been designed specifically to target the particular
causal-mechanisms at the local, neural, vascular,
or endocrine level. In fact, in both conditions, the
causal abnormalities can often progress despite the
ongoing treatments and thereby eventually limit the
effectiveness of the medication being administered.
Further complicating these issues is the knowledge
that certain cardiovascular treatments drugs (e.g.
certain antihypertensive agents) as well as other
medications (antidepressants) actually induce sex-
ual dysfunction even when the patients previously
had normal sexual function[140-142]. Thus, the
common association between ED and other co-
morbidities, combined with considerable failure rates
for current ED treatment, should signal that modifying
lifestyle and intervention-associated risk factors (e.g.
medications, overweight and obesity, inappropriate
diet, smoking, excessive alcohol consumption, and
physical inactivity) should be a fundamental step in
a holistic approach toward the treatment of both ED
and cardiovascular disease

As indicated, the available evidence indicates that
sexual dysfunction can be induced or exacerbated
by certain antihypertensive drugs. It is noteworthy
that reduction of blood pressure per se should not be
considered as the major cause of this drug-induced
effect, since not all agents have the same negative
impact. These data suggest that depressor agents
from disparate classes including centrally acting
sympatholytic drugs, diuretics and beta-adrenocep-
tor blockers are most likely to impact deleteriously
on sexual function. In contrast, the results of vari-
ous clinical and experimental studies suggest newer
therapies that antagonize the renin-angiotensin sys-
tem (ACE inhibitors and AT1 receptor antagonists)
or long acting calcium channel blockers either have
neutral or possibly even beneficial actions with re-
gards to sexual function[142-145]. The mechanisms
proposed to account for the beneficial effects found
in these studies include improved endothelial dys-
function, reduced vascular reactivity to vasocon-
stricior influences, decreased inflammation and nor-
malization of vascular remodeling, effects that have
even been shown to persist after the treatment was
stopped.

7. CONCLUSION

| Endothelial dysfunction and inflammation are common pathophysiological pathways of ED and systemic vascular disease | LOE 1 |
| Endothelial dysfunction is not confined to penile tissue, but is widespread in other vascular beds | LOE 1 |
| Presence and severity of ED are associated with markers and mediators of subclinical inflammation | LOE 1 |
| The presence of ED suggests there is an incremental inflammatory and endothelial-prothrombotic activation on top of that found in patients with CAD | LOE 1 |
| Patients presenting with ED as their initial condition have an increased prevalence of silent CAD | LOE 1 |
| ED can precede an acute coronary event, stressing the need to develop means of detecting nonobstructive, but vulnerable, coronary lesions | LOE 1 |

8. RECOMMENDATIONS

| Emerging noninvasive tests could be integrated as biomarkers to assess the risk for future coronary syndromes | Grade B |
| ED diagnosis should prompt assessment of cardiac risk and meticulous risk factor treatment | Grade A |
| Available risk assessment charts (e.g. Framingham, SCORE) should be used to stratify the risk of CAD events in each patient | Grade A |
| Patients with ED and no clinical CVD who carry an increased risk of CAD events (>10%) should undergo cardiological assessment and noninvasive testing (mainly ECG exercise stress test) to reveal silent CAD and to further stratify risk | Grade A |
| Additional noninvasive tests of arterial damage may aid in the determination of risk for future cardiac events | Grade B |

V. TESTOSTERONE

1. INTRODUCTION: CARDIOVASCULAR EFFECTS OF TESTOSTERONE

Life expectancy for women exceeds that for men,
and one mechanism for this discrepancy may be
speculated as the differences in sex hormone profiles
as a contributor to accelerated atherogenesis in men.
Heart disease prevalence in women lags behind that
in men until postmenopausal age; after that time,
women outpace men[146] leading to speculation
that sex hormone profile differences are contributors to risk. Evidence associates aberrant circulating androgen levels with increased risk for CAD in both genders, but the precise relation remains to be well defined[147].

In men increasing evidence suggest that low androgen levels are associated with all-cause death and, in particular, CVD death[148]. This begs the question: could this be causal or simply coincidence, with testosterone modulating established risk factors? If testosterone is causative, could replacement be beneficial and safe over time? Clearly, age-related decline in androgens has important clinical implications for CVD management.

The relationship between androgens and coronary artery disease has been extensively reviewed. Observational studies show a consistent inverse relationship between endogenous testosterone and adverse cardiovascular events[149-151]. While these studies provide no support for the suggestion that plasma estradiol or testosterone are primary risk factors for IHD, the associations between plasma testosterone and other probable risk markers (triglycerides, insulin, body mass index, and high density lipoprotein cholesterol) indicate the possibility that testosterone may play an indirect role in the pathogenesis of IHD. These findings may be interpreted as suggesting the hypothesis that chronically lowered blood testosterone may increase risk of cardiovascular disease. However, such findings from cross-sectional studies cannot distinguish the direction of causality or exclude a common cause. The opposite interpretation is that blood testosterone is mildly lowered due to heart disease, as occurs for many chronic disorders[152,153]. Longitudinal studies do not support the predictive value of lowered blood testosterone or dihydroepiandrosterone concentration for further cardiovascular events[154,155] which favors the decrease in cross-sectional studies being an effect, rather than a cause. The only definitive test of this important concept is a prospective interventional study of sufficient power and duration of surveillance to estimate or exclude an important protective effect size with use of testosterone and cardiovascular endpoints.

The 2004 analysis, published by the US Institute of Medicine[156] recommends that the National Institutes of Health support small efficacy trials aimed at treatment of androgen deficiency-related clinical conditions, but not a large, randomized trial to elucidate risk: benefit ratios. Although rigorously conducted, this was largely a qualitative review of the literature, and doubts have been expressed about the accompanying recommendations. Limitations of that research prompted subsequent investigations that have attempted to quantify (using objective and reproducible methods) the effects of testosterone. In 2005, two separate meta-analyses[157,158] were published on the 4 major areas in which an adequate number of randomized placebo-controlled trials were available: body composition; bone density; lipid profiles; and sexual function. Another two important meta-analyses published in the Mayo Clinic Proceedings[159] added to the unexpected findings of effects and adverse effects of testosterone[160]. These analyses revealed the following: a 6% reduction in body fat; a 3-4% increase in lean body mass and bone density; a diversified threshold effect on libido and erectile function.

Haddad and others[159] in their well-constructed meta-analysis of testosterone and cardiometabolic risk demonstrated that in men supplementation is relatively safe in terms of cardiovascular health. They noted that testosterone use in men with low testosterone levels led to inconsequential changes in blood pressure, glycemic control and all lipid fractions. Several reports have described consistent improvement in both anginal symptoms and ischemia on stress electrocardiograms in men treated with older injectable testosterone preparations. More recent studies have reported that low blood levels of androgens are associated with osteoporosis, adverse cardiovascular risk factors (including an atherogenic lipid profile), systolic and diastolic hypertension, obesity, insulin resistance and increased fibrinogen levels[161]. Other authors have published a series of articles[162,163] that consistently document that testosterone replacement is beneficial for cardiovascular disease. In addition, testosterone replacement has been demonstrated as having positive effects on numerous metabolic parameters (e.g. insulin sensitivity, glucose control, visceral obesity and hyperlipidemia) in patients with type 2 diabetes and heart failure[164].

Unfortunately, none of the randomized controlled trials were designed to assess the outcome of ‘safety’. Only large randomized placebo-controlled studies expressly designed to investigate the safety of androgen treatment will provide an authoritative answer[165].

2. TESTOSTERONE AND CVD RISK FACTORS

In 2004, Phillips et al[166] reported that low total and free testosterone levels were inversely linked to coronary artery disease, even after adjusting for age and adiposity. This observation still holds true as supported by a study showing that men with angiographically proven coronary artery disease had lower levels of testosterone than those of controls[167]. Also of significance, testosterone was negatively correlated to the degree of coronary involvement. Recently, a prospective population-based study of 794 men, 51 to 91 years of age, in the Rancho Bernardo community, looked at the relationship of testosterone with all-cause death over the subsequent 2 decades[151]. The authors found that men whose total testosterone levels were in the lowest quartile,
defined as <241 ng/dL, were 40% more likely to die than were men with higher androgen levels. These findings were independent of age, adiposity, lipids, adipokines, and lifestyle. In cause-specific analyses, low testosterone predicted increased risk of death due to cardiovascular and respiratory disease. It is thus clear that low testosterone is independently associated with many of the individual risk factors for heart disease. What are these risk factors, and how are they impacted by testosterone?

a) Visceral obesity, body mass index and fat mass

Studies of body fat and low testosterone levels have demonstrated an inverse relationship of testosterone with visceral fat accumulation. The term ‘lean body mass’ is often used synonymously with fat free mass. The description of age-related sarcopenia in the setting of the decline in serum testosterone in older men, and the knowledge that testosterone replacement increases fat-free mass and muscle volume has led to the hypothesis that testosterone therapy in older men will increase lean body mass and skeletal muscle, thereby improving quality of life increasing strength and stability. The largest placebo-controlled trial to date to test this hypothesis found that over 36 months of treatment, an increase in serum testosterone from 12.7 to 21.7 nM led to a 1.9 kg (3.5%) increase in lean mass. A linear regression analysis showed an inverse relationship to pretreatment testosterone levels[168] in parallel with the decrease in lean body mass seen in hypogonadal men, there is also an increase in fat mass. In a study of men aged 22-69 years (mean age 53 years), hypogonadal subjects had 26% body fat, compared to 19% in eugonadal men[169]. Quantitative CT analysis of hypogonadal men (mean age 52 years) has shown that they have a greater subcutaneous fat area and a trend towards an increased visceral fat area when compared to age-matched eugonadal men[170]. Testosterone replacement, in addition to decreasing fat mass, decreased subcutaneous fat by 12% and visceral fat by 6%[169]. Thereby, as fat mass (obesity) independently predicts cardiovascular risk, the likelihood that testosterone replacement can regulate this risk is equally appealing.

b) Carbohydrate metabolism: the association between low testosterone and glucose intolerance and type 2 diabetes.

Epidemiological studies show that low testosterone levels are independently associated with type 2 diabetes mellitus after adjusting for potential confounders[171]. In fact, lower concentrations of free and bioavailable testosterone even in the normal range are associated with diabetes, independent of adiposity[172]. Men in the lowest tertile of free testosterone were 4 times more likely to have diabetes compared to men in the highest tertile. Furthermore, low testosterone levels independently predict the development of the metabolic syndrome in middle-aged men[173].

Basaria and Dobs have postulated a clinical model that further establishes the role of testosterone in the mediation of glucose metabolism in their series of articles on testosterone and cardiovascular disease in men with prostate cancer. They note that in men undergoing androgen deprivation for prostate cancer, insulin resistance develops within a few months of initiation of the androgen-deprivation therapy[174,175]. In addition, when men who undergo long-term androgen-deprivation therapy are studied, in addition to hyperinsulinemia, they have a higher prevalence of hyperglycemia and metabolic syndrome[175,176]. This relationship between hypogonadism and hyperglycemia persists even after adjustment for age and body mass index, and the degree of hyperglycemia is directly related to the duration of sex hormone suppression[177]. Thus, hypogonadism appears to be an early marker for disturbances in insulin and glucose metabolism and may contribute to the pathogenesis of metabolic syndrome and type 2 diabetes, thus again contributing to the overall cardiometabolic risk.

c) Vasomotor regulation, vascular effects and coronary calcium

As previously mentioned, a clinical trial showed that transdermal testosterone improved exercise-induced myocardial ischemia (measured as time to ST depression) during an exercise stress test in men with stable angina[162]. These vasodilatory effects of testosterone on coronary and other vasculature are confirmed by the findings that men undergoing androgen-deprivation therapy for prostate cancer experience an increase in central arterial pressure (reflecting stiffening of large arteries)[174]. Similarly, in population studies, systolic and diastolic blood pressures have been shown to be inversely correlated with testosterone level[178].

In a study of 106 middle-aged men free testosterone was inversely correlated with intima-media thickness (IMT) of the common carotid artery and vascular adhesion molecule-1 (VCAM-1)[179]. The initial steps in the formation of an atherosclerotic lesion involve the adherence of circulating monocytes to dysfunctional endothelium and transmigration into the arterial intima, so the expression of vascular cell adhesion molecule-1 might be a key regulatory point in controlling the atherosclerotic process. Endothelial cells produce VCAM-1, therefore endothelial cell dysfunction or inflammation may signal an increase noted.

Testosterone has a direct effect on vascular smooth muscle by an action on either calcium or potassium channels[180] (Figure 8). In animal models using isolated coronary, pulmonary, and femoral arteries, a dose-dependent vasodilatory effect exists that is
independent of the endothelium[181]. Experimental studies in animals have demonstrated coronary dilation after acute testosterone administration.

Lastly, testosterone levels appear to be inversely related to arterial calcification. In the Rotterdam Study, the association between total and bioavailable testosterone with aortic atherosclerosis was evaluated in 504 nonsmoking men > 55 years of age[182]. Compared with men with levels of total and bioavailable testosterone in the lowest tertile, men in the highest tertile had a risk reduction of 60% to 80% of severe aortic atherosclerosis. Given that this was assessed by radiographic detection of calcification in the abdominal aorta, it is likely that subclinical atherosclerosis was not detected in this study. Another prospective study of elderly men (mean age 77 years) showed free testosterone concentration to be inversely related to the progression of intima-media thickness of the common carotid artery (CIMT) after adjustment for age and other risk factors[183]. The Tromso study also demonstrated an inverse association between total testosterone levels and intima-media thickness of carotid artery that is present even after exclusion of men with established cardiovascular disease[184].

Therefore, it appears that arterial stiffening, endothelial dysfunction, and increased atherosclerosis are means by which male hypogonadism may contribute to a higher risk of death.

d) The association of androgens with lipids, abnormalities of coagulation and inflammatory cytokines

Epidemiological data suggest that testosterone levels are associated with a beneficial lipid profile, with negative correlations with total cholesterol, LDL-cholesterol, and triglycerides, and a positive association with HDL-cholesterol[185]. Other various cross-sectional studies in men have reported a positive correlation of testosterone levels with HDL-C[186,187] and a negative correlation with total cholesterol, LDL-C and triglycerides[188,189] thereby suggesting that hypogonadal men have a pro-atherogenic lipid profile. There are also inverse associations between inflammatory cytokines and testosterone[190]. An inverse relationship between testosterone and interleukin-6 and C-reactive protein suggests a role for replacement, modifying the inflammatory response to CRP and cytokines, a theory that needs to be supported by further randomized trials. These associations are further validated by clinical trials showing improvement in lipid profile and reduction in inflammatory cytokines with testosterone replacement[191]. Additionally, inverse associations between testosterone and plasminogen activator inhibitor I, fibrinogen, and factor VII have been reported in men[182].

In summary, testosterone may influence cardiovascular disease via multiple mechanisms including changes in body composition, fat metabolism, glucose regulation, vascular mechanisms, and clotting.

Figure 8: Sites of androgen action on the vasculature, including sites where androgens have been shown to interact with the vessel wall and bloodstream components to initiate early stages of atherosclerosis, to propagate and enlarge the lesions, and to modify the late stage of plaque rupture.
3. TESTOSTERONE AND CARDIOVASCULAR OUTCOMES AND ALL-CAUSE MORTALITY

Several studies have evaluated the link between testosterone levels in men and the development of cardiovascular disease[149,150,192]. A prospective study of 794 men aged 50-91 years, in the Rancho Bernardo area of California evaluated the relationship between testosterone and all-cause mortality over approximately 20 years[151]. They found that men with testosterone levels <241 ng/dL i.e. in the lowest quartile, were 40% more likely to die than those with higher levels of testosterone. These findings held true regardless of age, lipid levels and other variables. Furthermore, low testosterone levels were associated with death from cardiovascular disease (HR, 1.98, 95% CI, 1.02-1.85) and respiratory disease (HR, 2.29: 95% CI, 1.25-4.20), but were not associated significantly with cancer-related deaths (HR, 1.34, 95% CI, 0.89-2.00).

A study conducted in Seattle by Shores and colleagues[149] evaluated whether low testosterone levels were associated with an increased risk of mortality in male veterans. This retrospective study included men older than 40 years without a diagnosis of prostate cancer. Men classified as having a low testosterone level- approximately 20% of the overall study population- had an increased mortality (HR 1.88; 95% CI, 1.34-2.63) after adjustment for clinical covariables, compared with those men with equivalent or normal levels. This suggests an increased mortality of 12%.

A third study, the largest study of testosterone levels and mortality ever conducted, called the European Prospective Investigation in Cancer in Norfolk (EPIC-Norfolk) Study[150] examined the relationship between testosterone levels and mortality due to all causes, cardiovascular disease, and cancer. The authors conducted a nested case-control study to determine the association of endogenous testosterone with all-cause mortality. They compared 825 men, who did not have any cardiovascular disease or cancer at baseline but died during the course of follow-up (entry between 1993-1997 through follow-up in 2003), with the 1489 men who were still alive. The cases and controls were matched for age and date of baseline visit. The authors found that the baseline testosterone levels were inversely related to deaths due to all causes, cardiovascular disease and malignancy, after controlling for the usual confounders (plus dehydroepiandrosterone and sex hormone-binding globulin).

The protective effect of testosterone increased with increasing quartiles, such that men in the highest quartile had a 30% lower risk of death than that of those in the lowest quartile. Even after excluding for deaths during the first 2 years of follow-up, this inverse relationship was maintained. Indeed, every 6-nmol/L (173 ng/dL) increase in serum testosterone decreased the death rate by 14%, and this benefit was irrespective of a patient’s age (above or below 65 years of age).

The study has limitations, though it is well conducted. It included on a single testosterone measurement, and thus did not control for any measures of transient variation in testosterone secretion. Second, the authors did not measure or calculate the free or bioavailable testosterone, the moiety that binds most closely to the androgen receptor. These measures are more accurate than total testosterone, especially in subjects with obesity or diabetes or older age because of the changes in sex hormone-binding globulin levels expected in these patient populations. Lastly, the authors did not measure estradiol levels, and it would be of interest to know if the beneficial effects of testosterone are mediated solely by testosterone or the aromatization of testosterone to estradiol[148].

The question remains: “Does testosterone serve as a marker, an association for increased cardiovascular mortality, or does it have a pathogenic role?” Even though Khaw and the other investigators of the EPIC-Norfolk study excluded men with serious disease and those who died within the first 2 years of the study (assuming they had subclinical illness) the authors were cautious in mentioning that they might have included men with subclinical disease[150]. However, given the results of these 3 large studies, the Rancho Bernardo study, the Shores study, and now the EPIC-Norfolk study, it is conceivable that testosterone has a pathogenic role in the development of cardiovascular disease, and is more than simply a marker of disease. The exact pathogenesis is still being debated.

This landmark study suggests that high endogenous testosterone concentrations appear to be beneficially associated with mortality due to all causes, cardiovascular disease and cancer. These findings require replication in other population studies, and safety outcomes in large-scale controlled trials.

4. TESTOSTERONE REPLACEMENT AND CARDIOVASCULAR DISEASE

Haddad and others[159] performed a systematic review and meta-analysis of 30 randomized, placebo-controlled trials to assess the effect of testosterone use on cardiovascular events and risk factors in men with different degrees of androgen deficiency. The included 1642 men of whom 808 were treated with testosterone. The trials had limited reporting of methodological features that prevent biased results (only 6 trials reported allocation concealment), enrolled few patients and were of brief duration (only 4 trials followed patients for > 1 year). Testosterone
use in men led to inconsequential changes in blood pressure and glycemia, and in lipid fractions. The OR between testosterone use and any cardiovascular event pooled across trials that reported these events (n=6) was 1.82 (95% CI, 0.78-4.23). Several trials failed to report data on measured outcomes.

Low-dose physiological testosterone therapy can improve cardiovascular functional capacity and symptoms in men with moderately severe CHF. In a randomized, double-blind placebo controlled study with Androderm 5 mg daily, Malkin et al demonstrated significant improvements using the parameter of the incremental shuttle walk test (ISWT) [164] (Figure 9).

Though this meta-analysis demonstrated that testosterone supplementation was relatively safe in terms of cardiovascular health, the problem of the study in evaluating safety of androgen replacement is that none of the available randomized controlled trials were designed to assess this outcome.

Therefore, no current evidence indicates that testosterone replacement reduces CVD. Testosterone replacement at present should be reserved for those who are symptomatic of testosterone deficiency. However, chronic illness is associated with low testosterone, and therefore, testosterone levels should be screened in those with diabetes and chronic CVD, including heart failure.

Another significant issue is whether testosterone should be conceived as a treatment versus prevention of common maladies of aging in older men. Studies of the sort as recommended by the Institute of Medicine[156] that the NIH support small and medium-sized randomized trials with one or more conditions or symptoms potentially attributable to hypogonadism, in order to determine whether or not testosterone treatment would improve or ameliorate these conditions. As mentioned earlier in this review, therapeutic targets included sarcopenia and muscle weakness, osteoporosis, sexual and erectile problems, cognitive impairment and depression.

Harman[193] astutely notes that “treatment and prevention are different strategies and frequently require different approaches. It is the failure to differentiate between prevention and treatment with regard to atherosclerosis that has led to the widespread misinterpretation of the Women’s Health Initiative regarding hormone therapy and increased cardiovascular risk, given that one cannot ‘prevent’ currently incident disease.” He goes on to note that most middle-age and older men are currently embarking on a regimen of testosterone treatment in order to slow progression or avoid onset of perceived age-related debilities such as diminished sexual capacity, loss of muscle mass and strength and bone loss.

In order to implement the large data we are collecting regarding testosterone and cardiovascular disease, we need to answer questions regarding the critical level for starting treatment, optimal dose, target testosterone level to be reached, duration of treatment, and long term safety. We argue what is needed is a Men’s Health Initiative Study, to critically evaluate the effects of testosterone treatment in long-term, double-blind, randomized, placebo-controlled trials of androgen replacement. “With all these data, androgens should no longer be considered as mediators of only sexual function or skeletal health, nor should they be discarded by defaming them as a fountain of youth.” [194]
5. CONCLUSION

<table>
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<tr>
<th>Recommendation</th>
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<tr>
<td>There is a consistent inverse relationship between endogenous testosterone levels and adverse cardiovascular events</td>
<td>LOE 1</td>
</tr>
<tr>
<td>Arterial stiffening, endothelial dysfunction, and increased atherosclerosis are means by which male hypogonadism may contribute to a higher risk of death</td>
<td>LOE 2</td>
</tr>
<tr>
<td>Low testosterone levels are independently associated with many of the individual risk factors for heart disease</td>
<td>LOE 2</td>
</tr>
<tr>
<td>High endogenous testosterone concentrations appear to be beneficially associated with mortality due to all causes, cardiovascular disease and cancer</td>
<td>LOE 1</td>
</tr>
<tr>
<td>No current evidence indicates that testosterone replacement reduces CVD</td>
<td>LOE 2</td>
</tr>
<tr>
<td>Testosterone supplementation in men is relatively safe in terms of cardiovascular health</td>
<td>LOE 2</td>
</tr>
<tr>
<td>Testosterone use in men with low testosterone levels led to inconsequential changes in blood pressure, glycemic control ad all lipid fraction</td>
<td>LOE 1</td>
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6. RECOMMENDATIONS

Because there is no evidence that testosterone replacement reduces overall cardiovascular risk, testosterone replacement at present should be reserved for those who are symptomatic of testosterone deficiency

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Men with clinical signs of hypogonadism and cardiovascular risk factors should be offered a screening testosterone level</td>
<td>Grade A</td>
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VI. TREATING ED IN THE CARDIAC PATIENT

1. IS THE PATIENT OR THE DRUG HARMFUL?

ED is frequent in patients with diagnosed CAD and PDE-5 inhibitors are widely used in such patients[195]. A strong body of clinical data shows all 3 agents (sildenafil, tadalafil and vardenafil) do not increase the risk of nonfatal myocardial infarction, stroke, or cardiovascular deaths. These drugs do not exacerbate ischemia or worsen exercise tolerance in patients with known CAD who achieve levels of exercise comparable or greater than that achieved during sexual intercourse. Even in patients with severe CAD, sildenafil does not adversely affect coronary artery diameter, coronary blood flow, or coronary vascular resistance, while it even increases coronary flow reserve[196,197]. It has also been shown that PDE-5 inhibitors might reduce cardiovascular morbidity and mortality in diabetic patients with silent CAD and ED. These data support the American College of Cardiology/American Heart Association Consensus and the Princeton Consensus Conference statements that PDE-5 inhibitors are safe for patients with stable CAD who are not taking nitrates[133]. Nitrates in combination with PDE-5 inhibitors may cause a profound and unpredictable decline in blood pressure and are contraindicated. The 24-hour period between nitrate use and short-acting PDE-5 inhibitor administration (up to 48 hours for the long-acting tadalafil) appears prudent until additional data, including information on outliers and patients with CAD are available. After cessation of oral nitrate, and provided there has been no clinical deterioration, PDE-5 inhibitors can be used safely[198].

Regarding the effect of concomitant medication, while previous studies indicated the negative influence of cardiovascular drugs such as P-blockers and thiazide diuretics on erectile function, recently, baseline data of ONTARGET/TRANSCEND showed that only calcium-channel antagonists had a significant adverse effect on erectile function[199]. Treatment with β-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin I (AT1) antagonists was not associated with a decreased erectile function, whereas statins had a beneficial effect. Follow-up data will provide more solid information on the effect of concomitant medication on sexual function.

Recognizing the need for advice on management of erectile dysfunction, two consensus panels (in the UK and the USA) have produced similar guidelines dividing cardiovascular risk into three practical categories, with recommendations for management[37,133]. The Princeton consensus guidelines have been updated. It is recommended that all men with erectile dysfunction should undergo a full medical assessment. Baseline physical activity needs to be established and cardiovascular risk graded as low, intermediate, or high (Table 5). Most patients with low or intermediate cardiac risk can have their erectile dysfunction managed in the outpatient or primary care setting.

There is no evidence that treating erectile dysfunction in patients with cardiovascular disease increases cardiac risk; however, this is with the provisos that the patient is correctly assessed and that the couple or individual (self-stimulation may be the only form of sexual activity) is appropriately counseled. Oral drug treatment is the most widely used, because of its acceptability and effectiveness, but all treatments have a place in management. The philosophy is to be always positive during what, for many men and their partners, is an uncertain time.

2. LIFESTYLE CHANGES

The commonest modifiable lifestyle factors associated with ED are obesity, cigarette smoking, hyperlipidaemia, and a sedentary lifestyle. In the Second Princeton Consensus on Sexual Dysfunction and
Cardiac Risk the role of lifestyle factors was emphasized regarding associated risk and evidence of benefit from intervention[133].

Due to their especially strong association with ED and CVD as well as their high prevalence in the population, physical inactivity and obesity present as ideal treatment targets for improving erectile function as well as the underlying vascular disease. For instance, overweight/obese men have up to double the risk of ED as compared to normal weight men[200] while sedentary men have twice the risk of ED as compared to active men[201]. Consistent with multiple disease outcomes, the emerging evidence suggests that abdominal obesity is the one phenotype most strongly associated with risk of ED[202]. When both abdominal obesity and physical inactivity are present men have a four-fold greater chance of developing ED in comparison to lean and active men[200]. Furthermore, even among men with ED, those who are overweight have significantly poorer erectile function than those who are not[203]. The strength of the causal relationship between obesity, inactivity and ED is further supported by the fact that changes in physical activity and obesity explain over 50% of the variance for changes in ED[202].

Thus, given that four out of five men with ED are obese or overweight and nearly half of these are also sedentary it is surprising that only limited prospective research has been conducted on the role of lifestyle changes on erectile function[202,204]. That said, the situation is complicated because while obesity and physical inactivity, are directly associated with both endothelial and erectile dysfunction they also contribute to insulin resistance, dyslipidemia, hypertension, and inflammation which are also distinctive risk factors for both endothelial and erectile dysfunction. Almost all of the risk factors (diabetes, dyslipidemia, smoking, obesity, hypertension, inactivity, and inflammation) have been suggested to have a final common pathway via disruption of normal endothelial function, in part, by the reduction of NO bioavailability through increased oxidative stress. Further complicating the issue, the use of some pharmacotherapy to control the underlying risk factors has been shown to result in an exacerbation of ED[19,205]. For example, as indicated in other sections the use of antihypertensive medication, such as beta-blockers and diuretics, as well as statins and fibrates, to control dyslipidemia have all been associated with hindered erectile function.

3. PHYSICAL INACTIVITY

Although the available clinical evidence is not yet definitive, overall the data strongly suggests that increased physical activity should be used as a preventative strategy against the development of ED[202] as well as a treatment strategy to improve erectile responses in those already suffering from ED. Coupled with the fact that increased physical activity can also improve other risk factors (obesity, insulin resistance, hypertension, dyslipidaemia, and inflammation) associated with endothelial and erectile dysfunction, cardiovascular disease, as well as poor response to PDE-5 inhibitors, it becomes an obvious strategy for improving both erectile function and systemic vascular health.

Some of the prospective evidence in this regard suggests that approximately one to two years of increased physical activity can improve erectile function[202,206]. Indeed, White et al[206] performed a 9 month aerobic exercise intervention trial in healthy middle-aged men, although with no diagnosed erectile dysfunction. Subsequently, as assessed by a non-validated self-report questionnaire, the exercising men reported less difficulty in maintaining erection from baseline measures as compared to the control group[202]. In the only randomized controlled trial to date, Esposito et al performed a 2 year lifestyle intervention including physical activity and caloric restriction in 110 healthy obese men with ED. The 55 men in the intervention arm attended monthly sessions aimed at improving exercise and diet in order to achieve a 10% weight reduction, while those in the control group received general information regarding exercise and diet. After the 2 years, men in the intervention group significantly increased their physical activity, reduced their caloric intake, improved the quality of their diet and accordingly, improved their erectile function from baseline, as compared to the control group. Indeed, the intervention lead to complete return of erectile function in over 30% of men.

In other experimental and clinical[207,208] studies, single exercise sessions have been shown to acutely enhance endothelial function for at least 24 hours by 1.5 to 2 fold, but are abolished by 48 hours[208]. In addition, aerobic exercise interventions of variable length (1-12 weeks) have found marked improvements in endothelial function, in particular increased bioavailability of NO as well as delayed progression and even regression of atherosclerosis[209]. More specifically, enhanced protein expression and increased phosphorylation of endothelial NO synthase (eNOS), the enzyme responsible for the synthesis of NO from its precursor, L-arginine, are likely responsible for the augmented NO availability post acute exercise. Considering that NO is the principal mediator of the penile erection, greater availability of endothelial NO should lead to enhanced physiological erectile function after acute exercise. Taken from another perspective, acute exercise has also been shown to counteract the postprandial endothelial dysfunction induced by high-fat and high-carbohydrate feeding, and improve brachial artery flow-mediated vasodilation in healthy adults[210].
4. OBESITY
Separate from physical inactivity, numerous studies have found obesity per se to be a clear risk factor for ED and reduction of obesity has been linked with improvements in erectile function[202]. Importantly, the health risk associated with obesity appears to be highly dependent on the regional deposition of adipose tissue[211]. Indeed, it is now well established that abdominal obesity is a strong predictor of various health outcomes irrespective of total obesity. The relationship between abdominal obesity and ED was first documented in 1956, and more recent studies demonstrate that abdominal obesity, as assessed by anthropometric measures may be a better predictor of ED risk than total obesity, as assessed by body mass index (BMI)[202]. The association between anthropometric measures of abdominal obesity (e.g. waist circumference) and ED may be explained by excess accumulation of adipose tissue in two distinct depots within the abdomen, namely abdominal visceral (VAT) and subcutaneous adipose tissue (SAT). Of the two abdominal fat depots, VAT has emerged as a strong and independent predictor of dyslipidemia and insulin resistance, cardiovascular disease, type 2 diabetes, inflammation, metabolic syndrome, and not surprisingly, endothelial function[212-214]. Various studies have established, that reductions in VAT are associated with consequent improvements in metabolic status, however, while it is a plausible link, no studies to date have assessed the effect of exercise-induced reductions of VAT per se on changes in erectile function[215].

5. CHANGES IN PHYSICAL ACTIVITY VERSUS OBESITY
Increased cardio-respiratory fitness is associated with reduced morbidity and mortality independent of total and abdominal obesity[216]. Indeed, obese and fit individuals are reported to have lower health risk than lean but unfit individuals. This is consistent with White et al observing that the improvements in self-reported erectile function following nine months of aerobic exercise were strongly correlated with individual improvements in cardio-respiratory fitness[206]. Furthermore, Esposito et al using a multivariate analyses, showed following two years of lifestyle intervention in obese men with ED, that increased physical activity was associated with an improvement in erectile function independent of changes in the obesity indices, and additional confounders[202]. These results are mechanistically corroborated by numerous exercise trials showing correlations between improvements in cardio-respiratory fitness and enhanced endothelial function. Indeed, it has been suggested that improved endothelial function, that is, greater endothelium-dependent vasodilatory function would lead to greater oxygen delivery to working muscle and thus augmented cardio-respiratory fitness. However, to date, no study has assessed the independent association between improvements in cardio-respiratory fitness and erectile function. Taken together, the above evidence suggests that both visceral adiposity and cardio-respiratory fitness mediate independent effects on the health risk associated with obesity, and that changes in these variables will likely causally impact erectile function.

6. SMOKING
In the Health Professionals’ Study, smoking increased the risk of developing ED by 50%[200]. In the Massachusetts Male Aging Study men who smoked at baseline increased their risk of developing moderate or total ED to 24%, compared with non-smokers at 14% \(P = 0.01\)[3]. Smoking has been shown to significantly adversely interfere with the cavernous veno-occlusive mechanism and to reduce the erectile response to intracavernous injections. When considering overall vascular health, advice and support to enable individuals to stop smoking are an essential lifestyle intervention.

7. THE METABOLIC SYNDROME
The metabolic syndrome, as discussed previously, consists of a cluster of risk factors that increase the risk of cardiovascular disease and type 2 diabetes. The Mediterranean-style diet (rich in whole grain, fruits, vegetables, legumes, walnut and olive oil) was evaluated in 35 men, with 30 active as control subjects[217]. All had the metabolic syndrome and ED. The intervention group was given detailed dietary advice, targets were set, and monthly small-group sessions were held to offer support. Men in the control group were given general oral and written information about healthy foods but no individualized support. After 2 years, markers of endothelial function and inflammation significantly improved in the intervention group but not in the control group. In the intervention group, 13 men achieved an IIEF of 22 or higher, compared with only two in the control group. The intervention group had a significant decrease in glucose, insulin, low-density lipoprotein cholesterol, triglycerides and blood pressure, with a significant increased in high-density lipoprotein cholesterol. Fourteen men in the intervention group had glucose intolerance and six had diabetes at baseline, but by 2 years the numbers had reduced to eight and three respectively.

We see here the evidence that multiple risk factor reduction benefits a multiple risk factor state in terms of both ED and CAD risk. A potentially important link is also emerging between inflammatory markers and their modification in the ED/CAD context and its therapy.

8. ALCOHOL
Excessive alcohol intake per se increases cardiovascular risk but there is little evidence of ED risk other than the acute effect of binge drinking. In addition, men with a very high alcohol intake are unlikely to
9. DEPRESSION

Depressive disorders range from mild symptoms to major depression with core symptoms of sadness or loss of interest/pleasure in usual activities for a period of at least two weeks accompanied by at least five of the following: sleep difficulties, fatigue, low self esteem, guilt, psychomotor agitation/retardation, loss of appetite. Not surprisingly, depressive symptoms may cause loss of libido and reduced sexual function, but conversely, ED may also lead to depression. Cross sectional studies have demonstrated a relationship between ED and depression but it remains unclear whether depression causes ED and, if so, what the underlying mechanism may be. The evidence that depression promotes coronary artery disease events in clinically healthy individuals as well as patients with known coronary heart disease is more established[218]. By analogy, it is conceivable that depression may cause vascular disease in the penile arteries therefore providing another link to ED.

Analysis of cross section results from the MMAS a decade ago established a relationship between erectile dysfunction and depression independent of aging, level of education, heart disease, diabetes, physical activity and other potential confounders[219]. Symptoms of depression (measured using the Centre for Epidemiologic Depression Scale (CES-D) and defined as a score ≥16)) were present in 12% of men across all ages. The estimated OR for ED was 1.82 in men who had depressive symptoms as compared with those who did not.

In the MMAS men were followed up for an average of 8.8 years, enabling a prospective analysis of a possible causative relationship between depression and ED[220]. Excluding men with ED, diabetes or heart disease at baseline as well as those who had undergone radical prostatectomy, 778 men were studied. Symptoms of depression were present in 9% at baseline. At follow up 168 of the men were classified as having moderate or complete ED (self-administered questionnaire with specific items as well as a single-item global self assessment). However, the presence of depressive symptoms at baseline was not a significant predictor of incident ED (p=0.12), with a greater percentage of men without depressive symptoms developing ED than those with depressive symptoms at baseline (21.3% vs 13.2%).

This result is at odds with the conclusion of a study of 1,683 men aged 50, 60 or 70 years from a Finnish cohort, 11.4% of whom demonstrated depressive symptoms (a score of ≥16) on the five-item version of the Mental Health Index) at baseline in five years follow up study[221]. In men free of ED at baseline (determined by two self-report items, adapted from the questionnaire used in the MMAS) the incidence of ED at five years was 59/1000 person-years (95% CI 39-90) in men with depressive mood and 37/1000 person years (95% CI 32-43) in men without depressive symptoms. After controlling for possible confounding variables (age, education, marital status, body mass index, smoking, diabetes, hypertension, heart disease, cerebrovascular disease and medication use), the incidence of ED was 4.5 times higher in men with treated depressive symptoms, but just 1.2 times higher in those with untreated depressive symptoms at follow up than those free of depressive symptoms and medication use for psychological disorders at baseline. In men free of depressive symptoms but who used antipsychotic medication, the risk of ED was doubled. The adjusted incidence density ratio of depressive mood was 1.9 (95% CI 1.1-3.3) in men with ED compared to those without it at baseline. The authors describe a bidirectional relationship between depression and ED, stating that ED may independently cause or increase depression, and moderate or severe depressive mood or antidepressant medication may cause ED. A suggested mechanism is decreased blood flow to the penis and inhibition of penile smooth muscle relaxation resulting from depression inhibiting the activity of parasympathetic nerves. The authors suggest low power in the MMAS as an explanation for the discrepancy between the MMAS results and their study.

The results of the Finnish study highlight the potential for antidepressant medication to cause ED. Drugs such as tricyclic antidepressants and selective serotonin reuptake inhibitors which are commonly used to treat depression may be associated with male sexual dysfunction including new onset erectile dysfunction and should be taken into consideration when treating depression[222].

Further evidence is needed to support a bidirectional relationship but given the well supported association between ED and depression, it is appropriate that patients presenting with ED should be screened for depression and vice versa.

VII. DRUG THERAPY

1. PHOSPHODIESTERASE (PDE) TYPE 5 INHIBITORS

PDE-5 inhibitors have transformed the management of erectile dysfunction[196]. The mechanism of action by blocking the degradation of cyclic guanosine 3’5’-monophosphate (cGMP) by PDE-5 promotes blood flow into the penis and the restoration of erectile function. They do not initiate an erection and sexual stimulation is needed to obtain an erection. They are not aphrodisiacs.

Hemodynamically, PDE-5 inhibitors have mild nitrate-like actions (sildenafil was originally intended to be a drug for the treatment of stable angina). As
PDE-5 is present in smooth muscle cells throughout the vasculature and the nitric oxide/cGMP pathway involves in the regulation of blood pressure, PDE-5 inhibitors have a modest hypotensive action. In healthy men, a single dose of sildenafil 100 mg transiently decreased blood pressure by an average of 10/7 mm Hg with a return to baseline at 6 hours after the drug was given[197]. There was no effect on heart rate. As nitric oxide is an important neurotransmitter throughout the vasculature and is involved in the regulation of vascular smooth muscle relaxation, a synergistic and clinically important interaction with oral or sublingual nitrates can occur, and a profound decrease in blood pressure can result. The mechanism involves a combination of increased formation of cGMP when nitrates activate guanylate cyclase, and decreased breakdown of cGMP as a result of the action of PDE-5 inhibitors. The concomitant administration of PDE-5 inhibitors and nitrates is thus contraindicated, and this recommendation also extends to other nitric oxide donors such as nicorandil. Clinical guidelines recommend that sublingual nitrate should be taken 12 hours after the PDE-5 inhibitors sildenafil or vardenafil; tadalafil, which has a longer half-life, ceases to react with nitrates only after 48 hours[133]. Oral nitrates are not prognostically important drugs, and they can therefore be discontinued and, if necessary, alternative agents substituted[198]. After cessation of oral nitrate, and provided there has been no clinical deterioration, PDE-5 inhibitors can be used safely. It is recommended that the time interval before the use of a PDE-5 inhibitor be five half-lives, which equates to 5 days in the case of most popular once-daily oral nitrate agents.

2. SILDENAFIL (VIAGRA)

Sildenafil was the first oral treatment for erectile dysfunction and is the most extensively evaluated[223]. Overall success rates of 80% or more in patients with cardiovascular disease have been recorded with no evidence of tolerance. Patients with diabetes, with or without risk factors, in whom the pathophysiology is more complex and extensive, have an average success rate of 60%. To date, randomized trials, open-label studies, and outpatient monitoring studies have not found the use of sildenafil to be associated with any excess risk of myocardial infarction, stroke, or mortality.

In patients with stable angina pectoris, there is no evidence of an ischaemic effect caused by coronary steal, and in one large, double-blind, placebo-controlled exercise study, sildenafil 100 mg increased exercise time and diminished ischaemia[224]. A study of the haemodynamic effects of sildenafil in men with severe CAD identified no adverse cardiovascular effects, and a potentially beneficial effect on coronary blood flow reserve[225]. Studies in patients with and without diabetes have demonstrated improved endothelial function acutely and after long-term oral administration, which may have implications beyond the treatment of erectile dysfunction. Sildenafil has also been shown to attenuate the activation of platelet IIb/IIIa receptor activity[196]. Hypertensive patients receiving monotherapy or being treated with several drugs have experienced no increased in adverse events, with the exception of those receiving doxazosin, a non-selective α-adrenoceptor antagonist. Occasional postural effects have occurred with sildenafil when it was taken within 4 hours of doxazosin 4mg; advice to avoid this time interval is now in place[226]. Sildenafil has also been proved to be effective in patients with heart failure who were deemed suitable for treatment of erectile dysfunction; the incidence of erectile dysfunction in patients with heart failure is 80%, making this finding of major clinical importance[227]. On average, the dose of sildenafil is 50 mg; 25 gm is advised initially for those older than 80 years because of delayed excretion. Onset of action is 30-60 minutes with a peak effect from 1-12 hours. A dose of 100 mg is invariably needed in patients with diabetes. An empty stomach and the avoidance of alcohol or cigarette smoking facilitate the effect of the drug. Sildenafil 100 mg has no adverse cardiac effects additional to those associated with the 50 mg dose and should be routinely prescribed if, after four attempts, the 50 mg dose is not effective.

Adverse effects are generally mild in nature (Table 11) with drop out rates similar to placebo in the randomized studies.

Table 11: Common adverse events of all three PDE-5 inhibitors (from EMEA statements on product characteristics).

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Sildenafil</th>
<th>Tadalafil</th>
<th>Vardenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>12.8%</td>
<td>14.5%</td>
<td>16%</td>
</tr>
<tr>
<td>Flushing</td>
<td>10.4%</td>
<td>4.1%</td>
<td>12%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4.6%</td>
<td>12.3%</td>
<td>4%</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>1.1%</td>
<td>4.3%</td>
<td>10%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.2%</td>
<td>2.3%</td>
<td>2%</td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>1.9%</td>
<td>&lt;2%</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>6.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>5.6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The short half-life of sildenafil makes it the drug of choice in patients with more severe cardiovascular disease, allowing early use of supportive treatment if an adverse clinical event occurs.

3. TADALAFIL (CIALIS)

Tadalafil also has been extensively evaluated in patients with cardiovascular disease, and has a safety and efficacy profile similar to that of sildenafil[228]. Studies have shown no adverse effects on cardiac contraction, ventricular repolarization or ischaemic threshold. A similar hypotensive effect has been recorded with a dose of doxazosin 8 mg so caution is needed: as hypotension does not occur when the patient is in the supine position, and as tadalafil has a long half-life, it is suggested that tadalafil is taken in the morning and doxazosin in the evening. There is no interaction of tadalafil with the selective α-adrenoceptor antagonist, tamsulosin, which can therefore be prescribed as an alternative to doxazosin for benign prostate hypertrophy[229]. Tadalafil is effective from 30 minutes after administration, but its peak efficacy occurs at 2 hours. Efficacy is maintained for up to 36 hours and is not influenced by food. It is administered in 10 to 20 mg doses. The recommended starting dose is 10 mg and should be adjusted according to the patient’s response and side effects. Adverse events (Table 11) are generally mild in nature and the drop-out rate due to adverse events is similar to placebo.

Tadalafil improved erections by 67% and 81% in men taking 10 mg and 20 mg of tadalafil compared with 35% of men in the control placebo group[230]. Tadalafil also improved erections in difficult to treat subgroups. In diabetic patients 64% reported improved erections compared to 25% of patients in the control group.

Because of its long half-life, tadalafil may not be the drug of first choice for patients with a more complex cardiovascular disease. However, as 80% of patients with cardiovascular disease stratify as low risk it does represent an alternative for the majority.

Tadalafil is now approved as a daily therapy (2.5 and 5mg) which may improve spontaneity and effectiveness[231].

4. VARDENAFIL (LEVITRA)

Because vardenafil has a chemical structure very similar to that of sildenafil, it is not surprising that it has a similar clinical profile. One study has reported no impairment of exercise ability in patients with stable CAD receiving vardenafil 20 mg[232]. Daily therapy provides no advantage probably due to the short half-life[233].

Vardenafil is effective after 30 minutes from administration. Its effect is reduced by a heavy fatty meal. It is administered in 5,10 and 20 mg doses. The recommended starting dose is 10 mg and should be adjusted according to the patient’s response and side effects. Adverse events (Table 11) are generally mild in nature with a drop-out rate similar to placebo.

After 12 weeks of treatment in a dose-response study, improved erections were reported by 66%, 76% and 80% of men taking 5 mg, 10 mg and 20 mg of vardenafil respectively, compared with 30% of men taking placebo[234]. Vardenafil has also improved erections in difficult to treat subgroups. In diabetic patients 72% reported improved erections compared to 13% of patients taking placebo.

5. CARDIOVASCULAR SAFETY

Clinical trial results and post-marketing data of sildenafil, tadalafil and vardenafil have demonstrated no increase in myocardial infarction rates in patients that received these agents compared to expected rates in age-matched populations of men[235]. None of the PDE-5 inhibitors were found to adversely affect total exercise time or time to ischaemia during exercise testing in men with stable angina. In addition to established benefit in treating pulmonary hypertension, these are encouraging results in cardiac failure.

Organic nitrates (e.g. nitroglycerine, isosorbide mononitrate, isosorbide dinitrate) and other nitrate preparations used to treat angina, as well as amyl nitrite or amyl nitrate (‘poppers’ used for recreation) are absolute contraindications to the use of PDE-5 inhibitors. They result in cGMP accumulation and unpredictable falls in blood pressure and symptoms of hypotension. The duration of interaction between organic nitrates and PDE-5 inhibitors is dependent upon the PDE-5 inhibitor and nitrate under study.

If a PDE-5 inhibitor is taken and the patient develops chest pain, nitroglycerine must be withheld for at least 12 hours if sildenafil (and likely vardenafil) was used (half-life 4 hours) and for at least 48 hours if tadalafil was used (half-life 17.5 hours). If a patient develops angina while taking a PDE-5 inhibitor he should be told to discontinue sexual activity and stand up, as the venous pooling will imitate a nitrate[133]. If pain continues under hospital supervision alternate agents should be prescribed, though intravenous nitrates can be used under careful medical observation.

Co-administration of PDE-5 inhibitors with antihypertensive agents (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium blockers, betablockers, diuretics) may result in small additive drops in blood pressure, which are usually minor. In general, the adverse event profile of the PDE-5 inhibitor[226] is not worsened by a background of antihypertensive medicines, even when the patient is on multiple antihypertensive agents.

6. INJECTION THERAPY

Direct intracavernosal injection of vasodilating agents
began in the 1980s. Prostaglandin E1 is a natural substance that relaxes smooth muscle cells and dilates the arterioles, increasing blood flow into the penis. Alprostadil is a commercially available form of prostaglandin E1 that is effective in 5 to 15 minutes, with an erection that usually lasts 30 minutes but occasionally may persist for several hours[236]. The starting dose is 1.25 µg and can be increased to 40 µg, depending on effect. It is important that patients be taught the correct technique for injection; men with poor dexterity (e.g. arthritic hands or tremor) will need their partner’s help with the injection. In fact, partners may often perform the injection as part of the sexual activity. On removal of the needle, firm pressure is applied and the drug should be gently massaged into the penis for approximately 30 seconds. Men on anticoagulants, however, should compress the injection site for 5 to 10 minutes. The resulting erection occurs without stimulation, although stimulation may enhance its effects. The erections are occasionally painful, but usually feel natural. It is recommended that this treatment not be used more frequently than every four days. Alprostadil is effective in up to 80% of the cases and is associated with a return to spontaneous erections in 35%. It is safe and effective in diabetic patients who are used to self-injection of insulin. Although its efficacy rates are impressive, the discontinuation rate for alprostadil is high, with local pain and loss of spontaneity being the most commonly cited reasons.  

7. TRANSCUTRAL THERAL THERAPY  
Intraurethral therapy of alprostadil presents an alternative to injections[237]. Medicated Urethral System for Erection (MUSE) is a single-use transurethral system that involves the insertion of a 1.4 mm pellet into the urethra using a hand-held applicator just after micturition and about 15 minutes prior to sexual activity. As with injection therapy, the patient must be taught the correct technique of insertion. Patients should receive an initial dose of 250 µg with dosage titration between 125 and 1000 µg under medical supervision until the patient achieves a satisfactory response. These numbers are much higher than with injection therapy due to drug loss in the general circulation. A maximum of two doses are allowed per 24 hour period. Once the correct dose has been identified, success rates of up to 60% have been recorded, although in a comparative study with injections this fell to 43% (injections 70%).

VIII. NON-DRUG THERAPY  
1. PSYCHOSEXUAL THERAPY  
If psychogenic ED is present, appropriate counselling should be arranged. Even organic cases of ED may have a psychological component secondary to the dysfunction itself. Cooperative teamwork between the physician and the therapist is valuable when the organic and psychological causes of ED overlap.

2. ROLE OF COUNSELLING IN THE TREATMENT OF CAD PATIENTS WITH ED  
Patients may become noncompliant with their medical regimen for CAD or hypertension, fearing that such medications cause or worsen sexual function. On the other hand, they may defer sexual activity fearing either hypothetical risks of PDE-5 inhibitors or that their cardiac condition does not permit it. Many patients with CAD are uncomfortable discussing sexual function despite their informational needs and desire to discuss their sexual health. To dispel fear and anxiety, couples should receive information about the pathophysiology of cardiovascular disease (including its treatment) relative to sexual function, the physiologic requirements of sexual activity and the psychologic sequelae of CAD. It should be made clear that all of the currently recommended therapeutic methods (revascularization procedures, medications, aggressive risk factors management) aimed at reducing cardiovascular risk in general may also be effective in minimizing cardiac risks associated with sexual activity in particular.

Most patients at low risk may be permitted to engage in or resume sexual activity, and/or receive treatment for ED, provided that this does not include PDE-5 inhibitor use in the presence of concomitant nitrate regimens. Clinicians should reassure low risk cardiac patients that the stress on the heart during intercourse is no greater than that during normal working activities or moderate exercise and the existence of a stabilized cardiac condition does not increase the risk of a cardiac event during intercourse. Sexual activity should be resumed gradually and when the patient is rested and relaxed. Maintaining a moderate room temperature, as well as avoiding intercourse after a heavy meal or heavy drinking, can contribute to a relaxing and safe sexual encounter. If the patient is taking a PDE-5 inhibitor for ED, then he should not take a nitrate if angina occurs during sexual intercourse but should be advised to stop the activity. No further sexual activity should be undertaken until the patient has had an adequate medical evaluation. Patients should also be advised to report any angina, dyspnea, prolonged palpitations or dizziness, or intense and sustained fatigue experienced during sexual activity. Such symptoms may indicate a need to reappraise the safety of sexual activity. The need for lifestyle changes and intense risk factors management should be made clear. Further, physicians should remember that even organic cases of ED may have a psychological component secondary to the dysfunction itself. It is preferable that sexual counselling is provided to both the patient and their partner when this is feasible, since
the disease has great impact on relationship issues. Finally, the bottom-line of a successful counselling is to individualize the advice.

Patients and their partners should be provided with the opportunity to:

- dissolve misconceptions on the relationship between CAD (and its medication) and ED
- further their understanding of the risks associated with sexual activity and to adopt safe practices
- understand proper use of PDE-5 inhibitors and their contraindications
- be sensitized regarding warning symptoms of a cardiac condition
- to understand the importance of adhering to lifestyle changes and risk factors treatment

3. VACUUM CONSTRUCTION DEVICES

The vacuum constriction device is a long-established means of treating ED[238]. It is a non-invasive method that produces an erection by creating a pressure vacuum of up to 250 mm Hg, causing blood flow into the penis. The erection is then maintained with the placement of a rubber construction ring at the base of the penis. The constriction ring must not be left in place longer than 30 minutes, since ischaemic damage could occur.

It should be recognized that a significant hematoma (minor in 10% of cases) may occur in men on anticoagulants; so, this is a relative contraindication. Specific training and advice before commencing the use of a vacuum device are needed. Vacuum devices are also not recommended for men with penile curvature.

IX. POTENTIAL CARDIAC APPLICATION OF PDE-5 THERAPY BEYOND ERECTILE DYSFUNCTION

1. PULMONARY HYPERTENSION

Sildenafil has been shown to be beneficial to patients with pulmonary arterial hypertension, either idiopathic or secondary[239].

2. IDIOPATHIC PULMONARY HYPERTENSION

The treatment of idiopathic pulmonary arterial hypertension is the only non-erectile dysfunction PDE-5 inhibitors indication currently approved. Sildenafil has been approved at a dose of 20 mg three times daily for improving exercise tolerance in patients with pulmonary hypertension[240]. It significantly enhances exercise capacity by improving pulmonary hemodynamics and reducing right ventricular afterload[240,241]. It also reduces right ventricular mass, as determined by magnetic resonance imaging. Sildenafil might have the very desirable combination of primary inotropic, antihypertrophic, and afterload-reducing effects on the right ventricle without significantly affecting systemic hemodynamics. Thus, this agent appears very attractive for the treatment of pulmonary arterial hypertension involving the right ventricle[242].

The currently available PDE-5 inhibitors are not equally efficacious in the treatment of pulmonary hypertension[243]. Reduction in mean pulmonary artery pressure, in the pulmonary-to-systemic vascular resistance ratio and in right ventricle afterload, as well as an increase in cardiac index, has been reported with all three PDE-5 inhibitors. However, only sildenafil causes a significant improvement in arterial oxygenation. The etiology of these agent-specific characteristics may be related to the different selectivities of the three PDE-5 inhibitors with respect to other PDE isoforms or the difference in their binding capacity to PDE-5 during hypoxia[243].

3. SECONDARY PULMONARY HYPERTENSION

Pulmonary arterial hypertension is a life-threatening complication of several connective tissue diseases including scleroderma, systemic lupus erythematosus, mixed connective tissue disease, rheumatoid arthritis and dermatomyositis/polymyositis. Clinical studies suggest that sildenafil can be used as a pulmonary vasodilator in systemic sclerosis patients with secondary pulmonary hypertension[244]. Sildenafil also reduces pulmonary artery pressure and increases quality of life in patients with systemic lupus erythematosus[245].

CONCLUSION THERAPY

<table>
<thead>
<tr>
<th>Statement</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED may benefit from lifestyle changes</td>
<td>1</td>
</tr>
<tr>
<td>Physical activity and weight loss are beneficial to both ED and CAD</td>
<td>1</td>
</tr>
<tr>
<td>Depression is common</td>
<td>1</td>
</tr>
<tr>
<td>PDE-5 inhibitors are safe and effective in cardiac patients</td>
<td>1</td>
</tr>
<tr>
<td>All therapies are safe in cardiac patients providing they are fully evaluated (page 7)</td>
<td>1</td>
</tr>
</tbody>
</table>

RECOMMENDATIONS THERAPY

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle advice for all men with ED</td>
<td>A</td>
</tr>
<tr>
<td>PDE-5 inhibitors as first line therapy</td>
<td>A</td>
</tr>
<tr>
<td>Alternative therapies if PDE-5 inhibitors contraindicated or ineffective</td>
<td>A</td>
</tr>
<tr>
<td>Counselling therapy to appropriate patients</td>
<td>A (B)</td>
</tr>
</tbody>
</table>
4. HIGH-ALTITUDE ILLNESS

The term «high-altitude illness» is used to describe the cerebral and pulmonary syndromes that can develop in unacclimatized persons shortly after ascent to high altitude. Acute mountain sickness and high-altitude cerebral edema refer to the cerebral abnormalities, and high-altitude pulmonary edema to the pulmonary abnormalities. Because millions of visitors travel to high-altitude locations each year, acute mountain sickness is a public health problem and has economic consequences, especially for the ski industry. High-altitude pulmonary edema and high-altitude cerebral edema, though uncommon, are potentially fatal[246]. Exposure to high altitude causes alveolar hypoxia, induces pulmonary hypertension, and may even lead to pulmonary edema. The alveolar edema and ventilation/perfusion mismatch initiate a catastrophic downward spiral of worsening alveolar hypoxia[247]. PDE-5 inhibitors show promise in high altitude medicine, as, by virtue of their vasodilating effect on the pulmonary circulation, they suppress the altitude-induced pulmonary hypertension and they ameliorate pulmonary hemodynamics and gas exchange, thus limiting the altitude-induced hypoxemia and favoring cardiovascular adaptation to exercise[248].

5. SYSTEMIC HYPERTENSION

Because PDE-5 is present in artery and vein smooth muscle cells throughout the body, PDE-5 inhibitors have mild systemic vasodilatory effects and thus the potential to impact the vascular system. The vasodilating properties of PDE inhibitors in the systemic circulation account for the BP reduction observed in patients treated for ED[249]. Thus, these drugs would be theoretically suitable for treating hypertension in patients without ED. Additional benefits may be related to improved arterial stiffness and endothelial dysfunction, two early vascular abnormalities characterizing essential hypertension[250].

The potential of PDE-5 inhibitors as antihypertensive agents has not been thoroughly explored. Active midterm treatment with sildenafil reduced ambulatory and clinic blood pressure to a similar extent as that observed with other classes of antihypertensive drugs [251]. An incremental antihypertensive effect of a single dose of tadalafil has been demonstrated in uncontrolled hypertensive subjects on multiple agents[252]. However, at this stage, the use of PDE-5 inhibitors as antihypertensive agents cannot be advocated. More investigation is needed on PDE-5 inhibitors as antihypertensive drugs, especially with slow-release formulations or compounds with long half-life. Studies on safety during long-term administration, interactions with antihypertensive and non-antihypertensive drugs, and effect on target organ damage are needed.

Concomitant use of PDE-5 inhibitors with antihypertensive drugs results in either no or small additive reductions in blood pressure. Multiple trials support the safety of use of PDE-5 inhibitors in hypertensive men with ED being treated with monotherapy or a multidrug antihypertensive regimen. Concomitant use of PDE-5 inhibitors with α-blockers requires some caution, because some patients may develop orthostatic hypotension.

6. CORONARY ARTERY DISEASE

PDE-5 inhibitors have potential as cardiovascular drugs in patients with vasospastic angina or diffuse coronary microvessel disease and in patients undergoing coronary artery bypass grafting because of their favorable effects on vascular function and their ischemic preconditioning-like effects[253]. Furthermore, although their potency is modest compared with other agents that specifically target platelet adhesion/aggregation, their adjunctive use as antiplatelet agents could be also considered.

In a recent prospective study Gazzaruso et al., showed that in type 2 diabetic men with silent coronary artery disease, treatment with statins and 5-PDE inhibitors might reduce the occurrence of major adverse cardiac events.

7. HEART FAILURE

Treatment of heart failure is a challenging task. An impaired nitric oxide pathway contributes to several abnormal cardiac and vascular phenotypes typical of the failing cardiovascular system. Inhibition of phosphodiesterase-5 is a new therapeutic strategy for overexpressing nitric oxide signaling by increasing the availability of cyclic guanosine monophosphate[254].

Sildenafil at the dose of 50 mg twice per day for 6 months heightened ventilatory efficiency and exercise performance, tempered the peripheral stimulus to hyperventilation, and improved the NO-mediated vasodilation in patients with chronic systolic heart failure[255]. Furthermore, long-term treatment (12 weeks) with sildenafil improved peak VO2, 6-minute walk distance and right ventricular ejection fraction, in patients with systolic heart failure complicated by secondary pulmonary hypertension. Since many of the observed benefits of PDE-5 inhibition with regard to left ventricular hypertrophy, ventricular-vascular stiffening, renal dysfunction, and pulmonary hypertension may be particularly relevant to the pathophysiology heart failure in patients with preserved ejection fraction, there is compelling rationale for extending the preliminary physiologic benefits of sildenafil seen in <systolic> heart failure to the population with <diastolic> heart failure. The RELAX trial, which proposes to address this question, is currently in progress.
Landmark experiments by Takimoto et al performed in mice exposed to sustained pressure overload, have documented that chronic PDE-5 inhibition can prevent and reverse cardiac and myocyte hypertrophy and interstitial fibrosis[256]. Experimental data also suggest direct myocardial effects of PDE-5 inhibition that may counteract β-adrenergic, hypertrophic and pro-apoptotic signaling, three critical pathways in the development of left ventricle dysfunction[257]. Inotropic effects of sildenafil were shown in human and animal hypertrophied right ventricle models; however, whether this is present in failing right ventricles remains to be determined.

Inhibition of PDE-5 has been associated with improvements in endothelial function in patients with heart failure due to systolic dysfunction that are highly correlated with improvements in skeletal muscle perfusion, reduction in exercise-induced hyperventilation, and increased aerobic efficiency[258]. Associated reductions in large artery stiffness observed during sildenafil treatment may further contribute to improved baroreceptor function and enhanced heart rate recovery in patients with heart failure. Improvements in vascular function and pulmonary vascular resistance may account for the overall improvements in exercise capacity and health-related quality of life that have been observed during chronic administration of sildenafil to heart failure patients.

In summary, multiple lines of pre-clinical evidence support a therapeutic role for PDE-5 inhibitors in the management of heart failure patients. However, human trials to date are limited to small physiologic studies of patients with heart failure and reduced ejection fraction (most with associated pulmonary hypertension) followed for relatively short periods of time. Longer-term randomized trials are necessary to define the safety, tolerability, and efficacy of PDE-5 inhibitors for the management of heart failure across the spectrum of ejection fraction.

8. RAYNAUD’S PHENOMENON

Raynaud’s disease (RD) is a common disorder affecting 3% to 5% of the healthy population, and occurs in more than 90% of patients with connective tissue diseases. The therapeutic options remain limited, particularly in patients with secondary RD due to connective tissue disease. Theoretical considerations lead to the expectation that phosphodiesterase type 5 inhibitors may improve clinical symptoms and digital blood flow in patients with RD.

Digital ischemia results from vasoconstriction of the digital arteries, precapillary arterioles, and cutaneous arteriovenous shunts. Despite various hypotheses, the mechanism of local vasoconstriction is not well understood. Nevertheless, there is increasing evidence that the NO/cGMP system plays a major role. PDE-5 inhibitors, through their vasoactive and platelet-inhibitory effects, may lead to improved microcirculation, decreased frequency and shorter duration of attacks, and ulcer healing in patients with vasodilator-resistant Raynaud’s phenomenon[259,260].

Based on current data from small clinical trials, open-label pilot studies and case series and reports, phosphodiesterase 5 inhibitors may help some patients with very serious Raynaud’s. A large, well-conducted multicenter, double-blind study is needed to determine the benefit and risk of these agents in Raynaud’s phenomenon[261].

9. PERIPHERAL ARTERY DISEASE

Therapeutic use of PDE-5 inhibitors may extend to the chronic tissue ischemic states such as peripheral artery disease. In a recent study on limb ischemia, sildenafil therapy resulted in increased angiogenic activity through a PKG-dependent pathway that is independent of nitric oxide production or NOS activity and a finding which identify the angiogenic therapeutic potential of sildenafil for critical limb ischemia[262].

10. CONGENITAL HEART DISEASE

Endothelium-dependent pulmonary artery relaxation is impaired in young patients with increased pulmonary flow secondary to congenital heart disease. This impairment may be an important early event in the pathogenesis of pulmonary vascular disease. Sildenafil increases pulmonary blood flow and improves cyanosis in patients with Eisenmenger syndrome. Efficacy of sildenafil as treatment for idiopathic pulmonary arterial hypertension may be extended to patients with Eisenmenger syndrome[263]. Preliminary evaluation of tadalafil has shown efficacy and safety in selected patients with Eisenmenger syndrome[264]. Finally, sildenafil was reported to improve pulmonary arterial hemodynamics and right ventricular function and relieve symptoms associated with severe pulmonary arterial hypertension in patients with large atrial septal defects[265].

11. DIABETES

PDE-5 inhibitors have shown to display beneficial cardiovascular effects, suggesting that they may have other systemic benefits involving the endothelium. There is currently little evidence available regarding the effects of PDE-5 inhibitors—beyond treatment of ED—in patients with type 2 diabetes. In a double-blind, randomized, controlled trial in 40 male patients, with type 2 diabetes the administration of 50mg of sildenafil citrate for 30 consecutive days diminished microalbuminuria and the percentage of Hb A1c, suggesting a protective effect of this drug against target organ damage of diabetes[266].

12. CONCLUSION

<table>
<thead>
<tr>
<th>PDE-5 inhibitors are effective in pulmonary hypertension</th>
<th>LOE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE-5 inhibitors may have increasing use across a spectrum of vascular disease</td>
<td>LOE 5</td>
</tr>
</tbody>
</table>
13. RECOMMENDATIONS

| PDE-5 inhibitors for pulmonary hypertension | Grade A |
| Research to continue in other vascular conditions | Grade D |

X. CARDIOVASCULAR ASPECTS OF FEMALE SEXUAL DYSFUNCTION

Female sexual dysfunction (FSD) is defined as disorders of sexual desire, arousal, orgasm and/or sexual pain which result in significant personal distress and may have a negative effect on a woman's health and her quality of life[267]. It is an age-related, progressive and highly prevalent disease, affecting 22-76% of women. An analysis of data from the National Health and Social Life Survey found that sexual dysfunction is more prevalent in women than in men (43% vs. 31%)[268]. Shifren et al[269] found an age-adjusted prevalence of any sexual dysfunction and sexually related distress of 43.1% and 22.2%, respectively in a large (n=31,581) female population representative of U.S. women. The two conditions occurred together in 12% of cases and were more common in middle-aged women.

Sexual symptoms may signal serious underlying disease. Although the same diseases, risk factors and medications that are associated with male erectile dysfunction, such as heart disease, hypertension, diabetes, smoking and hypercholesterolemia, antidepressants and anti-hypertensives are also associated with FSD, specific underlying causes are not well described and the association with cardiovascular disease has not been fully explored[270].

The heterogeneity of the patient population enrolled into the studies, the change over time in either FSD definition or classification, the confounding factor of the menopause, the profound effect of psychological and psychometric variables, the different methods used to diagnose both FSD and underlying vascular disorders and the lack of direct, “user friendly” indices of FSD (compared for example with penile erection in men) accounts for many uncertainties and the wide gap of information in this field[271]. Thus, a comparison with male erectile dysfunction is difficult and requires further research (Table 12).

<p>| Table 12: Similarities and dissimilarities between male and female sexual dysfunction. |</p>
<table>
<thead>
<tr>
<th>Definition</th>
<th>Erectile Dysfunction</th>
<th>Female sexual dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>The consistent inability to reach and maintain an erection satisfactory for sexual activity*</td>
<td>Disorders of sexual desire, arousal, orgasm and/or sexual pain which result in significant personal distress and may have a negative effect on a woman's health and un impact on her quality of life **</td>
<td></td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>50$</td>
<td>42$$</td>
</tr>
<tr>
<td>Etiology (%)</td>
<td>Organic/Vascular</td>
<td>Psychogenic</td>
</tr>
<tr>
<td>90/40</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Confounding factor</td>
<td>-</td>
<td>Menopause</td>
</tr>
<tr>
<td>Self-reported test</td>
<td>IIEF-15 #</td>
<td>FSFI ##</td>
</tr>
<tr>
<td>Risk factors prevalence (%)</td>
<td>age-related increase</td>
<td>Loose relationship</td>
</tr>
<tr>
<td>Age</td>
<td>42, up to 83</td>
<td>37, up to 80</td>
</tr>
<tr>
<td>Diabetes (type 1 &amp; 2)</td>
<td>30, up to 68</td>
<td>40</td>
</tr>
<tr>
<td>Hypertension</td>
<td>65, up to 75</td>
<td>Lack of data</td>
</tr>
<tr>
<td>CAD / PAD</td>
<td>73, up to 87</td>
<td>Lack of data</td>
</tr>
<tr>
<td>Predictor of CV events</td>
<td>Proved $</td>
<td>Lack of data</td>
</tr>
<tr>
<td>Seeking medical help (%)</td>
<td>20-30</td>
<td>20</td>
</tr>
<tr>
<td>Major reason for not seeking medical help</td>
<td>Embarrassment to talk about sexual problem</td>
<td>Embarrassment to talk about sexual problem</td>
</tr>
<tr>
<td>Response to PDE-5-I’s</td>
<td>Mostly effective</td>
<td>Mixed results</td>
</tr>
</tbody>
</table>

CAD= coronary artery disease; CV= cardiovascular; IIEF= International index erectile function; FSFI= female sexual function index; PAD= peripheral arterial disease. PDE-5-I’s= phosphodiesterase type-5 inhibitors

*Lue T, NEJM 2000**; Reference [259]; $ Feldman HA, 1994; $$ Laumann EO, 2000; # Cappelleri JC, Urology 1999; ## Reference [277]; § Thompson J, 2005,
1. PATHOPHYSIOLOGY OF FSD

The sexual response in women schematically includes excitement/arousal, plateau, orgasm and resolution. Physiologic changes that take place during sexual activity start with increased flow to the genitalia with engorgement. Vaginal lubrication occurs and precedes vagina lengthening and dilation due to smooth muscle relaxation. The increased blood flow to clitoris increases intracavernous pressure, tumescence, protrusion of the glans clitoris and eversion and congestion of the labia minora[272]. Common vascular risk factors may alter the NO-mediated vasodilation process that ultimately leads to vaginal engorgement and clitoral erection (the "vascular phases" of female sexual activity). Thus, similarly to male sexual dysfunction, a preserved endothelium integrity and a patent hypogastric-pudendal artery supply are needed for a correct sexual response. Animal models have shown that atherosclerosis of the aorto-iliac arteries causes clitoral fibrosis and significantly inhibits the vasculogenic response to stimulation[273].

Despite the high prevalence of FSD, little attention has been paid to this disorder. The fault is equally distributed between physicians and patients. From one side, a recent survey of members of the American Urogynecologic Society has shown that only a minority screen for FSD, mainly due to lack of time and uncertainty about the treatment[274]. From the other side, a very small proportion of women seek medical attention for FSD. In a UK-based survey[275], despite 54% of women reported at least one sexual problem lasting at least one month during the last year which caused 65% of them to avoid sex, only 21% had sought help (>70% the general practitioner). The most frequent reasons for that were embarrassment and feeling that there was no remedy for this problem. Thus, women are reluctant to talk about sexual problems with their GP, and time constraints of the every day clinical practice lead to doctors failing to address sexual dysfunction.

2. SPECIFIC RISK FACTORS FOR FSD: ROLE OF DIABETES, CARDIOVASCULAR DISEASE AND HYPERTENSION

a) Diabetes

Among the common risk factors, diabetes plays a pivotal role in sexual dysfunction either in men and in women. Prevalence varies between 27% and 49% with values as high as 80% reported in type 2 diabetics over 50 years (10-12). The pathophysiology of the association between diabetes and ED/FSD is multifactorial including endothelial and smooth muscle dysfunction and autonomic neuropathy. Diabetic women are prone to develop a "global sexual dysfunction" leading to decrease sexual desire, dyspareunia, decrease sexual arousal and inadequate lubrication. Overall, results of the association between diabetes and FSD in women are far less consistent than in ED mainly due to the difficulty in quantifying the sexual response in women. Studies exploring the effect of diabetes on the vascular component of sexual function found that both vaginal lubrication and clitoral erection are frequently affected as compared to non diabetic women[276]. Interestingly, a poor correlation between FSD and either duration of diabetes or diabetic complications has been reported in previous studies reinforcing the concept of the role of "extra-vascular" causes, included depression, in determining FSD[277,278].

b) Cardiovascular disease

Evidence is accumulating in favor of a strong association between various CV disease and male sexual dysfunction. Coronary artery disease (CAD) is often associated with hypertension, obesity and metabolic syndrome, sharing endothelial dysfunction as the pathophysiologic background. These conditions have been found to produce FSD as well. Interestingly, many cardiovascular diseases lead to decrease physical activity which in turn has been found to be one of the primary determinants of FSD[279].

c) Hypertension

The prevalence of FSD in hypertensives averages up to 40% and it is usually higher than in normotensives (42.1% vs. 19%, p<0.001)[280,281]. Variables that have been reported to significantly affect FSD rate are duration of the hypertension, age and anti-hypertensive medications[280]. As previously shown in hypertensive males with ED, no significant difference was found between treated vs. untreated patients in the female sexual function index scores (26.5±5.4 vs. 24.8±6.2, p=0.11)[280] confirming the role of the hypertensive process per se in the determination of FSD.

d) Menopause as a confounding factor

Menopause is characterized by a series of neuroendocrine changes that ultimately lead to reduced estrogen production[282]. The decline in ovarian hormones accounts for an increased rate of both sexual disturbances and cardiovascular disease. Prevalence of FSD in post-menopausal women varies between 68% and 87%, mainly due to a decrease in sexual desire and onset of dyspareunia. Many factors, such as age, hypertension, hypercholesterolemia and diabetes, metabolic syndrome, come into play to explain the increased CV risk in postmenopausal women. All these factors negatively affect endothelial function and accelerate the systemic atherosclerosis process, included CAD. In this situation, the association between FSD and CAD should be sought as a frequent occurrence rather than a peculiarity and correction for many covariates should be taken into consideration.
3. SELF-REPORTED QUESTIONNAIRE FOR FSD DIAGNOSIS

Self-reported questionnaire to assess FSD are well standardized and inexpensive diagnostic tools, easy to administer and score and normative values are available in both clinical and nonclinical populations. As with ED questionnaires (e.g., the IIEF), differences in educational, ethnic or cultural background may hamper the results of these tests. Among the several assessment tools available to investigate sexual dysfunction, the Female Sexual Function Index (FSFI) is probably the most popular and widely accepted and is becoming the gold standard for the evaluation of FSD[283]. It is a brief (19 items) questionnaire that assesses sexual functioning in women over the past 4 weeks in six separate dimensions (desire, arousal, lubrication, orgasm, satisfaction and pain). The test has been validated and the measure was shown to have a high degree of internal consistency and reliability. Other tests include the Self Function Questionnaire (SFQ), the Brief Sexual Function Index for Women (BSFI-W) and the Female Sexual Distress Scale (FSDS).

4. FEMALE SEXUAL DYSFUNCTION-CAD LINK: CLINICAL EVIDENCE

The clinical evidence of a link between FSD and CAD is far less robust than between ED and CAD. The few studies that have dealt with this link addressed the general relationship between obstructive vascular disease and complaints of sexual disorders. Kaya et al[284] assessed sexual function in 20, sexually active, young women (mean age 38±3.8 years) with angiographically proved CAD compared to 15 age-matched healthy controls. The FSFI test was used. Patients with CAD had higher rate of sexual dysfunction (60% vs. 33%, p<.05) and significantly lower total FSFI score (18±3 vs 26±5, p=0.001) as compared to normals. The most affected domains were orgasm and lubrication. No comparison was made between the extent and severity of CAD and the FSFI score. Tessier et al[285] evaluated the prevalence of sexual dysfunction in a population of women who underwent elective abdominal aortic surgery either for dilative or occlusive disease using the FSFI and SF-36 questionnaires. Mean age was 67.8 years with 93% being post-menopausal women on hormone replacement treatment. They found that FSD was more frequent in women with occlusive rather than dilative aortic disease, supporting the role of obstructive vascular disease in the genesis of FSD.

In 2005 Salonia A. et al[286] first presented a preliminary report on 39 consecutive women with angiographically proved CAD who were assessed for sexual dysfunction by FSFI and SDS test. FSD was detected in 12/39 women (30%). Interestingly, 10/12 (83%) of those with both FSD and CAD developed sexual symptoms prior to CAD onset with a median time interval of 62 months (12-108 months). CAD women had a significantly lower total-FSFI and FSFI-arousal scores as compared to a normal control group (n=102). Finally, The Women’s Health Initiative Observational Study (WHI-OS) explored the association between sexual satisfaction and cardiovascular conditions at baseline, in 46,525 sexually active, postmenopausal women aged 50 to 79 years[287]. Women were classified as sexually satisfied or dissatisfied. In logistic regression modeling dissatisfaction was significantly associated only with peripheral arterial disease (adjusted odd ratios 1.44, 95% CIs, 1.15-1.82), whereas no correlation was found with myocardial infarction, stroke, coronary revascularization either with coronary artery bypass or percutaneous coronary angioplasty, congestive heart failure and angina pectoris. Women were followed up for an average of 7.8±1.4 years. No increased prevalence or incidence of cardiovascular disease among the sexually satisfied vs. dissatisfied was detected. Authors concluded that the lack of predictive value of sexual dissatisfaction in this specific subset of women may be the result of physiological differences in sexual functioning between sexes. In a commentary to this article by R. Lane and J. Thayer[288] authors pointed out that sexual satisfaction in women is determined by multiple factors, of which vaginal lubrication (not assessed in that study) is only one. Sexual satisfaction/dissatisfaction is driven by different determinants in women and in men and are assessed by direct/indirect indexes. They concluded that it is of paramount importance to establish equivalent psychological markers across the sexes and to fully consider the role of emotions, both negative and positive, as important factors influencing the CV outcome.

An additional issue that merits some comments is the resumption of sexual activity after an acute coronary event (usually acute myocardial infarction). A somewhat “physiologic” change in the patient’s sexual activity up to 6 months after hospital discharge is a frequent occurrence (40-50%) and may vary from a reduction in the frequency/intensity of sexual intercourse to a true sexual dysfunction[47]. Reasons include anxiety, depression, loss of libido, fear of worsening the cardiac condition in both the patient and the partner and side-effects of cardiovascular medications. Those patients who had a degree of pre-existing sexual dysfunction were more likely to develop severe and long-standing sexual dysfunction.

5. RECOMMENDATION FOR SCREENING IN FSD

While evidence is accumulating supporting the concept that every patients with ED should be considered as a cardiac patient until otherwise proved, results are much less than conclusive for women with sexual dysfunction. Nevertheless, the Princeton Consensus Conference recommendations or any others available CV risk assessment tool[47] should
be applied to any woman with suspected or proved sexual disorder in order to stratify her own 10-year CV risk. Additional diagnostic tests should be performed when indicated. In those with proved sexual function disorder and heart disease, especially CAD, priority should be given to cardiologic diagnostic and therapeutic strategies before starting a specific approach to sexual disturbances.

6. TREATMENT OF FSD

Cardiovascular aspect of the treatment of FSD relates primarily to the use of medications that can influence sexual function. Similarly to men with ED, the avoidance of specific drug categories, such as beta-blockers and diuretics, may help to reduce sexual side-effects[280].

The development of phosphodiesterase-type-5 (PDE-5) inhibitors, such as sildenafil, tadalafl and vardenafil, has certainly revolutionized the treatment of sexual dysfunction in men. While improving erection, they exert beneficial effects on the heart and coronary, peripheral and pulmonary circulations. Basically, the inhibition of cGMP breakdown by phosphodiesterase type-5, PDE-5 inhibitors enhance muscle relaxation allowing for subsequent vasodilation and cavernosal engorgement. Moreover, the presence of NO synthase and PDE-5 in both animal and the human clitoral and vaginal tissues have been reported in previous studies. Despite this background, clinical studies with sildenafil, the only tested PDE-5 inhibitors in FSD, gave mixed results, suggesting a more complex mechanism of sexual dysfunction in women[289,290].

7. CONCLUSION

Female sexual dysfunction is a complex, multi-faceted, widely under diagnosed disorder affecting a substantial number of women

It is affected by common risk factors and clinical co-morbidities

Unlike ED, the association with CAD, the role as warning sign of sub-clinical vascular disease and as a predictor of future CV events has not been demonstrated

8. RECOMMENDATIONS

FSD should be evaluated in all female cardiac patients

XI. CONCLUSION

Cardiac patients may have anxieties about sexual activity because of their false belief of substantially increased risk. ED is common in cardiac patients because of the shared risk factors that adversely impact endothelial function. Signs of ED often present before overt cardiac symptoms develop; therefore a cardiac workup may be warranted for these patients, even without relevant cardiovascular histories. There is now increasing awareness of therapy for ED, but many patients remain reluctant to come forward for advice. The question of sexual activity and ED therapy should be raised by healthcare professionals as a routine part of the management of cardiac patients. Treatment is available. With reassurance, support, and careful explanation, sexual relationships can be
enjoyed by cardiac patients who receive appropriate advice.

With the recognition that ED is an early warning sign for silent coronary and vascular disease, screening for men presenting with ED and no cardiac symptoms is widely advocated. According to the second Princeton Consensus Guidelines, all men with ED and no cardiac symptoms should be considered as cardiac (or vascular) patients until proven otherwise. Such patients should undergo a full medical assessment with stratification of cardiovascular risk as high, medium or low. Those patients at low risk should receive lifestyle advice regarding physical activity and weight control and undergo regular monitoring by their general practitioner. Patients at increased risk for cardiovascular events should ideally undergo stress testing and referral for risk reduction therapy.

Although an exercise ECG is advocated to identify patients at increased cardiovascular risk, this method will identify only those people with obstructive flow-limiting CAD. Wherever possible, intermediate and high-risk patients should be considered for elective computed tomography coronary angiography to identify the presence of non-flow limiting lipid plaques that are potentially vulnerable to rupture. By implementing these measures, it should be possible to initiate early aggressive cardiovascular risk reduction in ‘at-risk’ patients, thereby taking advantage of the 2-5 year window of opportunity between the development of symptomatic ED and CAD. However, for the full potential of this approach to be realized, comprehensive education programmes are required to encourage men with ED to present to their general practitioner as soon as possible. In addition, a multidisciplinary approach is required, involving teamwork between the family doctor, nurse, pharmacist, urologist, diabetologist and cardiologist.

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Committee 9

Sexual Function In Chronic Illness And Cancer

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Sexual Function In Chronic Illness And Cancer

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INTRODUCTION

I. COMPLEXITIES AND RELEVANCE OF SEXUAL FUNCTION WHEN LIVING WITH CHRONIC DISEASE

Advances in surgical and medical treatment have greatly improved survival for patients with chronic illness, including many types of cancer. Surveys of patients who had received treatment for a variety of cancers in recent years suggest some 50% of the respondents developed sexual difficulties, half of whom would definitely seek treatment were it available. [1] As well, sexual dysfunction can reflect serious medical complications. For example severe ED in men with renal failure is known to be typically associated with coronary artery calcification which in turn is reflective of coronary artery disease. [2] The treatment of sexual dysfunction resulting from a medical condition, or commonly, from its treatment, has become an important component of medical care. Improved understanding of sexual physiology allows more effective therapy of dysfunction and even the opportunity of preventing some disease-related or iatrogenic dysfunction. Many factors contribute to sexual dysfunction related to chronic illness as shown in Table I.

In this chapter, we will identify the prevalence and underlying pathophysiology of sexual dysfunction associated with chronic illness and its treatment. We will address psychosocial factors contributing to sexual problems. Particularly in women, mood and relationship issues may be more crucial determinants than medical or surgical interruption of the sexual response. Currently accepted treatments, as well as emerging treatments, will be summarized. Potential prevention of dysfunction will be included.

II. ASSESSMENT

Because the sexual problems related to chronic illness are multifactorial, assessment and treatment should be from a multidisciplinary perspective. The most important assessment tool remains the structured interview. For patients in committed relationships, it is optimal to include both partners, seeing them together and individually. In the conjoint interview, the history of the sexual difficulties and each partner’s reaction to them can be evaluated. In individual sessions, the interviewer can ask about sensitive topics including past and present psychosocial difficulties, sexual trauma, sexual function with self-stimulation, with other partners, or emotions difficult to reveal in the partner’s presence. Table 2 outlines items requiring assessment when chronic illness is present in one or both partners.

A. NEUROLOGICAL DISORDERS

“Be near me when the light is low, when the blood creeps, and the nerves prick and tingle.”

Tennyson

I. NEUROPHYSIOLOGY AND NEUROANATOMY OF SEXUALITY IN HEALTH AND DISEASE

During the second quarter of the 20th century Wilder Penfield, in his cortical mapping experiments upon the brains of awake neurosurgical patients, found that genital tingling could be elicited by stimulating a small area of the right or the left parietal cortex in the interhemispheric fissure [22]. Stimulation was by surface electrodes. Later, neurosurgeon Robert Heath (1964) published a remarkable series of experiments whereby depth electrodes were
<table>
<thead>
<tr>
<th>Type</th>
<th>Mechanisms</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct</td>
<td>Change in sexual desire from disease</td>
<td>Typically reduced e.g., from high prolactin and anemia of chronic renal failure[3]. May be increased e.g., from some brain injuries[4]</td>
</tr>
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<td></td>
<td>Disruption of genital response from disease</td>
<td>ED from multiple sclerosis[5], hypertension[6]; orgasmic disorder from multiple sclerosis[7]</td>
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<td></td>
<td>Disruption of genital response from surgery</td>
<td>Radical prostatectomy and ED[8]; radical hysterectomy and reduced genital congestion/reduced lubrication[9], orgasmic disorder after radical vulvectomy[10]</td>
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<td></td>
<td>Disruption of genital response from radiation</td>
<td>ED from vascular (and also likely nerve damage) after radiotherapy for prostate cancer[11]; vaginal stenosis and friability from radiation for pelvic cancer[12]</td>
</tr>
<tr>
<td></td>
<td>Dyspareunia and disruption of sexual desire and response from chemotherapy</td>
<td>Sudden ovarian failure after chemotherapy for breast cancer[13]; testicular failure after intensive chemotherapy for hematopoietic transplantation[14]</td>
</tr>
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<td></td>
<td>Disruption of sexual desire and response from anti-androgen treatment</td>
<td>GnRH therapy for prostate cancer[15]</td>
</tr>
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<td></td>
<td>Disruption of genital response from aromatase inhibitors</td>
<td>Loss of sexual genital sensitivity, and exacerbation of vaginal atrophy from aromatase inhibition post breast cancer[16]</td>
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<tr>
<td></td>
<td>Disruption of sexual desire and response from pain</td>
<td>Pain from any chronic condition is a potent sexual distraction</td>
</tr>
<tr>
<td></td>
<td>Disruption of sexual desire and response from non hormonal medications</td>
<td>Narcotics can depress desire through gonadotrophin suppression[17]; selective serotonin reuptake inhibitors reduce desire and response[18]</td>
</tr>
<tr>
<td>Indirect</td>
<td>Reduction of self-image</td>
<td>Reduced by disfiguring surgeries, stomas, incontinence, altered appearance (e.g., drooling and altered facies of Parkinson's, altered skin color and muscle wasting of renal failure)</td>
</tr>
<tr>
<td></td>
<td>Depressed mood</td>
<td>Depression and mood lability commonly accompany chronic illness; depression major determinant of sexual function in women with renal failure[19] or multiple sclerosis[20]; strong link between ED and subsequent depression[21]</td>
</tr>
<tr>
<td></td>
<td>Impaired mobility</td>
<td>Reduced ability to caress, hug, and hold a partner; to sexually self-stimulate, to stimulate a partner, to move into positions for intercourse, to pelvically thrust in spinal cord injury, Parkinson's, brain injury, post amputation</td>
</tr>
<tr>
<td></td>
<td>Reduced energy</td>
<td>Fatigue may take its toll on sexuality especially desire e.g. from renal failure or chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Partnership difficulties</td>
<td>Difficulties finding a partner, dysfunction in the partner who assumes a care giver role, institutionalization, fear of becoming a burden to a partner, lack of independence. Relationship discord from stressors of living with medicalised lives (e.g. three times weekly hemodialysis)</td>
</tr>
<tr>
<td></td>
<td>Sense of loss of sexuality from imposed infertility</td>
<td>From surgery removing gonads or uterus, from chemotherapy or radiotherapy causing gonadal failure</td>
</tr>
<tr>
<td></td>
<td>Fear of sex worsening medical condition</td>
<td>Avoiding sex fearing a pregnancy would provoke cancer recurrence; fearing sex will provoke another stroke.</td>
</tr>
</tbody>
</table>
implanted into the deep mesiolimbic structures and other dopamine-rich 'pleasure centres' of the brain including the septal nuclei in the vicinity of the nucleus accumbens [23] (Figure 1). The ambulant patients were able to elicit orgasms at will by stimulating the implanted septal electrode connected to an external self-controlled button device. Fortunately by the turn of the millenium it became possible to map the topographic areas of sexual activation non-invasively by functional imaging with positron emission tomography (PET) and magnetic resonance (fMRI) as reviewed elsewhere [5] and addressed in greater detail in chapters 13 and 22 of the present book.

The septal nuclei are located adjacent to the cingulate gyrus on the medial surface of the frontal lobe and have massive projections to other limbic/paralimbic centres including the hippocampus, hippocampal fornix, amygdala, and hypothalamus (Figure 1). In some of those areas androgen receptors are present, and there is complex interaction between these receptors and hypothalamopituitary peptides including oxytocin, prolactin, and beta-endorphin to possibly contribute to arousal and to the 'satiation' that follows orgasm.

Neuronal damage to the frontal and temporal lobes of the brain, including the more deeply-located limbic structures, is the main vehicle of organic sexual dysfunctions brought about by brain trauma and stroke. Limbic and paralimbic areas of the brain involved in stroke include the insular cortex (middle cerebral artery stroke), the mesofrontal cortex/cingulate gyrus (anterior cerebral artery), the hypothalamus (contributions from both the anterior and posterior cerebral arteries), and the mesiotemporal structures (anterior choroidal artery). Epilepsy commonly arises in the hippocampal/
amygadaloid circuitry of the temporal lobe to potentially affect sexuality which can be further compromised by side effects from medications used to treat the seizures. Sexual dysfunctions in Parkinson’s disease are linked both to central dopamine depletion and peripheral autonomic neuropathy. Spinal autonomic pathways and ascending sensory pathways from the genitalia are selectively implicated in multiple sclerosis as well as spinal cord injury. Compromising the peripheral link are interruptions to the lower motor neuron connections between spinal cord and genitalia, by way of somatic/autonomic peripheral neuropathies, cauda equina injury, and iatrogenic pelvic nerve plexus injury brought about by surgical disruption or irradiation of the genital autonomic nerve supply (chapters 9 and 13) [5]. Ubiquitous in many of these neurological disorders are co-morbid disturbances of mood including depression (section C of present chapter and chapter 3) to potentially generate sexual anhedonia by way of frontolimbic inhibition [24].

II. EPIDEMIOLOGY OF SEXUAL DYSFUNCTION IN NEUROLOGICAL DISEASE

Uncertainties cloud the true prevalence of sexual dysfunctions in neurological disorders (Table 3) particularly in women in whom prevalence rates carry uncertainty even in health. Sexual difficulties following traumatic injury to the brain or to the spinal cord present a special case. Firstly, sexual losses can be total following spinal cord trauma depending on the completeness of paraplegia or quadriplegia and its segmental level along the spinal neuraxis. Second, in brain and spinal cord trauma, co-existing multiple injuries - including orthopedic injuries - exert their own, confounding effects upon sexuality by way of pain and disturbed sleep. Therefore, without inclusion of a control population of non-cerebral injuries, published figures on prevalence are a blend of brain (or cord) injury together with the sexual effects of ‘other’ bodily injuries [38,39]. By similar token, published rates of sexual dysfunction after stroke are clouded by comorbid vascular disease affecting the genital engorgement capacity in both men and women.

III. TREATMENT

Co-morbid depression to require treatment is a recurrent theme across the spectrum of chronic neurological illness. Pharmacological interventions for mood disorder can impact both positively and negatively upon sexual well-being. We recommend to screen and treat comorbid depression in patients with all neurological illness [5]: Grade C outlined in Table 4 are levels of evidence on selected treatment options for sexual difficulties in neurological disorders.

IV. INDIVIDUAL DISEASES

1. HEAD INJURY

a) Brain trauma

Sexual sequelae are not always linked to duration of coma, to the degree of global brain tissue loss, or the focality of brain injury. An exception is severe trauma to the prefrontal regions to produce a spectrum of change that ranges from disinhibited hypersexuality at one extreme to apathy and hyposexuality at the other.

Our specific recommendations for the management of hypersexuality include: CBT, SSRIs, clobazam, antiandrogens, GNRH agonists, and atypical antipsychotics: [5] Grade C.

Hypoactive sexual desire disorder is linked to disturbances of mood at all grades of head...
b) Pituitary trauma

Head injuries may give rise to sexual disorders not only as a result of injury to the brain tissues but also from co-occurring damage to the pituitary gland located on the undersurface of the brain. Injury of this type occurs mostly with, but is not limited to, severe levels of head trauma. Herrmann et al [65] found that pituitary deficits mostly occur when trauma-induced coma has exceeded 10 days. A ‘red flag’ for pituitary injury is the detection of basal skull fracture involving the sphenoid bone that harbours the pituitary gland; or by the finding on acute-phase CT or MRI of diffuse cerebral edema with resultant compression of the third ventricle as an indirect marker of disruption to the neighbouring hypothalamus and the connecting portal veins within the pituitary stalk.

### Table 3: Epidemiology of sexual dysfunctions in neurological disorders [5, 7, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37]

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence of sexual difficulty</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head Injury</td>
<td>36-54% for severer levels of TBI compared to 15% of healthy controls [25] Mostly erectile/ejaculatory dysfunction in men, reduced lubrication/dyspareunia in women.</td>
<td>Depression more important than severity of TBI in both sexes [34] Medications (especially mood-altering) account for up to one-quarter of cases of ejaculatory failure[26]</td>
</tr>
<tr>
<td>Spinal Cord Injury</td>
<td>Orgasm is achieved by less than half of subjects of either gender. About 50% of men are able to ejaculate when incomplete cord lesions are included. As few as 4% of men with complete, high lesions achieve ejaculation even though reflex erections remain intact[35].</td>
<td>Chronic pain in relation to cord injury occurs in as many as one-third of cases at least in men to potentially interact with depression and the autonomic aspects of sexual dysfunction[35]</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>Of men who are still ambulant, 60% have ED and 40-50% ejaculatory/organic dysfunction with reduced desire[27]. In ambulant, newly diagnosed women (mean time since first symptoms of MS, 2.7 years), sexual dysfunctions according to FSFI scores were present in 34.9% of sample compared to 21.3% healthy controls[7].</td>
<td>Eventually well over half of either sex are affected, predominantly by ED in 75% of men and by loss of genital sensation in up to 62% of women[5]</td>
</tr>
<tr>
<td>Stroke</td>
<td>An internally controlled study of 75 men and 25 women showed a dissatisfaction rate of 58.6% of men compared to 21.3% before the stroke and in 44% of the women compared to 20% prior to the stroke[28].</td>
<td>With depression as one of the exclusion criteria, post-stroke libido in patients 40-80 years, was still decreased or absent compared to pre-stroke in 61.9% of men (n=63) and 52.5% of women (n=40) having mild or no neurological disability after 6 months[29]. ED has a better prognosis under age 65[33]</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Both men[30] and women[30,31] with PD report sexual dissatisfaction more commonly than controls – the major determinants being age, severity of disease, and depression.</td>
<td>Caregiver partners (especially women partners) show an important degree of sexual dysfunction in several studies[32]</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Hyposexuality follows but does not predate the onset of epilepsy[5] and is more common in TLE. Men with localization-related epilepsy taking no AED’s have abnormally low sexual function[36]. Women with epilepsy have higher rates of disinterest and orgasmic dysfunction compared to controls[37].</td>
<td>Epilepsy has biological as well as psychological effects upon sexual well-being.</td>
</tr>
</tbody>
</table>

**KEY**

Table 4: Levels of evidence for treatment of sexual dysfunctions in neurological disorders [5, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66]

<table>
<thead>
<tr>
<th>Option</th>
<th>Level of Evidence</th>
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<tbody>
<tr>
<td><strong>EPILEPSY</strong></td>
<td></td>
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<tr>
<td>AED-induced hypogonadism</td>
<td>1. Switch to a P450 enzyme-inhibiting or enzyme-neutral AED[40]</td>
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<tr>
<td></td>
<td>2. In men, testosterone replacement[41]</td>
</tr>
<tr>
<td>AED-induced polycystic ovary syndrome/weight gain</td>
<td>Switch from valproic acid to an enzyme-neutral AED[42]</td>
</tr>
<tr>
<td>AED-induced sexual disinterest secondary to drowsiness</td>
<td>Consider lamotrigine</td>
</tr>
<tr>
<td>Sexual automatisms of temporal lobe origin</td>
<td>Consider anterior temporal lobectomy[43]</td>
</tr>
<tr>
<td><strong>MULTIPLE SCLEROSIS</strong></td>
<td></td>
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<tr>
<td>Erectile dysfunction</td>
<td>1. Sildenafil[44]</td>
</tr>
<tr>
<td></td>
<td>2. PGE[45]</td>
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<tr>
<td>Vaginal lubrication</td>
<td>Minor increase from sildenafil but no improvement to orgasmic capacity or overall sexual response[46]</td>
</tr>
<tr>
<td>Spasticity to inhibit movement</td>
<td>Baclofen, tizanidine, botox, sclerosing agents[5]</td>
</tr>
<tr>
<td><strong>SPINAL CORD INJURY</strong></td>
<td></td>
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<tr>
<td>Erectile dysfunction and ejaculation</td>
<td>1. Tadalafil – Significant increase in erectile and ejaculatory capacities at all spinal levels[49]</td>
</tr>
<tr>
<td></td>
<td>2. Vardenafil – Significant increase in orgasmic awareness compared to baseline and in ejaculation success rates compared to placebo[50]</td>
</tr>
<tr>
<td>Ejaculation</td>
<td>Midodrine – Antegrade or retrograde ejaculation were more frequent after midodrine with penile vibratory stimulation (PVS) compared to PVS alone[51, 52], with poorer responses shown in injuries below T10[51]</td>
</tr>
<tr>
<td>Vaginal lubrication</td>
<td>Minor increase from sildenafil[53]</td>
</tr>
<tr>
<td>Spasticity to inhibit movement</td>
<td>Baclofen, tizanidine, botox, sclerosing agents</td>
</tr>
<tr>
<td><strong>PARKINSON’S DISEASE</strong></td>
<td></td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>1. Apomorphine[54]</td>
</tr>
<tr>
<td></td>
<td>2. Sildenafil[55] Caution re orthostatic hypotension</td>
</tr>
<tr>
<td></td>
<td>PGE, if sildenafil contraindicated[5]</td>
</tr>
<tr>
<td></td>
<td>Deep brain stimulation to subthalamic nucleus[56]</td>
</tr>
<tr>
<td>Hypersexuality</td>
<td>1. Stop dopamine agonist, continue levodopa[57, 58, 59]</td>
</tr>
<tr>
<td></td>
<td>2. Quetiapine, not dopamine antagonists[5] Consider CBT, SSRI’s, clozapine</td>
</tr>
<tr>
<td></td>
<td>3. Consider nonsteroidal anti-androgens (eg flutamide), GnRH agonists (leuprolin and others), spironolactone but avoid high doses (hypotension) No data for antiandrogen use in women[5]</td>
</tr>
</tbody>
</table>
Recently published rates of pituitary hypogonadism following head injury have shown a wide range of 1% to 22.7% [60, 61, 62, 64, 65] that varied according to laboratory methods, liberal interpretation of gonadotropin values, and the acceptance of low testosterone levels not always in accordance with those defined by the US Endocrine Society [68]. Two of the seven studies were uncontrolled, and none took account of sexual symptoms, so that diagnosis was solely on biochemical grounds.

Severe levels of pituitary growth hormone (GH) deficiency were at an incidence ranging from 2% to 25% [60, 61, 62, 64, 65, 69].

Trauma-induced hyperprolactinemia when severe produces hypoactive sexual interest and is associated with both elevated thyrotropin (TSH) and hypogonadism [70]. The commonest causes of hyperprolactinemia in men and women in the head-injured population, however, are antidepressants [71] and antipsychotics [72].

A consensus recommendation supports hormonal screening for pituitary injury at 3 months and at 12 months following severer brain trauma [73]. Acute-phase screening is only necessary if there is early diabetes insipidus to suggest an important degree of acute hypopituitarism. Regardless of whether there is trauma to the brain, temporary hypopituitarism can occur in any critical illness that requires intensive care especially in the presence of hypotension and hypoxemia.

Table 4: Levels of evidence for treatment of sexual dysfunctions in neurological disorders [5, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66] (continued)

<table>
<thead>
<tr>
<th>Option</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Option</td>
<td>Level of Evidence</td>
</tr>
<tr>
<td>STROKE</td>
<td></td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Sildenafil [5]</td>
</tr>
<tr>
<td>PGE1 if sildenafil contraindicated [5]</td>
<td></td>
</tr>
<tr>
<td>HSDD and arousal disorders including vaginal lubrication</td>
<td>No data</td>
</tr>
<tr>
<td>Spasticity to inhibit movement</td>
<td>Baclofen, tizanidine, botox, sclerosing agents [5]</td>
</tr>
<tr>
<td>Hypersexuality</td>
<td>As Head Injury</td>
</tr>
<tr>
<td>HEAD INJURY</td>
<td></td>
</tr>
<tr>
<td>(a) Pituitary trauma</td>
<td>Potential replacement of estrogen/testosterone or growth hormone [60, 61, 62, 63, 64, 65, 66]</td>
</tr>
<tr>
<td>(b) Brain Trauma</td>
<td></td>
</tr>
<tr>
<td>Erectile/ejaculatory and lubrication dysfunctions</td>
<td>No data</td>
</tr>
<tr>
<td>Spasticity</td>
<td>As stroke</td>
</tr>
<tr>
<td>Hypersexuality</td>
<td>CBT, SSRIs, steroidal antiandrogens (spironolactone), non steroidal antiandrogens, GnRH agonists, dopamine antagonists, and atypical antipsychotics (eg quetiapine). No data for antiandrogen use in women [5]</td>
</tr>
</tbody>
</table>

KEY: AED = anti-epileptic drug. PGE1 = intracavernosal prostaglandin E-1. CBT = cognitive behavioural therapy. SSRI = selective serotonin reuptake inhibitor. GnRH = gonadotrophin releasing hormone. HHSD= Hypoactive Sexual Desire Disorder

Our recommendation is to identify and treat deficiencies of gonadotrophins [68] and GH as defined by the U.S. Endocrine Society. Grade C

2. SPINAL CORD/CAUDA EQUINA INJURY

Of the various neurological disorders under discussion, the highest rates of sexual dysfunction come from severe cauda equina lesions and spinal cord injuries - yet 86% of cord-injured patients retain their libido according to one cross-sectional study [74]. This is particularly disturbing as the prevalence of spinal cord injury is skewed towards younger people.

Reflex erections of the penis and reflex clitoral swelling and vaginal lubrication are lost in very low cord lesions involving S2, 3, 4 while psychogenic erections and psychogenic lubrication remain possible [75]. The hypothesis is that psychogenic erection and female genital congestion/lubrication are dependent upon the T12-L2 sympathetic outflow from the spinal cord above the medullary cone (Figure 2). Injuries to the medullary cone itself, or to the cauda equina, will interrupt the innervation of the genitalia and the pelvic floor by way of the autonomic and somatic nerve fibres leaving the lower end of spinal cord to then 'hitch-hike' in the S2, 3 and 4 nerve roots (Figure 2). In men and women with complete lower motor neuron dysfunction from these injuries, orgasms are generally lost [53, 76].
A complete loss of genital sensation together with loss of voluntary control of bladder and bowel, may compound severe traumatic lesions of the cauda equina brought about by spinal fracture below L1 or stenosis of the central canal below L1 occuring usually with massive central disc herniation. Depending on the segmental level of cord injury, more than one-third of men overall are able to self-ejaculate even with complete lesions [77]. The climactic experience of ejaculation seems related to blood pressure surge and other vascular parameters of autonomic dysreflexia (AD), the climax being pleasurable in mild to moderate AD but unpleasant or even painful with severe AD [52]. When penile vibrostimulation is added to regular sexual stimulation, some three-quarters of men with higher lesions can ejaculate.

Our specific recommendation is for the addition of alpha-adrenergic agonist midodrine as an adjunct to facilitate ejaculation in injuries at T10 and above: [51, 52], Grade C

Remarkably, women with complete lesions of the cord can still experience orgasm from cervical vibro-stimulation mediated, perhaps, through intact neural supply to the cervix travelling separately in the vagus nerve outside of the spinal neuraxis [53, 78].

It is suggested that neuroplasticity occurs over time post-injury in the ascending sensory pathways of the spinal cord [35] with the result that body areas such as the torso and shoulders can become highly arousing when stimulated under sexual circumstances - even in Asia A injuries (ie no sensation in the anal or genital areas and no motor function below the lesion level).

Our recommendation for SCI associated ED is for sildenafil to enhance reflex and psychogenic erections [47, 48], PGE1 to enhance reflex and psychogenic erections [5], for tadalafil to increase erectile and ejaculatory capacities at all spinal levels [49], and for vardenafil to increase orgasmic awareness and likelihood of ejaculation [50]: Grade A. Sildenafil may increase vaginal lubrication [53]: Grade C. Recommended also is baclofen, tizanidine, botox, and sclerosing agents to lessen spasticity interfering with sexual engagement: Grade C.

3. MULTIPLE SCLEROSIS

Lesions in the spinal cord more so than brain, have been implicated as the main cause of sexual dysfunctions in multiple sclerosis [79]. Dysfunctions increase with time since diagnosis and with disease burden (Table 3). Co-morbid incontinence, fatigue, and spasticity, contribute to sexual difficulties in both genders.

In a sample of 63 newly diagnosed women, Tzortzis [7] found that the most significant differences compared to controls were in the parameters of desire, satisfaction, and lubrication. Reduced sensation of the genital area was the only presenting symptom in 4 out of the 63 women with early MS all of whom were pre-menopausal; depression and other psychiatric or psychological disorders formed part of the exclusion criteria in both the study sample and the control sample [7].

We recommend using sildenafil for ED [44]: Grade A, or PGE1 [45]: Grade B.

Sildenafil may assist vaginal lubrication [46]: Grade C.

Recommended also is baclofen, tizanidine, botox, and sclerosing agents for spasticity: Grade C.

4. STROKE

Major stroke has special propensity to influence bodily positioning and movements during sex, compounded by spasticity, hemisensory neglect, and aesthetic considerations including loss of sphincter control. Lowering of cavernosal pressure by antihypertensive agents commonly received by stroke patients, adds further challenge.

In a study of 50 stroke patients (38 men, 12 women), 28% had ceased having sexual intercourse at 2 months and partner dissatisfaction was also high.
At 6 months, sexual activity was resumed by half of those patients [80]. Men under the age of 65 usually regain their erections within months of injury [33].

Of interest is that ischemic lesions in the right cerebellum and the left basal ganglia can be associated with a significant ejaculation disorder [81]. In Korpelainen's series of 192 stroke patients [82], 10% reported increased libido. Hypersexuality appears to be more prominent in lacunar strokes that affect the frontolimbic connections or the thalamic/subthalamic nuclei [4]. In a study from China, fear of recurrent stroke from sexual activity was noted in more than half of the patients [83] even though the risk of stroke from sexual excitement is said to be very low [84].

Recommended is sildenafil for ED: [5] Grade C and to treat hypersexuality with CBT, SSRIs, antiandrogens, GnRH agonists, and atypical antipsychotics: [5] Grade C

5. PARKINSON’S DISEASE

Of great interest is that in 32,616 healthy male participants in a U.S. study reporting erectile dysfunction in 1986, there was a four-fold higher risk of developing Parkinson’s Disease (PD) over the next 16 years of followup - to suggest that erectile difficulties can precede the onset of the classic motor features of Parkinsonism by a substantial margin [85].

Central dopaminergic mechanisms have a role both in initiation of sexual desire and induction of penile erection [86, 87] and are especially vulnerable to the depletion of dopamine within the basal ganglia in Parkinsonism. Autonomic failure (which is present in up to 90% of patients with PD) [88] also has the potential of impairing function by way of (a) parasympathetic cholinergic denervation to impede genital congestion, and (b) sympathetic noradrenergic denervation to inhibit orgasm and ejaculation [88, 89]. Whereas sympathetic neuropathy is mostly peripheral (ganglionic or post-ganglionic) in PD it is exclusively central (pre-ganglionic) in the variant MSA, Multiple System Atrophy [90].

Much interest has accrued concerning hypersexual behaviour in PD arising out of treatment with levodopa and more particularly dopamine agonists. Of 300 patients with Parkinson’s disease taking dopamine agonists such as the D3 agonists ropinirole and pramipexole, 25 had sexual compulsions and 28 had co-morbid or separate compulsive gambling of whom 17 met criteria for pathological gambling; men were over-represented [59]. In a Mayo Clinic database, where there was hypersexual behaviour, this developed within 8 months of starting dopamine agonist therapy in the majority of cases [57]. When considering these reward-seeking behaviours, it is of note that positron emission tomography scans of healthy volunteers during orgasm and ejaculation show strong activation in the dopamine-rich mesiodiencephalic and ventral tegmental areas [91]. These areas are also activated during the orgasm-like ‘rush’ experienced by heroin addicts.

It is ironic that hypersexuality in Parkinsonism should be so predominantly iatrogenic. The combination of greatly enhanced sexual drive with disrupted genital function can be highly problematic in partner relationships in the home or in a nursing home environment. Sexual compulsions can completely resolve after stopping the agonist, despite continued levodopa therapy [57].

For ED, we recommend sildenafil [92] using caution re orthostatic hypotension: Grade A; or apomorphine [93]: Grade B.

Deep brain stimulation can improve sexuality in men only [56]: Grade C.

For hypersexuality, discontinue dopamine agonist and continue levodopa. If necessary, add quetiapine and not risperidone, olanzepine, haloperidol or other dopamine antagonist [5, 57, 58, 59].

6. EPILEPSY

Of neurological disorders, epilepsy is unique in its ability to provoke - during a seizure - involuntary sexual gestures. This occurs when the seizure is of focal onset in the mesolimbic temporal structures or (less commonly) the area of the interhemispheric parietal cortex subserving genital sensation [94]. An erotic aura can precede an attack. Genital automatisms during a partial seizure can take the form of self-fondling or scratching of the genitals, masturbatory movements, or pelvic thrusting [95]. Because amnesia usually accompanies such automatisms, their frequency is probably under-reported: automatic sexual gestures were recorded in 11% of more than 200 selected patients who underwent video-electroencephalography for medically refractory seizures [95]. Profound hyposexuality has been noted in women who have reflex orgasms with their seizures.

Older-style anti-epileptic drugs (AED’s) such as phenytoin, barbiturates, and carbamazepine (but not oxcarbazepine) are inducers of the hepatic P450 enzyme system. This in turn causes increase in levels of SHBG with subsequent hyposexuality either with [36] or without [96] a reduction in levels of free bio-available testosterone. The deleterious effect of these older AED’s upon sexuality is affirmed in men but not in women [96].

The P450 enzyme-inhibiting AED valproic acid, has some propensity to increase serum androgen levels and also estradiol levels in both sexes [97, 98, 99] but with the risk of an increased incidence of infertility due to polycystic ovary syndrome in women of childbearing age [99].
Theoretically, enzyme-neutral AED’s are less likely to cause sexual side effects. These include oxcarbazepine, gabapentin, pregabalin, levetiracetam, and lamotrigine.

There is limited evidence that lamotrigine has the lowest profile of sexual side effects [36, 40]. Carbamazepine in men, and gabapentin [100] and topiramate [101] in both sexes, may cause reversible anorgasmia due to uncertain mechanisms [102].

We recommend men with epilepsy having phenytoin or carbamazepine-induced hypogonadism to switch to a P450 enzyme-inhibiting or an enzyme-neutral anti-epileptic drug [36]: Grade C. For hypogonadal men unable to discontinue phenytoin or carbamazepine, treat with testosterone [41]: Grade B.

When valproic acid causes unwanted weight gain or symptoms of polycystic ovary syndrome, use an enzyme-neutral AED [99]: Grade C.

That lamotrigine lacks sexual side effects, remains unclear: Grade D.

Anterior temporal lobectomy may eliminate epileptic sexual automatisms [43]: Grade C.

B. END STAGE RENAL DISEASE (ESRD)

I. INTRODUCTION

Sexual dysfunctions are frequent in men and women with end-stage renal disease (ESRD) and their etiology is multi-factorial given the complex pathophysiology of chronic renal failure: co-morbid diabetes, hypertension, coronary artery disease and peripheral vascular disease are common. Sexual dysfunction increases as renal function deteriorates [103] such that the former is apparent well before renal replacement therapy is necessary, i.e. ESRD where usually <10% of kidney function remains [103]. Furthermore, dialysis and even transplantation may not improve sexual function [104,105]. Sexual dysfunction in men appears to have the same prevalence whether dialysis is peritoneal (PD) or hemodialysis (HD) [3] but may be more common with the latter in women [106,107].

1. HIGH BURDEN OF PHYSICAL SYMPTOMS

Patients’ sexual dysfunction must be understood in the context of multiple symptoms. As the estimated glomerular filtration rate (eGFR) reduces to below about 15 mL/min/1.73m² multiple symptoms commonly ensue including bone and joint pain from renal osteodystrophy, fatigue, anorexia, nausea, stomatitis, and an unpleasant taste in the mouth. Pruritus is common and malnutrition and generalized wasting can occur. Medical complications such as pericarditis, GI bleeding and cardiac complications may follow. Moreover, the underlying pathology of the ESRD may contribute to symptoms, for example the pain of diabetic neuropathy. Symptom burden may preclude motivation to seek treatment for sexual dysfunction: in one study of men with ESRD on PD of those who had ED only 50% were willing to enter a trial of Sildenafil [108] and only a minority actually completed the study. Even after transplantation, studying 161 men, only 78 of the 126 with ED were interested in treatment [109].

2. HIGH PREVALENCE OF COMORBID DEPRESSION

Depression is independently associated with sexual dysfunction in men [110] and women [19] and is frequently undiagnosed or undertreated [111]. Self image, known to be highly correlated with sexual function especially in women is vulnerable: physical changes including altered skin color and presence of AV fistula or PD catheter, muscle wasting and dependence on dialysis may all have negative impact. Frequently compounding depression is discord within the sexual relationship from the multiple stressors [103].

II. PREVALENCE AND PATHOPHYSIOLOGY OF SEXUAL DYSFUNCTIONS IN ESRD

Prevalence and pathophysiology of dysfunctions in men and women with uremia, receiving HD and PD are given in tables 5 and 6.

III. ASSESSMENT

In addition to the detailed assessment of dysfunction, (see previous pages) certain medical parameters need specific review including the adequacy of the dialysis regime to minimize the deleterious effect of uremia on nerve function and reduce the progression of vascular disease. Blood pressure and signs of autonomic neuropathy are reviewed and lipids, blood glucose, hemoglobin, testosterone and prolactin measured—all of these potentially impacting on sexual function. Levels of estradiol, LH and FSH may be indicated: amenorrhea, anovulation, a hypoestrogen state despite menstruation or premature menopause are all common. Mood, stress levels and fatigue are assessed along with pain and pruritis management—all of these modulating sexual desire and motivation, see tables 1 and 2.

IV. TREATMENT

Treatment modalities that have been shown to have benefit are shown in tables 1 and 2. Women have received minimal study.
Table 5: Pathophysiological Mechanisms Involved In Dysfunction Associated With End Stage Renal Disease In Men And Therapy Options.

<table>
<thead>
<tr>
<th>DYSFUNCTION</th>
<th>PATHOPHYSIOLOGICAL MECHANISM</th>
<th>COMMENTS RE THERAPY and LEVEL OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERECTILE DYSFUNCTION</td>
<td>Prevalence 55-85% in men with uremia or on peritoneal and/or HD with possible further increase after transplantation[112, 104, 113]</td>
<td>Endothelial dysfunction from associated HT, DM Potential improvement of endothelial function with antagonists of renin angiotensin system and calcium channel antagonists not yet investigated in renal failure</td>
</tr>
<tr>
<td></td>
<td>Decreased oxygen delivery to genital tissues associated with anemia decreases NO synthesis and increases EDRF</td>
<td>Recombinant human erythropoietin in some but not all patients with ESRD[114, 115, 116]. May be useful in 80% of men with ESRD on dialysis compared to only 20% of uremic men (i.e., not receiving dialysis)[117] level 3</td>
</tr>
<tr>
<td></td>
<td>Reduced NO production associated with increased production of dimethyl arginine[118]</td>
<td>Occlusive cavernosal artery disease</td>
</tr>
<tr>
<td></td>
<td>Structural changes in cavernosal smooth muscle[119]</td>
<td>Veno - occlusive dysfunction: may be marked in end-stage renal failure[120, 121]</td>
</tr>
<tr>
<td></td>
<td>Uremia - associated reduced bioavailability of arginase, reduced NOS expression, quenching of NO by increased reactive oxygen species and inhibition of NOS[122]</td>
<td>Uremia associated reduction of NOS expression possibly due to overexpression of arginase &amp; lack of NADPH an essential co-factor for NOS. Reduced NADPH also promotes smooth muscle contractility by increasing DAG and protein kinase C. Increased oxygen free radicals including those from advanced glycosylation end-products quench released NO[122]</td>
</tr>
<tr>
<td></td>
<td>ANS dysfunction associated with uremia[126]</td>
<td>Use PDE-5 inhibitors to magnify action of remaining NO assuming no nitrate therapy[123] level 2. Caution with α-blockers, hypotension, aortic stenosis, LV outflow obstruction, unstable angina[124, 125]. Avoid vardenafil with congenitally long QT, and IA antiarrhythmics[125]. Reduce dose in uremia but not when dialyzed Transplantation may improve ED[105] level 2 PGE1 benefits those non responsive to or unable to take PDE-5 inhibitors[109] level 3</td>
</tr>
<tr>
<td></td>
<td>Diabetes related changes[122]: reduction of NOS activity - possibly due to overexpression of arginase &amp; lack of NADPH an essential co-factor for NOS. Reduced NADPH also promotes smooth muscle contractility by increasing DAG and protein kinase C. Increased oxygen free radicals including those from advanced glycosylation end-products quench released NO[122]</td>
<td>ANS dysfunction associated with uremia[126]</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic: transplantation may worsen or induce ED [104, 127]</td>
<td>Sildenafil effective and safe post transplant [105, 127]</td>
</tr>
<tr>
<td></td>
<td>Associated depression</td>
<td>Effectively treating ED can encourage remission of depression in men without ESR[128]</td>
</tr>
<tr>
<td></td>
<td>Medications: Peripherally acting α-blockers, SSRI's, TCA's, benzodiazepines[129]</td>
<td>PDE-5 inhibitors - level I evidence for sildenafil for SSRI associated ED did not include men with ESR[130]</td>
</tr>
<tr>
<td>DYSFUNCTION</td>
<td>PATHOPHYSIOLOGICAL MECHANISM</td>
<td>COMMENTS RE THERAPY and LEVEL OF EVIDENCE</td>
</tr>
<tr>
<td>-----------------------------</td>
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<td>----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>LOW SEXUAL DESIRE</td>
<td>Low testosterone: Leydig cell dysfunction but rise in LH blunted. LH pulse amplitude ↓, GnRH pulsatility ↓[131]</td>
<td>Testosterone therapy of limited benefit due in part to anemia and high prolactin. Erythropoietin partially corrects low testosterone[132]</td>
</tr>
<tr>
<td>High prolactin secretion &lt;autonomous&gt; possibly stimulated by 20 hyperparathyroidism</td>
<td></td>
<td>In older studies, bromocriptine effectively reduced prolactin but with minimal sexual benefit. Prolactin reduced by dihydroxy vit D with possible sexual benefit. No recent studies</td>
</tr>
<tr>
<td>Anemia of renal failure and associated fatigue</td>
<td>Erythropoietin, despite only partial correction of low T, Hct and high LH/FSH and prolactin, shows some sexual benefit in male hemodialysed (but not uremic) patients[132]</td>
<td>Debil, fatigue, anemia may also improve with nandrolone concomitant with erythropoietin[133]</td>
</tr>
<tr>
<td>Depression is independently associated with sexual dysfunction[110]</td>
<td>Treating depression improves sexual function[3], RCT of sildenafil’s benefit of SSRI associated low desire did not include men with ESRD</td>
<td></td>
</tr>
<tr>
<td>ORGASMIC DISORDER</td>
<td>Low testosterone</td>
<td>See above re testosterone</td>
</tr>
<tr>
<td>21% with HD, 17% with PD &amp; 14% post transplant in one large study[112]</td>
<td>Neuropathy: uremic, diabetic: autonomic and somatic</td>
<td>Vibrostimulation as in other situations of nerve damage but no studies</td>
</tr>
<tr>
<td>Multiple distracting symptoms including pain</td>
<td></td>
<td>Holistic approach to therapy recommended</td>
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<tr>
<td></td>
<td></td>
<td>Minimal data but non specific benefit from EPO may benefit sexual arousability and potential for orgasm</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- AV: Arterio venous
- ANS: Autonomic nervous system
- CAD: Coronary artery disease
- DAG: Diacylglycerol
- ED: Erectile dysfunction
- EDRF: Endothelium-derived contracting factor
- DM: Diabetes mellitus
- GnRH: Gonadotrophin releasing hormone
- HT: Hypertension
- HD: Hemodialysis
- LH: Luteinizing hormone
- LV: Left ventricle
- NADPH: Nicotinamide adenine dinucleotide phosphate
- NO: Nitric oxide
- NOS: Nitric oxide synthase
- PD: Peritoneal dialysis
- RCTs: Randomized controlled trials
- SSRI: Selective serotonin reuptake inhibitor
- TCA's: Tricyclic antidepressants

**Table 5: Pathophysiologica...**

... continued...
<table>
<thead>
<tr>
<th>Dysfunction</th>
<th>Pathophysiological Mechanism</th>
<th>Comments re Therapy and Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Sexual Desire</td>
<td>Anovulation: no or decreased LH surge (the associated testosterone decrease not studied) but</td>
<td>No studies of investigational testosterone therapy in women</td>
</tr>
<tr>
<td></td>
<td>levels of LH are abnormally high in the follicular phase. LH levels fail to rise after</td>
<td>One small open controlled study showed transdermal estrogen plus progestin supplementation improved desire</td>
</tr>
<tr>
<td></td>
<td>administration of estrogen strongly suggesting a defect in the positive hypothalamic feedback</td>
<td>in dialyzed women[139]</td>
</tr>
<tr>
<td></td>
<td>mechanism[3]. 40% of women with ESRD are totally amenorrheic and less than 10% have regular</td>
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</tr>
<tr>
<td></td>
<td>menses. Premature menopause common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sexual motivation reduced from anemia due to uremic menorrhagia (although amenorrhea more common)</td>
<td>Progesterone cyclically or daily - sexual function not studied</td>
</tr>
<tr>
<td></td>
<td>No desire triggered during women's sexual experience as painful outcome expected from chronic</td>
<td>Local vulvar vaginal estrogen therapy not contraindicated but minimally studied</td>
</tr>
<tr>
<td></td>
<td>estrogen deficiency-associated dyspareunia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High prolactin secretion &lt;autonomic&gt; possibly stimulated by 20 hyperparathyroidism</td>
<td>In older studies, bromocriptine effectively reduced prolactin but with minimal sexual benefit. Prolactin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>reduced by dihydroxy vit D with possible sexual benefit. No recent studies</td>
</tr>
<tr>
<td></td>
<td>Anemia of renal failure and associated fatigue</td>
<td>Erythropoietin and women's sexuality minimally studied: general benefit to well being expected to improve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sexual motivation</td>
</tr>
<tr>
<td></td>
<td>Depression is independently associated with sexual dysfunction[19]. Sad experiences without</td>
<td>Treating depression improves sexual function[3]. SSRI associated low desire not helped by PDE-5 inhibitors</td>
</tr>
<tr>
<td></td>
<td>clinical depression is a risk factor for low desire[106]</td>
<td>in women without ESRD[130]</td>
</tr>
<tr>
<td></td>
<td>Chronic pain including bone pain, headaches, painful neuropathy reported by 85%[134]</td>
<td>No studies of sexual benefit of adequate analgesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psychosexual and interpersonal issues. Altered self image, medicalization of bed room for HD</td>
<td>Holistic approach to therapy recommended</td>
</tr>
<tr>
<td>Orgasmic Disorder</td>
<td>Anovulation associated low testosterone</td>
<td>No studies of investigational testosterone therapy in women</td>
</tr>
<tr>
<td></td>
<td>Neuropathy: uremic, diabetic: somatic and autonomic</td>
<td>Vibrostimulation: no studies</td>
</tr>
<tr>
<td></td>
<td>Depression and SSRIs</td>
<td>One RCT showing benefit from sildenafil but women did not have ESRD[130]</td>
</tr>
</tbody>
</table>
1. ERYTHROPOIETIN

Recombinant human erythropoietin (EPO) has been shown to benefit sexual desire and erectile function in some but not all men [114, 115, 116]. Women’s sexual function improves [141] but is minimally studied.

2. SILDENAFIL DURING DIALYSIS

The reported response to sildenafil for ED is from 33-80% [108, 123, 142, 143]. Clearance of the drug is decreased in renal failure, but for men receiving dialysis the pharmacokinetics resemble those of normal volunteers [144].

3. SLOW NOCTURNAL HEMODIALYSIS

There is some evidence of benefit for ED from nightly at home hemodialysis [145].

4. RENAL TRANSPLANTATION

a) Renal transplantation in men

Renal transplantation may or may not reverse ED with studies showing response rates of 32-81% [104, 105, 109, 120, 127, 146, 147]. Higher response rates may be associated with shorter duration of dialysis [105]. Transplantation may not improve testicular function. Possibly elevated FSH levels suggest testicular function will not return [148]. Prolactin levels do reduce after transplantation: sexual desire although minimally studied may increase [149].

b) Renal transplantation in women

Return of menses, fertility and successful pregnancy may occur with transplantation. Of 48 women, of whom 27 were post transplant, desire and arousal disorders were significantly lower than in the dialyzed women as was dyspareunia. However, when those willing to measure increase in genital congestion with VPP (7 out of 21 dialyzed women and 20 out of 27 transplanted women), no differences were seen [107]. Although minimally studied desire may improve [149].

5. SILDENAFIL FOR ERECTILE DYSFUNCTION POST TRANSPLANT

Sildenafil post transplant has been seen to be effective and safe [127, 147]. A useful increase in GFR has been seen in kidney transplant recipients after the use of sildenafil [150].

V. FUTURE RESEARCH

Further investigation of sexual benefit to women from EPO is needed along with study of benefit to both genders from slow nightly dialysis.
VI. RECOMMENDATIONS

Recombinant EPO therapy is guided by hemoglobin level. However, its use improves ED and low desire in men and women [132]: Grade C.

Sildenafil is of benefit for ED during hemodialysis and peritoneal dialysis [123]: Grade B. Transplantation may improve ED 105]: Grade C.

Sildenafil is effective for ED post-transplant [105, 127]: Grade B.

Transplantation may improve sexual desire in men and women [148]: Grade C.

C. PELVIC DISEASE NON MALIGNANT

I. HYSTERECTOMY FOR BENIGN CONDITIONS

When hysterectomy is performed for benign conditions the concerns for post operative quality of life and sexual functioning are paramount. Some women will report increased sexual satisfaction and pleasure following hysterectomy due to improved dyspareunia, dysmenorrhea or menorrhagia. [151, 152]. Studies examining sexual function and hysterectomy are often heterogeneous, complex and inconsistent, fraught with methodological errors, confounders and a lack of standardized instruments. Retrospective design and limited sample size often hinder global interpretation of medical data. However, the method of hysterectomy (abdominal, laproscopically assisted or vaginal, subtotal or total) has been studied and no differences between groups have been documented. Sexual satisfaction improved in a majority after surgery irrespective of surgical approach [153,154]. Of note simple hysterectomy does not damage the autonomic nerves subserving genital vasocongestion that traverse the lateral portions of the uterosacral and cardinal ligaments [155].

II. LOWER URINARY TRACT SYMPTOMS IN WOMEN

1. INTRODUCTION

A number of syndromes give rise to lower urinary tract symptoms (LUTS) in women. The symptom spectrum consists of storage symptoms (frequency, urgency, nocturia and urinary incontinence), voiding symptoms (slow stream, splitting or spraying, intermittent stream, hesitancy, straining and terminal dribble), and post micturition symptoms (feeling of incomplete emptying and post micturition dribble) [156]. The urinary urgency with frequency and nocturia (with or without urge incontinence) is defined as overactive bladder (OAB) syndrome [156]. Urinary urgency, frequency, nocturia, pelvic pain and dyspareunia in the absence of bacterial infection or other definable pathology are characterized as symptoms of interstitial cystitis/ painful bladder syndrome (IC/PBS) [157, 158]. Emerging epidemiologic evidences have shown that LUTS is linked to female sexual dysfunction (FSD), but the pathophysiology of this relationship is poorly understood. Clinical therapies, particularly surgical therapy for certain types of LUTS (such as urinary incontinence) and the causes of LUTS (such as pelvic prolapse) can either positively or negatively affect sexual function.

2. PREVALENCE AND RELATIONSHIP OF LUTS AND FSD

a) Epidemiology studies for LUTS

The prevalence of LUTS in women was studied with the use of the International Prostate Symptom Scores (IPSS)/American Urological Association Symptom Scores (AUASS) designed for both genders. IPSS/AUASS of 8 or greater were used as the definition of LUTS (Table 7). There was no significant culture variation or difference between racial/ethnic groups in the prevalence of LUTS.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Population</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyle et al</td>
<td>cross-sectional,</td>
<td>612 (France)</td>
<td>12.6</td>
</tr>
<tr>
<td>2003[159]</td>
<td>cross-cultural</td>
<td>1066 (Netherlands)</td>
<td>18.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1360 (South Korea)</td>
<td>19.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>722 (UK)</td>
<td>23.7</td>
</tr>
<tr>
<td>Litman et al</td>
<td>cross-sectional,</td>
<td>3205 (no difference among black, Hispanic and white)</td>
<td>18.6</td>
</tr>
<tr>
<td>2007[160]</td>
<td>cross-ethnic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LOE: N/A (epidemiology study)
Table 8: Association of LUTS and FSD [162, 163, 164, 165, 166, 167]

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design (with age-matched control)</th>
<th>Population</th>
<th>FSD (%)</th>
<th>OR</th>
<th>FSFI Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salonia et al</td>
<td>cross-sectional (with age-matched control)</td>
<td>216 (102)</td>
<td>46 (N/A)</td>
<td>desire 2.0 vs. 3.2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>lubrication 3.2 vs. 4.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>satisfaction 2.7 vs. 4.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pain 1.8 vs. 4.0</td>
<td></td>
</tr>
<tr>
<td>Aslan et al</td>
<td>cross-sectional (with age-unmatched control)</td>
<td>21 (18)</td>
<td></td>
<td>desire 2.8 vs. 4.0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>lubrication 3.9 vs. 4.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>orgasm 3.8 vs. 4.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>satisfaction 4.1 vs. 4.6</td>
<td></td>
</tr>
<tr>
<td>Møller et al</td>
<td>prospective non-randomized</td>
<td>2,284</td>
<td></td>
<td>2.9 – 5.7*</td>
<td>3</td>
</tr>
<tr>
<td>Kim et al</td>
<td>cross-sectional</td>
<td>3,372</td>
<td>5.2</td>
<td>4.16 – 5.08*</td>
<td>3</td>
</tr>
<tr>
<td>Özel et al</td>
<td>retrospective (LUTS with/without prolapse)</td>
<td>201</td>
<td>53(30)</td>
<td>no libido 2.87 vs. 3.35</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>g9(30) no orgasm 3.44 vs. 3.75</td>
<td></td>
</tr>
<tr>
<td>Sen et al</td>
<td>cross-sectional (with age-matched control)</td>
<td>153 (89)</td>
<td></td>
<td>desire 2.87 vs. 3.35</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>lubrication 3.44 vs. 3.75</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>satisfaction 3.39 vs. 3.83</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pain 3.96 vs. 4.28</td>
<td></td>
</tr>
</tbody>
</table>

N/A: no information for control. *: OR (odds ratio) varies by the type of LUTS. FSFI: Female Sexual Function Index (data with significant difference are included).

b) Association of LUTS and FSD

Epidemiological studies suggest an association of LUTS with FSD, but well designed population study is lacking in part to the complexity of FSD and the wide spectrum of LUTS. It is suggested that all women with FSD should be screened for the presence of bladder dysfunction regardless of age [161]. Studies regarding the risk or the severity of FSD in patients with LUTS are summarized in Table 8.

3. PATHOPHYSIOLOGY

The pathophysiology of FSD associated with LUTS is poorly understood. Both the anatomical proximity of the bladder and urethra to the vaginal canal and the shared spinal reflexes that are under descending control from higher centers may be relevant [168]. However, LUTS in women may also have a much more complex psychological impact relevant to FSD. The possible mechanisms involving in the development of LUTS and FSD are summarized in Table 9.

4. TREATMENT CONSIDERATIONS

a) Pharmacotherapy

Pharmacotherapy including anticholinergic oxybutynin, tolterodine, trospium chloride, solifenacin and darifenacin [181] is the mainstay of therapy for LUTS and the treatment of choice for OAB. However, there are very few publications regarding this class of medications on female sexual function (table 10).

b) Pelvic floor muscle training

Pelvic floor muscle (PFM) training has been shown to be effective in the treatment of genuine stress incontinence by multiple randomized controlled trials [174]. The PFM training for LUTS with electrical stimulation, biofeedback and/or Kegal exercises also appears to improve female sexual function (table 11).

c) Sacral neuromodulation implant

Sacral neuromodulation (SNM) has become an established treatment option for LUTS. Some benefits of SNM on sexual function were also observed recently in a very small study [185], but the mechanism by which SNM improves sexual function is unknown.

d) Impact of Urogynaecological operations for LUTS on sexual function

Available data show conflicting effects of urogynaecological surgeries for LUTS on female sexual function with improvement, no change or worsening reported after surgeries [180]. Improvements in sexual function following vaginal surgery may follow improved continence during sexual activity whereas the etiology of worsening sexual function is more complicated involving organic and psychological factors [179].
Table 9: Pathophysiology associated with FSD and LUTS [162, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179]

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Rationale</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryological and neurological relationship</td>
<td>(1) The urinary and reproductive systems are embryologically related and share common nerve pathways[168, 169].</td>
<td>LUTS are also common symptoms for patients with IC/PBS. Mechanical irritation of the urethra and/or bladder during intercourse may also cause dyspareunia in patients with IC/PBS and exacerbate their LUTS[171].</td>
</tr>
<tr>
<td></td>
<td>(2) Pelvic autonomic nerves innervating the vagina, urethra and bladder are critical for normal sexual function and urinary continence: the anterior and lateral vaginal walls are most densely innervated by neuronal nitric oxide synthase immunoreactive nerves involved in sexual function[170]. LOE: IV</td>
<td></td>
</tr>
<tr>
<td>Changes of pelvic floor muscle tension</td>
<td>Pelvic floor muscles are important in maintaining urinary continence and also play a critical role in female sexual function. Chronic increase of muscle tension may be associated with vaginismus and dyspareunia[172, 173]. LOE: IV</td>
<td>No evidence is available to link the degree of pelvic muscle tension to FSD. Pelvic floor muscle training improves urinary continence and sexual function in women with urinary stress incontinence[174, 175].</td>
</tr>
<tr>
<td>Decreased blood flow</td>
<td>Bladder wall resistance to bacteria seems to partially depend upon the amount of local parietal blood flow. Decreased local blood flow is suggested in patients with LUTS due to bacterial cystitis[162]. LOE: IV</td>
<td>Blood flow increase to the vagina and uterus leads to increased secretion which lubricates the vagina. The transudation of plasma from engorged vessels in the vaginal wall also contributes to the vaginal lubrication.</td>
</tr>
<tr>
<td>Hormonal change</td>
<td>(1) Estrogen plays a major role in regulating female sexual function and nitric oxide synthesis in the vagina and clitoris[172]</td>
<td>Estrogen is important in maintaining the integrity of vaginal and urethral mucosal epithelium and promotes vaginal lubrication. Estrogen cream is empirically used for atrophic urethritis associated LUTS but currently, there is no clear role for estrogen in improving LUTS[176].</td>
</tr>
<tr>
<td></td>
<td>(2) Lower levels of estrogen in the urogenital tract suggests a relationship to FSD and LUTS as they are more prevalent in menopausal women[162].</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3) Estrogen therapy improves vaginal lubrication in postmenopausal women[177, 178]. LOE: IV</td>
<td></td>
</tr>
<tr>
<td>Psychological distress</td>
<td>The distress from chronic urinary symptoms may lead to sexual difficulty. Psychological distress may predispose to both sexual dysfunction and to LUTS[179, 180]. LOE: IV</td>
<td>Fear of urinary leakage during penetration or at orgasm, dyspareunia due to urine dermatitis, lowered self esteem may all play a significant role.</td>
</tr>
</tbody>
</table>

Table 10: Effect of medications for LUTS on Female sexual function [182]

<table>
<thead>
<tr>
<th>Medication</th>
<th>Study design</th>
<th>Evaluation method</th>
<th>Outcome</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin</td>
<td>multicenter, prospective, randomized, open-label, community-based, 6 month, 87.2% of female[182].</td>
<td>King’s Health Questionnaire (analysis was not performed separately among female and male)</td>
<td>(1) Sex lives improved in 19.1% and worsened in 11.2%. (2) Relationships improved in 19.6% and worsened in 11.9%. (3) Sexual interest improved in 23.4% and worsened in 12.2%.</td>
<td>3</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>prospective, non-randomized, no control, follow monthly for 3 months, 28 women with OAB[183].</td>
<td>Arizona sexual experience scale</td>
<td>Improved scores of desire, arousal, lubrication, orgasm and satisfaction at each follow up.</td>
<td>4</td>
</tr>
</tbody>
</table>
1. SURGERY FOR UI

The variable effects on sexual function after suburethral slings are shown in Table 12.

2. SURGERY FOR PROLAPSE

Pelvic organ prolapse affects many women worldwide and is commonly associated with LUTS [192]. The effect of reconstruction surgery for prolapse on sexual function is controversial as shown in Table 13.

---

**Table 11: Effect of pelvic floor muscle training for LUTS on female sexual function. [174, 175, 184]**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Number of subjects</th>
<th>Outcomes</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Be et al 2000</td>
<td>randomized</td>
<td>29</td>
<td>sex-life affected by LUTS</td>
<td>3</td>
</tr>
<tr>
<td>Beji et al 2003</td>
<td>retrospective</td>
<td>42</td>
<td>16.7%/ 50% (p=0.03)</td>
<td>4</td>
</tr>
<tr>
<td>Giuseppe et al</td>
<td>cross-sectional</td>
<td>37</td>
<td>↑sexual desire</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>43</td>
<td>↑dyspareuria</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑orgasm</td>
<td></td>
</tr>
</tbody>
</table>

N/A: no information for control. UI: urinary incontinence. FSFI: Female Sexual Function Index

**Table 12: Sexual function (SF) after suburethral sling procedures [187, 188, 189, 190, 191]**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study type</th>
<th>No. of Pts.</th>
<th>SF%</th>
<th>Questionnaire</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maaita et al 2002</td>
<td>Retrospective</td>
<td>43</td>
<td>72</td>
<td>5 14</td>
<td>3</td>
</tr>
<tr>
<td>Yeni et al 2003</td>
<td>Prospective</td>
<td>32</td>
<td>26</td>
<td>1.6</td>
<td>3</td>
</tr>
<tr>
<td>Glavind et al 2004</td>
<td>Retrospective</td>
<td>48</td>
<td>60</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Ghezzi et al 2005</td>
<td>Prospective</td>
<td>53</td>
<td>62</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

* U= unchanged, I= improved, W= worsened.

**Table 13: Surgery for prolapse on Female sexual function [193, 194, 195]**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Type</th>
<th>No. of pts.</th>
<th>Questionnaire</th>
<th>Outcomes</th>
<th>Comment</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barber et al 2002</td>
<td>prospective</td>
<td>32</td>
<td>Custom made</td>
<td>33.3% 0%</td>
<td>better (p&lt;001)</td>
<td>3</td>
</tr>
<tr>
<td>Helströmm et al 2005</td>
<td>prospective</td>
<td>45</td>
<td>McCoy inventory</td>
<td>33.17 28.08</td>
<td>worse (p&lt;0.05)</td>
<td>3</td>
</tr>
<tr>
<td>Novi et al 2005</td>
<td>cross-sectional</td>
<td>30</td>
<td>PISQ</td>
<td>79.3 82.9</td>
<td>no difference (p&gt;0.05)</td>
<td>3</td>
</tr>
</tbody>
</table>

PISQ: Pelvic Organ Prolapse/urinary incontinence sexual function Questionnaire
5. PREVENTION
There is no publication to evaluate any prevention strategy for LUTS associated sexual dysfunction. Educating women about the anatomical relationship of urinary and sexual organs may encourage compliance with pelvic floor exercise. Studies are needed to address psychological aspects of LUTS and effects on sexuality.

6. CONCLUSION
Epidemiology studies suggest an association of LUTS with FSD. However, well designed population studies with validated questionnaires to look at this association are needed given the complexity of FSD and the wide spectrum of LUTS. The pathophysiology of LUTS associated FSD is poorly understood and research is greatly needed. Limited publications suggest that non-surgical treatment for LUTS appears to benefit sexual function. However, current urogynecologic pelvic surgeries for LUTS can improve, worsen or have no effect on female sexual function. All patients should be well informed regarding this conflicting information before their surgical procedures. Currently, there is no publication available to recommend any prevention strategy for LUTS associated FSD. Through better understanding of their pathophysiology, prevention of both conditions may be possible.

7. RECOMMENDATIONS WITH GRADES
There is no publication available to recommend any prevention strategy for LUTS associated female sexual dysfunction: Grade C.
Non-surgical treatment for female LUTS appears to benefit sexual function [182, 183, 174, 175, 184]: Grade C.
Current urogynecological pelvic surgeries for LUTS can improve, worsen or have no effect on female sexual function: Grade C.

III. LOWER URINARY TRACT SYMPTOMS IN MEN
1. INTRODUCTION
Male lower urinary tract symptoms (LUTS) and sexual dysfunction are conditions encountered on a daily basis in urology practice. There is an increasing focus on the study of the relationship between LUTS and sexual dysfunction, both conditions increasing with advancing age. Considerable epidemiologic and clinical research has shown that LUTS and sexual dysfunction are strongly linked and investigation continues into the etiology of both, with particular attention to common pathways. Current clinical research focuses on the overlap and interactions of therapies for these conditions.

2. PREVALENCE AND RELATIONSHIP OF LUTS AND SEXUAL DYSFUNCTION

a) Epidemiology studies for LUTS
Lower urinary tract symptoms in men are mainly the manifestation of benign prostatic hyperplasia (BPH), bladder outlet dysfunction and the underlying bladder storage dysfunction. Although BPH can lead to complaints of LUTS, not all patients with BPH develop the symptoms (table 14) [196]. Similarly not all patients presenting with LUTS have objective evidence of BPH.

b) Association of LUTS and sexual dysfunction
Epidemiologic data cannot establish causality between LUTS and sexual dysfunction, but they can and do demonstrate reproducible association between the two conditions. At the present time, most studies are focused on the association of LUTS and ED (table 15).
Ejaculatory dysfunction (EjD) was also related to LUTS severity (table 16).
LUTS is also a risk factor for low sexual drive (OR of 1.37) [159]. It is clear that the presence of LUTS and the severity of LUTS are closely linked to the presence and the severity of sexual dysfunction.

3. PATHOPHYSIOLOGY
Even though the underlying cause has not been established, a bi-directional relationship between LUTS and ED suggests a common underlying pathophysiology or etiology. Research has identified several possible pathways and their links through which LUTS and ED develop (table 20). Metabolic syndrome and atherosclerosis may induce
autonomic nervous system hyperactivity in the lower urinary tract, prostate and penis with the changes of adrenergic receptors sensitivity and density, increase Rho-kinase and ET1 activity, reduce NOS expression and eventually cause LUTS and ED. In addition to common risk factors, it is thought that the psychological impact of LUTS on quality of life may also alter a patient’s erectile function[206].

4. TREATMENT CONSIDERATIONS

Current treatment modalities for LUTS can have negative or positive effect on erectile function, while emerging evidence shows that medical treatment of ED has positive impact on LUTS.

a) Effect of medications used to treat LUTS on ED

Medications for LUTS include traditional therapy (α-adrenergic receptor antagonists and 5-α reductase inhibitors) and novel therapy (antimuscarinics and PDE5 inhibitors)[226]. Table 18 summarizes their effect on sexual function. Investigational therapy for LUTS (luteinizing hormone releasing antagonists, β3-adrenergic receptor agonists and Vitamin D3 agonist) will not be discussed.

b) Effect of Medications used to treat ED on LUTS: Phosphodiesterase-5 inhibitors

At the present time, the data from three large, multicenter, randomized, placebo controlled trials are available[242, 243, 244] (Table 19). These sets of preliminary evidence open many avenues for further investigation into the benefits of PDE-5 inhibitors on LUTS.

c) Effect of combined treatment with PDE-5 inhibitors and medications for LUTS

The greatest improvement of erectile function in recent pilot studies in patients with LUTS was found with the combination of α-adrenergic receptor antagonists and PDE-5 inhibitors (Table 20). Cardiovascular effect is a concern with using PDE-5 inhibitors in conjunction with α-adrenergic receptor antagonists[226, 245, 246]. In men who have been on long-term therapy with α-adrenergic receptor antagonists, the effect of PDE-5 inhibitors on blood pressure may be less significant[247, 248].

d) Effect of Surgery for BPH on Erectile Function

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Study design</th>
<th>Population</th>
<th>OR or RR Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin-Morales et al[197]</td>
<td>2001</td>
<td>cross-sectional</td>
<td>2,476</td>
<td>2.67 (OR) 3</td>
</tr>
<tr>
<td>Braun et al[198]</td>
<td>2003</td>
<td>cross-sectional</td>
<td>4,489</td>
<td>2.11 (OR) 3</td>
</tr>
<tr>
<td>Boyle et al[159]</td>
<td>2003</td>
<td>cross-sectional</td>
<td>4,800</td>
<td>1.39 (OR) 3</td>
</tr>
<tr>
<td>Rosen et al[199]</td>
<td>2003</td>
<td>cross-sectional</td>
<td>12,815</td>
<td>2.00 to 8.90 (OR)* 3</td>
</tr>
<tr>
<td>Vallancien et al[200]</td>
<td>2003</td>
<td>cross-sectional</td>
<td>1,274</td>
<td>1.18 to 1.94 (OR)* 3</td>
</tr>
<tr>
<td>Li et al[201]</td>
<td>2005</td>
<td>cross-sectional</td>
<td>1,155</td>
<td>1.72 to 4.00 (OR)* 3</td>
</tr>
<tr>
<td>Shiri R et al[202]</td>
<td>2007</td>
<td>prospective</td>
<td>1,683</td>
<td>1.5 to 2.3 (RR)* 2</td>
</tr>
<tr>
<td>Antunes et al[203]</td>
<td>2008</td>
<td>cross-sectional</td>
<td>1,008</td>
<td>1.06 (OR) 3</td>
</tr>
<tr>
<td>Mondul et al[204]</td>
<td>2008</td>
<td>prospective</td>
<td>17,086</td>
<td>1.47 to 2.0 (RR)* 2</td>
</tr>
<tr>
<td>Rhoden et al[205]</td>
<td>2008</td>
<td>cross-sectional</td>
<td>192</td>
<td>1.07 (OR) 3</td>
</tr>
</tbody>
</table>

*: OR or RR varies by the severity of LUTS.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Study Design</th>
<th>Population</th>
<th>OR</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosen et al[199]</td>
<td>2003</td>
<td>cross-sectional</td>
<td>12,815</td>
<td>1.71</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.13</td>
<td>2.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(abnormal ejaculations)</td>
<td>(pain with ejaculation)</td>
</tr>
<tr>
<td>Vallancien et al[200]</td>
<td>2003</td>
<td>cross-sectional</td>
<td>1,274</td>
<td>1.23</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.70</td>
<td>5.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(abnormal ejaculations)</td>
<td>(pain with ejaculation)</td>
</tr>
<tr>
<td>Li et al[201]</td>
<td>2005</td>
<td>cross-sectional</td>
<td>1,155</td>
<td>1.92</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.36</td>
<td>4.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(abnormal ejaculation)</td>
<td>(pain with ejaculation)</td>
</tr>
</tbody>
</table>

Table 16: Odds ratio (OR) of EjD in men with LUTS [199, 200, 201]
### Table 17: Common Pathophysiology for ED and LUTS.

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Evidence</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome/autonomic hyperactivity</td>
<td>(1) Metabolic syndrome may affect autonomic nervous system activity. Increased autonomic nervous system activity can induce BPH and ED in rats[207]. Spontaneous hypertensive rats revealed autonomic hyperactivity, prostatic hyperplasia with ED, increased voiding frequency and detrusor overactivity[208]. Clinical study showed significant association of sympathetic tone with the severity of LUTS that may co-exist with ED[209]. LOE: III. Noradrenaline and α&lt;sub&gt;1&lt;/sub&gt;-adrenergic receptors in the sympathetic nervous system mediate adrenergic contraction of smooth muscles in the prostate, bladder neck, urethra and the corpus cavernosum, therefore, constituting the common link.</td>
<td></td>
</tr>
<tr>
<td>Imbalance in α-adrenergic receptor regulation</td>
<td>(1) Various subtypes of α-1 adrenergic receptors have been studied and identified in the bladder, prostate, and penile tissue[196]. With age, glandular proliferation occurs and the density of α-adrenoceptors increases. α&lt;sub&gt;1a&lt;/sub&gt; receptors concentrated in prostate and bladder neck are involved in voiding problems and α&lt;sub&gt;1d&lt;/sub&gt; receptors found in hypertrophied detrusor muscles are involved in storage problems[210]. LOE: N/A (basic research).</td>
<td>Adrenergic receptors mediate smooth muscle tone. Aberrant smooth muscle contraction may be a common cause of both LUTS and ED.</td>
</tr>
<tr>
<td>Increased Rho-kinase activity</td>
<td>(1) Increased RhoA/Rho-kinase signaling is involved in the development of ED with aging in rats[211]. Inhibition of Rho-kinase in the rat model has been shown to decrease prostatic smooth muscle cell proliferation and to decrease adrenergic contractions[212]. Rho-kinase inhibitor, fasudil, can prevent atherosclerosis, endothelial injury, and ED in rats[213]. LOE: N/A (basic research).</td>
<td>Rho-kinase activation leads to increased smooth muscle contraction by modifying the sensitivity of contractile and regulatory proteins to intracellular calcium, which in turn contributes to impaired erectile function and changes in bladder outlet tone[214].</td>
</tr>
<tr>
<td>Endothelin-1 activation</td>
<td>(1) Endothelin-1 (ET-1) is a potent vasoconstrictor and acts by stimulating ET type a (ETα) and b (ETβ) receptors. ETα is the predominant receptor in the smooth muscle cells of the corpus cavernosum, prostate and bladder[215, 216]. ET-1 has been suggested to be an important regulator for ED associated with other ED risk factors, such as diabetes[217]. LOE: N/A (basic research).</td>
<td>Studies are needed to look at the direct link of ET-1 activity in the presence of LUTS associated ED.</td>
</tr>
<tr>
<td>Nitric Oxide (NO)/phosphod-esterase (PDE) theory</td>
<td>(1) NO/PDE pathway is well known in the regulation of the corpus cavernosum smooth muscle tone[218]. Nitrergic oxide synthase (NOS) gene expression is reduced with age in rat prostate tissue and may be a factor in the increased smooth muscle tone associated with LUTS[219]. PDE-5 signaling is involved in bladder smooth muscle tone and prostatic stromal proliferation in rat[220]. The most abundant PDE isoforms in the prostate are PDE 4 and 5[221]. LOE: N/A (basic research).</td>
<td>NO/PDE theory gives the most logical explanation to link LUTS to sexual dysfunction. Reduced NOS/NO is related to ED and may also cause structural changes in the prostate and increase contraction affecting outlet resistance and bladder compliance, leading to LUTS.</td>
</tr>
<tr>
<td>Atherosclerotic changes</td>
<td>(1) Similar smooth muscle atrophy and fibrosis of the detrusor and corpora with production of transforming growth factor (TGF-β1), and stromal fibrosis, glandular cystic atrophy with increases of smooth muscle contractility of the prostate are observed in animal models with pelvic ischemia and hypercholesterolemia[222, 223, 224].</td>
<td>Atherosclerosis causes chronic ischemia and hypoxia to pelvic organs, including the bladder, prostate and penis that may contribute to the pathogenesis of both LUTS and ED.</td>
</tr>
<tr>
<td></td>
<td>(2) (1) An analysis of 1,724 men with more than one major vascular risk factor had significant increased IPSS suggesting an impact of predisposing factors of atherosclerosis on the bladder and lower urinary tract[225]. LOE: III.</td>
<td></td>
</tr>
</tbody>
</table>
Table 18: Effect of medications for LUTS on sexual function [182, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241]

<table>
<thead>
<tr>
<th>Medication</th>
<th>ED (%)</th>
<th>EjD (%)</th>
<th>Comments</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>α – receptor antagonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamsulosin/placebo</td>
<td>4/4</td>
<td>9/1</td>
<td>(1) None of the four agents has a negative effect on erectile function when compared to placebo[227, 228].</td>
<td>1-3</td>
</tr>
<tr>
<td>Doxazosin/placebo</td>
<td>4/4</td>
<td>0.4/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terazosin/placebo</td>
<td>5/5</td>
<td>1/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alfuzosin/placebo</td>
<td>3/4</td>
<td>0.3/(N/A)</td>
<td>(2) Basic science and clinical studies have demonstrated a possible beneficial effect of these medications on sexual function through therapy for LUTS[229, 230, 231, 232, 233, 234].</td>
<td></td>
</tr>
<tr>
<td>McVary 2007[242]</td>
<td>1.93</td>
<td>6.32</td>
<td>(3) Tamsulosin has obvious side effect on ejaculatory function[235].</td>
<td></td>
</tr>
</tbody>
</table>

5α - Reductase inhibitors

<table>
<thead>
<tr>
<th>Medication</th>
<th>ED (%)</th>
<th>EjD (%)</th>
<th>Comments</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finasteride/placebo</td>
<td>16/6</td>
<td>8/2</td>
<td>(1) Both finasteride and dutasteride are associated with comparable adverse effects on sexual function[236, 237, 238].</td>
<td>1</td>
</tr>
<tr>
<td>Dutasteride/placebo</td>
<td>4.7/1.7</td>
<td>1.4/0.5</td>
<td>(2) The rates of these adverse effects become comparable to placebo after the treatment continued more than 2 years[237, 239].</td>
<td>1</td>
</tr>
</tbody>
</table>

Combination Therapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>ED (%)</th>
<th>EjD (%)</th>
<th>Comments</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3.32</td>
<td>0.83</td>
<td>There is a cumulative risk of sexual side effects with combination therapy when compared to monotherapy or placebo[240, 241]</td>
<td>1</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>3.56</td>
<td>1.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finasteride</td>
<td>4.53</td>
<td>1.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination (Do + F)</td>
<td>5.11</td>
<td>3.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>3.8</td>
<td>1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutasteride</td>
<td>6.0</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination (Du + T)</td>
<td>7.4</td>
<td>6.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Antimuscarinics

<table>
<thead>
<tr>
<th>Medication</th>
<th>ED (%)</th>
<th>EjD (%)</th>
<th>Comments</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybutynin</td>
<td>N/A</td>
<td>N/A</td>
<td>(1) There is no well designed study regarding this class of medications on male sexual function.</td>
<td>N/A</td>
</tr>
<tr>
<td>Tolterodine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trospium chloride</td>
<td>0.8</td>
<td>0.5</td>
<td>(2) Oxybutynin treatment for LUTS may have a beneficial effect on sexual function[182].</td>
<td></td>
</tr>
<tr>
<td>Solifenacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darifenacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Table 19: Effect of PDE-5 inhibitors on LUTS [242, 243, 244]

<table>
<thead>
<tr>
<th>Author</th>
<th>PDE-5i</th>
<th>Population</th>
<th>Study Duration</th>
<th>ΔIPSS</th>
<th>ΔEF</th>
<th>P</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>T</td>
<td>C</td>
<td>T</td>
<td>C</td>
<td>T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>180</td>
<td>189</td>
<td>12 weeks</td>
<td>1.93</td>
<td>6.32</td>
<td>1.86</td>
</tr>
<tr>
<td>McVary 2007[242]</td>
<td>Sildenafil</td>
<td>143</td>
<td>138</td>
<td>12 weeks</td>
<td>1.7</td>
<td>3.8</td>
<td>1.4</td>
</tr>
<tr>
<td>McVary 2007[243]</td>
<td>Tadalafil</td>
<td>113</td>
<td>109</td>
<td>8 weeks</td>
<td>3.6</td>
<td>5.9</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Δ: Change of scores
C: placebo group
T: treatment group
Surgical therapy remains the most effective modality in improving LUTS [251]. The risk of ED after transurethral resection of the prostate (TURP), holmium laser enucleating of the prostate (HoLEP) and open prostatectomy (oP) is approximately 10% [227, 252, 253]. However, there is a report of marginal improvement of erectile function after TURP or HoLEP [253]. The risk of EjD after TURP, HoLEP and OP is over 60% [254, 253]. The risk of ED after transurethral microwave thermotherapy or Transurethral needle ablation was less than the risk associated with TURP [227].

e) Effect of parenteral therapies for ED on LUTS

There is no evidence to show vacuum erectile device, intracavernosal injection and penile vascular surgery for ED have effect on LUTS. It is well known that intraurethral use of alprostadil can cause urethral pain in some patients. A side benefit of penile prosthesis implantation for ED has been improved urinary control for some patients with mild stress incontinence, but there has been no prospective study.

5. PREVENTION

No publication is available to evaluate any prevention strategy for LUTS associated sexual dysfunction. However, targeting the pathological conditions underlying LUTS and sexual dysfunction through dietary and lifestyle modifications or therapies may prevent or decrease both sexual dysfunction and LUTS. Specifically, decreasing the risk factors for metabolic syndrome and atherosclerosis may reduce the suspected autonomic nervous system hyperactivity in lower urinary tract, prostate and penis.

6. CONCLUSION

Compelling evidence has established an association of LUTS with male sexual dysfunction. Many theories on the pathophysiology of these two conditions have been proposed and their testing may lead to novel and integrated treatments. For now, available treatments are proving to be beneficial in ways not previously known or studied. As research continues, both conditions may prove preventable.

7. RECOMMENDATIONS

Alpha adrenergic receptor antagonists do not have a negative effect on erectile function. Tamsulosin does cause significant ejaculation dysfunction [235]: Grade B.

5-α-reductase inhibitors for LUTS are associated with adverse effects on sexual function in the first two years of treatment [236, 237, 238, 239, 240]: Grade A.

PDE5 inhibitors have significant and clinically relevant effect to improve LUTS [242, 243, 244]: Grade A.

Future studies are needed to target the pathogenesis pathways of LUTS associated ED to identify novel pharmacotherapy: Grade C.

D. CANCER IN MEN

I. PROSTATE

1. WATCHFUL WAITING

a) Introduction

The diagnosis of prostate cancer has increased dramatically following widespread introduction of prostate-specific antigen (PSA) testing [255]. However, prostate cancer treatment continues to be a controversial topic given the heterogeneous clinical presentation among the diverse patient population, the protracted natural history of the disease and the real risk of treatment related side effects [256]. The risk of over diagnosis and overtreatment poses a tremendous clinical and ethical dilemma [257]. Recent systematic review concluded that assessment of the comparative effectiveness and harms of localized prostate cancer treatments was difficult due to the limitations of the evidence [255]. Nevertheless, watchful waiting (WW) is still a viable treatment option for clinically localized disease with low grade and low volume of prostate cancer, particularly for older patients with a life expectancy of less than 10 years. One of the major considerations for WW is to preserve or maintain the patients’ quality of life (QoL) including their sexual function. However, very few randomized, controlled trials are available.

Table 20: Combination of PDE-5 inhibitors and α-receptor antagonists on sexual function. [249, 250]

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Medication</th>
<th>Study Design</th>
<th>Population</th>
<th>Sexual function</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Rose et al</td>
<td>2002</td>
<td>sildenafil &amp; doxazosin vs.</td>
<td>Randomized</td>
<td>28</td>
<td>↑ IIEF in 78% pts</td>
<td>2</td>
</tr>
<tr>
<td>Kaplan et al</td>
<td>2007</td>
<td>sildenafil &amp; alfuzosin vs.</td>
<td>Randomized</td>
<td>62</td>
<td>↑58.6% of IIEF</td>
<td>2</td>
</tr>
</tbody>
</table>

De Rose et al [249]

Kaplan et al [250]
to compare the QoL and sexual function for men who select WW, to age and cofactor matched men without prostate cancer, and to men with prostate cancer who received active treatment.

b) Sexual dysfunction in patients on WW

1. Sexual function in patients on WW versus in general population

No study has specifically compared sexual function in men with prostate cancer on WW to age and cofactor matched men without prostate cancer. However, limited publications suggest that men on WW for prostate cancer have increased risk for sexual dysfunction compared to men without prostate cancer (table 21).

2. Sexual dysfunction on WW versus other treatment groups

The recent comparison studies of WW to active treatment modalities on sexual function with relatively large numbers of patients are summarized in table 22. It appears that WW has less impact on sexual function compared with active treatment modalities.

c) Pathophysiology

There are no publications exploring the specific mechanism of sexual dysfunction in patients on WW for prostate cancer. Patients with prostate cancer on WW should have the same risk factors (such as cardiovascular diseases, metabolic syndromes) for developing sexual dysfunction when compared to age matched men in the general population. However, patients on WW may have psychological distress due to the uncertainty regarding the disease course and the possibility of regret for not receiving curative treatment [265]. This distress may be associated with increased sexual dysfunction. Patients on WW for prostate cancer also have worse LUTS (mostly obstructive symptoms) compared to patients after RP [261]. It is well known that LUTS is associated with male sexual dysfunction [266].

d) Treatment considerations

Treatment of sexual dysfunction for patients on WW for prostate cancer is the same as the treatment for patients without prostate cancer. This includes oral medications, vacuum erectile devices, transurethral use or intracavernosal injection of vasodilators, and surgical implantation of prosthesis for ED. However, particular attention should be given to counseling patients about the nature and history of prostate cancer to ease the psychological stress that may affect their sexual function. Also, identification and treatment of LUTS is needed in these patients.

e) Prevention

There is no publication discussing prevention strategy. Educating men about common risk factors for sexual dysfunction, counseling patients about the disease course of the prostate cancer and early treatment of any LUTS should be considered as the prevention modality at the present time.

f) Conclusion

Data are limited on sexual function in men on WW for prostate cancer as compared to men without prostate cancer. Most studies support that WW has less impact on sexual function compared to active treatment. Management of sexual dysfunction includes addressing the psychological distress associated with knowing the diagnoses as well as standard medical options. Included also is treatment of any associated LUTS.

g) Recommendations

Watchful waiting has less impact on sexual function compared to active treatment modalities [258, 259, 261, 263]: Grade C.

Treatment of sexual dysfunction for patients on watchful waiting should be the same as the treatment for patients without prostate cancer: Grade C.

---

Table 21: Sexual dysfunction on Watchful Waiting [258, 256]

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Population</th>
<th>Outcomes</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siegel et al. 2001</td>
<td>centralized prospective database f/u &gt; 6 months</td>
<td>64</td>
<td>↑ED (from 45% at the diagnoses to 63% at the last f/u).</td>
<td>When stratified for age, there was no significant effect of age on the increase of ED. LOE: 3</td>
</tr>
<tr>
<td>Arredondo et al. 2004</td>
<td>CAPSURE registry from 1990 to 2001, UCLA PCI for sexual function evaluation at the diagnosis and every 6 months</td>
<td>310</td>
<td>A random slope model revealed more decrease (p&lt;0.001) of sexual function than expected in patients on WW.</td>
<td>Men on WW for prostate cancer appear to have a lower sexual function compared to men without prostate cancer. LOE: 3</td>
</tr>
</tbody>
</table>

CAPSURE – Cancer of the Prostate Strategic Urological Research Endeavor Health Survey *
UCLA PCI – University of California Los Angeles Prostate Cancer Index *
Psychosexual counseling to patients regarding the natural history of prostate cancer and treatment of ED should be considered as the preventive strategy for sexual dysfunction during watchful waiting: Grade C.

2. RADICAL PROSTATECTOMY

a) Introduction

Different options are available for treating localized prostate cancer, with disease-free survival rates nearly equivalent, hence current major efforts to optimize treatment outcomes are aimed to reduce the morbidity of these procedures [267].

Today the majority of men usually achieve resumption of all physical activities, recovery of urinary control and normalization of bowel function within a few months of surgery. However, ED confronts all men as a long-term and sometimes permanent complication following this treatment even when maximal cavernous nerve sparing techniques are applied. Sexual function, an important aspect of quality of life [268], is reportedly more commonly influenced after prostate cancer therapy than other domains of health related quality of life [269, 270, 271].

b) Radical prostatectomy (RP): the gold standard for the treatment of localized prostate cancer

Radical perineal prostatectomy, first described by Young in 1905 for early (localized) prostate cancer was the standard of care until 1945 when Terrence Millin described the radical retropubic prostatectomy [272]. Surgery initially was associated with significant blood loss, incontinence, ED, and prolonged convalescence [273]. Breakthrough modifications to the surgical technique [274] have decreased the complication rate of total and stress-induced incontinence to less than 10% and significantly reduced ED without compromising oncological principles, leading radical prostatectomy to become the gold standard treatment for organ confined prostate cancer for several decades [275, 276, 277, 278]. However the above mentioned postoperative

<table>
<thead>
<tr>
<th>Authors</th>
<th>Total Patients</th>
<th>Evaluation</th>
<th>RP before</th>
<th>XRT</th>
<th>HA</th>
<th>WW before</th>
<th>WW after</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siegel et al. 2001[258]</td>
<td>771</td>
<td>ED (%)</td>
<td>23</td>
<td>90</td>
<td>39</td>
<td>85</td>
<td>45</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patients on WW had a lower incidence of ED compared to patients after RP and XRT (p &lt; 0.0001). LOE: 3</td>
</tr>
<tr>
<td>Bacon et al. 2001[259]</td>
<td>752</td>
<td>EF scores</td>
<td>better scores for WW</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patients on WW (even though they were older) had significantly better scores compared with those after RP, XRT or HA. LOE: 3</td>
</tr>
<tr>
<td>Steineck et al. 2002[260]</td>
<td>326</td>
<td>ED (%)</td>
<td>N/A</td>
<td>80</td>
<td></td>
<td>N/A</td>
<td>45</td>
<td>The only randomized controlled trial. The data were obtained more than 48 months after randomization. LOE: 2</td>
</tr>
<tr>
<td>Siston et al. 2003[262]</td>
<td>98</td>
<td>EF scores</td>
<td>worse</td>
<td>worse</td>
<td></td>
<td></td>
<td></td>
<td>Patients with RP and XRT had worsening of sexual function at the 3 and 12 month f/u (p &lt; 0.05). LOE: 2</td>
</tr>
<tr>
<td>Galbraith et al. 2005[262]</td>
<td>137</td>
<td>Sex symp-</td>
<td>worse</td>
<td>symptoms</td>
<td></td>
<td></td>
<td></td>
<td>Patients on WW were older and no statistical analyses were performed regarding the differences for the scores of sexual complaints. LOE: 4</td>
</tr>
<tr>
<td>Namiki et al. 2007[263]</td>
<td>385</td>
<td>EF scores</td>
<td>better scores for WW</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patients on WW had better sexual function compared with patients after RP, XRT, or HA. LOE: 3</td>
</tr>
<tr>
<td>Katz et al. 2007[264]</td>
<td>61</td>
<td>Sexually Ac-</td>
<td>73</td>
<td>42</td>
<td>53</td>
<td>38</td>
<td>60</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tive (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patients made their own choice of treatment. Sexual activity was evaluated before and at least 12 months after the treatment. LOE: 3</td>
</tr>
</tbody>
</table>

RP: radical prostatectomy; XRT: radiation therapy; HA: hormonal ablation; WW: watchful waiting
complications may encourage choosing alternative treatments such as brachytherapy or external beam radiotherapy. Other additional anatomic, technologic and pharmacologic advances to minimize morbidity have been developed [273]. Within the past decade a major development has been the introduction of laparoscopic radical prostatectomy (LRP) and robotic-assisted laparoscopic radical prostatectomy (RALRP) [279,280].

c) Better diagnostic tools increase the prevalence of early diagnosed cases, impacting both the choice and goals of treatment

Until recently ED following radical prostatectomy was not an overwhelming concern, as most prostate cancers were detected in older men [281]. However, since the advent of PSA screening in the late 1980s, more young patients are being detected at an earlier stage, making both cure and quality of life important issues. There is some research on how patients trade preservation of urinary continence, bowel and sexual function versus more certain cure when given a choice in treatment modality [282, 283, 284]. Sexual function outcome following prostate cancer surgery is now considered a major issue.

d) Pathophysiology of post-RP Erectile Dysfunction (pRPED) and factors contributing to erectile function recovery

1. PATHOPHYSIOLOGY

Despite major advances in the understanding of mechanisms involved in pRPED (see chapter 20 for a comprehensive review on this topic), to quote the first step of this ladder is of justice: “The etiology of "impotence" after radical prostatectomy is unclear, although a variety of potential factors have been cited: neurogenic, psychogenic and possible vascular” [274, 277]; this is a literal quotation from the paper by Walsh and Donker, where they conclude: “Based on the findings in this study it is unlikely that potency can be maintained in men with locally extensive disease with capsular penetration. Rather the principles outlined seem to be more applicable to patients undergoing prostatectomy at the time of cystectomy or to patients with organ-confined prostate cancer. Recognizing that radical prostatectomy is more effective than external beam radiotherapy in the management of localized prostate cancer [285], it is incumbent upon urologists to perfect surgical techniques so that fears about the morbidity of the procedure do not discourage patients and physicians from selecting the optimal form of treatment. In this study 60 percent of the patients who were < 60 years old and who had tumor microscopically confined to the prostate were potent postoperatively. With further refinements in surgical techniques it may be possible to improve this record. If so, fears about impotence may be dispelled and physicians may take a greater interest in diagnosing prostatic cancer in young men at an early stage when it is still curable”. This statement written in 1982 was foresight indeed.

2. FACTORS AFFECTING ERECTILE FUNCTION RECOVERY

Although the main and well accepted pathophysiological issue is the neurological damage, the inconsistency between a “good surgical preservation procedure” and the “functional outcome” lead investigators to look at the basics, and consequently there are emerging points to be considered. Nowadays, the role of Accessory Pudendal Arteries (APA) [286] is under debate as a major precipitator of cavernous hypoxia in those patients in whom the cavernous nerves has been preserved. The cascade of events ending in cavernous fibrosis can start not only as a consequence of neural but of vascular damage as well. This point must be considered when a preservation procedure is undertaken. Besides these considerations, the following issues should be taken into account, when expecting/aiming erectile function (EF) recovery:

i) EF recovery is influenced by many factors [287, 288, 289] including:

a) Preoperative erectile function [290, 291]

b) Age and comorbidities [268]

c) Preservation of the neurovascular bundles [292, 291, 268]

1. Surgical technique of excellence does not refer necessarily to surgical approach, i.e.: open versus laparoscopic or robot-assisted, but to refinement on the procedure itself which is related to the surgeon’s experience (volume) [293].

3. INCIDENCE AND PREVALENCE OF ED ACROSS DIFFERENT SURGICAL TECHNIQUES

The current dilemma about the ED rate following RP is due to wide variation in the potency rates reported in the literature. Almost all the reviews conclude that the data are of limited value due to the lack of standardized variables in the available studies. The variables include: number of nerve-sparing procedures, single versus multi-surgeons series, volume of procedures, potency assessment, preoperative status, the use of erectile aids post-operatively, means of data collection and analysis. Despite these limitations, all the reports in the literature confirm that nerve-sparing surgery significantly increases the return of natural erections after RP [294]. The reported potency rates after bilateral nerve-sparing RP in most series varies from 53 to 86% [276, 295, 296, 297]. Contrary to assumed beliefs, better outcomes are related to surgeon’s experience and skills rather than to the method of surgical removal. Minimally invasive approaches, i.e. laparoscopic, whether robot assisted or not, do not seem to be relevant to the sexual outcomes [291, 273, 283, 298].
Our immediate task is to support the development of randomized trials incorporating consensus criteria on design and sexual function assessment. In the absence of such studies, relevant studies published within the last 10 years, have been identified through a comprehensive literature review and grouped in three categories:

1. Studies including preoperatively potent patients without use of erectile aids postoperatively: raw (true) pRPED incidence (Table 23).

2. Studies including preoperatively potent patients, but using or not using erectile aids post-operatively: pharmacologically adjusted pRPED incidence (Table 24).

3. Studies reporting only prevalence of post-operative ED are omitted, because of the limited value of their results.

Those interested in a wider scope of sexual dysfunctions after RP are encouraged to read the mentioned excellent reviews by Stanford 2000 [289], Trabulsi 2003 [290], Menon 2005 [308], Penson 2005 [311], Zippe 2006 [294], Miranda-Sousa 2006 [316], Burnett 2007 [268], and Sanda 2008 [317].

e) Therapy of post-surgical ED

Currently, no standard treatment or prophylaxis exists for pRPED. Neuro-protective and regenerative therapies, including immunophilin ligands, hold promise to reduce the morbidity of localized prostate cancer therapy [318]. In the meantime, several treatment modalities are available to manage sexual dysfunction following RP. These are used in addition to penile rehabilitation (see chapter 20), or when recovery of spontaneous erections fails.

Treatment options are [316]:

- First-line therapies including patient education, lifestyle modification, psychotherapy, oral therapy, and the use of a vacuum device.

- Second line therapies include intraurethral alprostadil and intracavernous injection therapy.

- Third-line options include penile prosthesis implantation.

Steps to minimize ED: In order to prevent cavernous tissue damage, the ultimate responsible for the true pRPED, the available evidence encourages to:

Aim to surgical technique of excellence:
- Maximal nerve preservation
- Avoidance of vascular damage
- Avoidance of thermal and electrical energy sources [319]
- Minimize cavernous ischemia.

Neural damage takes time to recover even when the nerves are preserved: up to four years [320, 295, 321], so penile rehabilitation (see chapter 20), must be considered in all patients aiming to resume spontaneous sexual activity after a radical prostatectomy.

Ejaculatory and other sexual dysfunctions after RP

Other distressing effects of treatment include: penile shortening (68%), loss of sexual desire (60-80%), less satisfying orgasms (64-87%), overall sexual dissatisfaction (61-91%) [322, 323]. Climacturia, or orgasm associated urinary incontinence (OAI), is a known complication of RRP. The exact rate of this problem is not well established and varies from 45% to 93% [324,325, 326].

Literature is scant providing information on the management of these problems. Some report on penile length preservation by means of vacuum devices begins to appear [327].

f) Conclusions and Recommendations (including level of evidence, when feasible)

Long survival from a localized prostate cancer is nowadays a reality. Quality of life, closely related to sexual function becomes an issue [317]. We conclude that ED following RP can be potentially either prevented or treated if the patients request such intervention. We note almost 50% of bilateral-nerve-sparing RRP patients freely decided not to start any ED treatment postoperatively [328]. Roughly 73% of patients who started therapy eventually discontinued it [328]. We note that patients who underwent RALP were more likely to be regretful and dissatisfied, possibly because of higher expectations of “innovative” procedure [329].

There is an urgent need to standardize data collection and reporting in order to improve our evidence for a better understanding and management of sexual function after RP. Our recommendations are as follows:

Means to minimize ED after radical prostatectomy are recommended: refining surgical technique including avoiding cautery to accessory pudendal arteries along with bilateral-nerve-sparing RRP is recommended [295, 289, 305, 313, 315]: Grade C.

Given some 50% of bilateral-nerve sparing RRP patients may not begin any ED treatment postoperatively [328], the couple rather than the individual should be considered when sexual function and dysfunction is addressed: Grade C.

We recommend urologists carefully portray the risks and benefits of new technologies during preoperative counseling to minimize regret and maximize satisfaction [329]: Grade C.
Table 23: Incidence of Erectile Dysfunction after Radical Prostatectomy (Non and Nerve Sparing Techniques) Patients pre-operatively potent, Erectile Function assessed without erectile aids post-operatively. [299, 300, 301, 302, 303, 304]

<table>
<thead>
<tr>
<th>Author/Reference</th>
<th>Age Years±SD (Range)</th>
<th>N</th>
<th>Study Design</th>
<th>Follow-up</th>
<th>Post op EF assessment</th>
<th>Surgical treatment</th>
<th>ED Incidence</th>
<th>ED Treatment</th>
<th>Outcome/Conclusion</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catalona 1999[299]</td>
<td>63±7 (38-79)</td>
<td>1870</td>
<td>Consecutive retrospective series</td>
<td>&gt; 18 months</td>
<td>Recovery of erections</td>
<td>BNSRRP (798) UNSRRP (60)</td>
<td>32% (BNS)</td>
<td>53% (UNS)</td>
<td>None</td>
<td>Recovery of erections was more likely with bilateral than unilateral nerve sparing surgery in patients less than 70 years old (71 versus 48%, p &lt;0.001) compared with patients with age 70 years old or older (48 versus 40%, p = 0.6)</td>
</tr>
<tr>
<td>Fulmer 2001[300]</td>
<td>59 (43-77)</td>
<td>42</td>
<td>Prospective comparative study</td>
<td>18 months</td>
<td>UCLA Prostate Cancer Index. Return to baseline.</td>
<td>UNSRRP NSRRP</td>
<td>81.7% (Overall: BNS and UNS)</td>
<td>N/A</td>
<td>Alternate treatments: HBT &amp; HBTC also comprises sexual function.</td>
<td>3</td>
</tr>
<tr>
<td>Guillonneau, 2002[301]</td>
<td>550. Data on sexual outcome only on 47</td>
<td>Consecutive selected</td>
<td>12 months</td>
<td>Spontaneous Erection/ Intercourse</td>
<td>LRP</td>
<td>34%</td>
<td>No treatment</td>
<td>For 47 consecutive selected patients, spontaneous erection rate was 85 and 66% experienced spontaneous intercourse.</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Katz, 2002[302]</td>
<td>65,8±6,7 63,9±5,4 62,8±6,0 N/A N/A N/A</td>
<td>143</td>
<td>Consecutive</td>
<td>12 months</td>
<td>23% Successful intercourse</td>
<td>NNSLRP(50) UNSLRP(30) BNSLRP(63)</td>
<td>43,2%</td>
<td>No treatment was given. Bur, was sildenafil consumed?</td>
<td>The overall rate of patients who had erections preoperatively and maintained erections after surgery (53.8%) is comparable to the results for open surgery.</td>
<td>3</td>
</tr>
<tr>
<td>Kundu, 2004[303]</td>
<td>61 ± 7.4 (36–80)</td>
<td>1834</td>
<td>Consecutive serie</td>
<td>18 months</td>
<td>Erections firm enough for intercourse</td>
<td>1770 BN- SRRP 64 UNSRRP</td>
<td>24% BN- SRRP 47% UN- SRRP</td>
<td>N/A</td>
<td>Potency recovery is patient age and surgeon’s experience related</td>
<td>3</td>
</tr>
<tr>
<td>Potosky, 2004 [304]</td>
<td>N/A 55-74</td>
<td>901</td>
<td>Prospective consecutive series</td>
<td>24 months 60 months</td>
<td>Erections firm enough for intercourse</td>
<td>RRP (no nerve sparing is stated)</td>
<td>82,1% 79,3%</td>
<td>Non stated</td>
<td>External beam radiotherapy patients declined in function from 2 to 5 years nearly to the level of radical prostatectomy patients, who experienced little or no change.</td>
<td>3</td>
</tr>
</tbody>
</table>

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<tr>
<th>Author/Reference</th>
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<th>Outcome/Conclusion</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walsh, 2000[295]</td>
<td>57 (36-67)</td>
<td>64</td>
<td>Prospective cohort</td>
<td>18 months</td>
<td>Unassisted intercourse</td>
<td>BNSRRP 89%</td>
<td>14% overall (0% 30-39 years 12% 40-49 years 10% 50-59 years 25% 60-67 years)</td>
<td>1/3 of patients were using sildenafil, but only 2 stated that they could not have intercourse without it.</td>
<td>Surgical experience is the major factor that influences the morbidity of radical prostatectomy and not the method by which the data are collected.</td>
<td>3</td>
</tr>
<tr>
<td>Stanford, 2000[289]</td>
<td>62.9 39-79</td>
<td>1291</td>
<td>Unselected population based longitudinal cohort study</td>
<td>24 months</td>
<td>Erections firm enough for sexual intercourse. Data collected directly from patients</td>
<td>NNSRRP UNSRRP NSRRP</td>
<td>65.6% NNS 58.6% UNS 56% BNS</td>
<td>VED 26.8% ICI 21.4% Oral medication 9% Counseling 7.6% Penile implant 3.7%</td>
<td>On the 24 months survey 41.9% reported sexual function moderate to big problem: Radical prostatectomy is associated with significant erectile dysfunction and some decline in urinary function.</td>
<td>3</td>
</tr>
<tr>
<td>Anatasiadis, 2003[305]</td>
<td>64.8± 6.4 (50–75) 64.1±6.4 (46–77)</td>
<td>300</td>
<td>Consecutive series</td>
<td>12 months</td>
<td>Erection suitable for sexual intercourse</td>
<td>NNSRRP NNLRP UNSRRP UNSLRP BNSRRP BNSLRP</td>
<td>70% 59% 73% 54% 56% 47%</td>
<td>With or without sildenafil. Other treatments were excluded</td>
<td>These preliminary data demonstrate that the two techniques offer similar outcomes in terms of continence and erectile function 1 year after surgery.</td>
<td>3</td>
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</tr>
</thead>
<tbody>
<tr>
<td>Salomon 2003[306]</td>
<td>64.5±6.3 (46–77)</td>
<td>77-205</td>
<td>Retrospective series</td>
<td>12 months</td>
<td>Erections allowing sexual intercourse with penetration</td>
<td>RRP (no mention of nerve or non-nerve sparing technique)</td>
<td>67.3%</td>
<td>With or without sildenafil. Other treatments were excluded.</td>
<td>The objective of this study is to propose a new method, based on a simple score, in order to report the combined cancer control and functional (continence and sexual potency) results of radical prostatectomy</td>
<td>3</td>
</tr>
<tr>
<td>Link 2005[307]</td>
<td>58.3±6.2 N/A</td>
<td>50</td>
<td>Prospective EPIC questionnaire</td>
<td>12 months</td>
<td>Intercourse</td>
<td>BNSLRP</td>
<td>21.1%</td>
<td>With or without PDE5i</td>
<td>The results reflect the degree to which each individual experienced return of urinary and sexual function compared to his unique baseline HRQOL state.</td>
<td>3</td>
</tr>
<tr>
<td>Menon 2005[308]</td>
<td>N/A N/A &gt; 10 years life expectancy</td>
<td>715</td>
<td>Prospective (2000-2003)</td>
<td>At least 2 years</td>
<td>Median time to erection Median time to intercourse</td>
<td>RRP 100 LRP 50 VIP 565</td>
<td>440 days for RRP vs 0.4 (OR) for VIP &gt; 700 days for RRP vs 0.5 (OR) for VIP</td>
<td>N/A</td>
<td>VIP superior to other techniques</td>
<td>3</td>
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</tr>
</thead>
<tbody>
<tr>
<td>Menon 2005[309]</td>
<td>57.4±6.3 60.5±7.0</td>
<td>58</td>
<td>Prospective (January-August 2003)</td>
<td>12 months</td>
<td>SHIM&gt;21 or Intercourse with and without PDE5i</td>
<td>35 VIP 23 BNSLRP</td>
<td>17% control, 51% cases SHIM &gt; 21 without medication. 74% control and 97% cases erections enough for intercourse. 26% control, 86% study SHIM &gt; 21 with or without PDE5i</td>
<td>Patients &quot;encouraged&quot; starting PDE5i as needed 4 weeks after surgery. No report on control over accomplishment.</td>
<td>Patients undergoing fascia preserving radical prostatectomy have significantly better potency outcomes than patients undergoing conventional nerve sparing robotic prostatectomy at 12 month follow-up</td>
<td>3</td>
</tr>
<tr>
<td>Saranchuck, J 2005[310]</td>
<td>58 (39-75)</td>
<td>647</td>
<td>Consecutive</td>
<td>48 months</td>
<td>Erections</td>
<td>NSRRP</td>
<td>47%</td>
<td>62% use PDE5i</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Penson 2005[311]</td>
<td>39-79 years at diagnosis N/A</td>
<td>1288</td>
<td>Longitudinal population based study</td>
<td>5 years</td>
<td>Erections firm enough for intercourse (EFEFI), with or without erectile aids</td>
<td>NNSRRP BNSRRP UNSRRP</td>
<td>60% BNS 78% UNS 78% NNS</td>
<td>VED ICI Sildenafil Counseling Penile implants</td>
<td>EFEFI (among BNSRP) 61% 39-54 years old 49% 50-59 years old 44% 60-64 years old 18% older than 65 years</td>
<td>3</td>
</tr>
<tr>
<td>Ghavamian, 2006[291]</td>
<td>57.8 (44-72) 60.8 (43-72)</td>
<td>70 (74.2% potent preop) 70 (82.8% potent preop)</td>
<td>Consecutive comparative series</td>
<td>18 months</td>
<td>Score 3 or more to questions 2 and 3 of IIEF-5</td>
<td>BNSRRP UNSRRP NNSRRP BNSLRP UNSLRP NNSLRP</td>
<td>27.5% 54.5% 20.5% 44.4%</td>
<td>Sildenafil if not able to have satisfactory erections for intercourse by 3 months postoperatively</td>
<td>No statistically significant difference was found between the two surgical approaches.</td>
<td>3</td>
</tr>
</tbody>
</table>

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<th>Outcome/Conclusion</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Bianco, 2005[312]</td>
<td>58 (54-63)</td>
<td>758</td>
<td>Consecutive serie (20 years)</td>
<td>4 years (2.6-6.5)</td>
<td>Intercourse</td>
<td>BNSRRP 544 UNSRRP 210 NNSRRP 4</td>
<td>30% at 24 months</td>
<td>N/A</td>
<td>Achieve no recurrence, continence and potency</td>
<td>3</td>
</tr>
<tr>
<td>Curto, 2006[313]</td>
<td>62 (43-75)</td>
<td>137</td>
<td>Consecutive serie</td>
<td>12 months</td>
<td>Intercourse</td>
<td>LRP</td>
<td>41.5%</td>
<td>With or without PDE5i</td>
<td>Intrafascial technique provides better functional outcomes</td>
<td>3</td>
</tr>
<tr>
<td>Rassweiler, 2006[314]</td>
<td>64 (41-81)</td>
<td></td>
<td>Multicenter report (18 centers)</td>
<td>12 months</td>
<td>Intercourse</td>
<td>LRP</td>
<td>47.5% BNS 69% UNS</td>
<td>With or without PDE5i</td>
<td>First multi-center study focusing on the reproducibility of LRP.</td>
<td>3</td>
</tr>
<tr>
<td>Menon, 2007[315]</td>
<td>60.2</td>
<td>1113</td>
<td>Prospective</td>
<td>12 months</td>
<td>Intercourse</td>
<td>RALRP(VIP) SNS Veil</td>
<td>32% SNS 7% Veil</td>
<td>With or without PDE5i</td>
<td>The preservation of the “Veil of Aphrodite” helps in postoperative return of erectile function in patients with normal preoperative erectile function.</td>
<td>3</td>
</tr>
</tbody>
</table>

SNS: Standard Nerve Sparing technique; Veil: Aphrodite's Veil preservation technique.
3. RADIOTHERAPY

a) Introduction

Despite the decrease in overall cancer incidence and mortality rates in developed countries since the early 1990s, cancer remains a major public health problem. Among men, the most common cancer affects the prostate and occurs more often in the older population [330]. In recent years, the number of patients diagnosed with prostate cancer (PC) has increased dramatically because of the widespread use of prostate specific antigen testing and the possibility for cure of early disease. Standard treatments for PC are radical prostatectomy, external-beam radiotherapy (EBRT), brachytherapy, hormonal therapy or observation. In recent years patient’s quality of life, including sexual functioning, plays a more significant role in decision making about treatment type. In the 1980s and 1990s penile prostheses and penile injections provided limited options for male sexual dysfunction. With the introduction of sildenafil (Viagra®) in 1998, media attention to erectile dysfunction (ED) made sexual problems more normative and increased acceptance of help-seeking [331].

b) Methods of Evaluating Erectile Dysfunction

The most practical and quickest way to evaluate ED is by using a questionnaire such as the International Index of Erectile Function (IIEF) [332]. The IIEF has been translated and validated in many countries, though it has not been specifically developed for cancer patients. In the published literature on post-radiation ED different questions have been used, but these were mainly incorporated into a more general questionnaire on toxicity of radiation treatment, or quality of life in general. For an extensive review of the clinical evaluation and symptom scales for sexual dysfunction assessment, see Chapter 6.

c) Definition of Potency

A clear definition of potency is mandatory in order to make meaningful comparisons of the different studies. The 2nd International Consultation on Sexual Dysfunctions, held in Paris is 2003, defined ED as the consistent or recurrent inability to attain and/or maintain a penile erection sufficient for sexual performance [333]. Rigidity of erections, presence of spontaneous daytime erections or morning/night erections are also important issues. It is also necessary to differentiate between ED and not being sexually active, often due to reasons not correlated to erectile insufficiency such as absence of a willing partner, or the lack of interest in sex. Psychological factors in irradiated patients may play a role in post-radiation ED and have to be kept in mind.

In most published studies, authors referred to the general terms potency or impotence without giving a proper operational definition. In some articles, a detailed definition of potency was provided, though this was often not comparable. Only very recent studies have used the IIEF questionnaire [332] or the shortened IIEF-5 questionnaire [334].

d) Etiology of Post-Radiation Erectile Dysfunction

An extensive and critical review on the topic has been published previously [335,336,337].

A study by Zelefsky and Eid [338] concluded that the predominant etiology of radiation-induced impotence was arteriogenic. Several more recent clinical studies investigated the relationship between the radiation dose to the neurovascular bundles, the penile bulb and the penile bodies and post-radiation ED [339, 340, 341, 342, 343, 344, 345, 346, 347,348, 349, 350, 351, 352, 353, 354] presenting contradicting results (Tables 25 and 26). Most studies have only analyzed few patients and the statistical power can be questioned. Post-radiation ED has more likely a multifactorial etiology, and is not only based on the general terms potency or impotence without giving a proper operational definition. In some articles, a detailed definition of potency was provided, though this was often not comparable. Only very recent studies have used the IIEF questionnaire [332] or the shortened IIEF-5 questionnaire [334].

![Schematic of the Male Genitalia](https://example.com/schematic.png)

Fi.3: Schematic of the male genitalia.
Table 25: Correlation between radiation dose to the penile bulb and radiation-induced erectile dysfunction [341, 342, 343, 344, 345, 346, 347, 348, 350, 351, 352, 353]

<table>
<thead>
<tr>
<th>Authors</th>
<th>LOE</th>
<th>Other structures than PB</th>
<th>Prospective ED evaluation</th>
<th>n=</th>
<th>Radiation technique</th>
<th>Follow-up (months)</th>
<th>Significant correlation</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisch et al., 2001[344]</td>
<td>3</td>
<td>no</td>
<td>no</td>
<td>21</td>
<td>3D-CRT</td>
<td>24</td>
<td>yes</td>
<td>median D70 of the PB with a 70 Gy cut off point</td>
</tr>
<tr>
<td>Merrick et al., 2001[341]</td>
<td>3</td>
<td>no</td>
<td>no</td>
<td>46</td>
<td>BT</td>
<td>35</td>
<td>yes</td>
<td>minimum D25, D50, D70, D75, D90 and D95 of the PB</td>
</tr>
<tr>
<td>Merrick et al., 2002[342]</td>
<td>3</td>
<td>crura</td>
<td>no</td>
<td>60</td>
<td>BT</td>
<td>26-79</td>
<td>yes</td>
<td>minimum D50 of the PB</td>
</tr>
<tr>
<td>Merrick et al., 2005[343]</td>
<td>3</td>
<td>crura</td>
<td>yes</td>
<td>128</td>
<td>BT</td>
<td>13-42</td>
<td>no</td>
<td>minimum D50 of the proximal crura.</td>
</tr>
<tr>
<td>Kiteley et al., 2002[345]</td>
<td>3</td>
<td>NVB</td>
<td>yes</td>
<td>50</td>
<td>BT</td>
<td>24-45</td>
<td>no</td>
<td>no significant correlations</td>
</tr>
<tr>
<td>Wright et al., 2004[349]</td>
<td>3</td>
<td>NVB, crura</td>
<td>no</td>
<td>41</td>
<td>BT</td>
<td>12-41</td>
<td>yes</td>
<td>minimum D90 with a 10% cut off point of the prescribed dose. Paradoxical result in NVB analysis</td>
</tr>
<tr>
<td>Selek et al., 2004[346]</td>
<td>3</td>
<td>Penile bodies</td>
<td>no</td>
<td>28</td>
<td>3D-CRT</td>
<td>≥ 24</td>
<td>no</td>
<td>paradoxical result: potent patients had a higher dose to penile base structures</td>
</tr>
<tr>
<td>Roach et al., 2004[347]</td>
<td>2</td>
<td>no</td>
<td>yes</td>
<td>158</td>
<td>3D-CRT</td>
<td>n.a.</td>
<td>yes</td>
<td>median dose to the penile bulb ≥ 52.5 Gy</td>
</tr>
<tr>
<td>Wernicke et al., 2004[348]</td>
<td>3</td>
<td>no</td>
<td>yes</td>
<td>29</td>
<td>3D-CRT</td>
<td>18-42</td>
<td>yes</td>
<td>median dose to D30, D45, D60 and D75</td>
</tr>
<tr>
<td>MacDonald et al., 2005[350]</td>
<td>3</td>
<td>no</td>
<td>yes</td>
<td>226</td>
<td>BT</td>
<td>≥ 24</td>
<td>no</td>
<td>no significant correlations</td>
</tr>
<tr>
<td>Mangar et al., 2006[351]</td>
<td>2</td>
<td>no</td>
<td>yes</td>
<td>51</td>
<td>3D-CRT</td>
<td>24</td>
<td>yes</td>
<td>mean D90 with a cut point of 50 Gy and 60 Gy</td>
</tr>
<tr>
<td>Brown et al., 2007[352]</td>
<td>3</td>
<td>no</td>
<td>yes</td>
<td>32</td>
<td>IMRT</td>
<td>24</td>
<td>no</td>
<td>no significant correlations</td>
</tr>
<tr>
<td>Vd Wielen et al., 2008[353]</td>
<td>1</td>
<td>no</td>
<td>yes</td>
<td>96</td>
<td>3D-CRT</td>
<td>24</td>
<td>no</td>
<td>no significant correlations</td>
</tr>
</tbody>
</table>

LoE  Level of Evidence  
*D-CRT Three-Dimensional Conformal RadioTherapy  
PB Penile Bulb  
BT Brachytherapy  
D xx Dose delivered to xx % of an anatomic structure  

NVB NeuroVascular Bundles  
n.a. not available  
IMRT Intensity Modulated RadioTherapy
radiation dose to one single anatomical structure. If this is the case, it is much harder to find a correlation between ED and the dose to a specific structure. Furthermore, it is very well possible that the structure responsible for ED has not been investigated yet (i.e. internal pudendal arteries). To date, no final conclusions can be drawn whether or not the radiation dose to the penile structures correlates with post-radiation ED. Even in a prospective, randomized trial such correlation was not found [353].

e) Incidence of Erectile Dysfunction after Radiotherapy

1. Incidence of Erectile Dysfunction after External-Beam Radiotherapy

An extensive review on the topic has been published previously [356]. Only studies that prospectively evaluated erectile functioning using validated questionnaires and using a proper definition of potency are useful to draw conclusions on the incidence of post-radiation ED. Two recent prospective trials have shown an incidence of ED in 30-40% of the patients treated by EBRT [357, 358]. Time elapsed since radiation is important: prospective studies show an increase of ED between one and two years after radiotherapy, but it does not seem to change after three years [357, 358].

<table>
<thead>
<tr>
<th>Authors</th>
<th>LoE</th>
<th>Other structures than NVB</th>
<th>Prospective ED evaluation</th>
<th>n=</th>
<th>Radiation technique</th>
<th>Follow-up (months)</th>
<th>Significant correlation</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>DiBiase et al., 2000 [341]</td>
<td>3</td>
<td>no</td>
<td>no</td>
<td>14</td>
<td>BT</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Maximal NVB doses exceeded average values in 3 patients with post implant impotence</td>
</tr>
<tr>
<td>Merrick et al., 2000 [340]</td>
<td>3</td>
<td>no</td>
<td>yes</td>
<td>54</td>
<td>BT</td>
<td>37</td>
<td>no</td>
<td>no significant correlations</td>
</tr>
<tr>
<td>Merrick et al., 2001 [341]</td>
<td>3</td>
<td>no</td>
<td>yes</td>
<td>34</td>
<td>BT</td>
<td>13</td>
<td>no</td>
<td>no significant correlations</td>
</tr>
<tr>
<td>Kiteley et al., 2002 [345]</td>
<td>3</td>
<td>PB</td>
<td>yes</td>
<td>50</td>
<td>BT</td>
<td>24-45</td>
<td>no</td>
<td>no significant correlations</td>
</tr>
<tr>
<td>Wright et al., 2004 [349]</td>
<td>3</td>
<td>PB, crura</td>
<td>no</td>
<td>41</td>
<td>BT</td>
<td>12-41</td>
<td>no</td>
<td>paradoxical result: decreased ED risk with a higher dose to the right NVB</td>
</tr>
</tbody>
</table>

LoE Level of Evidence
BT Brachytherapy
NVB Neurovascular Bundle
ED Erectile Dysfunction

Brachytherapy was originally introduced not only to limit the detrimental effects of EBRT on bowel and urinary function, but also to help preserve sexual function. The introduction of sophisticated 3D computer-assisted dosimetry, and the availability of intraoperative TRUS after the 1990s, led to a more accurate and reproducible implants. In general, after permanent seed implantations, ED rates ranged from 5 to 51%, with the highest percentages found after the combination brachytherapy and EBRT. The highest ED rates, ranging from 29 to 89%, have been reported combining the temporary Iridium-192 implants with EBRT.
### Table 27: Erectile Dysfunction after External-Beam Radiotherapy (EBRT) for Prostate Cancer: Prospective studies [357, 358, 359, 360, 361, 362, 363]

<table>
<thead>
<tr>
<th>Authors</th>
<th>LoE</th>
<th>Patients</th>
<th>Mean age*</th>
<th>Patients potent</th>
<th>Mean follow-up</th>
<th>ED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>years (range)</td>
<td>prior to EBRT n (%)</td>
<td>months (range)</td>
<td>%</td>
</tr>
<tr>
<td>Pilepich et al., 1995[359]</td>
<td>3</td>
<td>230</td>
<td>n.a.</td>
<td>71[^1] (49-84)</td>
<td>102 (44)</td>
<td>54[^1] (n.a.)</td>
</tr>
<tr>
<td>Beckendorf et al., 1996[360]</td>
<td>3</td>
<td>67</td>
<td>68 (54-84)</td>
<td>40 (60)</td>
<td>n.a. (8-12)</td>
<td>33</td>
</tr>
<tr>
<td>Beard et al., 1997[361]</td>
<td>3</td>
<td>121</td>
<td>n.a.</td>
<td>69 (57)</td>
<td>n.a.</td>
<td>57 at 3 months 64 at 12 months</td>
</tr>
<tr>
<td>Borghede et al., 1997[362]</td>
<td>3</td>
<td>184</td>
<td>67 (46-83)</td>
<td>134 (73)</td>
<td>46 (24-96)</td>
<td>7</td>
</tr>
<tr>
<td>Turner et al., 1999[363]</td>
<td>3</td>
<td>290</td>
<td>69 (44-82)</td>
<td>182 (63)</td>
<td>23[^1] (n.a.)</td>
<td>38 at 12 months 59 at 36 months</td>
</tr>
<tr>
<td>van der Wielen et al., 2007[357]</td>
<td>1</td>
<td>174</td>
<td>68[^1] (48-60)</td>
<td>139 (72)</td>
<td>27 (6-36)</td>
<td>27 at 12 months 38 at 36 months</td>
</tr>
<tr>
<td>Pinkawa et al., 2009[358]</td>
<td>3</td>
<td>123</td>
<td>71[^1] (53-84)</td>
<td>54 (44)</td>
<td>16 (12-22)</td>
<td>73 at 16 months</td>
</tr>
</tbody>
</table>

LoE: Level of Evidence
n.a. = data not available
[^1] mean age for entire group
[^1] median

### Table 28: Erectile Dysfunction after Brachytherapy (BT) for Prostate Cancer [364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374]

<table>
<thead>
<tr>
<th>Author</th>
<th>LoE</th>
<th>EBRT</th>
<th>Patients</th>
<th>Mean age*</th>
<th>Patients potent</th>
<th>Mean follow-up</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n (range), years</td>
<td>before BT, n (%)</td>
<td>(range), months</td>
<td>%</td>
</tr>
<tr>
<td>Martinez et al., 1995[364]</td>
<td>2</td>
<td>Yes</td>
<td>59</td>
<td>n.a</td>
<td>n.a.</td>
<td>19 (4-36)</td>
<td>38</td>
</tr>
<tr>
<td>Arterbery et al., 1997[365]</td>
<td>3</td>
<td>No</td>
<td>51</td>
<td>n.a</td>
<td>35 (69)</td>
<td>n.a.</td>
<td>13 at 6 months</td>
</tr>
<tr>
<td>Joly et al., 1998[367]</td>
<td>3</td>
<td>Yes</td>
<td>71</td>
<td>68 (51-82)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>89</td>
</tr>
<tr>
<td>Sharkey et al., 1998[368]</td>
<td>3</td>
<td>No</td>
<td>434</td>
<td>73 (52-83)</td>
<td>n.a.</td>
<td>28 (12-60)</td>
<td>15</td>
</tr>
<tr>
<td>Kestin et al., 2000[369]</td>
<td>3</td>
<td>Yes</td>
<td>161</td>
<td>69[^1] (n.a.)</td>
<td>n.a.</td>
<td>34[^1] (5-86)</td>
<td>29</td>
</tr>
<tr>
<td>Sánchez-Ortiz et al., 2000[370]</td>
<td>3</td>
<td>No</td>
<td>114</td>
<td>69 (n.a.)</td>
<td>81 (71)</td>
<td>23 (4-72)</td>
<td>51</td>
</tr>
<tr>
<td>Sharkey et al., 2000[371]</td>
<td>3</td>
<td>No</td>
<td>299</td>
<td>73 (48-88)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>15</td>
</tr>
<tr>
<td>Potters et al., 2001[373]</td>
<td>3</td>
<td>Yes</td>
<td>1166</td>
<td>69 (n.a.)</td>
<td>482 (41)</td>
<td>34[^1] (6-92)</td>
<td>31</td>
</tr>
<tr>
<td>Stock et al., 2001[374]</td>
<td>3</td>
<td>No</td>
<td>416</td>
<td>66[^1] (41-83)</td>
<td>313 (75)</td>
<td>31[^1] (12-92)</td>
<td>21 at 36 months 41 at 72 months</td>
</tr>
</tbody>
</table>

LoE: Level of Evidence
EBRT = BT in combination with external-beam radiotherapy (EBRT)
n.a. = data not available
[^1] mean age for entire group;[^1] median
f) **Ejaculatory and other Sexual Dysfunctions**

A deterioration of sexual activity has been associated with the severity of ejaculatory dysfunction, particularly a decrease in volume or an absence of semen [375]. After radiotherapy, ejaculatory disturbances varied from a reduction or absence of ejaculate volume (2%-56%) to discomfort during ejaculation (3-26%) and haemospermia (5-15%). Dissatisfaction with sex life was reported in 25-60%, and decreased sexual desire in 12-58%. One study reported a decreased intensity of orgasm, decreased frequency and rigidity of erections, and decreased importance of sex [338, 373, 374, 339].

**g) Therapy of Post-Radiation Erectile Dysfunction**

Prior to the introduction of sildenafil, only one small study reported on the efficacy of intracavernosal injections (ICI) in the treatment of post-radiation ED [376]. All patients had erections sufficient for vaginal penetration with an ICI. Dubocq et al. reported a high satisfaction rate and low morbidity in 34 patients with a penile implant [377]. With the availability of oral drugs to treat ED, these methods of therapy are loosing popularity. The efficacy of sildenafil after radiotherapy in open-label studies has been reported in up to 90% of the patients. In the only randomized, double-blind trial performed so far, sildenafil improved erections significantly as compared to placebo; 55% of the patients had successful intercourse with sildenafil (18% with placebo) [382,383]. Similar results have been reported in one randomized, double-blind trial using tadalafil [384,385].

**h) Prevention of Post-Radiation Erectile Dysfunction**

Prevention is a difficult matter. If one accepts the hypothesis that radiation induces vascular damage, then decreasing the dose to pelvic vascular structures could decrease ED rate. As no reliable data are available to correlate the radiation dose in the penile structures and neurovascular bundles with the prevalence of post-radiation ED, to date no conclusions can be drawn. Possibly, reduction of treatment margins, the use of fiducials to visualize the prostate, more sophisticated radiation techniques such as the intensity modulated radiotherapy (IMRT), might all reduce the prevalence of post-radiation ED. However, prospective studies with large series of patients, and the use of standardized validated questionnaires, have to investigate this hypothesis.

**i) Conclusion**

The prevalence of post-radiation ED is high. There are still no conclusive data on EBRT techniques, field sizes, energy used and their specific influence on ED. Although vascular damage seems to play a role in post-radiation ED this has not confirmed so far. A multifactorial etiology has to be considered, taking into account age, comorbidity, previous prostate surgery, drugs, pre-treatment erectile function and hormonal manipulation. The definition of (im)potence advocated by the 2nd International Consultation on Sexual Dysfunctions should always be used [333], and ED evaluation should be standardized by using, prospectively, validated questionnaires on quality of life and sexual functioning, such as the IIEF. A better understanding of the etiology would allow for more specific therapeutic modalities. Finally, sexual counseling is an important aspect. Patients need to be correctly informed on the anatomy of the prostate, on the possible sequelae of radiation on their sexual life and functioning. Not only a functional penis but a functional couple, has to be the goal. Thus sexual desire, the importance of intercourse in their sexual experiences and both partners’ satisfaction with sexual life, has to be assessed as well.

**j) Recommendations**

We recommend to define ED using the definition advocated by the second international consultation on sexual dysfunction: Grade C.

Use internationally validated questionnaires and collect data on sexual functioning prospectively, because time since radiotherapy is an important factor: Grade C.

A likely multi-factorial etiology should guide treatment of ED: Grade C.

Take the time needed to discuss sexual matters after radiotherapy not only with the patient but with his partner: Grade C.

Phosphodiesterate-5 inhibitors are effective in about half of patients [382, 383, 384, 385]: Grade A.

4. **ANDROGEN DEPRIVATION THERAPY FOR PROSTATE CANCER TREATMENT AND SEXUAL DYSFUNCTION**

a) **Introduction**

Androgen deprivation therapy (ADT) is widely used for treating men with clinically localized or advanced-stage disease prostate cancer (PCa), and has served as both primary and salvage therapy in selected patient populations [386]. Classically, ADT was reserved for patients who had clinically evident metastatic disease or for those who were not candidates for more definitive local therapies, although the indications for early use of ADT are expanding [387,388,389].

Decreasing serum testosterone can have a significant negative impact on quality of life for patients treated with ADT due to adverse effects including decreased libido, osteoporosis, vasomotor flushing, fatigue, anemia, diabetes mellitus (DM),
metabolic syndrome, and altered body composition [386, 390, 391, 392, 393, 394]. Despite the induction of castrate testosterone levels with ADT and the potential for loss of libido and resulting ED, there is a subset of patients in clinical practice who maintain erectile and sexual function [395].

b) Pathophysiology of ADT related Sexual Dysfunction (SD)
Testosterone plays an important role in maintaining male sexual desire. Testosterone also modulates many aspects of the neurogenic vascular dilatation integral to the erectile response. Thus men who undergo ADT have a further decline in ability for sexual intercourse and a decrease in sexual desire compared with men who are not treated with ADT [396]. Sex steroid action in the brain results from the combination of rapid signaling as well as classic transcriptional regulation [397]. Amongst other actions, gonadal steroids act on brain regions involved in the control of sexual behavior and neuroendocrine regulation, modulating release of neurotransmitters including dopamine which is thought to modulate sexual desire. Available data from preclinical and clinical studies, suggest that in the corpus cavernosum, androgens regulate the multiple signaling pathways and the structure of cavernosal tissue. Androgens are involved in the regulation of: (i) NOS isoform expression and activity; (ii) phosphodiesterase-5 (PDE5) expression and activity; (iii) alpha adrenoceptor expression and function; (iv) smooth muscle cell growth and response to vasodilators; (v) connective tissue metabolism and deposition of the extra cellular matrix; (vi) differentiation of progenitor vascular-stroma cells into myogenic and adipogenic lineages; and in maintaining neural structure and function. Androgen reduction causes changes in tissue response to endogenous vasodilators causing reduced blood inflow (failure to fill); changes in the fibroelastic properties and expandability with poor compliance of the corpus cavernosum, resulting in increased blood outflow (failure to accumulate blood under pressure) and dysfunctional veno-occlusive mechanism, contributing to ED [398].

c) Incidence of SD across different treatment modalities
Heterogeneity in collecting data and defining outcomes makes the scant data on SD after ADT difficult to interpret and sometime surprising. We have reviewed data concerning:

i) Continuous Androgen Deprivation (CAD)
(1) Surgical
(2) Medical
   (a) LHRH agonists
   (b) LHRH agonists + antiandrogens: Combined Androgen Blockade (CAB)

ii) Intermittent Androgen Deprivation (IAD)
See Table 29 with relevant studies comparing sexual outcomes after ADT.

d) Management of ADT related SDs
Most standard treatments for ED such as oral agents, vacuum erection devices, intracorporal injection therapy, or placement of a penile prosthesis, are good options. Other forms of ADT, specifically antiandrogen monotherapy and intermittent androgen deprivation, have also been shown to be associated with significantly improved sexual function. In the study by DiBlasio [395] (2008) addressing treatment responsiveness, response rates were 33–80% with medical therapy, including 44% receiving PDE5 inhibitors monotherapy. The low desire as a consequence of ADT can improve during the "off treatment phases" when on IAD [401]. No specific data have been found on absent or delayed ejaculation.

e) Summary
In summary, studies demonstrate that sexual function is significantly impaired after ADT, and that these effects are similar for surgical versus medical ADT.

However, men receiving LHRH agonists reported more worry and discomfort and somewhat poorer overall health and were less likely to believe they are free of cancer compared to orchiectomy patients [395]. These results reflect treatment delivered to a heterogeneous group of patients in diverse health care settings but may provide representative information about the effects of hormonal therapy so as to guide treatment decisions.

In recent years the concept of IAD has passed from hypothesis to laboratory experiments and is now being investigated in randomized, controlled clinical trials. The potential benefits of IAD are an improvement in the ADT adverse event profile normally associated with CAD therapy, an increase in the patient’s overall QoL, and a prolongation of the time taken for the tumor to become androgen independent [401]. The whole question of allowing testosterone therapy for androgen deficient men with a history of prostate cancer is addressed by Committee 14.

f) Conclusions and Recommendations
Most endocrine-related health outcomes are similar after surgical versus primary hormonal therapy [399] (LOE 3). Adverse effects of ADT often mimic testosterone deficiency due to other causes. Symptoms such as hot flashes and sexual effects significantly affect quality of life [402] (LOE 2). We recommend the information comparing surgical and medical ADT is used by physicians and patients when making treatment decisions: Grade C.
We recommend further studies to help physicians carefully weigh the benefits against the morbidity associated with ADT and to optimize the management of adverse effects: Grade C.

II. TESTICULAR CANCER

1. INTRODUCTION

Testicular cancers are mainly germ cell tumors that are classified histopathologically into seminoma, nonseminoma and combined tumors. They account for about 1% of all male cancers [403]. Excellent cure rates have been achieved with greater than a 99% cure rate in the early stages by the standardization of treatment with surgery, radiation and platinum-based chemotherapy [404]. Since testicular cancer affects mostly young men aged 20-40 years, and these patients will survive many decades after successful treatment, the negative impact of the illness and its treatment on their sexual lives should be carefully addressed.

2. SEXUAL DYSFUNCTION

There are numerous studies reporting sexual dysfunction in patients with testicular cancer and after the cancer treatment. Nazareth et al [405] conducted a systematic review of literature from 1966 to 1999 and identified six controlled studies with end point data (table 30). They concluded, with cautions, that patients have increased risk for sexual dysfunction after testicular cancer treatment.

Jonker-Pool et al [406] conducted a meta-analysis of 36 empirical studies from 1975 to 2000 concerning 29 retrospective studies and 7 prospective studies with the mean follow-up of 6.9 years. The mean percentages for different sexual dysfunctions are summarized in table 31 for the entire patient population.

The outcomes of specific treatment modalities for testicular cancer were also analyzed but without comparing the retrospective with prospective data. This was due to the small number of patients in
the prospective studies who reported outcomes specified according to treatment modality (table 32). Obviously, patients’ sexual dysfunction varies after each treatment.

Interestingly, recent studies provide controversial results regarding the sexual function after the testicular cancer treatment. These studies are summarized in table 33.

3. PATHOPHYSIOLOGY

The mechanism of sexual dysfunction associated with testicular cancer and its treatment are complex. The known and proposed theories are summarized in table 34.

4. TREATMENT

Treatment of sexual dysfunction for testicular cancer survivors should follow the same principles as the treatment for patients without a history of testicular cancer. However, it is important to identify the psychological distress of testicular cancer and its treatment on patients and to include psychological therapy. Hormonal abnormalities should be identified and corrected unless there is a contraindication. All men undergoing orchectomy should be offered the option of testicular implantation and the realistic expectations of the testicular implantation should be discussed with the patients [413]. Because the

<table>
<thead>
<tr>
<th>Sexual Dysfunction</th>
<th>OR</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Libido</td>
<td>1.75</td>
<td>Study Source: 6 controlled studies. Population: 709 patients, 543 control</td>
</tr>
<tr>
<td>ED</td>
<td>2.47</td>
<td>Follow up: &gt; 2 years. LOE: 3</td>
</tr>
<tr>
<td>↓ Orgasm</td>
<td>4.62</td>
<td>Pitfalls of the Studies: poor design, poor response rates, inconsistency in outcome</td>
</tr>
<tr>
<td>EjD</td>
<td>28.57</td>
<td>me</td>
</tr>
</tbody>
</table>
### Table 33: Sexual function after testicular cancer treatment – recent data [404, 407, 408]

<table>
<thead>
<tr>
<th>Authors</th>
<th>Total patients</th>
<th>Evaluation</th>
<th>Testicular Cancer Treatment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incrocci et al.</td>
<td>123</td>
<td>sexual interest, sexual activity, sexual pleasure, ED</td>
<td>SL</td>
<td>CT</td>
</tr>
<tr>
<td>Lackner et al.</td>
<td>53</td>
<td>IIEF – EF scores</td>
<td>28</td>
<td>27.5</td>
</tr>
<tr>
<td>Wiechno et al. 2007</td>
<td>326</td>
<td>ED with IIEF – EF scores &lt; 22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 34: Pathophysiology of sexual dysfunction after testicular cancer treatment [403, 404, 405, 406, 407, 408, 410, 411, 412, 413]

<table>
<thead>
<tr>
<th>Theory</th>
<th>Rational</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve damage</td>
<td>EjD occurs in almost 100% of patients with bilateral radical RPLND due to the damage to the postganglionic nerves of the hypogastric plexus. Template RPLND with the nerve-sparing techniques can preserve the ejaculatory function. EjD can still occur in about 10-20% of patients after the use of current RPLND techniques[406, 409, 403]. More patients now have retroperitoneal surgery to debulk residual disease, and may end up with EjD because nerve-sparing is less effective in this context. [410] LOE: 3-4</td>
<td>It is suggested that RT could damage small blood vessels causing ED[405], but it is not known whether reported EjD after RT to bilateral para-aortic and ipsilateral hemipelvis to treat seminoma is associated with nerve damage[406].</td>
</tr>
<tr>
<td>Hormonal disturbance</td>
<td>Testicular cancer can cause hormonal disturbances with effects on gonadal function that independently influence sexual function[405]. In a cohort of 326 patients with cancer free &gt; 2 years, 55% and 49% of patients had elevated LH and FSH; 15% of patients had decreased testosterone and 7% of patients had abnormal estradiol levels. The correlation analysis revealed elevated LH and abnormal estradiol were significantly associated with sexual dysfunction[404]. LOE: 3</td>
<td>Platinum-based chemotherapy may contribute to the long term increase in gonadotropins and decrease in testosterone levels[411, 412]. However, a retrospectively study in 53 patients with a median following up &gt; 14 months found that chemotherapy for testicular cancer has no greater risk of developing a hormonal disorder than those following a surveillance strategy[408].</td>
</tr>
<tr>
<td>Body imaging effect</td>
<td>Correlation study revealed that changes in body image are statistically significant in association with negative impact on patients’ sexual life[407]. The appearance of normal male scrotum is important and orchiectomy per se can affect psychosexual function[413]. LOE: 3-4</td>
<td>Body image has been reported improved after testicular prosthesis implantation[403], but it is not known whether this would also significantly improve their sexual life.</td>
</tr>
<tr>
<td>Psychological effect</td>
<td>In a cohort of 326 patients with cancer free &gt; 2 years, more than 27% of patients had abnormal anxiety levels and more than 15% of patients had depression[404]. The symbolic nature of the testicular cancer in young men apparently will cause psychological distress[405], LOE: 3-4</td>
<td>There was no study specifically examining the interactions between psychological distress and sexual dysfunction in patients after testicular cancer treatment.</td>
</tr>
</tbody>
</table>
fertility outcome in testicular cancer patients varies so much between individuals, and because ultimate treatments are not always predictable at diagnosis, routine sperm banking is recommended before beginning chemotherapy or pelvic radiotherapy [414].

5. PREVENTION

Modified retroperitoneal lymph nodes dissection (RPLND) with nerve sparing surgery has proved to be and will continue, if indicated, to be the most effective preventive strategy to avoid EjD. Early psychological counseling should include accurate information about the sexual risks after specific treatment and psycho-sexual vulnerability that may evolve due to the intrinsic actual and symbolic danger of a genital tumor at a relatively young age. Study has shown that patients with testicular cancer who suffered sexual dysfunction reported extremely high needs for information and support [415]. Unfortunately, the latter was lacking for more than half of the patients both during cancer treatment and at the 5.9 year follow-up. Adequate information and support may prevent or reduce sexual anxiety and suffering.

6. CONCLUSION

With some conflicting studies, available evidence indicates that sexual dysfunction affects some patients after testicular cancer treatment. Higher level evidence is needed involving larger prospective controlled studies using standardized instruments and measures of sexual function before and after the treatment of testicular cancer. Nerve damage during the RPLND surgery is proven to be the responsible, yet preventable etiology in most cases for EjD. Hormonal disturbance maybe considered as a correctable cause for sexual dysfunction in some patients. Changes in body image are significantly associated with a negative impact on patients’ sexual life and all men undergoing orchiectomy should be offered the option of testicular implantation [407, 413, 403] (LOE 3/4): Grade C. Early psychological counseling should include accurate information and support regarding sexuality during and after testicular treatment: Grade C.

Routine sperm banking is recommended before beginning chemotherapy or pelvic radiotherapy; Grade C

III PENILE CANCER

1. INTRODUCTION

Penile cancer (PC) is rare in men in the USA and Europe, and accounts for 0.4-0.6% of all malignant diseases in men in these regions. However, it is a substantial health problem in developing countries, and can constitute up to 10% of malignancies in men in some African and South American countries [416]. In urban India, the age adjusted incidence rates vary from 0.7 to 2.3 per 100 000 people in the population-based cancer registries, and in rural India, the rate is three per 100 000 people - more than 6% of all malignant diseases in men [417]. The lowest incidence of PC has been reported in Jews [418]. It is a disease of older men, but is not unusual in younger men and has also been reported in children [419].

2. EFFECTS ON SEXUAL FUNCTION

Of all urogenital cancers, the one that most obviously jeopardizes sexual function is PC. It is an especially distressing disease because of its serious physical and psychosexual consequences. The conventional treatment for this cancer is partial or total penile amputation, radiation- or laser therapy. It appears that most patients can still enjoy a sexual life if laser treatment is used [420,421]. More invasive procedures reduce this likelihood [422]. If the lesion is early and noninvasive, conservative treatment with local resection, Mohs micrographic surgery, topical chemotherapy, external beam radiotherapy, brachytherapy, cryosurgery, or laser therapy can be used, with only marginal compromise of sexual function and satisfaction [423,424,425,426,427].

In partial penectomy, in spite of a reduction in the penile length, vaginal penetration is frequently possible as is the ability to reach orgasm and ejaculation. The main reason for not resuming sexual intercourse appeared to be related to feelings of shame owing to the small penile size and absence of glans penis found in 50% of sexually abstinent patients [422].

If total penectomy is necessary, the reason for not resuming sexual intercourse or masturbation is obvious [428], however, no studies have been found
addressing sexual function outcomes with regards to other sexual activities and satisfaction in these patients.

Surgical complications may also compromise resumption of sexual activity after amputation. Meatal stricture is the most frequent complication after partial penectomy. Excessive penile shaft skin has not been described as a complication; keeping it may give the post penectomy phallus an appearance of a short uncircumcised, but normal, penis. However, the excessive skin may interfere with function and require excision.

Few reviews have dealt with the quality of life and, in particular, sexual function of patients treated for PC. Table 35 shows the most relevant studies.

3. MANAGEMENT OF PC RELATED SEXUAL DYSFUNCTIONS

Given that PC most frequently appears later in life, some patients may develop ED after definitive treatment. This can be managed with current therapies, regardless of the therapeutic method used for the malignancy. The studies shown in Table 35 confirm that a high percentage of patients with partial penectomy maintain sexual function. This suggests that adequate follow-up possibly with a multidisciplinary team may improve sexual desire, function and satisfaction after partial penectomy, although this remains to be demonstrated [422].

4. SUMMARY

- Prevalence of PC varies widely between regions and races.
- Although PC is amenable for primary and secondary prevention, it has been ignored as a public health issue.
- Factors implicated in its etiology and suitable for intervention are: circumcision and poor genital hygiene.
- Conservative treatment, when feasible, should be aimed to preserve as much of the penis, hence sexual identity and activity.
- Partial penectomy seems to have a lesser impact on sexual function than expected.
- A proper follow up, including a multidisciplinary team should be considered, to optimize the outcome.
- The gap between “western” and “developing” countries, with regards to diagnose, treatment and outcomes, completely falls within the scope of this Consultation on Sexual Dysfunctions, raising the need for an effort on education on how to prevent PC incidence.

5. RECOMMENDATIONS

Pre-treatment education is recommended to minimize psychologically-based sexual dysfunction. Include confirmation that intercourse can occur with a short penis: Grade C.

Since penile cancer is a curable condition when diagnosis and treatment is implemented early, preservation of maximal penile shaft is advocated so as to allow continual sexual function [428, 423, 422]: Grade B.

Whether penectomy is partial or complete, multidisciplinary follow-up including clinicians trained in sex therapy is recommended: Grade C.

E. CANCER IN MEN AND WOMEN

1. PELVIC (NON GYNECOLOGICAL)

a) Introduction

Bladder cancer, usually transitional cell arising from the bladder mucosa, is the fourth most common cancer in men, although it is three times less frequent in women. The approximately two-thirds of tumors which do not spread beyond the bladder lining are treated locally, even when recurrent. When there is invasion of the bladder wall, radical cystectomy is indicated. Bladder cancer can spread locally into the prostate, vagina, or uterus. It may also metastasize to distant organs. Currently, metastatic bladder cancer cannot be eradicated. Regardless of the type of treatment, psychological concerns of cancer recurrence or of “being unclean” may add to sexual dysfunction from nerve damage and loss of sexual organs.

b) Intravesical Treatment

Superficial cancer is removed during cystoscopy, typically followed by chemotherapy or immunotherapy with Bacille Calmette-Juérin (BCG) instilled into the bladder [429]. There is little research on the impact of treatment for superficial cancer on sexual function in men or women. Intravesical therapy is typically followed by a week of pelvic pain [430] and sometimes temporary ED [431]. One small, cross-sectional comparative study suggested men and women receiving intravesical chemotherapy have similar sexual function as those receiving only cystoscopic tumor removal [432].

c) Pelvic Radiotherapy

Definitive radiotherapy is rarely used because long-term survival is much poorer than after radical cystectomy [433]. Radiation also typically decreases bladder capacity, causing problems...
Table 35: Sexual Function after Penile Cancer Treatment [422, 423, 428]

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Sample size (range)</th>
<th>Median age (range)</th>
<th>Treatment modality</th>
<th>Assessment</th>
<th>Follow-up: median (range)</th>
<th>Results</th>
<th>Conclusions</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Ancona/ 1997[428]</td>
<td>14 (50,5 (37-70))</td>
<td>Partial penectomy</td>
<td>Questionnaires OSFQ*</td>
<td>Median 11.5 months (range: 6-72)</td>
<td>64% overall sexual function, sexual interest, satisfaction remained normal or slightly decreased. Masculine self-image and partner’s relationship unchanged.</td>
<td>QoL, including sexual function is retained after partial penectomy in a majority</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Windahl/ 2004[423]</td>
<td>40 (64 (34-90))</td>
<td>Laser Structured face-to-face interview</td>
<td>Median 3 years (range 6 months-15 years)</td>
<td>72% unaltered EF**; 22% decreased EF; 6% improved EF. 50% satisfied very satisfied with their sexual life; 10% had dyspareunia.</td>
<td>Laser treatment of localized penile carcinoma preserves the penis and generally provides satisfactory sexual function and cosmetic results.</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Romero/ 2005[422]</td>
<td>18 (52(35-86))</td>
<td>Partial penectomy</td>
<td>Personal interview and IIEF***</td>
<td>23.5 months (range 6-62)</td>
<td>55.6% erection that allowed intercourse; 66.7% sustained the same and level of sexual desire; 72.2% continued to have ejaculation and orgasm with sexual stimulation or intercourse. Only 33.3% maintained preoperative sexual intercourse frequency and were satisfied with their sexual relationships with their partners and their overall sex life</td>
<td>Preoperative and postoperative scores were statistically different for all domains of sexual function after partial penectomy.</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

*OSFQ= Overall Sexual Function Questionnaire (Domains: Sexual Interest, Sexual Ability, Sexual Satisfaction, Relationship with Partner, Sexual Identity, Frequency of Coitus)

**EF= Erectile Function; ***IIEF= International Index of Erectile Function;
with urinary frequency, urgency, and incontinence. However, some small retrospective studies found male sexual function to be less impaired after definitive radiotherapy than after radical cystectomy [434,435,436] (LOE 4). Definitive radiotherapy remains an option for patients who refuse radical cystectomy or whose health makes them poor surgical candidates.

d) Radical Cystectomy and Nerve Sparing to Preserve Erectile Function

Standard radical cystectomy also removes the prostate, seminal vesicles and pelvic lymph nodes. When cancer is multi-focal, especially when it is present in the bladder neck or urethra, the entire urethra may be removed. Recently, the need for urethrectomy has been challenged and in the future, the procedure may be done less often [437]. Although orgasm is preserved, it is different due to the loss of ejaculate after radical cystectomy. ED is usual.

Nerve sparing techniques to preserve erectile function after radical cystectomy were suggested by Walsh and Mostwin in 1984 [438]. To provide a context for the success of nerve sparing cystectomy, Schover et al [439] interviewed 112 men about to undergo radical cystectomy, with a mean age of 63 years. Seventy three men provided follow-up data 13 months post surgery: sexual inactivity increased from 20% before cystectomy to 50% at follow-up. Preoperatively, 35% had ED vs. 94% at follow-up. Table 36 summarizes the outcome of nerve-sparing cystectomy. Some procedures remove the whole prostate, attempting to avoid the neurovascular bundles lateral to its surface [438,440]. Other modifications include sparing the prostate, seminal vesicles and vasa deferentia so that both erectile function and ejaculation and fertility can be preserved [441]. Originally intended only for benign bladder conditions, this procedure has been adopted by some urologic oncologists for men with high risk superficial disease. It remains controversial since invasive transitional cell carcinoma is found at the apex of the prostate in 17-48% of men and another 29-40% have occult adenocarcinoma of the prostate found in the pathology specimens, which had not been suspected before cystectomy [442,443,444]. Although nerve-sparing appears to reduce the risk of ED, particularly if the entire prostate is spared, the risk of local recurrence is also elevated (LOE 4). A recent review of 252 cancer patients who had some form of prostate-sparing cystectomy also found a suspiciously high rate of distant metastases [444]. Recovery of erectile function may be enhanced after nerve sparing prostatectomy during radical cystectomy by the use of penile injection therapy or the oral phosphodiesterase inhibitors within a few weeks of surgery. This sexual rehabilitation may also include a counseling component, which was shown to improve patient satisfaction with treatment outcome [448].

e) Types of Urinary Diversions

It is presumed that having urinary continence will increase the likelihood of remaining sexually active. Unfortunately, it is impossible to conduct a randomized trial comparing ileal conduits with the two major competing diversions. The continent cutaneous diversion, often called the Kock or

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Procedures</th>
<th>Erectile Function</th>
<th>Other Outcomes</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walsh &amp; Mostwin, 1984[438]</td>
<td>11</td>
<td>Radical cystectomy sparing nerve bundles</td>
<td>67% “able to have intercourse”</td>
<td>--</td>
<td>4</td>
</tr>
<tr>
<td>Zippe et al., 2004a[445]</td>
<td>16 NS 33 NNS</td>
<td>Radical cystectomy sparing nerve bundles</td>
<td>91% had ED at mean 48-mo. FU</td>
<td>Only 9% could use PDE5-inhibitors successfully</td>
<td>4</td>
</tr>
<tr>
<td>Hekal et al., 2008[446]</td>
<td>21 NS 24 NNS</td>
<td>Radical cystectomy sparing nerve bundles</td>
<td>0% ED 42% ED</td>
<td>Sildenafil worked in 21% with NS but none with NNS</td>
<td>4</td>
</tr>
<tr>
<td>Puppo et al., 2008[440]</td>
<td>37</td>
<td>Intrafascial prostatectomy, sparing SV, VD, nerve bundles</td>
<td>Only 14% had moderate/severe ED</td>
<td>No loss of urinary continence</td>
<td>4</td>
</tr>
<tr>
<td>Nieuwenhuijzen et al., 2005[441]</td>
<td>40</td>
<td>Spared prostate, SV, VD, and nerve bundles</td>
<td>Only 23% had ED</td>
<td>Was 42 mo. FU, but subjective criteria used</td>
<td>4</td>
</tr>
<tr>
<td>Davila et al., 2007[447]</td>
<td>15</td>
<td>Spared apex of prostate Spared whole prostate</td>
<td>IIEF EF score 20 IIEF EF score 30</td>
<td>At 30 months, excess local recurrence rates</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviations: NS: nerve-sparing; NNS: non nerve-sparing; ED: erectile dysfunction; FU: follow-up; PED5-Inhibitors: phosphodiesterase5-inhibitors; SV: seminal vesicles; VD: vasa deferentia; IIEF: International Index of Erectile Function
Indiana pouch, has an internal reservoir for urine that is drained every few hours by putting a catheter into a smaller, “continent” ostomy opening on the abdomen. The continent ostomy requires careful adherence to a schedule of emptying the pouch with a catheter, and if leakage occurs, it is difficult to manage. A neobladder is the second option. The ureters are connected to a new bladder reservoir, created from a bowel segment, which is also attached to the remaining urethra so that urination can occur through the urethral opening for men or women. A major drawback of the neobladder is that many patients have some stress incontinence during the day and more severe lack of urinary control during sleep [433]. Since surgery to create a neobladder is longer and more complex than that to make an ileal conduit, reconstruction is significantly more common in patients who are younger, male, Caucasian, well-educated, treated at an academic center, and with less comorbidity [449]. Given the differing pros and cons of the three diversions, a recent review of the literature found no clear evidence for superiority of one method over another in terms of general quality of life (LOE: 3) [450] in agreement with Table 37 which summarizes evidence of impact of varying urinary diversions on sexual function or activity.

f) Modifications to Female Radical Cystectomy

Radical cystectomy has typically included removing the uterus, ovaries, and front part of the vagina along with node dissection. Because bladder cancer becomes more common with age, many women may not be sexually active at diagnosis. One older study [456] identified only 9 sexually active women out of 39 who had received radical cystectomy during a 38-month period. In these women, the vagina had been repaired without any tissue grafting, resulting in a narrowed or shallower vagina. Nevertheless, therapy including lubricants, topical estrogen, dilators, counseling, and pelvic muscle relaxation helped 7 to resume intercourse with no or only mild discomfort. Orgasmic response remains intact after radical cystectomy.

For women with cancer at the bladder neck urethrectomy is usually necessary and prevents construction of a neobladder [444]. Direct sexual consequences of urethrectomy have not been studied in women.

Surgeons have also tried to use more limited resection and nerve-sparing to improve women’s quality of life after radical cystectomy. Reports in the literature have been limited to small case series. One concern has been that traditional cystectomy may cause clitoral numbness [457]. A study of sensory thresholds in 16 women after radical pelvic surgery showed, however, that sensation was only reduced in the area of the proximal urethra, whereas sensation in the distal urethra was intact [458]. The pelvic nerve plexus that mediates sensation in the upper urethra is often damaged in surgery, but the

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Procedures</th>
<th>Erectile Function</th>
<th>Other Outcomes</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bjerre et al., 1998[451]</td>
<td>27</td>
<td>Ileal conduit</td>
<td>81% of men had ED</td>
<td>26% sexually active at FU, less likely if .68 years</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>Cutaneous diversion</td>
<td>no difference by group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Henningsohn et al., 2002a[452]</td>
<td>95</td>
<td>Cutaneous diversion</td>
<td>94% ED at 1-year FU</td>
<td>No difference from controls in QOL</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>112</td>
<td>Healthy controls</td>
<td>40% ED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zippe et al., 2004[445]</td>
<td>8</td>
<td>Ileal conduit</td>
<td>86% at 4-year FU, no difference by group</td>
<td>Only 52% of men with ED sought help</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Cutaneous diversion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>Neobladder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kikuchi et al., 2006[453]</td>
<td>13</td>
<td>Ileal conduit</td>
<td>100% had ED, no difference by group</td>
<td>Desire for sex also low</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>Cutaneous diversion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Neobladder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studer et al., 2006[454]</td>
<td>442</td>
<td>Neobladder</td>
<td>78% ED</td>
<td>15% successful use of medical therapy for ED</td>
<td>4</td>
</tr>
<tr>
<td>Gilbert et al., 2007[432]</td>
<td>60</td>
<td>Ileal conduit</td>
<td>Both groups had poor sexual function</td>
<td>Continence worse if neobladder</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>93</td>
<td>Neobladder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frich et al., 2008[455]</td>
<td>37</td>
<td>Ileal conduit</td>
<td>81% had ED at 2- to 5-year FU, no difference by group</td>
<td>Continence worse if neobladder</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>Cutaneous diversion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>Neobladder</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ED: erectile dysfunction; FU: follow-up
pudendal nerve, which innervates the lower urethra, clitoris, and outer third of the vagina, is not in the surgical field. As in men, type of urinary diversion appears to have little impact on women’s sexual function after radical cystectomy [457, 431]. The Cleveland Clinic group [459,460] have described a technique to preserve the neurovascular bundles on the anterior vaginal wall by using careful sharp dissection to separate it from the urinary bladder. It is unclear whether sparing the neurovascular bundles can help even postmenopausal women to have better blood flow into the vaginal walls with sexual arousal, and therefore more normal vaginal lubrication, or if the benefit is due to sparing more of the anterior wall so that vaginal size remains optimal. It is also important to acknowledge a selection bias, in that women more interested in maintaining sexual activity may opt for nerve-sparing cystectomy. Retrospective comparisons of women who choose one procedure vs. another may not be very enlightening. Table 38 summarizes different cystectomy types and their impact on female sexuality. Operations that spare neurovascular bundles and vaginal tissue may help preserve sexual function (LOE 4).

g) Recommendations/ conclusions

Research is needed on the sexual impact of repeated treatment for superficial tumors with cystoscopy/intravesical chemotherapy: Grade C.

With cystectomy, type of urinary diversion does not predict sexual activity or function [451, 452, 457, 453, 455, 461]: Grade C.

Nerve-sparing cystectomy has limited impact on erectile function [445, 446] (LOE 4). Grade C.

Prostate-sparing cystectomy reduces ED but also increase local and distant recurrence rates [440, 447] (LOE 4): Grade C.

Table 38: Female Sexual Function and Radical Cystectomy [457, 459, 461]

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Procedures</th>
<th>Sexual Function</th>
<th>Other Outcomes</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zippe et al., 2004[457]</td>
<td>10</td>
<td>Cutaneous diversion</td>
<td>At 2-year FU no difference by group, 48% inactive, 37% low desire, 22% dyspareunia, 45% inorgasmic</td>
<td>Classic operative technique, no NS</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Neobladder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volkmer et al., 2004[461]</td>
<td>44</td>
<td>Neobladder, NNS</td>
<td>39% stayed sexually active and 65% of this group said better sex than before cystectomy</td>
<td>Classic operative technique, no NS; if &gt; age 60 at time of surgery, had benign disease, and a sexual partner, better sexual functioning</td>
<td>4</td>
</tr>
<tr>
<td>Bhatt et al., 2006[459]</td>
<td>6</td>
<td>NS</td>
<td>Preserved FSFI score</td>
<td>Anterior vaginal wall and neurovascular bundle spared</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>NNS</td>
<td>Big drop in FSFI score</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NS: nerve-sparing; NNS: non nerve-sparing; FU: follow-up; FSFI: Female Sexual Function Index

2. COLORECTAL CANCER

a) Introduction

Treatment for colorectal cancer has the potential to interfere with sexuality in a variety of ways. Despite surveys indicating intact quality of life after colorectal cancer, specific assessment of sexuality consistently reveals high percentages of men and women discontinuing sexual activity or experiencing sexual dysfunction [462,463,464,465]. Furthermore, in prospective cohorts, other psychosocial and physical symptoms improve over time while sexual function remains impaired [462, 466,467,468]. When thirty long-term survivors of colorectal cancer were interviewed, the two most distressing problems associated with their cancer were pain and sexual dysfunction.

If the tumor is in the rectum, cancer treatments are more likely to impair sexual function. In a recent comparison, 86% of survivors of rectal tumors had sexual dysfunction compared with 39% of colon cancer survivors [469]. Intuitively one would expect a colostomy to impair psychosexual functioning more severely than surgeries that preserve the anus. In a retrospective survey of 476 cancer survivors who had lived a mean of 10 years with a colostomy, complaints about interference with sex were common. Fifteen percent of cancer survivors had become sexually inactive. ED was present in 79% of men [470]. Interestingly, 71% of those remaining active were satisfied with their sex lives. Unfortunately, surgery that reconnects the colon and rectum typically leaves survivors with bowel frequency and some incontinence. In fact a recent Cochrane review of 8 published studies found no clear advantage of...
sphincter-saving surgical procedures over colostomy on quality of life [471].

b) Assessing Sexual Problems after Colorectal Cancer Treatment

Two major quality-of-life inventories have been validated for patients with colorectal cancer, the EORTC QLQ-CR38 [472] and the FACT-C [473], each with a few items assessing sexual function. It remains difficult to compare rates and types of dysfunction across studies, however, because some researchers use idiosyncratic questionnaires and some use the more detailed International Index of Erectile Function [463, 474, 475] and Female Sexual Function Index [476, 463] scales, which measure sexual function in any adult population. Some general conclusions can be drawn, however.

c) Rates and Types of Sexual Dysfunction

Table 39 lists treatments for colorectal cancer, their hypothesized impact on sexual dysfunction, and evidence in the literature. Tables 39 and 40 summarize research studies that report the prevalence of sexual dysfunctions in men and women treated for colorectal cancer. Unfortunately researchers have focused on the physiological impact of cancer treatment without exploring the relationship between sexual function or satisfaction and other indices of quality of life [471]. It is probable that emotional variables, including premorbid psychosocial adjustment, social support, and socioeconomic status interact with physiological impairment in determining sexual outcomes. Even from a physiological standpoint, many men in the age group at high risk for colorectal cancer already have erection problems related to comorbidities that damage the penile vascular system and/or autonomic nerves, such as obesity, diabetes, smoking, or alcohol abuse [477, 463]. Some surveys have found older age to be a better predictor of sexual function than a specific type of colorectal cancer treatment [478, 479].

Although a number of surveys have concluded that men are more likely to have sexual dysfunction than women after treatment for rectal cancer [478, 477, 481, 494], few data are available for women. Many elderly women are not sexually active at the time of cancer diagnosis [477, 463, 478, 495]. Typically they lack a partner or their partner is ill or has erectile dysfunction. Women also appear more likely than men to give up sexual activity after cancer treatment [477, 463]. For those women who remain sexually active (Table 41), prevalence and types of problems appear similar to those in women treated for other pelvic tumors, such as cancer of the bladder, ovaries, or uterus [456].

Finally, a greater proportion of women in the cohorts refuse to complete questionnaires that ask about their sexuality. As Table 42 illustrates, in six recent surveys that provided information on participation from men vs. women in completing sexual items, response rates for men ranged from 52% to 100% compared to 27% to 70% for women [477, 463, 488, 485, 486, 479].

d) Anal Cancer and Sexual Function

Unlike colorectal cancer, anal cancer is a type of skin cancer that is strongly related to the human papilloma virus (HPV). Risk for these lesions increases when a person’s immune function is compromised: from Human Immunodeficiency Virus (HIV) [497], chemotherapy, immunosuppressive drugs for example. Since the advent of HIV, rates of squamous cell carcinoma of the anus have been increasing. Research has not yet examined the impact of anal cancer on sexual behavior or satisfaction. Since treatment usually involves simultaneous local radiation therapy and chemotherapy [498], receptive anal intercourse would probably become painful and alternative types of sexual stimulation might need to be substituted. Radiation induced vaginal stenosis is also likely.

e) Recommendations / conclusions

Avoid abdominoperineal resection if possible, since it has a worse impact on sexual function [463, 479, 482] (LOE 4): Grade C.

The combination of radiotherapy and surgery leads to more dysfunction than either treatment alone [464, 467, 463, 468] (LOE 2): Grade B.

Nerve-sparing with a laparoscopic total meso-rectal excision is promising in preserving erections [486, 489] (LOE 4): Grade C.

II. HEMATOPOIETIC CELL TRANSPLANTATION

1. INTRODUCTION

Over the past 20 years survival after hematopoietic cell transplantation has increased dramatically, making quality of life more salientse [499]. The typical preparation for transplantation of bone marrow or of peripheral blood stem cells is intensive chemotherapy and/or whole body irradiation, destroying the patient’s bone marrow so that no new blood cells can be made. Transplanted bone marrow or blood stem cells then restore the patient’s ability to produce new blood cells. The transplant material may be gathered before preparation from the patient (autologous transplantation) or is obtained from a donor matched to the recipient on human leucocytic antigens (HLA), proteins on the surface of blood cells (allogeneic transplantation). Increasingly, less intensive regimens are used, followed by infusing blood stem cells and using growth stimulating factors
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Hypothesized Impact</th>
<th>Evidence in Men</th>
<th>LOE in men</th>
<th>Evidence in Women</th>
<th>LOE in women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominoperineal resection (APR), complete removal of rectum and anus with creation of colostomy</td>
<td>ED from damage to inferior hypogastric nerve plexus and prostatic nerve plexus, diminished arterial flow to penis[480]; Damage to emission when sympathetic nerve pathways in the superior hypogastric nerve are interrupted higher in the pelvis, orgasm preserved but no ejaculate[481]; Partial resection of posterior vaginal or BSO can cause dyspareunia. Impact of colostomy on sexual activity[463]</td>
<td>Retrospective cohort studies: Male sexual problems worse after APR than other rectal surgeries [463, 479, 482]</td>
<td>3</td>
<td>Female sexual problems, especially vaginal dryness and tightness [463]</td>
<td>4</td>
</tr>
<tr>
<td>Low anterior resection (LAR) of the rectum with reanastomosis, sometimes including J-pouch to minimize urgency and incontinence</td>
<td>May be better than APR because entire rectum is not mobilized, but if done with older, blunt dissection, may be more likely to damage nerves involved in erection. Need to compare LAR and APR when both done using TME. Also no colostomy.</td>
<td>Male sexual problems better after LAR than APR, retrospective cohorts [483, 477]</td>
<td>4</td>
<td>No evidence</td>
<td>4</td>
</tr>
<tr>
<td>Total Mesorectal Excision (TME) mobilizing the whole rectum using sharp dissection from the pelvis before removing it. Can be done with LAR or APR.</td>
<td>Easier to identify and spare autonomic nerves involved in erectile function and antegrade ejaculation of semen; May also spare nerves important to female sexual function. Minimizes damage to pelvic arteries and veins[484]</td>
<td>Rates of ED after TME still range from 50% to 90%[463, 465, 477, 485]; Slight advantage for TME over older techniques in ED and antegrade ejaculation, but small, historical control[486]</td>
<td>4</td>
<td>In one very small cohort, women who had total mesorectal excision still had more sexual dysfunction than women with resection higher in the pelvis for colon cancer[487]</td>
<td>4</td>
</tr>
<tr>
<td>Laparoscopic TME</td>
<td>Laparoscopic approach may facilitate sparing of nerves involved in sexual function.</td>
<td>RCT laparoscopic vs. open rectal cancer surgery: More ED with former especially if surgery included complications or a conversion to an open procedure or was done with TME[488]; However, case series of laparoscopic TME for 48 men caused NO changes in IIEF scores Liang et al 2008 Smaller case series of laparoscopic TME report similar rates of preserved erections to those from open cases (75% and 58%, respectively[489, 491, 492].</td>
<td>4</td>
<td>Case series of laparoscopic TME in 44 women caused NO changes in FSFI scores[490]</td>
<td>4</td>
</tr>
</tbody>
</table>

| Table 39: Colorectal Cancer Treatments and Their Impact on Sexual Function [463, 464, 465, 467, 468, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493] |
(usually granulocyte colony-stimulating factor) to increase stem cell production [499]. New techniques allow stem cells to be purified from the patient’s own blood, reducing the chance that a transplant will contain cancer cells [500]. Peripheral cells may also come from a donor or from umbilical cord blood that has been frozen soon after a baby’s birth. Since few people have stored their own cord blood, a matched donor is typically used. Cord blood is used most often for children, since it contains a limited number of stem cells [500].

2. GRAFT VERSUS HOST DISEASE

When a transplant is allogeneic, some degree of graft versus host disease (GVHD) often results, especially if the donor and patient are not well matched. The immune system attacks the patient’s own cells as if they were foreign, causing a variety of symptoms. Severe GVHD can be debilitating, but some degree of GVHD may actually mobilize the immune system to kill off any remaining cancer cells [501]. If peripheral stem cells from a donor are used along with a stimulating factor, chronic GVHD is especially common [502].

### Table 39: Colorectal Cancer Treatments and Their Impact on Sexual Function [463, 464, 465, 467, 468, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493] (continued)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Hypothesized Impact</th>
<th>Evidence in Men</th>
<th>Evidence in Women</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy pre- or post-op</td>
<td>Radiation therapy could exacerbate ED or orgasmic dysfunction by damaging pelvic vascular bed, and subsequent damage to nerves Radiation may cause vaginal fibrosis and stenosis</td>
<td>Preop radiation created more ED, dry orgasm, and sexual inactivity than surgery alone, prospective observational case control (201 men)[464]; Adjuvant radiotherapy exacerbated male sexual dysfunction in retrospective cohorts[463, 467]; RCT of 990 with TME ± brief pre-operative radiotherapy[468], more problems with erection and ejaculation</td>
<td>2</td>
<td>Adjuvant radiotherapy exacerbated female sexual dysfunction after rectal surgery [463]; Also in RCTI [468]</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Chemotherapy would not be expected to have a major impact on male sexual function, but could impair female function by causing abrupt ovarian failure</td>
<td>Chemotherapy for colorectal cancer does not appear to exacerbate post-surgical sexual dysfunction in men[464, 478, 479]; RCT of short course preop radiotherapy vs. chemoradiation, 68 men, no difference at 1 year in sexual function[493]</td>
<td>4</td>
<td>RCT of short course preop radiotherapy vs. chemoradiation, 50 women, no difference at 1 year in sexual function[493]</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- APR: abdominoperineal resection
- HAR: high anterior resection
- LAR: low anterior resection
- TME: total mesenteral resection
- Lap: laparoscopic
- ED: erectile dysfunction
- RCT: randomized controlled trial

### 3. PHYSIOLOGICAL SIDE EFFECTS OF TRANSPANTATION ON SEXUAL FUNCTION, AND PREVALENCE AND TYPES OF PROBLEMS

Table 43 illustrates how the physiological impacts of hematopoietic transplantation affect sexual function. Tables 44 and 45 summarize literature in last 10 years reporting the prevalence of major types of sexual dysfunction for men and women after transplantation. Most studies have small numbers of participants. Only two are prospective studies with baseline measures of pre-transplantation sexual function, and only two include comparison groups that have not been transplanted. Limited conclusions can be drawn. Sexual function is affected more severely for women than for men. Although some recovery of sexual activity and pleasure occurs in the first two years after transplantation, survivors remain more likely than controls to experience sexual dysfunction even 5 to 10 years after their cancer treatment. The relative contribution of different physiological and psychological factors to these problems is still not adequately studied, but the presence of significant sexual problems after conditioning and
<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Response Rate</th>
<th>Age</th>
<th>Months Since Surgery</th>
<th>Type of Surgery (N)</th>
<th>Nerve-Sparing</th>
<th>Pre-Op XRT</th>
<th>Post-Op Adjuvant TX</th>
<th>Rate of Sexual Problems</th>
<th>Dry Orgasm</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cöl et al., 2006[474]</td>
<td>91</td>
<td>--</td>
<td>Mean=56</td>
<td>Mean=31</td>
<td>APR: 38% LAR: 52% HAR: 10%</td>
<td>--</td>
<td>0%</td>
<td>100%</td>
<td>See IIEF scores</td>
<td>20%</td>
<td>--</td>
</tr>
<tr>
<td>Vironen et al., 2006[477]</td>
<td>52</td>
<td>69%</td>
<td>Mean=68</td>
<td>Md=21</td>
<td>APR: 75% LAR: 59% HAR: 53%</td>
<td>Yes, if possible</td>
<td>66%</td>
<td>18%</td>
<td>63%</td>
<td>59%</td>
<td>23%</td>
</tr>
<tr>
<td>Ameda et al., 2005[465]</td>
<td>28</td>
<td>77%</td>
<td>Mean=66</td>
<td>Md=60</td>
<td>APR: 54% LAR: 46%</td>
<td>Yes, if possible</td>
<td>--</td>
<td>--</td>
<td>64%</td>
<td>88%</td>
<td>68%</td>
</tr>
<tr>
<td>Hendren et al., 2005[463]</td>
<td>99</td>
<td>81%</td>
<td>Md=68</td>
<td>Md=58</td>
<td>APR: 33% LAR: 52% HAR: 15%</td>
<td>Yes, if possible</td>
<td>40%</td>
<td>--</td>
<td>69%</td>
<td>90%</td>
<td>42%</td>
</tr>
<tr>
<td>Jayne et al., 2005[488]</td>
<td>128</td>
<td>68%</td>
<td>Mean=65</td>
<td></td>
<td>Lap LAR: 43% Open LAR: 22% Lap HAR: 35%</td>
<td>Yes, if possible</td>
<td>16%</td>
<td>28%</td>
<td>47%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Sterk et al., 2005[496]</td>
<td>36</td>
<td>81%</td>
<td>Md=63</td>
<td>Md=6</td>
<td>TME</td>
<td>--</td>
<td>0%</td>
<td>56%</td>
<td>76%</td>
<td>76%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Abbreviations: APR: abdominoperineal resection
HAR: high anterior resection
LAR: low anterior resection
TME: total mesenteral resection
Lap: laparoscopic
Table 41: Sexual Function in Women after Treatment for Colorectal Cancer [463, 477, 488]

<table>
<thead>
<tr>
<th>Reference</th>
<th>Total N</th>
<th>Response Rate</th>
<th>Age (X±SD)</th>
<th>Mos. Since Surgery</th>
<th>Type of Surgery (N)</th>
<th>Nerve-Sparing</th>
<th>Pre-Op XRT</th>
<th>Post-Op Adjuvant TX</th>
<th>Rate of Sexual Problems</th>
<th>Vaginal Dryness</th>
<th>Dyspareunia</th>
<th>Other</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vironen et al., 2006[477]</td>
<td>30</td>
<td>30%</td>
<td>68</td>
<td>Md=21</td>
<td>APR: 25% LAR: 41% HAR: 7%</td>
<td>Yes, if possible</td>
<td>66%</td>
<td>18%</td>
<td>33%</td>
<td>--</td>
<td>11%</td>
<td>11%*</td>
<td>4</td>
</tr>
<tr>
<td>Hendren et al., 2005[463]</td>
<td>81</td>
<td>70%</td>
<td>Md=68</td>
<td>Md=52</td>
<td>APR: 31% LAR: 14% HAR: 56%</td>
<td>Yes, if possible</td>
<td>38%</td>
<td>--</td>
<td>29%</td>
<td>56%</td>
<td>46%</td>
<td>41%**</td>
<td>4</td>
</tr>
<tr>
<td>Jayne et al., 2005[488]</td>
<td>85</td>
<td>54%</td>
<td>65</td>
<td></td>
<td>Lap LAR: 35% Open LAR: 18% Lap HAR: 47%</td>
<td>Yes, if possible</td>
<td>16%</td>
<td>28%</td>
<td>16%</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>4</td>
</tr>
</tbody>
</table>

*Unable to engage in penetration due to anatomic changes
** Loss of desire
Abbreviations: APR: abdominoperineal resection
HAR: high anterior resection
LAR: low anterior resection
TME: total mesenteral resection
Lap: laparoscopic

Table 42: Response Rates for Sexual Questionnaires: Men vs. Women [463, 477, 479, 486, 488, 496]

<table>
<thead>
<tr>
<th>Reference</th>
<th>Male Response Rate</th>
<th>Female Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jayne et al., 2005[488]</td>
<td>68%</td>
<td>54%</td>
</tr>
<tr>
<td>Vironen et al., 2006[477]</td>
<td>71%</td>
<td>30%</td>
</tr>
<tr>
<td>Hendren et al., 2005[463]</td>
<td>94%</td>
<td>70%</td>
</tr>
<tr>
<td>Schmidt et al., 2005[479]</td>
<td>52%</td>
<td>50%</td>
</tr>
<tr>
<td>Sterk et al., 2005[496]</td>
<td>81%</td>
<td>44%</td>
</tr>
<tr>
<td>Maurer et al., 2001[486]</td>
<td>100%</td>
<td>42%</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Cancer Treatments</td>
<td>Impact on Sexual Function</td>
</tr>
<tr>
<td>-----------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Primary hypogonadism in men</td>
<td>Intensive chemotherapy, especially with alkylating agents; total body irradiation</td>
<td>Loss of desire for sex, ED, reduced semen volume Consider testosterone therapy if ED resistant to phosphodiesterase-5-inhibitors[503, 504].</td>
</tr>
<tr>
<td>Premature ovarian failure (POF) in women</td>
<td>Intensive chemotherapy, especially with alkylating agents, higher dose needed in younger women; after age 35, alkylating chemotherapy drugs typically cause permanent, premature menopause given depleted reserve of primordial follicles. The dose of radiation from TBI is also high enough to lead to premature ovarian failure[505, 506]</td>
<td>Loss of sexual desire, vaginal dryness and dyspareunia all common prior to actual transplantation due to premature ovarian failure from previous cancer treatment. Of 48 premenopausal women preparing for transplantation, 73% already had lost desire for sex and 48% were dissatisfied with their sex lives[507]. In women without specific contraindications to using estrogen replacement, either systemic or local treatments may help in treating vaginal atrophy. If vulvovaginal GVHD is present, 0.05% clobetasol propionate ointment may be added[508]. The safety and efficacy of testosterone therapy after POF is unclear[505]</td>
</tr>
<tr>
<td>Failure to begin puberty in children (male or female)</td>
<td>TBI or the chemotherapy drug busulfan are the most common antecedents of pubertal failure[509]. Direct radiation to the testes given to boys with leukemia to ensure no cancer cells are protected in those glands will prevent puberty. Although puberty is deferred during cancer treatment, or within a few years afterwards[509], a majority of females treated in childhood or adolescence retain sufficient follicles to be fertile, only to have an unusually early menopause[505]. In boys LH and FSH are often slightly elevated, but puberty occurs and testosterone remains in the lower normal range. It is unclear if these mild abnormalities lead to overt sexual dysfunction later in life.</td>
<td>Failure of spontaneous puberty is more common in girls than in boys. It is difficult to estimate the prevalence of failed puberty, since it varies with children's ages, type and dose of chemotherapy, and dose and field of radiation. Often treatments are combined. Reductions in recent years in treatment toxicity also may reduce the rate of gonadal damage.</td>
</tr>
<tr>
<td>Autonomic nerve damage</td>
<td>Neurotoxic types of chemotherapy (vincristine or platinum-based drugs) may cause damage to autonomic nerves, if given in high dosages, but evidence is only anecdotal[510]</td>
<td>May damage erection and/or ejaculation, but not even small cohort studies. No research on potential sexual impact in women.</td>
</tr>
<tr>
<td>Damage to pelvic vascular bed</td>
<td>TBI impairs the vascular supply to penis, vagina and vulva and the vascular supply to their autonomic innervation[511], but no research has examined the sexual consequences. TBI reduces uterine arterial blood flow and inhibits uterine growth, particularly when given before puberty[512] but effects on vaginal lubrication or expansion have not been studied.</td>
<td>May cause erectile dysfunction in men or reduced vaginal lubrication with sexual arousal in women. Much more research is needed. May be role for Phosphodiesterase-5-inhibitors to increase vaginal lubrication in women.</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Cancer Treatments</td>
<td>Impact on Sexual Function</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td><strong>Graft vs. Host Disease (Male)</strong></td>
<td>Contribution of GVHD to male sexual dysfunction has been largely ignored. Case reports of genital GVHD causing inflammation of fascia and penile curvature[513] adherence of foreskin to the glans (phimosis)[514]. GVHD may be one cause of Peyronie’s Disease which affects 3% to 9% of all men[515, 516]. Out of five surveys of sexual function in men and women after hematopoietic cell transplantation, only one[517] included GVHD as a potential factor in sexual problems, finding a correlation with loss of sexual desire and pleasure, and inability to have sex. More recent studies have not investigated GVHD[518, 519, 520, 521]</td>
<td>Penile curvature, pain, and ED, or pain with erection due to failure of foreskin to retract. Men often puzzled and embarrassed by pain with erection and penile curvature, and do not seek medical help. Nelson and colleagues (2008)[515] documented that about half of men with Peyronie’s have high rates of chronic depression that does not decrease with time. It will be important in future research to see if genital GVHD in men is more prevalent than has been suspected.</td>
</tr>
<tr>
<td><strong>Graft vs. Host Disease (Female)</strong></td>
<td>Women with systemic GVHD often have vaginal inflammation and scarring, especially women receiving allogeneic peripheral blood stem cell transplants with growth factors: some 25% to 50% may be affected[522, 508]. Genital GVHD begins about 9 months post-transplantation with systemic GVHD almost always present. The earliest symptoms resemble provoked vestibulodynia, with redness on the vulva and exquisite tenderness around the vaginal introitus. If untreated, vulvar GVHD progresses into the vagina, where fibrous wisps of scar tissue attach to the vaginal walls, ultimately narrowing of the vagina by tough scar tissue (stenosis), and closing the vagina as the inflamed vaginal mucosal walls adhere to each other.</td>
<td>Pain with genital caressing and intercourse is common. If diagnosed early, genital GVHD can often be treated successfully with a combination of high-dose steroid topical cream and low-dose vaginal estrogen. Two recent case series of 29 women in an Australian cohort of 81 followed prospectively[522] and 29 American women referred for assessment of vaginal symptoms after transplantation[508] reported that all women responded to the local vaginal treatment, none needing surgery. Those who wanted to stay sexually active worked with vaginal dilators plus topical steroid and estrogen and were able to stretch the adhesions and open their vaginal canals.</td>
</tr>
</tbody>
</table>

**Key**
- ED: erectile dysfunction
- FSH: follicle-stimulating hormone
- GVHD: Graft versus Host Disease
- LH: Luteinizing Hormone
- TBI: Total Body Irradiation
<table>
<thead>
<tr>
<th>Reference</th>
<th>Men N</th>
<th>Design</th>
<th>Median F-U</th>
<th>Disease Types</th>
<th>Transplant Types</th>
<th>Rates of Sexual Dysfunction %</th>
<th>Factors Associated with Higher Rates of Sexual Problems and Level of Evidence (LOE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson et al., 1999[517]</td>
<td>218</td>
<td>Cross sectional</td>
<td>1 year</td>
<td>Acute myeloid leukemia</td>
<td>Allo, autol, vs. chemotx</td>
<td>Male Low Desire: *; Male Orgasm Problem: *; Pain with Sex: 0.5%; Sexual Inactivity: *</td>
<td>BMT &gt; chemotx, GVHD, hormonal, female &gt; male, older age, fatigue, emotional distress, and poor quality of life (LOE 3)</td>
</tr>
<tr>
<td>Lee et al., 2002[523]</td>
<td>12</td>
<td>Cross sectional</td>
<td>1 year</td>
<td>Mixed</td>
<td>Allo and autol</td>
<td>0% 17% 42% 8% *</td>
<td>Only desire for sex was correlated with quality of life (LOE 4)</td>
</tr>
<tr>
<td>Monti et al., 2003[524]</td>
<td>30</td>
<td>Cross sectional</td>
<td>10 years</td>
<td>Germ cell</td>
<td>Autol marrow or stem cell</td>
<td>10% 27% 23% 0% 20%</td>
<td>63% felt they did not get enough information on sex and cancer (LOE 4)</td>
</tr>
<tr>
<td>Syrjala et al., 2005[520]</td>
<td>66</td>
<td>Cross sectional, matched controls</td>
<td>10 years</td>
<td>Mixed</td>
<td>Allo and autol</td>
<td>* * * * 14%</td>
<td>Transplant survivors had significantly more sexual dysfunction than controls, but similar marital satisfaction (LOE 3)</td>
</tr>
<tr>
<td>Claessens et al., 2006[518]</td>
<td>34</td>
<td>Cross sectional</td>
<td>11 years</td>
<td>Acute or chronic leukemia</td>
<td>TBI &amp; allo from HLA matched siblings</td>
<td>56% 38% 47% 12% 15%</td>
<td>20% felt they did not get enough information on sex and cancer. Male sex problems increased with age (LOE 4)</td>
</tr>
<tr>
<td>Humphreys et al., 2007[519]</td>
<td>42</td>
<td>Prospective pre-transplant, 1 year, 3 years</td>
<td>3 years</td>
<td>Mixed</td>
<td>Allo</td>
<td>23% 15% 14% 40%</td>
<td>At 3 years, men and participants who were not depressed had fewer sexual problems. Only half recalled getting info on sexuality (LOE 4)</td>
</tr>
<tr>
<td>Syrjala et al., 2008[521]</td>
<td>45</td>
<td>Prospective baseline to 5 years, matched controls</td>
<td>5 years</td>
<td>Mixed</td>
<td>98% allo</td>
<td>23% 27% 23% * 0%</td>
<td>Men’s sexual problems improved at 1 year vs. 2 years for women, but were still worse than controls at 5 years (LOE 3)</td>
</tr>
</tbody>
</table>

Abbreviations: Allo: allogeneic; Autol: autologous; Chemotx: Chemotherapy; TBI: total body irradiation; *: Not reported separately
Table 45: Hematopoietic Cell Transplantation and Female Sexual Function [517, 518, 519, 520, 521, 523]

<table>
<thead>
<tr>
<th>Reference</th>
<th>Women N</th>
<th>Design</th>
<th>Median F-U</th>
<th>Disease Types</th>
<th>Transplant Types</th>
<th>Rates of Sexual Dysfunction %</th>
<th>Associated Factors and Level of Evidence (LOE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson et al., 1999[517]</td>
<td>261</td>
<td>Cross sectional</td>
<td>1 year</td>
<td>Acute myeloid leukemia</td>
<td>Allo, autol, vs. chemotx</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Lee et al., 2002[523]</td>
<td>26</td>
<td>Cross sectional</td>
<td>1 year</td>
<td>Mixed</td>
<td>Allo and autol</td>
<td>54%</td>
<td>50%</td>
</tr>
<tr>
<td>Syrjala et al., 2005[520]</td>
<td>71</td>
<td>Cross sectional, matched controls</td>
<td>10 years</td>
<td>Mixed</td>
<td>Allo and autol</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Claessens et al., 2006[518]</td>
<td>36</td>
<td>Cross sectional</td>
<td>9 years</td>
<td>Acute or chronic leukemia</td>
<td>TBI &amp; allo from HLA matched siblings</td>
<td>56%</td>
<td>53%</td>
</tr>
<tr>
<td>Humphreys et al., 2007[519]</td>
<td>37</td>
<td>Prospective pre-transplant, 1 year, 3 years</td>
<td>3 years</td>
<td>Mixed</td>
<td>Allo</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Syrjala et al., 2008[521]</td>
<td>45</td>
<td>Prospective baseline to 5 years, matched controls</td>
<td>5 years</td>
<td>Mixed</td>
<td>98% allo,</td>
<td>44%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Abbreviations: Allo: allogeneic; Autol: autologous; Chemotx: Chemotherapy; TBI: total body irradiation; *Not reported separately
before transplant suggests that the long-term sexual dysfunction has complex causes. Not only may prior cancer treatment have damaged pelvic nerves and vasculature or reduced hormone production, but the intensive conditioning to prepare for hematologic transplantation, as well as the ongoing psychological stress exacerbate sexual problems. GVHD after transplantation may compound the dysfunctions further.

4. RECOMMENDATIONS

Men may become hypogonadal and require testosterone plus other medical treatments for ED [503, 504] (LOE 4): Grade C. After allogeneic transplants, women should watch for symptoms of vulvo/vaginal GVHD and seek early treatment with estrogen/steroids [522, 508] (LOE 4): Grade C. Local estrogen therapy is recommended for women with premature ovarian failure and dyspareunia. Systemic estrogen may be appropriate in some cases: Grade C.

We recommend giving information to men and women about sexual problems and rehabilitation before starting cancer treatment, with further assessment and counseling during planning for transplantation as well as at repeated follow-up visits: Grade C.

III. CANCER IN CHILDREN AND TEENS

1. QUALITY OF LIFE AND MARRIAGE IN SURVIVORS OF CHILDHOOD AND ADOLESCENT CANCER

Despite the increasing success of treatment for pediatric cancer in Western nations, men and women who survive these malignancies remain vulnerable to increased mortality from cancer recurrence, second malignancies, and late health effects of their cancer treatment [525]. Research on the quality of life of survivors of cancer in childhood and adolescence has rarely investigated sexual function, however. Rates of marriage have been compared with population norms. Survivors also are less likely to attain college degrees or be employed fulltime compared to population norms. Most have little idea that they may be at risk not only for infertility, but for sexual problems as well. A survey of 217 cancer survivors aged 18 to 40 at approximately 3-5 year follow-up from treatment found that about half desired counseling on sexuality, just as many as wanted assessment of infertility or counseling on adoption services [533]. Unmet needs were particularly acute in the group aged 18 to 29, whose age at diagnosis put them in the Adolescent and Young Adult (AYA) population that is now a focus of attention [534] (LOE: 4).

Even once these young people reach adulthood, research on sexual function seems to be off limits. In the past ten years, only two surveys of small, selected groups have been published. Relander and colleagues [535] used interview techniques and medical examinations to study 77 men treated for childhood cancer in Sweden at a median of 13-year follow-up. Eleven men were treated for low testosterone resulting from radiation for craniopharyngeal tumors, direct radiation therapy to the testes to treat leukemia, or high-dose alkylating chemotherapy agents. Only 2 of these men had "normal" sex lives, characterized by having desire for sex, being able to get erections, and being able to reach orgasm. Seventy percent of the 66 eugonadal men met criteria for being sexually functional, but this still suggests a higher rate of problems than expected among young men. A more recent Dutch study of childhood cancer survivors [536] included 31 young men and 29 young women with a mean age of 25. Although both genders were included, rates of problems were mainly cited for the group as a whole. In those over age 25, experience with sexual intercourse was significantly lower than age norms for the Dutch population. Being diagnosed during adolescence led to delays in sexual development in terms of dating, experimenting with intimate touch, intercourse, and for women, with masturbation. Although this sample also reported worse physical and mental health on the SF-36 than their peer group, general quality of life measures were not significantly associated with sexual function. Sexual problems were common: 41% reported low sexual desire, 45% sexual dissatisfaction, 44% feeling unattractive, and 14% feeling their cancer history interfered with their chance to have a future romantic relationship. Of note, these two surveys were conducted in
Northern Europe, where adolescent sexuality is not stigmatized as it is in the United States [537]. Clearly more detailed research is needed to enable clinicians to understand risk factors for sexual dysfunction after cancer in childhood and adolescence so that services can be directed to the subgroups most in need (LOE: 4).

3. TREATING SEXUAL PROBLEMS IN CANCER SURVIVORS

One intervention study used a psychoeducational model to counsel AYA patients about reproductive health issues [538]. A written workbook, using clip art and text layouts designed to appeal to teenagers and young adults included the following topics: male and female sexual anatomy and response, the impact of cancer treatments on sexual function and fertility, ways to develop a positive body image, making good decisions about whether or not to be sexually active, using contraception for safer sex and pregnancy prevention, being able to be assertive in sexual situations, and dealing with dating and relationships after cancer. Half of participants were randomized to a 3-month waiting list condition and half to 2 90-minute sessions of counseling from an expert psychologist, along with receiving the workbook. Questionnaires were administered at baseline, after the waiting list period, at the end of counseling, and at 3-month follow-up. Only 24 participants were recruited, and 3 could not complete the study because of illness. The only change during the waiting list period was an increase in emotional distress. However, gains at the end of treatment, and maintained at 3-month follow-up, included increased knowledge of the material, decreased general emotional distress, more positive body image, and less anxiety about sexuality and dating. Despite having the AYA programs of two large pediatric oncology centers participating, recruitment for this trial was very slow and difficult, limiting its generalizability (LOE: 3). In the future, it might be more acceptable to teens to use an internet-based or peer counseling model along with the material in the workbook.

4. RECOMMENDATIONS

Given the minimal research on sexuality compared to data on fertility and marital status, surveys of current young adult survivors are needed: Grade C.

F. CANCER IN WOMEN

I. GYNECOLOGICAL CANCERS

1. INTRODUCTION

Gynecologic cancer involving vulva, vagina, cervix, uterus, fallopian tubes or ovaries accounts for 13.4% percent of all cancers in women [539] with endometrial cancer being the most common: in the US some 40,000 women are diagnosed annually. In office endometrial biopsy or operative curettage for postmenopausal bleeding has lead to early diagnosis coupled with a favorable prognosis and a survival of 85-90% at five years. Surgical removal remains the mainstay of treatment for many gynecological cancers especially ovarian in origin. Pelvic radiation is often the primary or main adjunctive treatment for cervical and some endometrial cancers: external beam if often followed by intravaginal or brachytherapy. The majority of women (62-88%) are at high risk for developing vaginal agglutination and stenosis within the first 3 months after radiotherapy [540]. Recent studies demonstrate that between 30-63% of women who undergo treatment for cervical cancer experience some sexual complaint [541]. The sudden loss of ovarian hormones from surgery or chemotherapy also contributes to sexual dysfunction.

Surveys confirm the need to address sexual repercussions of gynecological cancer. Women with these diagnoses consider their sexual health to be one of the three most important aspects of quality health care [542] and while 74% in one study believed their physicians should discuss sex [543] such discussions did not occur in 62% of the time. Moreover, sexual dysfunction can be the primary source of distress from symptoms related to cervical cancer treatment [544]. However, data on prevalence and optimal treatment are scant especially for endometrial and fallopian tube cancers.

2. PREVALENCE

The prevalence studies (Table 46) of sexual dysfunction after specific gynecological cancers are often difficult to compare as sample size, oncological stages and follow up times are variable. Most studies are retrospective and do not have baseline sexual functioning. According to the National Cancer Institute, research shows that approximately one-half of women who have been treated for breast and gynecologic cancers experience long-term sexual dysfunction. Qualitative study highlights the importance of lost femininity and fertility and the fear of dyspareunia in women with endometrial and cervical cancer [545].

3. PATHOPHYSIOLOGY

The sexual side effects of treatment for gynecologic cancer are of multifactorial etiology and include direct and indirect mechanisms (table 47). Cancer treatment modalities and psychological reactions can both influence sexual function.

4. SPECIAL SURGICAL CONSIDERATIONS

Radical hysterectomy for cervical cancer is noted to have persistent negative ramifications on sexual desire whereas lubrication and other vaginal
<table>
<thead>
<tr>
<th>Cancer</th>
<th>Author &amp; year</th>
<th>Number of Patients</th>
<th>Mean Age of Patients</th>
<th>Stage</th>
<th>Mean Follow-up</th>
<th>Prevalence of FSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gynecological</td>
<td>Anderson et al (1997) [546]</td>
<td>47</td>
<td>NA</td>
<td>Early</td>
<td>12 mo</td>
<td>50% of all patients with all types of gynecological malignancies had at least one sexual complaint</td>
</tr>
<tr>
<td>Cervical</td>
<td>Greimel et al (2008) [547]</td>
<td>121</td>
<td>NA</td>
<td>Variable</td>
<td>NA</td>
<td>43.3% not active. 23.1% no interest</td>
</tr>
<tr>
<td>Cervical</td>
<td>Jensen et al (2004) [541]</td>
<td>173</td>
<td>NA</td>
<td>1A1-11</td>
<td>All pt followed up 5wk, 3 mo, 6 mo, 18 mo and 24</td>
<td>At 24 mo: 57% no interest. 5% dyspareunia. 36% orgasmic concerns</td>
</tr>
<tr>
<td>Cervical</td>
<td>Lindau et al (2007) [543]</td>
<td>221</td>
<td>49</td>
<td>Cervical and vaginal</td>
<td>Mean survivorship was 26.8 years (5.5-39.7)</td>
<td>25% orgasmic dysfunction. 43% decreased desire</td>
</tr>
<tr>
<td>Cervical</td>
<td>Pieterse et al (2008) [548]</td>
<td>94</td>
<td>Mean age of 43.3</td>
<td>Stage 1-11a</td>
<td>2yrs</td>
<td>Significant negative effects on sexual function: less lubrication, narrow short vagina, area around labia non sensate, dyspareunia and sexual dissatisfaction</td>
</tr>
<tr>
<td>Cervical</td>
<td>Bergmark et al (1999) [549]</td>
<td>332</td>
<td>26-80</td>
<td>Stage 1B or 11A</td>
<td>Variable</td>
<td>26% insufficient lubrication. 26% short vagina. 23% inelastic vagina all causing dyspareunia</td>
</tr>
<tr>
<td>Cervical</td>
<td>Bergmark et al (2002) [544]</td>
<td>332</td>
<td>26-80</td>
<td>1B-11A</td>
<td>variable</td>
<td>Increased distress over reduced orgasm frequency, overall intercourse dysfunction, dyspareunia</td>
</tr>
<tr>
<td>Cervical</td>
<td>Frumovitz et al (2005) [550]</td>
<td>37 surgery 37 Xrt</td>
<td>Surg:43.6 Xrt 46.9</td>
<td>Stage 1</td>
<td>5yrs</td>
<td>XRT caused worse sexual functioning than surgery. XRT women had more arousal, lubrication &amp; orgasm problems &amp; sexual dissatisfaction.</td>
</tr>
<tr>
<td>Cancer</td>
<td>Author &amp; year</td>
<td>Number of Patients</td>
<td>Mean Age of Patients</td>
<td>Stage</td>
<td>Mean Follow-up</td>
<td>Prevalence of FSD</td>
</tr>
<tr>
<td>-----------------</td>
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<td>----------------------</td>
<td>-------</td>
<td>----------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cervical</td>
<td>Park et al (2007) [552]</td>
<td>860</td>
<td>NA</td>
<td>I-IVa</td>
<td>5.86</td>
<td>Worse body image &amp; sexual function, more anxiety about sexual performance &amp; dyspareunia than controls</td>
</tr>
<tr>
<td>Cervical</td>
<td>Burns et al (2007) [553]</td>
<td>13</td>
<td>NA</td>
<td>NA</td>
<td>2-3 years</td>
<td>Physical problems i.e. bowel &amp; bladder dysfunction lead to difficulties with sexual desire, body image &amp; anxiety concerning maintaining a sexual relationship.</td>
</tr>
<tr>
<td>Cervical</td>
<td>Donnovan (2007) [554]</td>
<td>50</td>
<td>45.3+/−9.9</td>
<td>0-11B</td>
<td>1-5 years</td>
<td>Significantly more lowered interest, sexual dysfunction, &amp; sexual dissatisfaction than controls</td>
</tr>
<tr>
<td>Ovarian</td>
<td>Carmack et al (2004) [555]</td>
<td>232</td>
<td>NA</td>
<td>NA</td>
<td>Variable</td>
<td>47% low desire 62% dyspareunia 75% orgasm disorder</td>
</tr>
<tr>
<td>Ovarian</td>
<td>Liavaag et al (2008) [556]</td>
<td>287</td>
<td>51.5 at DX 57.8 at survey</td>
<td>FIGO 1 - 111</td>
<td>Mean 6.3 yr</td>
<td>Pleasure, desire decreased, dyspareunia increased compared to controls</td>
</tr>
<tr>
<td>Ovary</td>
<td>Gershenson et al (2007) [558]</td>
<td>132</td>
<td>DX: 25.7 Surgery: 35.9</td>
<td>Early or advance germ cell tumor</td>
<td>10.2</td>
<td>Less sexual pleasure, low SAQ. No difference with sexual discomfort compare to controls</td>
</tr>
<tr>
<td>Vulvar Intraepithelial Lesion</td>
<td>Likes et al; (2007) [559]</td>
<td>43</td>
<td>47.5</td>
<td>VIN</td>
<td>NA</td>
<td>Significant loss in desire, arousal, lubrication, orgasm and satisfaction compared to controls</td>
</tr>
</tbody>
</table>

**KEY**

NA not applicable: the article did not specify or information unavailable
XRT: radiation treatment
SAQ : The Sexual Activity Questionnaire
FSFI: Female Sexual Function Index
<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Negative impact on sexual self image</th>
<th>Other Sexual symptoms</th>
<th>Treatment &amp; LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature ovarian failure (estrogen and testosterone)</td>
<td>Loss of fertility</td>
<td>Estrogen deficiency</td>
<td>Local estrogen via silastic ring (LOE 1) [560]</td>
</tr>
<tr>
<td>Loss of ovarian androgen and precursor sex hormones (DHEA, A4) from post menopausal ovaries</td>
<td>Prematurely 'old' Alopecia Loss of pubic hair Loss of eyelashes</td>
<td>related dypareunia Deficient lubrication Reduced sexual genital sensitivity Reduced desire Reduced subjective arousal</td>
<td>Via vaginal pill estradiol 25μg (LOE 1)[560] (12.5 μg in future) Via CEE cream 0.5g 2x / week (LOE 1) – [560] Systemic E if recommended for non sexual reasons (LOE 1)[561]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Delayed or absent orgasm Vaginl or Eros device (LOE 4) [562]</td>
</tr>
<tr>
<td><strong>Gynecological surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Removal of sex organs</td>
<td>Sense of loss of womanhood Loss of fertility</td>
<td>Arousal and orgasmic disorders</td>
<td>Consideration for nerve sparing hysterectomy for neural preservation (LOE 4)</td>
</tr>
<tr>
<td>Disruption of uterosacral plexus</td>
<td></td>
<td></td>
<td>Physical therapy may decrease lymphedema</td>
</tr>
<tr>
<td>Lymph node dissection</td>
<td>Appearance &amp; possibly painful lymphedema of leg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible scars from reconstruction</td>
<td>Appearance &amp; possibly painful</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Radiation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin fibrosis</td>
<td>Altered appearance &amp; sensitivity of skin</td>
<td>Loss of sexual sensitivity of genital skin</td>
<td>Sex therapy to adapt to limited cardio/ respiratory reserve</td>
</tr>
<tr>
<td>Cardiac or respiratory damage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal narrowing &amp; foreshortening</td>
<td>Loss of sexual confidence</td>
<td>Fatigue, cardiac or respiratory compromise limit sexual activities</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decreased lubrication dyspareunia</td>
</tr>
</tbody>
</table>

**KEY & NOTES**

CEE: CONJUGATED EQUINE ESTROGEN
A4 ANDROSTENEIDONE
DHEA DEHYDROEPANDROSTERONE
LUBRICANTS: WITHOUT PERFUME, MICROBICIDES, FLAVOUR
DILATORS: SUPPORTIVE BEHAVIORAL THERAPY INCREASES COMPLIANCE
VITAMIN PREPARATIONS E.G. ZESTRA NOT STUDIED IN THESE POPULATIONS.
concerns may dissipate over time, as noted in one study where the autonomic nerves in the cardinal and uterosacral ligaments were likely spared [541]. However, nerve sparing radical hysterectomy is in its infancy [563] but early data suggest neurovascular preservation leads to improved sexual function [548, 564].

Ovarian removal signifies both reproductive loss and the advent of menopause (see table for effects) [565] Bowel resections and anterior/posterior exenerations for advanced gynecologic malignancy can result in stomas, colostomies, and ileoconduits impacting on self image. Some surgical techniques are becoming less aggressive without impact on survival as oncological surgeons consider sexual health concerns: clitoral preservation surgery for vulvar cancer offers selected women decreased morbidity with preservation of sexual function [566]. There are on going studies of radical tracelectomy (which preserves fertility) for early cervical disease and subsequent sexual function. The emerging trend is to provide adequate cancer treatment, but with minimal surgical removal of tissue and to minimize long-term negative sexual consequences [567] In all cases, adequate preparation and information may facilitate sexual adjustment after surgical intervention [568].

5. PSYCHOLOGICAL CONSIDERATIONS
Sexual self schema, sexual self concept, create the cognitive view about sexual aspects of oneself derived from past experiences and often manifest in current experience. Sexual self schema may account for variance in predicting current sexual behavior in cancer survivors; those with positive sexual self concept may adapt more positively [546]. Recently studies have noted the success of brief psychosexual interventions and of addressing the informational and sexual needs of cancer patients [569, 570, 571]. Mindfulness training, that has been incorporated into a psychoeducational program for women with arousal disorder subsequent to gynecological cancer, has been effective in preliminary studies [572,573]. An effective method of treatment for sexual difficulties in cancer patients is through the coordinated provision of information, support, and symptom management [570], preferably at one site. Many cancer institutions have established comprehensive multi-disciplinary programs. The focus is on both the psychosexual and physical aspects of sexuality. Limited study has shown increased compliance with therapy and subjective improvement in sexual symptoms [574]. Palliative care providers can also be involved as they reassure patients and their partners that even at the end of life, when intercourse may not be feasible, physical sexual intimacy and emotional closeness can be encouraged.

6. FUTURE RESEARCH
Further randomized clinical trials are needed to

<table>
<thead>
<tr>
<th>7. Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>The highly prevalent but commonly ignored sexual sequelae of gynecological cancer should be addressed: Grade C.</td>
</tr>
<tr>
<td>Nerve-sparing during radical hysterectomy, radical trachelectomy and clitoral preservation during vulvar cancer surgery may allow neurovascular preservation which may lead to improve sexual function [541, 548, 563, 564, 566, 567] (LOE 4)): Grade C.</td>
</tr>
<tr>
<td>Vaginal dilators may be helpful in maintaining vaginal patency after damage to the vaginal tissue. Compliance is linked to health care provider’s support [574]: Grade C.</td>
</tr>
<tr>
<td>Minimally absorbed local vaginal estrogen is recommended for most gynecological cancer survivors for dyspareunia from estrogen deficiency: the clinical implication of the minimal absorption remains to be further elucidated: Grade C.</td>
</tr>
<tr>
<td>Mindfulness training and psychoeducational programs may be useful adjuncts [572, 573] (LOE 4): Grade C.</td>
</tr>
</tbody>
</table>

II. BREAST CANCER

1. INTRODUCTION
Breast cancer is the most common malignancy in women [576]. Some 2.5 million women in the United States are breast cancer survivors: the 5 year survival rate is estimated to be close to 90%. Twenty-five percent of new cases present before menopause and 15% present before the age of 45 [577, 578, 579]. Sexual concerns are distressing complications for women during their diagnostic, treatment, and survivorship phases of breast cancer. Etiological factors include premature menopause, premorbid sexual dysfunction and negative self-concept [580, 581] relationship discord and depression [582].
2. PREVALENCE:

Table 48 shows the prevalence of sexual dysfunction after a diagnosis of breast cancer.

Women of Asian [583] or African American [584] [585] descent may be less communicative about sexual health concerns and possibly more prone to sexual dysfunction after breast cancer, but this has yet to be determined. There is limited study on breast cancer survivors who are lesbian, bisexual or single.

3. PATHOPHYSIOLOGY OF DYSFUNCTION

Living with a diagnosis of breast cancer can negatively affect sexual self image and function. There may be fear of recurrence, hesitancy to start a new relationship with need to disclose medical details, fear of rejection by a partner, coupled with the stress and sadness of possible changed fertility, life plans and finances. However, studies conclude that major factors negatively influencing sexual are also treatment related, see table 49.

4. SPECIAL SURGICAL CONSIDERATIONS

Surgical excision may affect sexual image and impact sexual responsiveness. Sexual problems may be more significant immediately after surgery and some gradually decrease with time, but there is still a need to address sexual problems related to the breast surgery and possible iatrogenic menopause, especially in younger breast cancer survivors [587]. Up to 10% of women with breast cancer may have a genetic predisposition for the development of ovarian cancer because of BRCA gene mutations and some of these women may choose to undergo a risk-reducing bilateral salpingo-oophorectomy (RRBSO). In a recent study [590], women who underwent a RRBSO were negatively impacted, experiencing dyspareunia and reduced body image [591]. In addition many women choose to undergo prophylactic mastectomy of the breast unaffected by cancer fearing bilateral involvement or another primary breast cancer. Study of subsequent sexual function is scant but cosmetic results are not always favorable and may negatively impact sexual self esteem.

5. SPECIAL RADIATION CONSIDERATIONS

Radiation therapy may cause direct and indirect affects (see table 64) that promote sexual dysfunctions. Skin damage, fatigue, alopecia, diarrhea, nausea, vomiting and radiation-induced symptoms contribute to general malaise and negatively impact sexual desire and response. Studies are lacking with respect to Mammocyte®, a novel minimally invasive intramammary placement of radiation at the time of surgical intervention and its implications on female sexual function.

6. SPECIAL CHEMOTHERAPY CONSIDERATIONS

The probability that a woman will enter menopause as a result of chemotherapy increases dramatically at the age of 35. More than 40% of women receiving chemotherapy at the age of 40 become amenorrheic [592]. Weight gain with chemotherapy and hormonal manipulation has been linked to women's feelings of lost attractiveness [593]. Goodwin et al [594] noted a mean overall weight gain of 1.6 kg, with an average gain of 2.5 kg, in newly diagnosed breast cancer patients receiving chemotherapy, and a 1.3-kg gain in those taking tamoxifen.

---

Table 48: Prevalence of Sexual Complaints after Breast Cancer [546, 569, 583, 586, 587, 597]

<table>
<thead>
<tr>
<th>Estimated Prevalence</th>
<th>Sexual Complaint</th>
<th>Research Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.4-38 %</td>
<td>Dypareunia</td>
<td>Barni et al [586]</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Negative impact on sexual self image</td>
<td>Other Sexual symptoms</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Loss of fertility</td>
<td>Estrogen deficiency relations, dypareunia</td>
</tr>
<tr>
<td></td>
<td>Prematurely ‘old’</td>
<td>Deficient lubrication</td>
</tr>
<tr>
<td></td>
<td>Alopecia</td>
<td>Reduced sexual genital sensitivity</td>
</tr>
<tr>
<td></td>
<td>Loss of pubic hair</td>
<td>Reduced desire</td>
</tr>
<tr>
<td></td>
<td>Loss of eyelashes</td>
<td>Reduced subjective arousal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delayed or absent orgasm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast surgery</td>
<td>Loss of sexual self image</td>
<td>Loss of breast &amp; nipple sensitivity</td>
</tr>
<tr>
<td>Partial or complete or bilateral mastectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cosmesis may not always be favorable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Appearance &amp; possibly painful lymphedema of arm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Appearance &amp; possibly painful</td>
<td></td>
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<tr>
<td></td>
<td>Possible non breast scars from reconstruction</td>
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<td></td>
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</tr>
<tr>
<td>Radiation</td>
<td>Altered appearance &amp; sensitivity of skin</td>
<td>Loss of sexual sensitivity of affected skin</td>
</tr>
<tr>
<td>Skin fibrosis,</td>
<td>Feeling prematurely ‘old.’ Concern about being “radioactive”</td>
<td></td>
</tr>
<tr>
<td>Cardiac or respiratory damage</td>
<td>Fatigue, cardiac or respiratory compromise limit sexual activities</td>
<td></td>
</tr>
<tr>
<td>Hormonal</td>
<td>Severe menopausal symptoms often at young age</td>
<td>Dyspareunia Loss of genital and non genital sexual sensitivity Possible vaginal bleeding from tamoxifen may impact sexual responsiveness</td>
</tr>
<tr>
<td>manipulation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7. SPECIAL HORMONAL THERAPY CONSIDERATIONS

Tamoxifen, a first generation selective estrogen receptor modulator (SERM), is prescribed to block estrogen receptors in the breast, but it also acts as a weak estrogen agonist on the uterine lining requiring monitoring for adverse endometrial effects. It is probably neither agonist nor antagonist in the vagina: studies that have looked at the impact of tamoxifen on sexual function have proven inconclusive [596].

Aromatase inhibitors (Anastrozole, Letrozole, and Exemestane) are rapidly becoming the mainstay of treatment for various stages of breast cancer. These drugs prevent the production of any estrogen and many women complain of vaginal dryness, moderate and severe dyspareunia, exacerbated menopausal symptoms, and loss of sexual desire [596]. Scientific data are limited. Management may include encouragement of non penetrative sex if non estrogen vaginal products to ease dyspareunia are insufficient.

8. PSYCHOLOGICAL CONCERNS

The literature confirms that many women adapt well after they learn of their diagnosis. Never the less, there is a subset of women who report continued anxiety, depression, and concerns regarding body image, fear of recurrence, post-traumatic stress disorder, and sexual problems well after treatment completion [592]. Sometimes women link prior negative sexual experiences, past sexual behavior (promiscuity, extra marital affairs or acquisition of sexually transmitted diseases) to their cancer diagnosis. Sexual well being in partnered women with breast cancer recurrence demonstrates substantial stress as they attempt to maintain their sexual lives. Younger and distant recurrence patients may have the greatest risk for sexual disruption. [597] The frequency of both intercourse and kissing declines significantly. Data demonstrate that sexuality declines after the recurrent cancer diagnosis and does not significantly improve over time.

The dynamics of relationships can be strained and changed with a cancer diagnosis. Survivors' levels of relationship distress, depression and age rather than hormonal levels have proved the most significant variables affecting arousal, orgasm, lubrication, satisfaction and sexual pain [598]. One study of women receiving ongoing anti estrogen therapy involved multiple regression analysis to determine what influenced desire, arousal, orgasm, pain and satisfaction. It was found that relationship factors predicted desire and a history of chemotherapy predicted problem-atic arousal, lubrication, orgasm and pain. However, there was no relationship between sexual function and hormonal levels including androgen metabolites [582]. The experience of chemotherapy rather than the resulting low hormones appeared to be highly detrimental to sexual function.

9. ASSESSMENT

Assessment of the breast cancer patient with sexual health concerns should be focused on the multimodal approach as outlined in the beginning of the chapter. Careful attention should be addressed to her relationship and social support network as well as her coping styles for her disease.

10. TREATMENT CONSIDERATIONS

It is imperative to counsel patients concerning possible sexual remedies including treatments for vaginal dryness [587]. Since breast cancer is often hormonally sensitive and tumor cells possess estrogen and progesterone receptors, treatment of menopausal sequelae with systemic replacement hormones is almost always contraindicated. The use of alternative medications, including serotonin reuptake inhibitors, antihypertensive medications, and environmental modifications (rhythmic breathing, acupuncture, avoiding spicy foods and alcohol, dressing in layers) may help decrease the intensity and severity of menopausal symptoms, though evidence of efficacy is limited. Sexual health resources to enhance body image (wigs, special lingerie, attachable nipples etc) should be widely available to help the survivor reclaim her sexual self esteem. The use of minimally absorbed local vaginal estrogen products remains an individual decision that requires informed consent and consultation with the oncology team [560, 599]. Several small reports [600] noted increased estradiol levels in women who take aromatase inhibitors and vaginal estrogen tablets. New lower dose tablets need further investigation and safety in breast cancer populations is lacking. Preliminary studies suggest that 0.5 G of Premarin Vaginal cream applied twice weekly has no endometrial effects and is not systemically absorbed; however it remains officially contraindicated in hormonally sensitive cancer survivors [560, 599]. Long term safety data are lacking such that the use of local estrogens for the treatment of vaginal atrophy after breast cancer women remains experimental: the amount of escape in to the systemic circulation has the potential to interfere with aromatase inhibition [575]. Non hormonal water based lubricants and moisturizers remain the primary treatment. Delivery of DHEA to the vaginal tissue may allow strictly local androgen action to benefit vaginal atrophy from aromatase inhibition and be a preferable choice in the future for women who must be strictly systemically estrogen-deplete [602]. A phase III RCT of 216 postmenopausal women without breast cancer, has confirmed maturation of epithelial cells and decrease in pH without significantly increasing serum estrogen or testosterone levels, with all steroid values remaining in the range seen in post menopausal women. All domains of sexual function improved [602, 603].
The safety of androgen replacement in the breast cancer population has not been adequately studied. There is a concern that testosterone can be aromatized to estrogen, which may reactivate or promote further tumor growth. The use of androgen replacement in estrogen deficient breast cancer patients was not effective for lowered libido in a recent randomized placebo controlled crossover clinical trial [604]. Future studies are needed to examine the safety and efficacy of androgens in this population. Psychosexual counseling and possible psychological therapies for sexual dysfunction should be offered to all breast cancer survivors with sexual complaints specifically addressing possible anxiety, stress, and mood changes from the imposed infertility.

11. Recommendations

Comprehensive assessment of sexual function is recommended given the multifactorial etiology and premorbid risk factors including past dysfunction, negative self-concept, depression, relationship discord as well as premature menopause [580, 581], Grade C.

Tamoxifen is likely sexually neutral [596], Grade C.

The clinically observed markedly negative impact of aromatase inhibitors on vulval vaginal health and coital comfort must be addressed: Grade C.

The short and long-term safety of minimally absorbed local vaginal estrogen for vaginal atrophy remains in question: their use is officially contraindicated by the FDA in the USA. The North American and the European Menopause Societies recommend individual decisions dependant upon each woman’s preference in consultation with her oncologist [560, 599]. We concur with these recommendations by the Menopause Societies: Grade C.

Local DHEA to allow tissue production of estrogen and testosterone without release of any sex hormones into the systemic circulation holds promise and research in this population is needed [601, 602, 603] (LOE 2): Grade C.

Non-hormonal water-based lubricants and moisturizers remain a safe treatment for dyspareunia: Grade C.

G. SEXUAL DYSFUNCTION AND PSYCHIATRIC DISEASE

I. INTRODUCTION

Sexual dysfunction should be acknowledged as a common and frequent symptom of psychiatric disease. Enquiry about possible changes of sexual performance including libido, arousal, orgasm, ejaculation, vaginal lubrication and erectile function should be made initially, before treatment is initiated. This information should be periodically reviewed in follow up visits in order to identify sexual problems and their acceptability to the patient and partner.

II. DEPRESSION:

1. DEPRESSION AND SEXUAL DYSFUNCTION

Depression is associated with low interest, lack of energy, low self-esteem as well as anhedonia. The associated deterioration of communication skills can impair personal relationships. Unfortunately patients frequently delay seeking help such that unsatisfactory sexual relationships are common. Social isolation and irritability can also contribute to decreased ability to initiate and maintain new intimate relationships.

a) Prevalence of sexual dysfunction from depression

Sexual interest is decreased in almost all depressive patients: it is a classical and frequent symptom. The Zurich Cohort study highlights a double prevalence of sexual dysfunction in depressed patients compared with controls (50% vs. 24%) [605]. Case controlled studies are shown in table 66. Approximately 40% of men and 50% of women with major depression suffer decrease in libido and problems regarding sexual arousal, as shown by specific questionnaires used to investigate sexual activity during the month prior to diagnosis. Orgasmic problems occur in a lower percentage, 15% to 20%, prior to taking the antidepressant drug.
Table 50: Studies of sexual dysfunction in depression [606, 607, 608, 609]

<table>
<thead>
<tr>
<th>Study</th>
<th>Depressed subjects</th>
<th>Control subjects</th>
<th>Problem investigated, method of assessment</th>
<th>Prevalence in depressed patients (%) (where stated)</th>
<th>Prevalence in controls (%) (where stated)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angst, 1998[606]</strong></td>
<td>Random selection of 126 subjects from a population scoring above 85th centile on SCL-90-R. Includes major depression, dysthymia and recurrent brief depression</td>
<td>Random selection of 365 subjects from population scoring below 85th centile on SCL-90-R</td>
<td>SPIKE interview Increased libido Decreased libido Sexual dysfunction <strong>Any sexual problem</strong></td>
<td>Men 23.3 Women 8.8 Men 6.9 Women 1.7</td>
<td>Men 25.7 Women 35.3 Men 6.9 Women 18.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48.2 50.9</td>
<td>17.6 31.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14.0 14.6</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42.0 32.0</td>
<td>17.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32.0 13.1</td>
<td>10.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>63.0 45.1</td>
<td>25.8</td>
</tr>
<tr>
<td><strong>Kockott and Pfeiffer, 1996[607]</strong></td>
<td>58 outpatients with stable manic-depressive illness</td>
<td>30 age- and sex matched dermatological outpatients</td>
<td>Sexual dysfunction according to semi-structured interview for assessing sexual behaviour and function</td>
<td>36.2</td>
<td>13.3</td>
</tr>
<tr>
<td><strong>Kennedy et al, 1999[608]</strong></td>
<td>134 patients with Major Depression</td>
<td>None</td>
<td>Sexual function assessed by Sex FX Questionnaire</td>
<td>Any Sexual dysfunction Male 50% Female 65%</td>
<td></td>
</tr>
<tr>
<td><strong>Bonierbale M, 2003[609]</strong></td>
<td>4557 depressed patients</td>
<td>With versus without treatment</td>
<td>Sexual dysfunction assessed by ASEX</td>
<td>65% in non treated patients, 71% in treated patients</td>
<td></td>
</tr>
</tbody>
</table>

2. ANTIDEPRESSANTS AND SEXUAL PROBLEMS

Selective serotonin reuptake inhibitors (SSRIs) venlafaxine, duloxetine and tricyclic agents (particularly those with a high serotonin reuptake blocker profile such as clomipramine) show a higher incidence of sexual dysfunction than other antidepressants that work through different mechanisms of action: bupropion [610], mirtazapine, moclobemide [611] tianeptine and agomelatine [612]. However, sexual dysfunction is the most frequent adverse effect of the serotonergic drugs [613, 614, 615, 616, 617, 618, 619]. This problem, which has a high incidence (30 - 50%), affects the patient’s quality of life and can lead to therapeutic noncompliance in long-term treatments, and was the most common side effect leading to a 50.8% dropout in the GAMIAN Survey [620].

Antidepressant drugs can deteriorate previous sexual activity by negatively affecting desire, arousal, orgasm, and ejaculation. Anecdotal reports also describe less frequent alterations such as penile anaesthesia [621] clitoral anaesthesia, painful orgasm [622], orgasm associated to yawning [623] priapism (associated with paroxetine and trazodone) [624], increased libido, spontaneous orgasm [625] and decreased ejaculation volume [626].

Only direct questioning will identify the real incidence of drug related dysfunction. Spontaneous reports are uncommon, even though this side effect can considerably affect drug compliance. In a specific study only 14% of the patients reported SD spontaneously but this increased to 58% when sexual questionnaires were used [613]. Patients are reluctant to speak about sexual problems with the physician because they are afraid of finding themselves in an embarrassing situation and they expect little help from their doctors in this regard [616].

a) Mechanisms involved in antidepressant-related sexual dysfunction

The normal sexual response includes the combination of neurogenic, psychogenic, vascular, and hormonal factors that are coordinated by hypothalamic, limbic system, and cerebral cortex centers (Table 67). Nowadays, it is accepted that human sexual function is influenced by the intervention of many neurotransmitters: dopamine, serotonin, noradrenaline, acetylcholine, GABA, oxytocin, arginine-vasopressin, angiotensin II, GRH, substance P, neuropeptide Y, and cholecystokinin-8, melanocortins among others. [616, 627] Dopamine enhances sexual function acting on D₂ receptors...
while serotonin inhibits sexual desire, ejaculation, and orgasm acting on postsynaptic 5HT2 receptors [616, 628, 629].

Although the central role of noradrenergic activity in human sexual activity is unclear, it is linked to the onset and maintenance of copulatory behavior in male rats. Blocking of the peripheral-adrenergic and cholinergic receptors in the genitourinary tract impairs sexual function [630]. Drugs with potent anticholinergic and/or α-1 receptor blocking action such as antidepressants (clomipramine) and some antipsychotic agents (risperidone) have a great capacity to impair sexual arousal. Reduction of nitric oxide (NO) activity has been related to SD secondary to antidepressant agents [631].

Table 51: Mechanism involved in Psychotropic related Sexual Dysfunction

- Increase of serotonin activity
- Anticholinergic effect.
- D₂ blockade
- Nitric Oxide Inhibition
- Alpha 1 blockade (priapism)
- Endocrine changes: Increase of Prolactin

b) Frequency of antidepressant-related Sexual Dysfunction

In agreement with previous studies which have shown frequencies of SD between 30% and 70% [613, 618], a very significant increase in SD incidence (59.1%) was found when patients were examined using the PRSexDQ Scale [614]. Only 24% of the patients with SD reported the problem spontaneously. Table 68 shows the overall frequency of SD for each of the antidepressants obtained by the Spanish Working Group using the specific PRSexDQ-SALSEX Questionnaire [612] and some important differences between them. Citalopram, venlafaxine, and paroxetine present the highest incidence values. A greater frequency of SD and sedation has been reported with paroxetine than with other SSRIs when a meta-analysis is used [632]. Citalopram and paroxetine are the most potent SSRIs. In this group of patients, fluoxetine had a slightly lower incidence of SD when compared with the other SSRIs [614]. The increase in serotonin activity is clearly related to low levels of libido and delayed or absent ejaculation and orgasm.

Moclobemide, a reversible MAO-A inhibitor has very little effect on sexual function, probably due to stimulation of dopaminergic activity and the absence of serotonergic effect.

Bupropion has shown little SD due to its dopaminergic mechanism of action. Clayton et al in a large sample of 6300 patients comparing SSRIs, buproprion, and placebo showed SD from bupropion to be no different from placebo [633]. Orgasmic dysfunction from bupropion is less than from SSRIs and also sexual dysfunction is less compared to venlafaxine [634]. Because bupropion is a selective norepinephrine and dopamine reuptake inhibitor with no serotonergic activity, other common antidepressant-associated side effects such as weight gain and sedation that could also impact sexuality, are absent.

Erectile dysfunction from serotonergic drugs is significantly less than orgasmic problems, suggesting a different mechanism of action perhaps not related to serotonin but rather to the peripheral adrenergic and cholinergic pathways. Paroxetine was associated with a significantly greater incidence of erectile dysfunction and insufficient vaginal lubrication [614]. This might be explained by the greater capacity of paroxetine to bind to the cholinergic receptors, as it is 5 to 160 times more potent in its cholinergic blocker capacity than the remaining SSRIs [635]. As well, it has been recently found that paroxetine is

<table>
<thead>
<tr>
<th>%</th>
<th>Libido Decrease</th>
<th>Orgasm delayed</th>
<th>Anorgasmia</th>
<th>Arousal problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine</td>
<td>64</td>
<td>64</td>
<td>53</td>
<td>41</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>47</td>
<td>48</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>50</td>
<td>50</td>
<td>39</td>
<td>22</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>48</td>
<td>54</td>
<td>37</td>
<td>21</td>
</tr>
<tr>
<td>Sertraline</td>
<td>55</td>
<td>56</td>
<td>47</td>
<td>29</td>
</tr>
<tr>
<td>Citalopram</td>
<td>62</td>
<td>63</td>
<td>51</td>
<td>34</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>60</td>
<td>61</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>53</td>
<td>50</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>20</td>
<td>18</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Bupropion XR</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Agomelatine</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Pooled data from different observational studies

472
a potent inhibitor of nitric oxide (as it inhibits oxide-nitric-synthase) both in vitro as well as in vivo [636].

Mirtazapine causes SD much less frequently (24.4%) than SSRIs and venlafaxine, and less severely [614]. However, erectile dysfunction occurs with the same intensity as with the other drugs, due to the different mechanisms involved in orgasmic and erectile function. Never the less, patients switched to mirtazapine because of SD related to other antidepressants may show improvement in all sexual items [637]. Although mirtazapine can improve sexual difficulties in depressed men and women, other adverse effects can appear (weight increase or somnolence). The global improvement found (64.7%), suggests that mirtazapine is a good therapeutic alternative in patients with severe SD secondary to other drugs, especially orgasmic problems [638].

Limited data suggest that duloxetine (with a dual serotonergic and adrenergic activity) has few sexual adverse events compared with paroxetine and escitalopram [639]. Agomelatine, a new antidepressant, an agonist of melatonin receptors MT1 and MT2, and antagonist at 5HT2C has shown a very low degree of SD [640,641]. A comparison of sexual functioning in depressed patients treated with either agomelatine or venlafaxine indicated that agomelatine 50 mg/day had a better sexual profile than venlafaxine XR 150 mg in remitted patients after 12 weeks of treatment in both orgasm and preorgasm measures; both treatments showed comparable antidepressant efficacy. Agomelatine caused significantly less sexual dysfunction, (similar to placebo, <10%), compared to paroxetine (>80%) in a sample of 90 healthy volunteers [641]. Due to its unique pharmacological profile, agomelatine has been shown to positively influence disturbed circadian rhythms in depressed patients by improving all phases of disturbed sleep and the overall quality of sleep, with a favourable impact on daytime alertness. Clinical studies suggest that this compound offers a novel approach to the treatment of depression combining efficacy, even in severe depression, with an extremely favourable side-effect profile including lack of sexual effects [641].

c) The need to use specific questionnaires to identify sexual problems

Recently validated questionnaires have been developed to measure psychotropic-related SD. The PRSexDQ-SALSEX, Psychotropic Related Sexual Dysfunction Questionnaire [642]; CSFQ Changes in Sexual Functioning Questionnaire [615], and ASEX Arizona Sexual Experiences Scale [643] have been used worldwide. SeeTable 53.

The “Psychotropic-Related Sexual Dysfunction Questionnaire” (PRSexDQ) has been used in samples of depressed and schizophrenic patients on medication [644]. Used in a direct clinical interview for the Spanish Group to Study Psychotropic Related Sexual Dysfunction, it has shown adequate feasibility and good psychometric properties. It consists of 7 items assessing 5 dimensions of SD according to severity or frequency: loss of libido, delayed orgasm or ejaculation, absence of orgasm or ejaculation, erectile dysfunction, vaginal lubrication dysfunction and patient’s acceptability of SD. In addition to scores for each item, an overall score may be obtained as a summated rating scale with items 3 to 7 ranging from 0 to 15 (severe SD).

d) Acceptability of sexual dysfunction by the patient and the partner

The acceptability of sexual dysfunction seems to be very relevant to the risk of dropouts, see table 54. As previously mentioned, data from large surveys show between 41.7% and 50.8% of the

| Table 53: Assessment Instruments for Psychotropic-Related Sexual Dysfunction, [615, 617, 642, 643] |
|-----------------------------------|---|---|---|---|
| Scale | ASEX | CSFQ | Sex Fx | PRSexDQ(Salsex) |
| Questions | 5 | 14 | 13 | 5 |
| <10 minutes | yes | yes | yes | yes |
| Validated for Depression | yes | yes | yes | yes |
| Validated for Schizophrenia | yes | no | no | yes |
| Sensitivity to Change | yes | yes | yes | yes |
| Likert Scale | yes | yes | yes | yes |
| Specific for medication | no | no | no | yes |
| With Interview | no | no | yes | yes |
| Multilanguage | no | yes | yes | yes |
| Acceptability of patients | no | no | no | yes |
| Spontaneous communication | no | no | no | yes |

ASEx: Arizona Sexual Experiences Scale, CSF-Q: Changes in Sexual Functioning Questionnaire, SEX Fx: Sex Effects Scale, PRSexDQ(Salsex): Psychotropic Related Sexual Dysfunction Questionnaire
total withdrawals are due to adverse effects. Thus, the use of alternative treatments that can decrease the frequency or intensity of SD in patients with poor tolerance, and at risk of discontinuing treatment, must be considered.

**e) Management Strategies for antidepressant associated sexual dysfunction.**

Past strategies have included waiting for spontaneous remission, dose adjustments, drug holidays, drug substitution, antidote therapy, and nonpharmacologic strategies, but their efficacy remains insufficiently proven or unknown [616, 645]. See table 55.

Gradual reduction of the dose may be useful in some patients especially in patients who are also experiencing other side effects. However, it should be attempted only in patients who have responded well to the medication, and clinician and patient must be watchful for any signs of relapse or discontinuation symptoms.

Drug holidays, in which a patient is advised to skip his or her antidepressant treatment for a day or two, can be effective but can also undermine treatment compliance and cause drug discontinuation symptoms or relapse of depressive symptoms.

Substituting one SSRI with another one may help alleviate sexual side effects; however, few patients (about 10%) benefit from this method of management [614]. Substituting SSRIs with drugs that work through a different mechanism of action, including bupropion [646], and mirtazapine [638] appears to be a more effective option. Patients on SSRIs for Generalised Anxiety Disorder were switched to Tiagabine (GABA agonist with anxiolytic effect) allowing remission of their SD [647]. The previously mentioned new antidepressant, agomelatine, may be a good alternative for patients suffering moderate to severe SD.

Agents currently used as antidotes that have been evaluated in placebo-controlled trials include drugs approved for the treatment of erectile dysfunction, such as sildenafil [648] or tadalafil [649]. A recent clinical trial with extensive exclusion criteria showed that sildenafil treatment of sexual dysfunction in women taking SSRIs was associated with a reduction in drug induced orgasmic dysfunction [650].

Sometimes no pharmacologic treatments alleviate the depression induced or the medication induced sexual dysfunction. Validating and explaining their sexual problems may be enough to help some patients, while others may require psychological treatments including CBT, sex therapy and mindfulness – see chapters 3 and 24

### III. PSYCHOSIS: SHIZOPHRENIA

#### 1. INTRODUCTION

Dependant on the course of their psychosis, patients suffering from schizophrenia have a variety of sexual difficulties. Patients with persistent illness tend to suffer significant sexual deterioration accompanied by other mental disturbances [651]. In contrast, patients with a good evolution of their disease maintain interest in their sex lives, although they have emotional difficulties in expressing their sexual needs [652,653]. Some 89% of chronically psychotic patients may have sexual dysfunction and this incidence may be related to the illness itself and how it affects the patients’ motivation, relationships with others, affective deficit, difficulties in finding or keeping a partner [654] or may be secondary to antipsychotic therapy. A significant group of patients are very dissatisfied when they develop sexual dysfunction following treatment, reducing compliance with treatment and clearly worsening the long-term prognosis [655].

**Table 54: Acceptability of the Sexual Dysfunction by patients**

<table>
<thead>
<tr>
<th>Good</th>
<th>27.2 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair</td>
<td>34.5 %</td>
</tr>
<tr>
<td>No acceptance*</td>
<td>38.3 %</td>
</tr>
</tbody>
</table>

*Patients with high risk of treatment drop-outs.

**Table 55 Managing Antidepressant Associated Sexual Dysfunction with Levels of evidence**

<table>
<thead>
<tr>
<th>Strategies</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switching to Bupropion and Mirtazapine</td>
<td>2</td>
</tr>
<tr>
<td>Switching to Moclobemide, Trazodone, Reboxetine, Maprotiline, Tianeptine, Agomelatine</td>
<td>4</td>
</tr>
<tr>
<td>Antidotes buspirone, amantadine, selegiline and Ginkgo Biloba are NO better than placebo</td>
<td>2</td>
</tr>
<tr>
<td>Sildenafil is useful to reverse male sexual dysfunction</td>
<td>2</td>
</tr>
<tr>
<td>Sildenafil is useful to improve female orgasmic disorder</td>
<td>2</td>
</tr>
</tbody>
</table>
2. SEXUAL DYSFUNCTION FROM ANTIPSYCHOTIC MEDICATION

a) Mechanism of antipsychotic drug induced sexual dysfunction

The most frequent dysfunctions are decreased libido, delay or lack of orgasm/ejaculation and arousal problems both in men and women. In general, antipsychotics that increase prolactin levels (haloperidol and typicals, risperidone, amisulpride, paliperidone) are associated with more sexual problems than those which do not (aripiprazol, quetiapine, ziprasidone and olanzapine). However, despite clozapine producing little or no change on serum prolactin concentrations, comparable and relatively high rates of sexual side effects were found for clozapine and haloperidol. Also, prolactin levels per se may not correlate with sexual dysfunction or psychosis control. Rather, the increased ability for emotional regulation from effective anti-psychotic therapy seems to benefit sexual function [656]. This finding also supports that, in addition to hyperprolactinemia, there are several possible mechanisms of antipsychotic induced SD including sedation due to histaminic blockade, cholinergic blockade, and adrenergic blockade [657]. Conventional antipsychotic drugs block D2 receptors on pituitary lactotrophes and so prevent inhibition of prolactin secretion by dopamine. The increase in prolactin levels also occurs at low doses and has a dose-dependent relationship as well. There is a greater prolactin elevation in women with chronic antipsychotic treatment at equivalent doses [658].

b) Prevalence of sexual dysfunction from antipsychotic medication

New atypical antipsychotics were expected to be associated with a lower incidence of sexual adverse events compared to conventional/typicals (chlorpromazine thioridazine) [659]. However, high rates of SD have been consistently reported with risperidone, ranking from 43% to 67% [660]. olanzapine, quetiapine, ziprasidone and aripiprazol exhibit a significantly lower incidence of SD as compared with risperidone. Moreover, olanzapine induced SD has been reported to be dose-related [658].

The disparity of incidence rates may be due to confounding factors such as difficulties in evaluating sexual function, use of small patient series and non-specific questionnaires and variably selecting sexually active and/or inactive subjects. When semi-structured sexual function interviews are used, SD frequency figures of between 49% and 63% are detected in treated schizophrenic outpatients [661]. In contrast, much lower frequency rates are found using the same methods in non-medicated psychotic patients, and in normal controls [662]. The highest figures for SD – 60% – (mainly erectile dysfunction and retrograde ejaculation) have been associated with thioridazine, decreasing to 25% with other antipsychotics[660, 663, 664, 665, 666, 667].

Sexual changes may include decreased libido, problematic ejaculation, orgasm, erection, vaginal lubrication, as well as priapism, menstrual disturbances, gynaecomastia, or increased breast size in women [644, 658, 668]. The frequency of SD in patients receiving antipsychotic medication is shown in Table 56.

c) Consequences of sexual dysfunction from antipsychotic medication

New atypical antipsychotics were expected to have a lower incidence of sexual adverse events compared to conventional/typicals (chlorpromazine thioridazine) [659]. However, high rates of SD have been consistently reported with risperidone, ranking from 43% to 67% [660]. olanzapine, quetiapine, ziprasidone and aripiprazol exhibit a significantly lower incidence of SD as compared with risperidone. Moreover, olanzapine induced SD has been reported to be dose-related [658].

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Table 56: Frequency of Sexual Dysfunction after Antipsychotic

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMISULPRIDE</td>
<td>74</td>
</tr>
<tr>
<td>RISPERIDONE</td>
<td>68</td>
</tr>
<tr>
<td>OLanzAPine</td>
<td>50</td>
</tr>
<tr>
<td>ZIPRASIDONE</td>
<td>40</td>
</tr>
<tr>
<td>QUETIAPINE</td>
<td>18</td>
</tr>
<tr>
<td>ARIPIPRAZOLE</td>
<td>9</td>
</tr>
<tr>
<td>TYPICAL</td>
<td>11</td>
</tr>
<tr>
<td>LONG ACTING</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

A major problem arising from SD is treatment non
compliance increasing the risk of relapse leading to significant healthcare, economic, family, and social consequences [669]. SD has recently been identified as one of the adverse effects that patients find most bothersome and that clearly compromises long-term treatment objectives [670]. Using specific Questionnaires it has been shown that patients, especially men (36% in one study), are very likely to drop out due to SD [644]. Much higher frequency rates are found when specific questionnaires (SALSEX) are used versus recording spontaneous reporting. Selecting patients who are sexually active will prevent falsely low prevalence rates of dysfunction (since patients who do not engage in sexual activity may not report/ be aware of adverse sexual effects); however, those who have discontinued due to sexual side effects will not be included.

d) Management of antipsychotic drug induced sexual dysfunction

There is minimal study to guide management. The efficacy of waiting for spontaneous remission, dose adjustments, drug holidays, drug substitution, antidote therapy and nonpharmacologic strategies, remains insufficiently proven or unknown [616, 645] (Table 57).

Spontaneous remission occurs only in a few cases and gradual reduction of the dose may be useful in some patients but relapses and discontinuation must be monitored. Drug holidays have been explored in anecdotal cases but undermine treatment compliance.

There is a lack of controlled data to support the use of antidotes such as amantadine, or cabergoline. The use of sildenafil shows significant improvement in erectile dysfunction [671].

Substitution may be helpful. Switching to olanzapine, quetiapine, aripiprazol or ziprasidone has decreased sexual dysfunction in observational studies [644, 658, 672]. When prolactin was measured an association between improved sexual function and decreased prolactin levels was found when risperidone was substituted for olanzapine [673].

IV. OVERALL CONCLUSIONS ABOUT SEXUAL DYSFUNCTION IN PATIENTS WITH PSYCHIATRIC DISEASE

- Sexual dysfunction may be present before psychotropic medication is initiated
- Direct and detailed examination of sexual function with specific scales is a decisive factor in the detection of dysfunction at treatment onset and in follow up
- The incidence of psychotropic drug related SD is underestimated and occurs mainly with serotonergic agents and hyperprolactinaemic drugs.
- Psychotropic drug related SD is associated with poor compliance with treatment
- There is a role for drug substitution to lessen sexual sequelae from medications in both depression and schizophrenia
- Phosphodiesterase inhibitors have a role as antidotes for psychotropic drug related SD
- Though minimally studied, non pharmacological therapy for sexual dysfunction during psychiatric disease may allow treatment compliance and improve quality of life

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<td>Wait...</td>
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<td>Low success rate</td>
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<td>Lower dose</td>
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<tr>
<td>Drug holiday</td>
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<tr>
<td>Substitution to another APS (quetiapine, olanzapine, ziprasiodone,</td>
<td>Single agent successful</td>
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<tr>
<td>Antidotes (cabergoline, amatadine)</td>
<td>No good success rate of</td>
<td>Increased side effects</td>
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<tr>
<td>Sildenafil improves erectile dysfunction</td>
<td>efficacy in men</td>
<td>Cost</td>
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Table 57: Strategies for managing sexual dysfunction with antipsychotic medication
V. RECOMMENDATIONS WITH GRADES

Psychotropic drug related sexual dysfunction should be addressed given the known risk of non-compliance as well as impaired quality of life [620]: Grade C.

Sexual history using specific scales prior to initiating drug and at follow up is strongly recommended: Grade C.

Sexual side effects should be important factors when initially selecting long-term psychotropic drugs: select drugs with low risk of sexual dysfunction.: Grade C.

Though minimally studied, non-pharmacological therapy for sexual dysfunction during psychiatric disease may allow treatment compliance and improve quality of life: Grade C.

To lessen drug-induced dysfunction, choose olanzapine, quetiapine, aripiprazole, ziprasidone instead of risperidone, amisulperide or paliperidone, [642, 644]: Grade B.

Avoid serotenergic anti-depressants [633, 634, 614, 641]: Grade C.

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Kessler, R. Advocacy Groups: A cross-national compari-


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Committee 10

Sexually Transmitted Diseases and Sexual function

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Daniel Richardson
David Goldmeier
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It is a reasonable assumption that people who contract sexually transmitted infections (STIs) do not have sexual dysfunction and that those who are dysfunctional would not have the capacity to develop STIs. In this chapter we have put forward what we believe is a raft of compelling scientific evidence showing that these realms do, in fact, interact, often in causative fashion. Because sexual dysfunction symptoms may be found in up to half of non biased populations studies and the rates of STIs are measured in tens of millions, these issues potentially affect a sizeable proportion of sexually active men and women in most countries. To date, a systematic and broad review of the interaction of these two major themes has not been undertaken, but with the spread of HIV and other STIs worldwide, it is a timely mission that we have been asked to tackle. Although much of the material in this chapter has high grade references, the evidence base levels are low in some instances. This is due to the newness of the topic, a fact that positively opens many future possibilities for future research and improved evidence based levels.

I. OVERVIEW OF HIV AND HIV IN MEN

1. EFFECTS OF HIV ITSELF
   a) Introduction

The first cases of AIDS in 1981 described in young homosexual men in the US with severely impaired cellular immunity lead to the discovery of the human immunodeficiency virus - HIV [1] [2]. HIV is a novel retrovirus infecting CD4+ lymphocytes which are pivotal to cell mediated immunity. Those most affected in North America, Western Europe and Australia are men who have sex with men and intravenous drug users. Other marginalised populations are also at risk for example black and Hispanic residents of the United States. In the developing world, heterosexual sexual intercourse and vertical (mother to child) remain the primary routes of transmission [3].

Lack of any effective treatment for AIDS and HIV in the early years coincided with a reduction in the transmission of STIs due to a reactive increase in the use of barrier contraception and so-called “safe sex.” Unfortunately, since the advent of effective HIV treatment [highly active antiretroviral therapy (HAART)] in the mid 1990s, sexual behaviour has changed and the incidence of STIs has increased again; even among those who are HIV Infected [4] [5]. In developing countries, the incidence of HIV has been and remains explosive, and, without effective treatment and STI prevention measures, the outlook seems potentially devastating [3].

HAART generally produces a sustainable suppression of plasma HIV virus (viral load) and an increase in circulating CD4 cells. More than 25 antiretroviral drugs from six therapeutic classes are now available for the management of HIV infection and mortality in HIV infected patients now approaches that of the uninfected population [6].

Logically, it is untenable that men with sexual problems including erectile dysfunction, low sexual desire, and ejaculatory disorders should be at significant risk of STIs. Similarly, it is untenable that young, sexually active people who are at greatest risk of STIs should experience sexual problems. In reality, these paradoxical situations are common in clinical practice. In a nationally representative sample of HIV-infected outpatients in France, sexual difficulties were reported by 33.3%
of individuals; immuno-virological outcomes were not associated with sexual difficulties [7]. A study in London, UK demonstrated that Hiv infected MSM are 5 times more likely to report sexual problems than uninfected MSM and that those on HAART are more likely to complain of loss of sexual desire which is associated with endocrine abnormalities [8]. Furthermore patients on HAART with Sexual difficulties are more likely to report poor adherence to HAART [9]. Amongst Hiv infected MSM, there is a complex, but important organic and psychosocial interaction between recreational drug use, use of PDE5 inhibitors and poor condom use (and probably Hiv transmission) [10].

b) Hiv encephalopathy

The primary cause of Hiv encephalopathy (HivE) is the infection of the CNS caused by Hiv. If untreated, some 15-20 % of patients will eventually develop the disease [11]. Since the introduction of (HAART), the incidence of the disorder has decreased [12], [13]. Other terms used for this condition are AIDS dementia complex, AIDS dementia, Hiv dementia, and Hiv associated cognitive motor complex. HivE generally only occurs in the later stages of the Hiv infection when there is a profound immune suppression (CD4+ T-cells < 200/μl) [14] [15].

Hiv encephalopathy is a subcortical dementia which emerges over the course of weeks and months. Typical complaints are slowing of reasoning, forgetfulness, difficulties concentrating, lack of energy drive, mild depressive symptoms and emotional blunting. Impairment of alertness, neck stiffness and focal or lateralisning neurological signs (e.g. hemiparesis, aphasia) are not typical for Hiv associated encephalopathy. The coincidence of psychosis with HivE is rare. Focal and generalized epileptic seizures are rare manifestations of HivE [11] [13].

There are no systematic reviews of sexual functioning of Hiv patients with encephalopathy. Anecdotal reports by the authors had clinical pictures of low sexual desire, erectile dysfunction and sexual disinhibition. It is likely that patients with Hiv have altered neuropsychological functioning which may impact on sexual functioning. Hiv associated encephalopathy and other CNS manifestations are less likely in individuals on HAART and are more likely to improve on HAART [16], [17].

c) Adjustment disorders, depression and anxiety in Hiv

At the beginning of the AIDS pandemic, affective disorders such as depressed mood were seen in a considerable number of Hiv-1-infected individuals [18]. These disorders were a result of the poor physical condition of patients, brain involvement by the virus (e.g. encephalopathy), or a reaction to disadvantageous living conditions (losing friends, jobs, etc.). In the era of highly active antiretroviral therapy (HAART), mental illness related to physical weakness is declining [19].

A survey of patients in the US found that 54% of Hiv patients had Axis I psychiatric disorders, including 20% with major depression and 18% with depressive symptoms associated with adjustment disorder [20]. Patients with mild adjustment disorders resulting from bad news (i.e. giving the patient an Hiv diagnosis or the worsening of Hiv disease status) and patients with major depression may benefit from supportive psychotherapy. Regular meetings with a health provider to discuss feelings and to encourage treatment compliance are often of great benefit [21].

Anxiety and depression are common among persons living with Hiv, with a prevalence of nearly 50% in a U.S. screening sample of 2,864 Hiv-infected persons [22]. It is not known whether the introduction of HAART has led to a decline in depression and anxiety disorders among Hiv-infected persons, although recent studies showed that the incidence and prevalence of Hiv-1-associated dementia and minor cognitive motor disorders have significantly declined in the HAART era [13], [23]-[28]

The presence of depression and anxiety has been shown to be an important patient-related barrier to adequate adherence to HAART, as it has to adherence to medications for other disorders [29], [30]. Despite the consistent association between depression and HAART adherence behavior, there have been few detailed analyses of this issue. It is also possible that Hiv associated neurocognitive disturbances, which become more prominent as Hiv disease advances, might be responsible for non-adherence. However, to our knowledge, the relationship between adherence to HAART and neuropsychological performance has been assessed in only one recent study, which suggested a negative effect of neuropsychological impairment on adherence to antiretrovirals [31].

Men with Hiv who have multiple sexual problems were likely to suffer from major depression. Factors independently associated with multiple sexual problems among the Hiv-negative gay men were poorer general health and interpersonal isolation, whereas for the Hiv-positive gay men, they were adoption of avoidant strategies to cope with daily life stress, sexual risk-taking in casual encounters, and the use of antidepressants [32].

d) Endocrine

Hypogonadism was a well recognised clinico-pathological problem in the pre HAART era [33]. Hypogonadism is now less common among Hiv-infected men in the HAART era and is usually attributable to hypothalamic/pituitary dysfunction [34]. The prevalence and aetiology remains unclear,
however given its association with increasing age, the prevalence of hypogonadism may rise as Hiv-infected men survive to older ages [34]. Hypogonadism appears to be associated with decreased muscle mass quantity and function, changes in corporal fat mass distribution and quantity, secretion of adipocytokines and endothelial dysfunction. This may be due to the metabolic syndrome which is likely to be a feature of the lipodystrophy syndrome [35]. Hiv associated hypogonadism is also associated with sexual dysfunction, namely erectile dysfunction and low sexual desire [8], [34], [36], [37]. Furthermore, there is increasing evidence that men with Hiv complain of low sexual desire, particularly those on HAART who have raised estradiol levels [8], [36], [37].

2. DIRECT EFFECTS OF HIV INFECTION

**a) Lipodystrophy**

Lipodystrophy is a recognized side effect of older antiretroviral therapy [38]. Lipodystrophy is a pathological fat redistribution problem manifesting in central obesity and peripheral, including facial, fat atrophy. Lipodystrophy is associated with protease inhibitors and lipoatrophy is likely to be due to thymidine analogue reverse transcriptase inhibitors; however, the exact physiological mechanisms are unknown [38]. The psychological effects of lipodystrophy are potentially devastating. Patients fear disclosure and often exhibit features of depression, which can affect sexual function; self-image and self-esteem are compromised [39]. Aromatization of testosterone to estrogen in pathological lipodystrophic tissue has been noted as a biological mechanism for increased estradiol levels in Hiv-infected men [37]. Clinical trials demonstrating the role of aromatase inhibitors in preventing raised estradiol levels in lipodystrophic individuals have shown early encouraging results [36]. The incidence of lipodystrophy and lipoatrophy is decreasing due to newer antiviral agents.

**b) Neuropathy**

Peripheral neuropathy is a well-documented complication of both Hiv infection by direct viral toxicity and HAART, most notably thymidine analogue nucleoside reverse transcriptase inhibitors i.e. zidovudine-AZT [40]. There is little data on the relationship of peripheral neuropathy and sexual dysfunction in patients with Hiv. There is a significant association in this group of men with peripheral neuropathy and retarded ejaculation [41]. The relationship between retarded ejaculation and peripheral neuropathy is complex and often included. Although within the context of Hiv is likely to be an autonomic neuropathic process, other relevant causes of retarded ejaculation need to be considered [41], [42]. In non-Hiv settings, men with diabetes and consequent associated peripheral neuropathy have been reported to complain of retarded ejaculation [43].

**c) Iatrogenic low sexual desire**

Low sexual desire in the post-HAART era appears to be related to their Hiv therapy [44]-[46]. Experience in a previously reported study from a London Hiv centre showed that 2% of a convenience sample of unselected healthy MSMs admitted to low sexual desire, compared with 26% in Hiv positive men who were well but not on HAART and 48% for men with Hiv on HAART [8]. The mean estradiol level in the latter group was significantly raised (228 pmol/L). Clearly, the difference between 26% of non-HAART-taking men having low sexual desire and 48% of those taking HAART having low desire suggests there might be a causal relationship between HAART and raised estradiol levels [8]. Other workers have also found significant changes in testosterone and estradiol levels in men on HAART [37]. Using aromatase inhibitors in men with Hiv and low sexual desire has an effect suggesting that the organic mechanism is raised estradiol [36].

**d) New treatments**

Efavirenz, a commonly used antiretroviral agent since the late 1990s, has been shown to have CNS side effects; however, there does not exist any evidence for increased sexual dysfunction in controlled studies [47]. Currently, newer antiretrovirals are licensed on a yearly basis; however, effects on sexual dysfunction or interaction with current pharmaceutical agents used to manage sexual dysfunction are not systematically investigated. Protease inhibitors, cause increased plasma levels and clinical effects of all PDE5 inhibitors via the inhibition of cytochrome p450 liver isoenzymes [48]-[50].

3. PDE5I USE AND SEXUAL FUNCTION WITH PARTICULAR REGARD TO MSM

Common sense would suggest that MSM using PDE5i to maintain strong erections would lead to safer sex e.g. a man who feels his erection might fail whilst putting on condom would not do so and so have unprotected high risk sex but would have a hard erection under PDE5i cover and so feel able to use a condom. However, the current evidence appears contradictory to this concept. Rosen et al reported at the Bolger conference that PDE5i use is associated with recreational drug use (e.g. crystal meth or cocaine ) which in turn may lead to central excitement, but peripheral ( penile) vasoconstriction [10]. In order to overcome this recreational drug induced ED, MSM resort to PDE5i use, which seemingly in the USA is frequently obtained online, not via a physician, and with little or no safer sex counselling [10]. Furthermore, the disinhibition induced by these recreational drugs may well be enhanced by similar CNS effects of the PDE5is themselves [51]. A further problem is that PDE5i use has been shown to be much more likely to lead
to condom breakage and has also been suggested to lead to anal vasoengorgement in MSM with consequent facility of transfer of Hiv at anal sex [10]. Recent qualitative and quantitative work in MSM who have recently Hiv seroconverted shows that use of recreational drugs, past and current sexual assault and current depression are cumulatively associated with unsafe sex and Hiv acquisition [52]-[53]. Addressing these issues is important both to ensure good HAART compliance as well as safer sex [54]-[56].

The committee’s opinion is that intracorporeal alprostadil or Trimix for the treatment of ED should be injected further towards the glans than is usually recommended so that the puncture site is covered by the condom.

II CIRCUMCISION AS A STRATEGY TO REDUCE HIV INFECTION IN MEN

The merits of circumcision in the neonatal period or in later years have been debated for ages. Proponents of the procedure have argued that the public health benefits of circumcision including a protective effect against urinary tract infections in childhood, sexually transmitted diseases, penile cancer, and inflammatory conditions of the penis far outweigh the risks. Those against circumcision have traditionally held the view that this procedure poses an unnecessary surgical risk, that the benefits do not justify the potential exposure to risk, and question its ethical foundation. Three recent randomized studies in sub-Saharan Africa have conclusively demonstrated that circumcision is associated with a significantly decreased risk of Hiv infection in the male. The following is a summary of these more recent findings and their impact on forming current and future global health policy, as well as a brief review of the history, ethical aspects, and potential complications of circumcision.

1. HISTORY AND INTRODUCTION

Circumcision is believed to have originated in Egypt more than 6000 years ago and may be the “oldest” elective operation in the history of man [57]. Six millennia later, circumcision has resurfaced as a hotly debated topic and come to occupy center stage in public health policy directed toward the control of the Hiv epidemic. Recently, many “anti circumcision” activists have argued that the presence of foreskin and the associated Meissner’s corpuscles is necessary for maximized sexual pleasure and that removal of foreskin, especially in infancy and adolescence, is a form of unnecessary forced trauma [58] Detailed review of the merits of circumcision in relation to health benefits other than Hiv control is beyond the scope of this manuscript, but studies have shown reduced relative risk of urinary tract infections in boys, carcinoma of the penis, genital ulcer diseases, and human papilloma virus transmission in association with male circumcision [59]-[64].

2. CIRCUMCISION AND HIV RISK

The prevalence rates of Hiv are strikingly variable in different parts of sub-Saharan Africa, a finding that has been attributed to varying rates of male circumcision in different parts of the continent and the assumption that male circumcision reduced susceptibility to Hiv, syphilis and chancroid [65]. The protective effects of circumcision in preventing Hiv infection can be traced back to the observational studies performed in the 1980s [66]-[67]. In addition to these observational studies, the recommendations for MC in sub-Saharan Africa were based on three landmark, randomized controlled studies in Africa demonstrating unequivocally that non-ritual, properly performed circumcision can reduce Hiv acquisition by 50% or more [68]-[70]. The results of the first of these trials in Orange Farm, South Africa were published in 2005. In late 2006, the remaining two randomized controlled trials of male circumcision in Africa were terminated by the National Institutes of Health (NIH) due to a preponderance of evidence supporting the protective effect of circumcision against Hiv infection. In March of 2007, the World Health Organization (WHO) and UNAIDS issued statements recommending circumcision as an intervention in heterosexual men to reduce the risk of acquiring Hiv infection. The findings from these trials, published between 2005 and 2007, confirmed the considerable benefit of circumcision in reducing Hiv incidence in men [68]-[70]. Westercamp and Bailey identified thirteen studies from 9 countries in order to evaluate the acceptability of MC in sub-Saharan Africa and to assess factors that will influence uptake of circumcision in populations where circumcision is not routinely and traditionally performed. It was found that the level of acceptability was fairly homogeneous and consistent in the evaluated nations and that 65% of uncircumcised men were willing to undergo circumcision. Acceptability among female partners was similarly high with 81% of women willing to circumcise their sons and 69% of women favoring circumcision for their partners[71]. Today, much of the discussion and the challenges revolve around development of sound policy and budgetary planning for widespread implementation of circumcision in Hiv endemic areas.

3. BIOLOGICAL RATIONALE FOR PROTECTIVE EFFECTS OF MC ON HIV ACQUISITION

A number of investigators have looked at the biological rationale for the protective effects of circumcision against Hiv acquisition and have found the effect biologically plausible. The Langerhans’
cells, macrophages, CD4+ T cells, and dendritic cells are amply found in the foreskin and are all considered to be Hiv target/receptor cells. Other important factors supporting the biological protective effect of circumcision include exposure of the inner mucosa of the penile shaft to vaginal and cervical fluids, as well as mucosal breach of the frenulum and the distal shaft due to the minor trauma of intercourse. Other studies have documented the lower incidence of genital ulcer disease in the keratinized penile skin of circumcised men, yet another factor that may be protective against acquiring Hiv infection [72] [64], [70],[73]-[77].

4. POTENTIAL COMPLICATIONS AND ETHICAL ASPECTS

Muula et al performed a systematic review of complications of male circumcision in Anglophone Africa in March 2007 and included such factors as indications for MC, complications reported, age of patients and category of circumcisers. 8 articles and 2 abstracts were found to be suitable for the analysis and the prevalence of reported complications ranged from 0% to 50.1%. One study on hemophilic patients reported a very high complication rate of with 50.1%, but excluding this series, most of the reported complications in the reported studies were of only minor severity without serious sequelae. Interestingly, the prevalence of complications of MCs performed by physician surgeons was not significantly different than those performed by non-physician health professionals. Given the relatively short duration of the studies and inadequate long-term follow-up, it is evident that the information pertaining to at least some adverse events (i.e. keloid formation) may not be properly captured to date. The authors concluded that there is inadequate data to conclusively assess the prevalence of complications of MC in the region [78]. The overall complication rate reported in the 1,475 patients constituting the intervention arm of the South African randomized study was 1.8% which is not dissimilar to rates reported in the West and the industrialized nations [79]. The reality of complications associated with any surgical procedure, as well as the complexities of the various religious, cultural, and societal values pertaining to circumcision mandates careful attention to the ethical aspects of circumcision in Africa and the developing world. Some of the medical, legal, and ethical aspects of treating sexual dysfunction in the Hiv positive male have been previously addressed [10], [80], [81]. In the context of circumcision as it relates to Hiv prevention, attention to human rights and ethical considerations are paramount, especially as they relate to children. Stemple points to the nature of the disease typically affecting the marginalized and the poor, as well as the fact that the spread of disease can lead to further inequality and hardship, to encourage debate that is focused on informed consent and children’s rights [82]. He also urges an increase in the use of treaty-based judicial mechanisms and rewarding human rights compliance with preferential trade agreements [82].

5. CIRCUMCISION OUTCOMES AND EFFECTS ON SEXUAL FUNCTION

Implementation of policies for mass circumcision as a measure to control the Hiv epidemic has raised concerns about possible impairment of sexual function. A number of investigators have evaluated the effects of circumcision on a range of sexual satisfaction measures. Despite conflicting results in some of the historical observational studies, most recent papers do not show evidence of adverse effects on sexual function [83]. Senkul et al. evaluated the effects of adult circumcision on sexual function using the Brief Male Sexual Function Inventory (BMSFI) and ejaculatory latency time in men circumcised only for religious or cosmetic reasons. After a 12 week interval, the BMSFI evaluation and ejaculatory latency time measurements were repeated and it was noted that despite a post-circumcision increase in the mean ejaculatory latency time which the authors suggested can be considered an advantage, differences in the mean BMSFI scores were not statistically significant [84]. Similarly, a small prospective study of the effects of circumcision using the BMSFI administered before and after the procedure with a minimum 12 week follow up revealed no statistically significant difference in the BMFSI composite scores of reported sexual drive, erection, ejaculation, problem assessment, or overall satisfaction [85].

In the randomized trial of male circumcision performed in Rakai, Uganda, Kigozi et al investigated self-reported sexual satisfaction and function among 4456 sexually experienced Hiv-negative males. The study participants were randomized such that 2210 in the intervention arm had immediate circumcision and 2246 in the control arm had the procedure delayed for 24 months. Overall, less than 2% of the participants in either arm of the study reported problems with sexual satisfaction and function at 6,12, and 24 month follow-up. After a review of all analyzed domains, the authors concluded that sexual satisfaction and sexual function are not adversely affected by circumcision [86].

The effect of adult male circumcision on men’s sexual function and pleasure was also evaluated by the investigators of the previously reviewed Kisumu, Kenya, randomized controlled trial of circumcision to reduce Hiv. The arms of the study included immediate or delayed circumcision after 2 years similar to the Rakai trial. Both the circumcision and control groups had significantly decreased rates
of any sexual dysfunction from 23.6% and 25.9% at baseline to 6.2% and 5.8% at month 24 [87]. Changes pertaining to increased penile sensitivity were reported by 64.0% of the circumcised men and approximately half of the circumcision group reported significantly increased ease of reaching orgasm at month 24. These changes notwithstanding, the authors had concluded that male circumcision was not associated with sexual dysfunction [87]. The same group examined male circumcision outcomes among healthy, sexually active, uncircumcised, Hiv-seronegative men aged 18-24 in an African setting and reported 27 adverse events in 26 procedures (1.8%) out of a total of 1,475 procedures. It was further reported that among the study participants, 92% were “very satisfied” with the procedure outcome 3 months after the surgery [79]. (Table 1) below is a summary of these findings:

6. THE FUTURE AND GLOBAL HEALTH POLICY

Dickerman has authored an article provocatively titled: “Circumcision in the time of Hiv: when is there enough evidence to revise the American Academy of Pediatrics’ policy on circumcision?” where he strongly urges the Academy to issue more direct statements in support of the medical benefits of circumcision [88]. Comparative evaluation of the costs of neonatal circumcision in the United States in relation to later health benefits has confirmed that the post-neonatal circumcision is significantly (10X) more expensive than neonatal circumcision and that the latter will confer life-time benefits at little or no cost [89]. Although these findings are not directly applicable to the setting in sub-Saharan Africa, it is likely that the future trend for Hiv prevention will gradually evolve toward earlier circumcision. Any global policies for undertaking large scale circumcision programs must take into consideration the important ethical dilemmas as well as the delicate cultural sensitivities of each region. The landmark findings of the 3 randomized controlled trials on the protective effects of circumcision on reducing Hiv acquisition are major breakthroughs in the public health arena and will hopefully have a meaningful impact in areas ravaged by the epidemic. However, health care practitioners and global health policy engineers cannot overstress the dictum that circumcision will be most effective in disease prevention if combined with patient education and low-risk sexual behavior.

III. HIV IN WOMEN

1. INTRODUCTION

In almost all societies, women are disadvantaged compared to men to a greater or lesser extent. This has a significant impact on women’s health. Nowhere is this discrimination more vividly seen than in Hiv infection. Some of the sociocultural factors that prevent women from obtaining good quality health services and attaining the best possible level of health are included in the table below: [90]

**TABLE 2: Who Factors that prevent good quality health in women**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unequal power relationships between men and women</td>
<td>No change except slight increase in IVELT</td>
</tr>
<tr>
<td>Social norms that decrease education and paid employment opportunities</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>An exclusive focus on women’s reproductive roles</td>
<td>No change</td>
</tr>
<tr>
<td>Potential or actual experience of physical, sexual and emotional violence</td>
<td>No difference</td>
</tr>
</tbody>
</table>

**Table 1. Sexual outcomes of circumcision in adults**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Number</th>
<th>Sexual dysfunction assessment tool</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senkul</td>
<td>Observational cohort 12 weeks</td>
<td>?</td>
<td>BMSFI inventory</td>
<td>No change except slight increase in IVELT</td>
</tr>
<tr>
<td>Kigosi</td>
<td>Randomized trial</td>
<td>4996</td>
<td>IIEF + supplementary questions</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>Collins</td>
<td>Observational cohort 12 weeks</td>
<td>?</td>
<td>BMFSI</td>
<td>No change</td>
</tr>
<tr>
<td>Krieger 2008</td>
<td>24 month randomized trial</td>
<td>2784</td>
<td>Non validated Likert + dichotomized scales</td>
<td>No difference</td>
</tr>
<tr>
<td>Krieger 2007</td>
<td>Observational cohort</td>
<td></td>
<td>Non validated questionnaire</td>
<td>Very satisfied</td>
</tr>
</tbody>
</table>
It is estimated that up to 17 million women over the age of 15 are infected with HIV worldwide. Globally, this represents 50% of the disease burden. However, in sub-Saharan Africa, young women may be three times more likely to be infected than young men [91].

Women in high-income countries seem to find it particularly difficult to come forward to discuss their sexual problems, so that as few as 3% of women with sexual dysfunction have discussed these issues with a health care professional [92], [93]. Reasons given by women for non-consultation include a “perceived lack of perception or lack of bothersomeness of their problem”, not perceiving it as medical problem and embarrassment [94]. It may be surprising that as few as 4% of HIV health care providers in the UK ever ask their HIV positive female patients about sexual functioning [95]. This neglect of clinical care is likely underpinned by ignorance, lack of time and embarrassment [95], [96].

Sexual functioning issues in women with HIV in developing countries worldwide are more likely to be focused on male coercive sex and domestic violence[97]-[99]. Gender power differentials and poverty can force women to engage in unsafe forced sex in order to secure food and economic security for themselves and their children [99].

The best predictors of female sexual dysfunction (FSD) in general are lack of general emotional well being states found in conditions such as depression, anxiety and relationship difficulties [100], [101]. The evidence to date pertaining to FSD in HIV positive women bears this out, although important organic correlates may co-exist.

Overall, the literature on the interaction of HIV and FSD is sparse and not of the highest quality. The majority of the reported evidence comes from Europe and North America.

2. RATES OF SEXUAL DYSFUNCTION AND GENERAL ETIOLOGY.

a) Studies reported pre HAART

Small studies on socially disadvantaged and intravenous drug user women in the 1990s in North America suggested that FSD was commoner in women who were HIV positive compared to HIV negative, and that a sexual adjustment period after being told the diagnosis persisted for up to a year [102], [103]. In spite of needing to adjust to having HIV, 44% had resumed sexual intercourse after 4 weeks [103]. Hypoactive sexual desire disorder (HSDD)(DSM-III-R) was reported by 39% of such women over the previous 4 weeks in the absence of clinical depression [104]. Brown and colleagues carefully followed up 54 HIV-positive women from the US armed forces for over 5 years [16]. Heterosexual intercourse was the presumed mode of transmission in most cases. By their third follow up visit, 14 of the 28 still attending had developed HSDD (DSM III-R) for at least 4 weeks in the absence of psychiatric illness [105]. These rates of HSDD appear significantly higher than the 16% recently reported in a large general population study[106]. However, it is questionable whether HSDD reported for only 4 weeks is clinically meaningful [107].

b) HAART era- quantitative studies

Denis and Hong, in an Australian study in 2003 compared 43 HIV+ to 73 non HIV women from a community sample. They pointed out that the two groups were not ideally matched, particularly in regard to the level of psychosocial stress that HIV itself can impart. Using an adapted version of the Sexual Function Questionnaire (SFQ) for women they found the HIV + women had significantly lower total SFQ scores, plus lower scores on a number of the subscales including sexual interest, activity, satisfaction and orgasm [108]. Two clinically based European surveys [20],[21] suggest that such sexual problems, particularly low desire, might be caused either directly by protease inhibitors (PIs) or as a secondary effect via iatrogenic lipodystrophy (see below)[46], [109]. Unfortunately the data for women in these studies are not reported separately. A recent Italian cohort study demonstrated a strong correlation between FSD and self reported non adherence to HAART (the authors offer a number of explanations for this including medication side effects and advancing HIV disease)[9]. Two further studies on women with HIV; one European cross sectional and the other from New York comparing cross sectional data pre and post HAART do not show that PIs or indeed any antiretrovirals have any great impact on women’s sexual dysfunction or psychosocial status [110], [111]. This contention is supported by data that women in general in the HAART era perceive these medication as beneficial and in a positive light compared to the pre-HAART era [112].

Three recent cross-sectional studies show strong associations between FSD and psychiatric illness (Table 3) [110], [113], [114].

c) HAART era- qualitative studies

Further understanding of the psychosocial issues that underpin FSD in the HAART era has been explored in recent qualitative studies [115], [116] (Table 4).

3. GENERAL PSYCHOSOCIAL MANAGEMENT

Studies looking at socially disadvantaged HIV-positive women in North America suggest that focus groups may enhance the social support of these patients, and that using psychological coping styles rather than physical coping mechanisms (i.e. enhancing positive cognitions rather than attending to practical issues) may be associated with significantly less distress and depression [117], [118].
### TABLE 3. HAART era cross sectional studies

<table>
<thead>
<tr>
<th>DESIGN</th>
<th>NUMBERS</th>
<th>FINDINGS</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross sectional descriptive study women New England. Wide CD4 count range Majority low income 64% drug use Wide ethnic background</td>
<td>101 women</td>
<td>Good sexual functioning in the main. Sexual dysfunction correlated to poorer mental health, less positive meaning to Hiv, poorer life quality, fewer Hiv symptoms, ever drug used</td>
<td>Bova C et al 113</td>
</tr>
<tr>
<td>Cross sectional Self selected UK 75% Black Africans Wide CD4 count range HAART status unknown</td>
<td>82 women</td>
<td>35% depressed; 60% anxiety 42% sexually dysfunctional Significant correlation between depression and sexual dysfunction; 40% had been sexually abused</td>
<td>Lambert S et al 114</td>
</tr>
<tr>
<td>Cross sectional study Pan European 83% Caucasian CD4&gt; 500 in 60% Most women using HAART</td>
<td>166 women</td>
<td>FSFI&lt;10 (high grade dysfunction) 25% Low FSFI NOT associated with organic illness/HAART but with anxiety/depression</td>
<td>Florence E 110</td>
</tr>
</tbody>
</table>

### TABLE 4. Qualitative Studies in HAART era

<table>
<thead>
<tr>
<th>SUBJECTS</th>
<th>THEMES</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>74 women in pre HAART era 74 women in HAART era(30% on HAART) New York City Mixed race Low Income</td>
<td>Similar findings both eras:- Fear of Hiv transmission Loss of sexual spontaneity and freedom Diminished participation in sex Fear of rejection Relationships a hassle Diminished sense of self attractiveness</td>
<td>Siegel K et al 111</td>
</tr>
<tr>
<td>21 women London UK 67% Black African in HAART era 81% currently taking HAART No history of drug abuse</td>
<td>Fear of Hiv transmission Fear of disclosure Relationship avoidance Reduced sense of intimacy Sex with casual partners to avoid disclosure Dislike of condoms</td>
<td>Keegan A et al 115</td>
</tr>
</tbody>
</table>
4. OTHER ISSUES

a) Genital arousal

There are good theoretical reasons as to why genital arousal in HIV+ women might be impaired i.e. genital arteriosclerosis and impaired vascular response because of autonomic neuropathy. However, there are no studies directly addressing these issues. Indirect evidence comes from a number of studies such as the large Women’s Interagency HIV study in the USA where insulin resistance was found to be significantly associated with HIV (compared to HIV negative women) - particularly with use of the NRTI stavudine [119]. Arteriosclerosis has been found to be associated with HIV infection itself, likely via local cytokine release, the duration of infection, age, abnormal fat distribution, nadir CD4 count and protease inhibitors [120], [121]. Screening for autonomic neuropathy by history suggests it is a not uncommon problem in women and men in a population with a mean CD4 count of just over 300 [122].

b) Body image

The pathogenesis of HIV associated lipodystrophy is multifactorial. However, the protease inhibitors have been incriminated in fat accumulation and the nucleoside analogue reverse transcriptase inhibitors with lipoatrophy [123]. A recent pan USA cross sectional study involving 183 HIV+ women and 142 well matched negative controls however demonstrated that peripheral fat atrophy (face, cheeks, arms, legs, buttocks) occurred in 28% of the HIV women but only 4% of the controls. Central (visceral) hypertrophy was present in around 60% of both groups, was associated with HAART use, and was not associated with peripheral atrophy [124]. Two further HIV negative matched cross sectional studies in women from the USA confirmed that lipodystrophy is significantly associated with poor body image and depression and may result in patients stopping HAART [125]-[127]. In an African setting fat redistribution (facial and buttock atrophy and abdominal adiposity) can render these women easily recognisable, and hence significantly effects psychological and social domains of the quality of women’s lives to the extent that they feel stigmatised and marginalized socially and sexually [128]. Exercise training (level 1) and facial lipofilling with either autologous fat or polylactic acid infiltrates (level 3) can result in a marked improvement in self image and self esteem [129], [130].

### c) Sex hormones

When HIV disease becomes advanced in women, low body mass index is associated with significant reduction in free testosterone [131]. An early studies suggested that iatrogenic visceral lipodystrophy was associated with significantly raised free testosterone levels, but this was not confirmed in a later study of similar design [132], [133]. In terms of sexual desire and arousal, it is likely that some women are more sensitive than others to falling levels of androgens [134]. Replacing testosterone in women with HIV associated weight loss appears to be safe and well tolerated at least in the short term (level 2) and significantly increases muscle strength (level 2) [135, 136]. Its effect on sexual responses in women are not known.

It has been argued that oestrogens may be protective against Tat protein induced inflammatory pathways in human vascular endothelium induced arteriosclerosis, and may be protective against HIV dementia [137], [138]. However, oestrogen containing contraceptives may interact with antiretrovirals and consideration should be given to this therapeutic scenario in each individual case, along with consideration of dual methods of contraception [139].

d) Unsafe sex

A French cohort study followed up 176 men and 47 women over a median of 24 months who initially had primary HIV infection. Sexual behaviour at risk for transmission of HIV (SBR) was defined as inconsistent use of condoms at sex, compared with always using condoms. SBR rates for women were higher than for men, but mostly occurred with seropositive partners. After a mean of 5 year follow up, 21% of patients had had SBR with a casual partner (9% at study outset). SBR sex with steady partners however remained constant at about 5%. Other risk factors for SBR were the onset of lipodystrophy and anxiety/depression [140].

Adolescents who had acquired HIV non sexually either at birth or via transfusion appear to have little knowledge of safer sex, and in an African context are both marginalized by short stature and low weight as well as worrying if they can ever marry [141], [142].

However, condom use in post menopausal women with HIV does not appear to decrease after the menopause, unlike typical HIV negative women [143].

In a recent UK study 80% of women who attended a clinic for emergency contraception after unprotected sex had not heard of post exposure HIV prophylaxis [144].

5. HUMAN PAPILLOMA VIRUS (HPV) AND SEXUAL DYSFUNCTION

Human papilloma virus (HPV) causes benign condylomata or genital warts and is known to have oncogenic strains. More than 120 HPV subtypes have been identified. Of the 120 subtypes of HPV, 30 infect genital epithelium. HPV is spread through direct skin-to-skin contact during oral, genital, or anal sex with an infected partner. Genital warts can
be caused by strains 6, 11, 30, 42, 43, 44, 45, 51, 52 and 54. However, types 6 and 11 are responsible for 90% of genital warts cases [145]. Most infected individuals do not develop genital warts: the rate of subclinical infection is high. HPV is also associated with cervical cancer and anal cancer; types 16 and 18 account for 70% of HPV associated cancers including oral cancers [146]. The incidence of HPV infection has increased in the last 35 years, likely the result of earlier age of initial sexual contact and an increased number of sexual partners [145]. The estimated prevalence rate of HPV genital infection in the US adult population is 10-20 percent. The incubation period of HPV varies from 3 weeks to 8 months, with a mean of 2-3 months after initial contact [145].

There are now two prophylactic vaccines for HPV; a bivalent vaccine Cervarix which induces protective immunity against HPV 16 & 18; and a quadrivalent vaccine, Gardasil, a quadrivalent vaccine inducing protective immunity against HPV 6, 11, 16 & 18 [147], [148]. There is also unpublished evidence that these vaccines reduce both the incidence and virulence of genital cancers in men. Public health officials in Australia, Canada, Europe and United States recommend vaccination of young women against HPV to prevent cervical cancer and genital warts and possibly oral cancers.

There is currently conflicting data to link sexual problems including emotional distress in men and women with HPV infection [149]-[153]. In practice, many clinicians managing men and women with genital warts realize the association between genital warts and changes in sexual functioning and relationship issues. Clearly more research is required.

6. GENITAL HERPES

Genital herpes (GH) is usually caused by type 2 herpes simplex virus (HSV) but type 1 is becoming an increasingly common cause nowadays [154]. A recent population study in the USA estimated that 17% of those between the ages of 14 and 49 had acquired HSV type 2 [154]. Up to 90% of those who acquire HSV type 2 antibodies have never knowingly had a clinical outbreak of GH [155]. Symptoms can be severe in a primary outbreak, particularly in women, where fever, headache, malaise and myalgia are reported in up to 70% of cases [156]. Classically, the lesions progress from erythema to vesicles to pustules, and then break down to form erythematous-bordered painful ulcers [156]. The ulcers heal by crusting in non moist areas. About 30% of patients have a milder clinical course, likely either because of pre-existing HSV 1 or HSV 2 [156].

Routine diagnostic testing is either via cell culture or nowadays, increasingly commonly in house polymerase chain reaction testing [157].

Patients are usually in too much pain to even consider intercourse during a primary infection. Untreated, the symptoms can persist for weeks, but antivirals such as acyclovir can resolve the symptoms within days. Recurrences of genital herpes are less common where the initial infection was HSV type 1 [158].

Many patients have frequent recurrences. These are usually confined to a small area of the genitals and rarely persist for longer than 7 days even if untreated. It is not so much the pain of the genital lesions that may prevent some patients from having intercourse but rather the concern of transmission even if they do not have any current outbreak. Other important patient issues are the stigma of having a sexually transmissible disease as well as the psychosocial and psychosexual issues that may accompany recurrences in some vulnerable patients.

There is little doubt that recurrent GH is associated with psychological distress and psychosexual problems. However opinion differs as to whether these problems are the result of the stress of having genital herpes, caused by pre-existing stressors or a combination of the two [159],[160]. Many patients with recurrent GH complain of feeling low in mood, tense and having sleep disturbances for a day or two prior to a recurrence. This may be because of release of systemic cytokines prior to the clinical manifestations of the recurrence [159].

Disclosure to partners may be problematic. Patients with recurrent GH appear less likely to tell partners their diagnosis if they perceive them as "casual" and if they are depressed. Decisions to inform partners are more based on perceived likelihood of discovery and honesty rather than control of transmission [161].

Patients who have frequently recurrent GH need to be empowered with information regarding their illness and likely transmission to others. Even if they abstain from intercourse at outbreaks there is about a 5% chance per year that the partner will acquire GH (via asymptomatic shedding of virus) [162]. This rate can be halved if the patient takes continuous antiviral prophylaxis and is significantly decreased with regular condom use [162], [163]. Patients should be told that even if the recurrence is not in the genital area e.g. buttock region, that asymptomatic genital shedding of virus is a common contemporaneous event [164].

Continuous antivirals for patients with regular and frequent recurrences, such as acyclovir, valacyclovir or famcyclovir will significantly decrease the clinical outbreak rate, increase the quality of the patient's life in general, decrease anxiety, illness concern and the chance of transmission at sex [162], [165], [166]. It is
of psychological distress compared to those who did not suffer sexual abuse in the past [179]. A Danish study of 277 men and women based in general practice showed that 10% of those who found out they were CT positive ended their current acquisition onto others rather than themselves [175]. Both qualitative research and a thematic analysis of the literature strongly suggest that CT positive patients are at increased risk of psychological distress [176], [177]. In particular, women tended to blame themselves for acquiring CT and feel stigmatised, whereas men are less concerned in general about CT, less willing to disclose to partners and tend to project the blame of infection onto others rather than themselves [175]-[177]. A Danish study of 277 men and women based in general practice showed that 10% of those who found out they were CT positive ended their current relationship as a direct result of the infection [178]. A history of past sexual abuse in patients with recurrent bacterial STIs was associated with a higher degree of psychological distress compared to those who did not suffer sexual abuse in the past [179].

Consistent and correct condom usage has been shown to confer a statistically significant degree of protection against bacterial STIs such as CT and Gc [180]. CT and Gc are the most likely organisms to cause acute PID but other conditions such as bacterial vaginosis (see BV section) and Mycoplasma genitalium may be involved [181], [182]. Gonococcal PID is usually more severe, but less likely than CT to cause long term sequelae. The incidence of PID in women who are CT infected ranges from 5% to 30% [183]. The important outcomes of PID are pelvic pain, infertility and ectopic pregnancy. Deep dyspareunia may or may not be present with background pelvic pain- it is associated with anxiety, depression and a history of sexual abuse [184].

Young women may continue to have intercourse in spite of dyspareunia because they feel sexual intercourse affirms them being a normal woman and to satisfy their partner’s sexual needs [185].

Tubal infertility can be associated with distress, anxiety, depression and relationship problems. In one study of tubal infertility about a third of women felt this had a negative effect on their sex lives [186].

7. CHLAMYDIA TRACHOMATIS (CT), GONORROEA (GC) AND ASSOCIATED PELVIC INFLAMMATORY DISEASE (PID)

Recent WHO estimates estimate the prevalence of CT in European women as between 2.7% and 8.0%, with rates of up to 13% in African countries [172]. Rates for Gc world-wide ranged from between 0.1% and 3.5% and resulted in a total of 62 million cases between 1995 and 1999 [173].

Mass screening programs are important in order to decrease the prevalence of CT and its complications. Careful assessment of 20,000 men and women randomly screened from general practice in the UK showed that the screening process did not have a negative impact on psychological well being where the results were negative; in fact they suggested that the process can lead to a general decrease in anxiety [174]. Both qualitative research and a thematic analysis of the literature strongly suggest that CT positive patients are at increased risk of general anxiety, fear of infecting their partner and concern about infertility [175]-[177]. In particular, women tended to blame themselves for acquiring CT and feel stigmatised, whereas men are less concerned in general about CT, less willing to disclose to partners and tend to project the blame of acquisition onto others rather than themselves [175]-[177]. A Danish study of 277 men and women based in general practice showed that 10% of those who found out they were CT positive ended their current relationship as a direct result of the infection [178]. A history of past sexual abuse in patients with recurrent bacterial STIs was associated with a higher degree of psychological distress compared to those who did not suffer sexual abuse in the past [179].

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IV SEXUAL DYSFUNCTION AND CHRONIC PROSTATIS/CHRONIC PELVIC PAIN SYNDROME (CP/CPPS)

1. INTRODUCTION

In spite of the known impact of prostatitis-associated symptoms on sexual dysfunction, limited data is available to suggest a proven association between the two entities. Since a high percentage of men with prostatitis-like symptoms do not have a known infectious or inflammatory prostate-related etiology for their symptoms , the investigation of the relationship is complicated and must be based on the generally accepted definition of the National Institutes of Health(NIH) prostatitis panel (Table 5) [187], [188]. The evaluation of the effects of prostatitis on sexual function should take into consideration the adverse effects of drug therapy of CP/CPPS on sexuality, as well as the more interesting direct interactions between prostatitis symptoms and disorders of libido, erectile function and ejaculation. In this context, it is noteworthy that some investigators are convinced that “prostatitis” does not necessarily impair sexual function, whereas others suggest a rather strong association [189], [190]. The failure to demonstrate a concrete link between sexual dysfunction and prostatitis may be based on the following two factors: a) The use of unaccepted classifications of “prostatitis” and b) analysis of a generally dysfunctional or disturbed sexuality without clear definition of the different entities. An acceptance of the new prostatitis definition and a clear identification of the items of disturbed sexuality are necessary to improve the understanding of the association.
2. PROSTATITIS – CLASSIFICATION AND RELATED UROGENITAL INFECTIONS INFLAMMATIONS.

The NIH classification of prostatitis syndromes is supported by the International Prostatitis Collaborative Network (Table 5) [187].

Type I, Acute Bacterial Prostatitis is a severe infection with fever, inflammatory host response, and voiding disturbances excluding active sexuality. Type IV prostatitis is considered an asymptomatic inflammatory condition in patients in whom white blood cells are found in prostatic tissue or in prostatic secretions and is thus difficult to relate to sexual dysfunction. Therefore, when considering disturbed sexuality, only type II Chronic Bacterial Prostatitis and type III Chronic Prostatitis/Chronic Pelvic Pain Syndrome have to be considered.

Chronic Bacterial Prostatitis (NIH II- typically caused by coliform bacteria) is a rare disease in about 5 percent of all men presenting with “prostatitis” symptoms which are indistinguishable from CP/CPPS [188], [191]. Recurrent UTIs in the history and the evidence of bacteriospermia in semen are other clinical findings common for this entity [192]. In CP/CPPS (NIH III), men with “prostatitis” symptoms, mainly pelvic pain, are classified to the inflammatory (NIH III a) or non-inflammatory (NIH III b) group. The differentiation is made by the finding or exclusion of leukocytes in the urine after prostatic massage, EPS or in semen [187], [188], [191], [192]. It is an ongoing debate whether both entities are really to be considered as different [193], [194]. There remain also major concerns regarding the validity of the NIH-CPSI questionnaire as instrument for diagnosis, classification and severity of CP/CPPS [193], [194]. The WHO has pointed out that the symptoms of CP/CPPS may relate not only to pathology in the prostate but also to the whole male pelvic genital region, especially to the epididymides and the seminal vesicles [195]. There is little direct evidence that sexually transmitted bacteria such as Chlamydia Trachomatis or Mycoplasma species cause CP/CPPS, in part due to problems of urethral contamination of prostatic secretions [187], [196-198]. Hopefully, the interaction between IL-8 and antichlamydial mucosal IgA in the ejaculate provides a new opportunity to establish a better organ-related diagnosis of potentially sexually transmitted infections of the prostate in the future [196].

3. ANALYSIS OF THE LITERATURE

We searched the PubMed database covering the last 8 years (English-German) using the search terms: urogenital infections, prostatitis, chronic urethritis, Chronic Bacterial Prostatitis, CP/CPPS, MAGI, ejaculate infection, ejaculate inflammation, sexual dysfunction, erectile dysfunction, libido disorders, sexual excitation, ejaculatory dysfunction, premature ejaculation, ejaculatory pain, loss of ejaculate volume. Furthermore, all supplements (2000-2008) were included. These topics have been looked through for items addressing sexual disorders in their relation to infections/inflammations of the urogenital tract.

These searches identified a total of 62 articles. This was followed by a review of the titles and abstracts following the modification of the US Department of Health and Human Services (1992)* giving an evidence-based guideline. 51 papers met the criteria for inclusion. Astonishingly, no systematic reviews or meta-analyses could be included.

Most of the papers detailed results of case series and cohort studies (Level 2 and 3 evidence).

4. SEXUAL DYSFUNCTION AND "PROSTATITIS" SYMPTOMS

Early anecdotal experience in the 1980s suggested a significant association between "chronic prostatitis" and sexual dysfunction [199]. Later on, these postulated interactions between chronic prostatitis, the psychological and physical health status and the direct influence on sexual activity were addressed in two overviews [200], [201]. In 2005, Lutz et al were the first to analyze systematically the interaction between urogenital (pelvic) pain and sexual function [202]. The authors used the NIH-CPSI with a cutpoint of >4 in the pain score and the Brief Male Sexual Function Inventory [193], [203]. In this study men with significant “pelvic pain” had a higher chance of suffering from ED than patients without pelvic pain (level 3 evidence). Recently, Marszalek et al analyzed the prevalence of CP/CPPS in an urban population (Vienna) in association with erectile function [204]. The study confirmed a significant correlation between CP/CPPS symptoms measured by the NIH-CPSI and erectile dysfunction measured.

Table 5: Prostatitis NIH Classification

<table>
<thead>
<tr>
<th></th>
<th>Acute Bacterial (ABP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Chronic Bacterial (CBP)</td>
</tr>
<tr>
<td>III</td>
<td>Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS)</td>
</tr>
<tr>
<td></td>
<td>a) inflammatory</td>
</tr>
<tr>
<td></td>
<td>b) non-inflammatory</td>
</tr>
<tr>
<td>IV</td>
<td>Asymptomatic, Inflammatory</td>
</tr>
</tbody>
</table>

NIH (National Institutes of Health)
by the IIEF (level 2 evidence). Using the same questionnaires Qiu et al. were not able to confirm such a significant correlation (level 3 evidence) [205, 206].

4 studies analyzed the percentage of ED measured by the IIEF in men suffering from CP/CPPS according to NIH criteria (Table 6). Anderson et al. analyzed 146 patients with CP/CPPS defined by NIH criteria and stated erectile dysfunction in 45%, meaning a percentage of 31 percent (level 3 evidence) [207]. Liang et al. analyzed the prevalence of sexual dysfunction, meaning erectile dysfunction and premature ejaculation in “prostatitis” patients demonstrating a prevalence of ED in only 15% (level 3 evidence) [208]. Most of these patients revealed erectile dysfunction and/or problems with premature ejaculation: 7.7% suffered from both pathologies. In a recently published study from China, 296 participants seeking help for CP/CPPS have been evaluated, 72.3% reported sexual dysfunction (level 3 evidence) [209]. In this study, in most of men ejaculatory dysfunction was common and in men, reporting both ED and ejaculatory difficulties, worse CP/CPPS symptoms and a reduced quality of life became evident (level 3 evidence). Finally, one study from Italy has to be mentioned. This study included not only men with CP/CPPS, but also men with CBP. The authors demonstrated an incidence of ED in about 23% of the patients (level 3 evidence) [210].

Table 6: Percentage of Erectile Dysfunction in Men with CP/CPPS

<table>
<thead>
<tr>
<th>Author</th>
<th>Reference</th>
<th>Percentage of ED in CP/CPPS %</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al</td>
<td>21</td>
<td>31</td>
<td>-</td>
</tr>
<tr>
<td>Liang et al</td>
<td>22</td>
<td>15</td>
<td>additionally ejaculatory dysfunction</td>
</tr>
<tr>
<td>Lee et al</td>
<td>23</td>
<td>72</td>
<td>cases of NIH II included</td>
</tr>
<tr>
<td>Trinchieri et al</td>
<td>24</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

In conclusion, symptoms of sexual dysfunction, especially ED, do occur in between 15 to 72 percent of all patients seeking help for “prostatitis” related symptoms. This is particularly notable in cases of CP/CPPS. A significant correlation between severity of ED and increasing CP/CPPS symptoms remains debatable. Unfortunately, age-matched control studies including the general accepted risks for ED are not published in this context to date. Until an evidence-based confirmation of this association becomes available, it is difficult to ascertain the validity of the proposed links between the two conditions.

Another very important concern is the interaction between CP/CPPS symptoms and ejaculatory dysfunction. As already mentioned, two Chinese studies demonstrated the relevance of premature ejaculation (PE) in symptomatic prostatitis patients [208], [209]. This finding was later corroborated by a study from Turkey where a modern definition of PE using the intravaginal ejaculation latency time was utilized: 77% of all men with CP/CPPS suffered from this disorder (level 3 evidence) [211]. In a very similar study from Italy, Screponi et al. reported a high incidence of “inflammatory prostatitis signs” in men with PE [212]. Their findings are more controversial and debatable due to the use of poorly-defined “prostatitis” diagnostic tools (no evidence).

Besides PE, “prostatitis” patients may be bothered by ejaculatory pain [213]. Despite lack of concrete evidence, many patients may be encouraged to refrain from ejaculation when suffering from this condition [189]. Conversely, other investigators have suggested that improvement of prostatitis symptoms may follow better prostatic fluid drainage with regular sexual activity and increased ejaculatory frequency [214] (no evidence).

5. “PROSTATITIS” AND BPH

The impact of infection/inflammation on the pathogenesis of BPH is the subject of ongoing discussions. It is well known that histologically proven inflammation can be demonstrated in the majority of BPH pathologic specimens and that the presence of inflammation may be a predictor of progression outcomes of BPH (level 1 evidence) [215]. The interaction between chronic immune response and fibromuscular growth of BPH is one possible explanation for the similar pathogenesis [137]. A second arguably more important pathway may be the similar cytokine expression by epithelial and stromal prostate cells in men suffering from BPH and CP/CPPS [216]. In men presenting with LUTS, an important diagnostic goal is to establish or to exclude the pathogenesis of the symptoms as being related to BPH [217]. Usually, the AUA Symptom Index or the IPSS are recommended for symptom assessment. A recommendation for special questionnaires pertaining to other items such as altered sexual function is not routinely given [217]. The Alf-One study elegantly demonstrated the direct interaction between severity of LUTS and sexual dysfunction, especially ejaculatory disorders (level 2 evidence) [218]. The key message of this study and consecutive papers is that in sexually active men with LUTS suggestive of BPH, those with painful ejaculation have more severe LUTS, more frequently suffer from ED, and have reduced ejaculatory
6. THERAPEUTIC CONSIDERATIONS.

The 6th International Conference on New Developments in Prostate Cancer and Prostate Diseases in Paris 2005 summarized all types of therapy based on an evidence-based approach for all types of prostatitis and CP/CPPS [188]. In this context, it seems to be the consensus that only therapeutic strategies reducing symptoms, especially against pelvic pain, are of relevance in relation to changes of sexual function. The use of alpha-blockers has to be addressed since one study demonstrated a special benefit on painful ejaculation in LUTS patients. In patients with CP/CPPS, alpha-blockers are often prescribed as the first therapeutic choice for several reasons [222], [223]. Besides the proven efficacy for LUTS, the blockage of alpha-adrenergic receptors located in the nervous system has been discussed as a possible strategy in long-term pain syndromes [224]. Furthermore, a direct effect on neurogenic inflammation has been noted [223]. Concerning CP/CPPS, a new randomized study using alfuzosin did not demonstrate a reduction of symptoms in comparison to placebo (level 2 evidence) [225]. This outcome is contrary to the widespread use of alpha-blockers in all types of prostatitis and especially not in concordance with several trials in the last decade. Nevertheless, there is similarity to the study of Alexander et al who did not find a reduction of symptoms in a 4-arm study using a fluoroquinolones, tamsulosin, both drugs or placebo (level 2 evidence) [226]. Discussing these negative findings, Weidner argued in 2004 against the efficacy of alpha-blocker therapy due to highly variable treatment periods, different populations, and inhomogeneous inclusion criteria of the different studies [227]. In conclusion, it is questionable whether the effects of alpha-blocker therapy are thoroughly directed against the symptoms that comprise CP/CPPS. A subgroup of men with proven subvesical obstruction and/or proven CBP (NIH II) may benefit from alpha blockers, but adverse effects on ejaculatory function typical for at least some alpha-blockers have to be taken into account. Unfortunately, all other types of treatment of CP/CPPS have been evaluated without a clear effect on sexual symptoms in comparison to placebo including phyotherapeutic agents such as pollen extract, quercetin or saw palmetto [223], [228]. Unfortunately, a new randomized study with pollen extract in patients with inflammatory CP/CPPS did not show an improvement of the mean sexuality domain of a life satisfaction questionnaire, although compared to placebo, the pollen extract significantly improved total symptoms, pain and quality of life (level 2 evidence) [229]. These results are to be interpreted as a weak interaction between CP/CPPS symptoms and disturbed sexuality.

Concerning the combined use of alpha-blockers and a PDE 5-inhibitors in men suffering from LUTS and ED, it seems to be the consensus that this combination may be more effective than each drug administered alone [230]. Stimulated by these results, different authors speculate on the benefit of PDE 5-inhibitors in CP/CPPS. A relaxation of prostatic duct smooth muscles increasing the washout of prostatic reflux products interacting with pain receptors was suggested as one beneficial pathway [231]. Furthermore, the better arterial vasodilatation provided by the degradation of cGMP into GMP catalyzed by cyclic nucleotide phosphodiesterase enzymes in the prostate has been suggested to be useful in the treatment of CP/CPPS [231], [232]. Unfortunately, recently published studies concerning the interaction of the effect of PDE 5-inhibitors on CP/CPPS symptoms and disturbed sexuality do not show significant effect either due to the study design or to the missing correlation between CP/CPPS symptoms and ED (Table 7) (no evidence).

V. SEXUAL, SOCIO-CULTURAL AND ECONOMIC ISSUES OF HIV WITH PARTICULAR REFERENCE TO SUBSAHARAN AFRICAN WOMEN

1. INTRODUCTION

Every day, over 6800 persons become infected with HIV and over 5700 persons die from AIDS, mostly because of inadequate access to HIV prevention and treatment services [91]. AIDS continues to be the single largest cause of mortality in sub-Saharan Africa and of the global total of 2.1 million [1.9 million–2.4 million] adult and child deaths due to AIDS in 2007, 1.6 million [1.5 million–2.0 million] occurred in sub-
Saharan Africa. There are an estimated 11.4 million [10.5 million–14.6 million] orphans due to AIDS1 in this region [91].

Women and young people are especially vulnerable to HIV. Half of all new infections occur in young people aged 15-24 and young women account for 62% of the 11.8 million people living with HIV [233].

Differences in the spread of the epidemic can be accounted for by a complex interplay of sexual behavior and biological factors that affect the probability of HIV transmission per sex act and sexual behavior patterns are determined by cultural and socioeconomic context [234]. In sub Saharan Africa the subordinate position of women, impoverishment and decline of social services, rapid urbanisation and modernization, wars and conflicts have contributed to extensive spread of HIV [234].

In addition to these macrocosmic parameters there are microcosmic influences to this epidemic. Stulhofer’s study on Croatian youth indicates that peer pressure, sensation seeking, personal risk-assessment, behavioral intention, condom use at first sexual intercourse and sexual victimization were significant predictors of sexual risk taking behaviors [235]. An integrated sociobehavioral approach to communication as a means of prevention of HIV/AIDS is thus of vital importance [236].

2. THE FEMINIZATION OF HIV

In sub Saharan Africa, young women (15-24 years) are approximately three times more likely to be HIV infected compared to young men of the same age [237]. 50% of infected people worldwide are women and half of new infections occurred between spouses with women often at risk from their main male partner [238]. This has been described as the “feminization of HIV/AIDS” [238].

Gender based violence (GBV) is the most significant reason for women’s greater vulnerability to HIV. It is partly explained by women’s inability to negotiate the terms and conditions of sex as well as very high levels of sexual and domestic violence [239]. A study of more than 1500 South African women indicates that “women with violent or controlling male partners are at increased risk of HIV infection. [239]” A review of research articles from 1996 to 2002 found 9 studies showing that women who experienced sexual coercion were more at risk of HIV transmission [239]. Ackermann looked at the social factors that make South African women vulnerable to HIV infection and concluded that the degree to which women are able to control various aspects of sexual lives is critical to HIV prevention [240]. The high rate of rape, the unfavorable economic position of women and the inability to insist on condom usage render these women powerless to protect themselves against HIV/AIDS [240], [241]. Poor women are especially vulnerable to coercion from and compliance to their male partners [236].

A study examined gender attitudes and sexual violence-supportive beliefs (rape myths) in a sample of South African men and women at risk for HIV transmission. The authors speculated that women’s risks for STI/HIV are the product of partner characteristics and male dominated relationships. Some of these men’s characteristics include a sexual assault history and rape myth acceptance, along with alcohol and other drug use history [241]. Studies conducted in the USA show that women in violent or abusive relationships are less likely to use condoms, more likely to incur abuse as a result of requesting condoms and more likely to contract a STI than women who have not been in violent relationships [241].

This is supported by research conducted in a township in Cape Town [241]. A total of 40% of the women surveyed had been sexually coerced. They were significantly more likely to have exchanged sex to meet survival needs, to have had multiple male sex partners, greater rates of unprotected vaginal intercourse, lower rates of condom use, more sexual

<table>
<thead>
<tr>
<th>Author</th>
<th>Reference</th>
<th>Type of study</th>
<th>Effect on CP/CPPS symptoms</th>
<th>Effect on Sexual Dysfunction</th>
<th>Association between both symptoms</th>
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<tbody>
<tr>
<td>Yang et al</td>
<td>48</td>
<td>prospective study</td>
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<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Aliyev et al</td>
<td>49</td>
<td>cohort study</td>
<td>not analysed</td>
<td>no better prostatic arterial flow</td>
<td>no</td>
</tr>
<tr>
<td>Lin et al</td>
<td>50</td>
<td>prospective study</td>
<td>yes</td>
<td>yes</td>
<td>negative correlation</td>
</tr>
<tr>
<td>Esilevskii et al</td>
<td>51</td>
<td>prospective study</td>
<td>not analyzed</td>
<td>better arterial status of the prostate</td>
<td>unclear</td>
</tr>
</tbody>
</table>
AIDS cases due to the perinatal transmission of HIV infection, by year of diagnosis, 2001-2005, United States [233].

Contacts involving blood and greater rates of STI’s. This suggests that the potential for women to reduce their risks for STI/HIV is seriously limited by socially constructed gender roles and sexual scripts [241].

Intimate Partner Violence (IPV) or “Femicide” is violence perpetrated by an intimate partner [237]. Globally between 10 and 69% of women report physical abuse by an intimate partner at least once in their lives. Between 6 and 47% of adult women worldwide report being sexually assaulted by intimate partners in their lifetime. Between 7 and 48% of girls and young women age 10-24 years report their first sexual encounter as coerced [237]. Gielen et al reviewed 35 US studies on the intersection of HIV and IPV. HIV positive women appear to experience any IPV at rates comparable to HIV negative women.
from the same underlying populations. However their HIV positive women’s IPV seems to be more frequent and more severe than women who are HIV negative. Their research suggest interventions need to focus on both causal pathways of IPV and HIV [242].

The intersection of IPV, GBV and HIV is explained by biological as well as socio-cultural and economic factors [237]:

a) Direct transmission through sexual violence [237]

The biological risk of transmission of forced coercive sexual intercourse with an HIV infected partner is determined by type of exposure (vaginal, anal or oral). HIV risk increases in presence of other STI’s and also degree of trauma, vaginal lacerations and abrasions that occur when force is used. Vaginal tracts of younger women are immature and tear easier during sexual intercourse thus increases risk. Two studies form USA suggest that while women who are raped are at high risk for pre-existing STI, sexual assault itself presents a small but substantial additional risk of acquiring STI (236).

b) Indirect transmission through sexual risk taking

Studies show that women’s experience of violence is linked to increased risk taking. This includes multiple partners, non-primary partners or engaging in transactional sex [237]. In Zimbabwe, Kenya, South Africa and Zaire increasing financial insecurity that exists among female –headed households makes transactional sex a “rational means of making ends meet [236].” Jewkes and colleagues have shown that women who enter transactional relationships are more likely to be HIV positive. They may be more vulnerable as they tolerate unfaithful partner and also seek out additional concurrent sexual relationships for themselves [243].

In more than two thirds (68%) of households women or girls are the primary caregivers for those sick with AIDS related Illnesses [239]. Similar trends are present in parts of Asia and Latin America [236]. Sexual abuse during childhood and forced sexual initiation during adolescence are associated with HIV risk taking among women. In USA several studies show that experience of childhood sexual assaults is associated in adults with early sexual initiation, anal sex, sex with unfamiliar partners and low rates of condom use [237].

c) Indirect transmission through inability to negotiate condom use.

Suggesting condom use with a resistant partner has dire consequences for women: threatens his masculinity, raises his suspicions about the woman’s monogamy or sexual history. Dunkle and Jewkes found that traditional men’s gender roles lead to “more negative condom attitudes and less consistent condom use” [239]. Women find themselves vulnerable to further violence, being rejected and potentially loosing partner’s financial support. This was confirmed in a study conducted in South Africa by the international Centre for Research on Women [241]. A study from USA African-American women who had physically abusive partners were four times more likely to be verbally abused and nine times more likely to be threatened with physical abuse when they asked their primary partner to use condoms compared to those who did not have partner abuse 237. In a South African study women who experienced forced sex were found to be nearly six times more likely to use condoms inconsistently than women who did not experience coercion. And women with inconsistent condom use were 1.6 times more likely to be HIV positive [237]. However another South African study found that women who were physically abused prior to the past year were 1.5 times more likely to ask their current partner to use condoms than women who were not abused [237]. As these have been cross sectional studies measures of condom use and violence have differed across studies. Thus it is difficult to draw definite conclusions about how partner violence is linked to condom use. Condom use is economically dependent as evidenced in Thailand. They experienced initial success with this structural intervention that enforced 100% condom use in collaboration with sex workers, brothel owners, clients of sex workers and the police. But the Asian financial crisis caused widespread unemployment. This worsened the economic situation for women and youths [238]. Girls, women and sex workers found it difficult to insist on condom use. Evidence suggests that when faced with economic duress women are more likely to acquiesce to intercourse with no condoms when offered more money by men [238].

d) Indirect transmission by partnering with riskier/older men

A review of over 40 studies from sub-Saharan Africa suggests that a significant proportion of adolescent girls have sexual relations with men five to ten years older than themselves [237]. Emerging evidence form a study conducted among women (16-23 years) in South Africa suggests that women who have partners older than them (i.e. age difference of three or more years) have 1.6 fold higher odds of being HIV infected. Young women with older partners are 1.5 times more likely to experience physical and sexual violence than women with partners in their peer age group [237]. Several studies highlight that men’s use of violence is linked to their own sexual risk taking. This increases both their and partners risk of HIV/STI’s [237]. In India a study showed that men who had extra marital sex were six times more likely to report sexual abuse of their wives than men.
who remained faithful [237]. The men in this study who reported an STI were 2.5 times more likely to report abuse of wives than men who did not report an STI. Thus these researchers concluded that abusive men were more likely to engage in extra marital sex, acquire STI, and place their wives at risk for STI possibly through sexual abuse [237].

e) Violence as a consequence of being Hiv positive.

Between 16-86% of women in developing countries choose not to disclose their HIV status to their partners [237]. Disclosure is essential as it ensures HIV positive person get access to services including prevention of mother-to-child transmission (MTCT) antiretroviral treatment (ART) and psychosocial support. In most studies between 3-15% of women report negative reactions from disclosure. Blame, abandonment, anger and violence result. Between 16-51% of women in studies from Tanzania, South Africa and Kenya say they do not disclose their status due to their fear of violence [237].

A study was conducted in South Africa to examine if non-disclosure of HIV positive status placed sexual partners at risk. Sample was 69 sexually active, heterosexual, married (62%), cohabitating (38%) patients recently diagnosed as HIV positive. Results showed that 78% had not disclosed and 46% had no knowledge of their partner’s serostatus [244]. These non disclosures were more likely to be male, to not have used a condom during their last sexual encounter, to have used alcohol heavily before sex, to have multiple sexual partners and to have engaged more frequently in sexual intercourse in the six months prior to the study [244].

Kalichman’s study on risk behaviors of men and women living with HIV/AIDS is disturbing [245]. Across populations one in three persons with HIV/AIDS continues practicing HIV transmission risk behaviors. This behavior is related to relationship factors, economic conditions, emotional states, substance abuse and personality dispositions. From this study it appears that risk behavior is increasing with HIV negative partners and partners of unknown HIV status. Kalichman’s study observed that risk practices are also affected by perceptions of how ART’s may affect infectivity [245].

Similarly a study by Marks and Crepaz (14) of 206 HIV positive men (41% homosexual, 35% bisexual, 24% heterosexual) showed that 25% of the men engaged in unsafe sex and 48% of the total sample withheld disclosure from the partner. Risky behavior patterns repeat what has been noted in other studies: alcohol and drug use before sex, having a HIV unknown partner, being less emotionally involved with one’s partner and testing seropositive in the previous 3 years [246].

A cornerstone of HIV prevention in South Africa is voluntary HIV antibody counselling and testing (VCT), only one in five South Africans aware of VCT have been tested. Kalichman’s study results on 224 men and 276 women living in a black township in South Africa showed that individuals not tested for HIV demonstrated significantly greater AIDS related stigmas; greater shame, guilt and social disapproval to people living with HIV.

f) Mother-to-child (perinatal) HIV transmission

HIV transmission from mother to child during

(Strengthening the Linkage between Reproductive Health and HIV/Aids Program, by Elizabeth Lule, Population and Reproductive Health Advisor)
pregnancy, labor and delivery, or breastfeeding is called perinatal transmission [247].

VCT testing allows pregnant HIV women ARV’s to reduce the risks of MTC (perinatal) transmission. However a study by Gaillard et al shows that a major obstacle to compliance is partner disclosure [248]. Only a third of the 290 HIV infected women included in an intervention study to reduce mother-to-child transmission of HIV in Mombasa, Kenya, informed their partners of their results. Despite careful counselling, 10% subsequently experienced violence or disruption of their relationship.

g) Women who have sex with women (WSW)
The belief that female same sex relationships are low risk of contracting HIV and other STI’s continues to dominate. WSW who are in both same sex and heterosexual relationships needs attention [249]. Data on HIV risk faced by WSW are scarce. Several surveys have reported that that certain groups of WSW engage in risky behavior such as unprotected sex with men, unprotected sex or sharing sex toys with women and injection drug use [250]. Self reported HIV rates among lesbian women in a study show that 8% of those tested were positive [249]. In Post-apartheid South Africa, a large number of lesbian black women have fallen victim of hate crimes and violent sexual attacks, being victim to “conversion rapes” some of which have led to HIV infection or even death [249]. Numerous studies indicate higher prevalence of BV, hepatitis C and HIV risk behaviors in WSW [251], [252]. These data support the hypothesis that sexual exchange of vaginal secretions is a possible mechanism for acquisition of BV. A study by Marazzo JM et al indicates that Genital HPV infection and squamous intraepithelial lesions are common among WSW [252]. In summary women’s physiological susceptibility due to hormonal changes, vaginal microbial ecology and physiology plus a higher prevalence of STI’s, and it is understood that behaviors that put WSW at risk for HIV need attention [253].

3. SEXUAL BEHAVIOR AND HIV/AIDS/STI’S

Although HIV has been identified as the etiological agent causing AIDS, transmission of this virus depends on human behavior related largely to sexuality and drug use [239]. It is important not to assume that individuals make rational decisions when engaging in sexual activity. It is impulsive and driven by physiological needs [236]. Add to this “contextual personal” and socio cultural variables such as gender and racial/ethnic culture and the complexity of HIV/AIDS becomes clearer [236].

Concurrent partnerships are a major contributing behavior that places people at risk. Morris’s study examined how concurrent partnerships amplify the rate of HIV spread. Their results indicate that concurrent partnerships exponentially increase the number of infected individuals and the growth rate of the epidemic during its initial phase. Adimora and Schoenbach’s study similarly found that mathematical modelling demonstrates that concurrent sexual partnerships spread transmission of HIV through sexual networks more effectively than does serial monogamy for the same total number of sexual partners [254], [255]. Helen Epstein gives an excellent description of concurrency and the effects of sexual networking on HIV transmission as an explanation of why HIV rates are so high in Africa [243].

4. THE VULNERABILITY OF MEN AND HIV/AIDS/STI’S

Although the first cases of AIDS were reported in gay men little is known about the current prevalence of HIV among lesbian, gay, bisexual, transsexual (LGBT) and now that the dominant mode of transmission is seen as heterosexual, and women at most risk, less data exists on heterosexual men and HIV/AIDS.

Decker et al did a study on sex purchasing and HIV among a clinic based sample of US men [256]. They found that men engaging in sex purchasing were more likely to be HIV/STI infected and thus represent a risk to the sexual health of both commercial and non-commercial sex partners. In summary heterosexual men put their close partners at risk through lack of awareness of their actual HIV status, practicing unprotected sex with close committed partner whose status is also unknown, intravenous drug user and sex purchasing [257].

Dunkle and Jewkes name the following as male factors that increase their risk for HIV [239]:

1. Men and low condom use
2. Men and VCT: Recent national studies in South Africa found that only one in five South Africans aware of VCT have been tested and that men accounted for only 21% of all clients receiving VCT3. Men and ART: A study conducted at Johannesburg General Hospital indicated women accessing ARV’s outnumbered men 2:1. Men were also likely to use ARV’s later in the disease trajectory than women.
4. Men and alcohol: World Health report noted that South African men were more likely to be “heavy drinkers”. Alcohol is a risk factor for GBV and HIV
5. Men and male circumcision (see section on this topic above)
6. Men and partner reduction: surveys suggest that the spread of HIV is accelerated where men have multiple concurrent partners and practice unsafe sex [243], [254], [255].
5. MEN WHO HAVE SEX WITH MEN (MSM)

Recent studies demonstrate that unprotected anal sex between men is a factor in HIV prevalence. In Zambia one in three surveyed tested MSM tested HIV positive; in Kenya 43% of MSM were living with HIV; in Senegal HIV prevalence rate of 22% was found among 463 MSM surveyed [258].

Lieb et al examined estimated numbers of MSM in Miami-Dade County by race, ethnicity and mortality rates. An estimated 63,020 men aged >=18 in the country are MSM with mortality rates higher for black men than other races [259].

Mckellar et al tested MSM aged 15-29 years for HIV at 263 randomly selected sampled venues in 6 US cities from 1994-2000. Of 5649 participants 10% tested positive for HIV. Of these 77% overall were unaware of their infection [260]. A study was conducted with MSM who use the internet to meet sexual partners. 53% used condoms consistently, 47% reported having sexual partners that were older >4 years. In this study MSM engaged in behaviors such as unprotected anal intercourse that place them at risk for HIV /STI's [261].

Research into MSM in Africa is limited. Johnson reports that most Africans have also engaged in sex with women [262]. Once again myths make men more vulnerable to HIV, as does economic exchange, and inconsistent condom use. Sexual abuse of MSM is common.

In summary, management and prevention requires all people get tested, use condoms, and choose partners carefully. In addition long term sustained strategies should address the social, cultural, economic, and political factors that influence the spread of HIV/AIDS.

<table>
<thead>
<tr>
<th>COMMITTEE RECOMMENDATION</th>
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<td><strong>1. HIV</strong></td>
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**RECOMMENDATIONS**

- early diagnosis of HIV associated sexual dysfunction is important in the context of HIV infection and HIV units should have provisions to diagnose/manage or refer to specialists as indicated.
- physicians caring for both HIV infected and HIV negative msm should be aware of the likely psychosocial interaction between recreational drugs, pde5 inhibitors, unprotected sexual behaviour and HIV transmission
- Level of evidence 3, Grade B

HIV encephalopathy

- There should be recognition that there is a likely association between HIV encephalopathy and sexual dysfunction.
- Level of evidence 3, grade B
- Specialist management of HIV associated sexual dysfunction should be in collaboration with HIV physicians
- There should be recognition that there is an interaction between HAART and sexual dysfunction
Level of evidence 3, grade B

Endocrine:

Patients with HIV and endorinopathy should have an assessment of sexual functioning.
Level of evidence 3, grade B

Direct Effects of HIV infection

Lipodystrophy

Recognition of possible association between HIV lipodysrophy and sexual dysfunction is important
Level of evidence 3, grade B

Neuropathy

- Physicians looking after HIV patients should recognize that associated neuropathy may include symptoms of sexual dysfunction
Level of evidence 3, grade B

Iatrogenic low sexual desire

- HIV patients with low sexual desire should be formally assessed for endocrinopathy
Level of evidence 3, grade B

New treatments

Caution and vigilance using newer anti-HIV therapy should include assessment of sexual function
Level of evidence 4, grade C

Circumcision as a strategy to reduce HIV infection in men

1. Male circumcision reduces the risk of acquisition of the HIV virus in HETEROSEXUAL men
Level of evidence: Level 1
Grade of recommendation: Grade A

2. Heterosexual Male circumcision is not associated with behavioral disinhibition and engaging in high risk sexual behavior
Level of evidence: Level 1
Grade of recommendation: Grade A
3. There is a paucity of literature pertaining to the complications of male circumcision in Africa. The available literature does not allow a complete comparison among various studies as there is great heterogeneity with regard to indications, follow-up duration, and the skill set level for the circumcisers.

Level of evidence: Level 3
Grade of recommendation: Grade B

4. Adult male circumcision can be performed in the developing country setting with acceptable outcomes and complications rates similar to those observed in developed nations.

Level of evidence: Level 3
Grade of recommendation: Grade B

HIV IN WOMEN
- Female Hiv infection is associated with sexual dysfunction.
  Level of evidence 3 Grade C.
  - All women with HIV should have a sexual dysfunction screen.
  GRADE B

2. GENITAL HERPES
- All patients with primary and recurrent GH should be seen and counselled about the condition
  level of evidence 4 Grade C
- Those with frequent recurrences of GH should be assessed psychologically and psychosexually and given appropriate treatment for any co-existing psychological illness
  level of evidence 4 Grade C
- Patients with frequent recurrences of GH should be assessed regularly by a clinician and can have their sexual functioning and quality of life enhanced by giving continuous antiviral cover
  level of evidence 1 Grade A

3. CHLAMYDIA TRACHOMATIS (CT), GONORRHOEA(GC), AND ASSOCIATED PELVIC INFLAMMATORY DISEASE (PID)
- Chlamydia trachomatis (CT), gonorrhoea(Gc), and associated pelvic inflammatory disease (PID) are associated with sexual dysfunction.
  Level of evidence: 4
  Grade C

4. HUMAN PAPILLOMA VIRUS RECOMMENDATIONS
HPV infection is likely to affect sexual function, however more research is needed.
Level of evidence: 3 Grade C

5. SEXUAL DYSFUNCTION AND CHRONIC PROSTATITIS / CHRONIC PELVIC PAIN SYNDROME (CP/CPPS)
- Acute bacterial prostatitis (abp) interferes with sexual function due to the severity of the acute disease
  Level OF EVIDENCE 1 Grade A
- CBP may be associated with ejaculatory pain
  Level OF EVIDENCE 4 and ED Level OF EVIDENCE 3.
  Grade C
- CP/CPPS is associated with ED in 15 to 72 %
  Level OF EVIDENCE 3 Grade C
- Premature ejaculation has been described in 77% of men with cp /cpps
  Level OF EVIDENCE 3 Grade C
- Therapy of CP/CPPS is limited by a 40% placebo effect.
- An improvement of symptoms with PDE-5 inhibitors remains debatable.

6. SEXUAL, SOCIO-CULTURAL AND ECONOMIC ISSUES OF HIV WITH PARTICULAR REFERENCE TO SUBSAHARAN AFRICAN WOMEN MANAGEMENT INTERVENTIONS
MACROCOSMIC:
1. Programs targeting gender attitudes and norms should be supported. For example, the subordinate position of women must be acknowledged and addressed.
  EVIDENCE LEVEL 3
  RECOMMENDATION GRADE C
2. Economic empowerment of women. For example micro finance.
  EVIDENCE LEVEL 4
  RECOMMENDATION GRADE C
3. Role of health services in addressing gender based violence should include strengthening the
MICROCOSMIC:

1. Early coital debut should be delayed as it is a significant predictor of Hiv.

EVIDENCE LEVEL 2
RECOMMENDATION GRADE B

2. Negotiation and disclosure skills should be taught in school programs.

EVIDENCE LEVEL 3
RECOMMENDATION GRADE B

3. VCT should be vigorously encouraged at every clinic, and educational seminar. VCT should be widely accessible. There should be increase demand for availability of VCT.

EVIDENCE LEVEL 3
RECOMMENDATION GRADE B

4. Stigmatizing attitudes towards people living with AIDS should be discouraged to promote VCT.

EVIDENCE LEVEL 3
RECOMMENDATION GRADE C

5. Hiv prevention strategies must be blended with Hiv/AIDS care services.

EVIDENCE LEVEL 3
RECOMMENDATION GRADE B

6. Sexual assertiveness, condom self efficacy for women and parental monitoring, traditional morality, Hiv knowledge, and talking about sex with partners should be taught and encouraged.

EVIDENCE LEVEL 4
RECOMMENDATION GRADE C

7. More interventions should be targeted towards male clients of sex workers.

EVIDENCE LEVEL 3
RECOMMENDATION GRADE B

8. Prevention interventions are needed to address behaviors that put WSW at risk for Hiv infection.

EVIDENCE LEVEL 4
RECOMMENDATION GRADE C

9. Pap smears must be encouraged for WSW.

EVIDENCE LEVEL 4
RECOMMENDATION GRADE C
10. Disclosure must be encouraged.

EVIDENCE LEVEL 3
RECOMMENDATION GRADE B

11. “Knowledge gaps” should be filled and seen as primary intervention in communication campaigns.

EVIDENCE LEVEL 3
RECOMMENDATION GRADE B

12. Knowledge and appropriate attitudes are necessary for bringing about risk reduction behavior but they are not sufficient.

EVIDENCE LEVEL 4
RECOMMENDATION GRADE C

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Committee 11

Future Sexual Medicine
Physiologic Treatment Targets

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Future Sexual Medicine
Physiologic Treatment Targets

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INTRODUCTION

Sexual function incorporates physiologic processes and regulation of the central and peripheral nervous systems, the vascular system, and the endocrine system, similar but different in men and women. Recent advances in sexual medicine research have led to an increased understanding of the underlying molecular factors and mechanisms governing the display of sexual functions. Understanding the molecular basis for penile erection has led to treatment of erectile dysfunction with oral phosphodiesterase type 5 (PDE5) inhibitors. Little is known, however, about the physiology and regulatory biology of the erectile/arousal response. Scientific investigation in this field is needed to increase knowledge and foster development of the future line of treatments for all forms of sexual dysfunction. This paper addresses the current knowledge of the major cellular and molecular targets of biologic systems responsible for sexual function. Scientific discovery is critically important for developing new and increasingly effective treatments in sexual medicine. Future treatment targets include growth factor therapy, gene therapy, stem and cell-based therapies, and even regenerative medicine. All directions should be vigorously explored and considered for future management sexual disorders.

I. CNS TARGETS FOR MALE SEXUAL DYSFUNCTIONS

1. INTRODUCTION

The use of drugs that act on the central nervous system (CNS) is possible and fascinating although a very complicated strategy for the therapy of several male sexual dysfunctions (erectile dysfunction, [ED], hypoactive sexual desire disorder [HSDD], and premature ejaculation [PE]). This strategy is feasible only when neural pathways, which originate from the CNS and control the vascular and muscular structures of the genital apparatus, are intact. Among neurotransmitters and neuropeptides which control sexual behaviour and its various phases and components at the CNS level, the best known are dopamine, serotonin, oxytocin, nitric oxide (NO) and adrenocorticotrophic hormone-melanophore-stimulating hormone (ACTH-MSH) derived peptides [1 - 24]. Cannabinoid (CB1) receptors, endogenous vascular growth factor (VGF)-derived peptides and growth hormone (GH) secretagogues have been recently added to this list [25 - 32]. This makes these compounds and their receptors valuable targets for the therapy of male sexual dysfunctions (33).

2. CNS TARGETS FOR ERECTILE DYSFUNCTION

a) Dopamine and Dopamine Receptors

Dopamine agonists are perhaps the best known compounds that facilitate penile erection in male mammals, including man. Apomorphine is the best known dopaminergic agonist commercially available and labelled for the therapy of ED (34) activates dopamine receptors of the D2 family in order to facilitate penile erection [35-37]. Molecular biology studies have shown that D2 receptors may be divided into D2 (long and short variants), D3 and D4 receptor subtypes [38]. Recent studies revealed that selective D4 agonists or partial agonists induce penile erection when injected systemically or into the paraventricular nucleus of the hypothalamus (PVN), with a potency similar to that of apomorphine (Figure 1). Perhaps most importantly for therapeutic use in men, some of these compounds are ineffective in mammal models...
of emesis [39]. This reopened the research aimed at the identification of new dopamine agonists, which are capable of inducing penile erection after systemic administration and are devoid of emetic properties. These studies make central D4 receptors one of the most promising central targets for the therapy of ED and suggest that the synthesis of selective pro-erectile D4 agonists may provide a valuable strategy for the treatment of this sexual dysfunction.

Figure 1. D4 Receptor agonists [PD 168887 (PD), PIP-3A (PI)] induce penile erection when injected into the PVN: comparison with apomorphine and prevention by L-745,870 (L), a selective D4 antagonist, or haloperidol (H), a D2 antagonist, given into the PVN. DA agonists were dissolved in the appropriate vehicle (V) and injected into the PVN at the dose of 100 ng each. DA antagonists were dissolved in the appropriate vehicle and injected into the PVN 15 min before the DA agonists. Each value is the mean ± SEM of 7 rats per group. * P < 0.01 when compared to vehicle-treated rats, # P < 0.01 when compared to the corresponding group treated with DA agonist alone (Student's t test)

b) Oxytocin and Oxytocin Receptors

Oxytocin is one of the most potent compounds discovered to induce penile erection when given into the PVN, mediated by the stimulation of oxytocinergic receptors located there as well as the hippocampus and spinal cord (40) (Figure 2). Unfortunately, oxytocin given systemically does not cross the blood brain barrier in amounts capable of inducing penile erection, and it is unfeasible to treat ED by injecting oxytocin or other drugs directly into brain nuclei controlling penile erection. The only way to overcome this problem is to synthesize molecules (possibly non peptidergic) that pass the blood brain barrier and have the same potency and selectivity of oxytocin when given systemically at central oxytocinergic receptors. The synthesis of such non peptide molecules, however, would be very complicated and expensive.

c) CNS Oxytocinergic Neurons

Drugs that stimulate neurotransmitter/neuropeptide receptors located in the cell bodies of oxytocinergic neurons in the PVN can facilitate or inhibit penile erection by activating or inhibiting oxytocinergic neurons at level of the PVN [40]. The most promising are dopamine receptor agonists of the D2 family, or the D4 receptor subtype without emetic properties. Other neurotransmitter/neuropeptide receptor agonists or antagonists meant to facilitate erectile response by increasing oxytocin neurotransmission would have to be given directly into the PVN in order to avoid other side effects often incompatible with sexual activity. The CB1 receptor antagonist, SR 141716A, may induce penile erection by increasing the release of glutamic acid in the PVN, in turn activating oxytocinergic neurons mediating penile erection [41] (Figure 3).

d) Melanocortins and Melanocortin Receptors

The stimulation of central, mainly hypothalamic melanocortin (MC) receptors by ACTH-MSH peptide or non peptide molecules is another way to facilitate erectile function [42], melanotan II and its carboxylate derivative PT-141, new a-MSH analogues with high agonist and antagonist potency and selectivity at specific receptor subtypes, induce penile erection in men when given subcutaneously [43]. The increase in intracavernosal pressure induced by α-MSH is not antagonized by a classical oxytocin receptor antagonist in contrast to that induced by oxytocin [44-46]. In contrast, the pro-erectile effect of tetrahydroisoquinoline (THIQ) [47], a non-peptide putative MC4 receptor agonist induces penile erection when injected in male rats. Although the role of oxytocin in the pro-erectile effect of ACTH-MSH peptides and non peptides may be very modest, the ability of these derivatives to induce penile erection after systemic administration makes MC3 and MC4 receptors a valuable target for ED and these compounds new possible therapeutic agents for ED treatment.

3. CNS TARGETS FOR HYPOACTIVE SEXUAL DESIRE DISORDER

a) Dopamine, Oxytocin and their Receptors

Hypoactive sexual desire disorder often occurs with erectile dysfunction, and is not always associated with low levels of testosterone [48 - 50]. In these cases drugs that act at the CNS level may represent a successful strategy for the therapy. Different neurotransmitters are known for their ability to increase or decrease sexual motivation and sexual arousal, the best known being dopamine. The nucleus accumbens is the brain area in which dopamine is thought to act to facilitate sexual motivation and sexual arousal [51]. Male rats exposed to an inaccessible receptive female often show non-contact erections, pheromone-dependent penile erection episodes indistinguishable from those induced by drugs and/or neuropeptides. Recent studies have shown that extracellular dopamine also increases in the medial
Figure 2. Oxytocinergic neurons as a target for the central therapy of ED. These neurons originating in the PVN and projecting to extra-hypothalamic brain areas, mediate penile erection. When activated by neurotransmitters such dopamine, excitatory amino acids, NO, oxytocin, hexarelin peptide analogues, VGF peptides or by the blockade of CB1 receptors in the PVN, facilitate penile erection, while when inhibited for instance by GABA or opioid peptides this sexual response is reduced. Appropriate references are cited in the References list.

Figure 3. The pro-erectile effect of SR 141716A, a CB1 receptor antagonist, when injected into the PVN is mediated by the blockade of CB1 receptors located in GABAergic synapses impinging on glutamatergic synapses that stimulate oxytocinergic neurons mediating penile erection. Such a block reduces GABA release increasing glutamic acid release that activates in turn oxytocinergic neurons to facilitate penile erection. Alternatively, SR 141716A may block CB1 receptors exerting an inhibitory control on glutamic acid release, and which are located in the above glutamatergic synapses. Whatever mechanism operates in the PVN, this facilitates glutamic acid release increasing oxytocinergic neurons mediating penile erection. Both mechanisms have been identified in other brain areas rich in CB1 receptors. Appropriate references are cited in the References list.
preoptic area [52] during copulation and in the PVN not only during copulation but also during non-contact erections. Finally, dopamine agonists injected into the PVN not only induce penile erection but also increase extracellular dopamine in the nucleus accumbens. This increase is negated by oxytocin antagonists injected intracerebroventricularly or into the VTA, where mesolimbic dopamine neurons originate [4, 51].

If a neural circuit connects the mesolimbic and incerto-hypothalamic dopaminergic systems where oxytocinergic neurons originate, it may be involved in the integration of neural activities controlling of consummatory (erectile – ejaculatory) and anticipatory (motivational and rewarding) aspects of male sexual behaviour in physiological contexts. Dopamine may contribute to modulating the activity of incerto-hypothalamic dopaminergic neurons in the PVN, which causes either penile erection (via activation of oxytocinergic neurons projecting to the spinal cord) or sexual motivation and reward (via activation of oxytocinergic neurons projecting to the VTA) (Figure 4).

Thus, this neural circuitry may be a valuable target for drugs capable of increasing its activity, and dopamine agonists represent a valuable strategy for the therapy of both ED and HSSD, as they act both in the nucleus accumbens and in the PVN. However, considerations against these drugs are the emetic properties of D2 agonists and their potential to produce marked dependence and addiction by increasing dopamine release (e.g., amphetamine-like drugs) from or by inhibiting dopamine reuptake (e.g., cocaine-like drugs) in central synapses. Oxytocin and oxytocin receptors also might be targeted for activating this neural circuitry, although the capability of oxytocin receptor agonists crossing the blood brain barrier seems still far from being realized.

4. CNS TARGETS FOR PREMATUR EJACULATION

a) Serotonin and Serotonin Receptors

Stimulation of serotonin receptors of the 5HT2 subtypes is often followed by inhibition of seminal emission and ejaculation in many animal models...
II. PERIPHERAL PHARMACOLOGIC TARGETS FOR ED

1. INTRODUCTION

Penile erection is initiated after central processing and integration of peripherally and/or centrally generated stimuli (e.g. tactile, visual, olfactory, and imaginative). The signals generated by peripheral penile tissues depend on the balance between factors that control the degree of contraction of the smooth muscle of the corpora cavernosa (CC) and the penile vessels, in turn determining the functional state of the penis. Many details of neurotransmission, impulse propagation and intracellular transduction of signals in penile smooth muscles have been described [61-63], but information on the peripheral control mechanisms involved in erection is rapidly expanding, and new details are continuously added. This review summarizes new information on some established and some new potential targets for drugs potentially useful for control of penile erectile mechanisms.

2. PERIPHERAL NEUROMEDICATION

The different structures of the penis receive sympathetic, parasympathetic, somatic, and sensory innervation [61-63]. The nerves contain different transmitters, and the nerve populations have been categorized as adrenergic, cholinergic, and non-adrenergic, non-cholinergic (NANC), dependent on the transmitter content. However, it should be stressed that these nerves often contain more than one transmitter or transmitter/modulator generating enzymes, such as NO synthases (NOS) and heme oxygenases (HO) [64-67]. One important population of nerves in the CC contains not only acetylcholine (ACh), but also NOS, vasoactive intestinal polypeptide (VIP), and neuropeptide Y [68,69]. If co-released, the different transmitters/modulators may interact, implying that the end result may be more complex than would be suggested from an experimental situation, where often the effect of a single agent is investigated.

It is not only the nerves, but also the endothelium of the CC and vessels of the penis, that produce and release transmitters and modulators that can influence the contractile state of the CC smooth muscle. In addition, they may also have other important functions. There is no question that among the contractile transmitters, noradrenaline (NA) plays an important role, and that for CC relaxation NO derived from nerves and endothelium is a major factor. These transmitters, their receptors and their signalling pathways remain to be the main targets for drugs meant for the treatment of ED. However, other transmitters/modulators, either directly or indirectly, can affect the CC and penile vessels and change the balance between relaxation and contraction and thus influence penile function [70-72].

a) Acetylcholine and Cholinergic Receptors

The importance of parasympathetic nerves for producing penile erection is well established [61-63]. Penile tissues from humans and several animal species are rich in cholinergic nerves [73,74] from
which ACh can be released by transmural electrical field stimulation. ACh released from these nerves acts on muscarinic receptors located on CC smooth muscle and on the endothelium of sinusoids and vessels. Four muscarinic receptor subtypes (M₁₋M₄) were shown to be expressed in human CC [76-77]. The receptor on smooth muscle was suggested to be of the M₂ subtype [76-77], whereas that on the endothelium was of the M₃ subtype [77]. ACh causes endothelium-dependent relaxation of CC, penile arteries, circumflex and dorsal vessels *in vitro* [61-63]. In isolated CC cells, carbachol consistently produces contraction. This means that relaxation induced by ACh can be produced either by inhibition of the release of contractant factors, e.g., NA, and/or by the release of relaxation-producing factors, e.g., NO.

It is important to stress that ACh also acts on nicotinic receptors. Bozkurt et al. (2007) analyzed the presence of neuronal nicotinic ACh receptors in rabbit CC tissue and possible mechanisms underlying nicotine’s potentiation of electrical field stimulation-induced relaxation [78]. The authors showed that nicotine acts on the nicotinic ACh receptors located on nitrogic nerves, thereby evoking release of NO from these nerve terminals. Since most nitrogic nerves are cholinergic, it may be speculated that ACh, released by the parasympathetic stimulation causing erection, acts not only via stimulation of ACh, released by the parasympathetic stimulation nerves are cholinergic, it may be speculated that ACh, released by the parasympathetic stimulation causing erection, acts not only via stimulation of 

**b) Noradrenaline and Alpha Adrenoceptors**

Noradrenaline (NA), released from adrenergic nerves, stimulates α-adrenoceptors (ARs) in the penile vessels and CC, producing contraction. It is generally accepted that this tonic activity keeps the penis in the flaccid state [79]. Both α₁- and α₂-ARs have been demonstrated in human CC tissue, but available information supports the view of a functional predominance of α₁-ARs. This may be the case also in the penile vessels, although a contribution of α₂-ARs to the contraction induced by NA and electrical stimulation of nerves cannot be excluded.

The mRNAs of all subtypes of α₁-AR have been shown to be expressed in human CC [81-82]. Their results demonstrated the presence of α₁A-, α₁B-, and α₁D-ARs, and they suggested that the NA-induced contraction in this tissue is mediated by two or possibly three receptor subtypes.

An additional α₁-AR subtype with low affinity for prazosin (α₁L), and which probably represents a conformational state of the α₁A-AR, has been suggested to be of importance in human penile erectile tissues. In rats, α₁B-, and α₁D-AR subtypes seem functionally relevant for erectile function, and α₁B-, and/or α₁L-AR subtype selective antagonists were suggested to represent advantages in the treatment of ED [83]. The distribution of α₁-AR subtypes in the penis and systemic vessels, however, may not be the same in rats and humans, and the method of study may influence the results. For example, Hussain and Marshall [84] found that the α₁D-AR predominated in several systemic rat vessels *in vitro*, which may not be the case in humans [85]. Similarly, Tong and Cheng [86] found α₁A-ARs to be responsible for the contractile response of rat CC, which does not seem to be in agreement with the *in vivo* data.

Expression of mRNA for α₁A-, α₁B-, and α₁D-ARs in whole human CC tissue has been demonstrated. Radioligand binding revealed specific α₁-AR binding sites, and functional experiments showed that the selective α₁A-AR agonist, UK 14,304, induced concentration-dependent contractions of isolated strips of human CC smooth muscle [87-88]. Whether or not these α₁-ARs are of importance for the contractile regulation of tone in CC smooth muscle is still unclear. Prejunctional α₁-ARs have been shown to inhibit stimulus-evoked release of NA from nerves in the human CC. Stimulation of prejunctional α₁-ARs in horse penile resistance arteries was also shown to inhibit NANC-transmitter release [89]. This might be one of the mechanisms by which NA maintains detumescence.

Morton and co-workers assessed the response of dorsal and cavernous penile arteries on alpha-AR-selective agonists and antagonists in the rabbit [90]. They found a predominant, functional α₁A-AR population with little evidence of other α₁-AR subtypes in cavernous arteries; there seems to be evidence for the presence of α₁D-AR in dorsal arteries. The authors concluded that α₁A-AR-agonists with affinity for both α₁A-AR and α₁D-AR would potentially have pro-erectile properties, with the combination of these perhaps being most effective.

**c) Endothelins and Endothelin Receptors**

Endothelins (ETs) have been demonstrated in penile erectile tissues and may contribute to the maintenance of CC smooth muscle tone [61-63]. In the endothelium of human CC tissue, intense
ET-like immunoreactivity has been observed; immunoreactivity has also been observed in the CC smooth muscle. Binding sites for ET-1 have been demonstrated by autoradiography in the vessels and in CC tissue. As both ET_A and ET_B receptors have been found in human CC smooth muscle membranes, it cannot be excluded that both receptor subtypes are functional [91].

ET-1 potently induces slowly developing, long-lasting contractions in different smooth muscles of the penis: CC, cavernous artery, deep dorsal vein, and penile circumflex veins. Contractions can also be evoked in human CC tissue by ET-2 and ET-3, although these peptides have a lower potency than ET-1. The contractions induced by ET-1 are dependent on both transmembrane calcium flux (through voltage-dependent and/or receptor-operated calcium channels) and on the mobilization of inositol trisphosphate- (IP_3-) sensitive intracellular calcium stores [92-93].

Becker [94] investigated the plasma ET levels in 33 healthy adult males and in 25 ED patients. In the healthy males, no changes in ET-1/2 levels were observed in the systemic and cavernosal blood during penile tumescence, rigidity and detumescence. However, in the patients, mean plasma ET-1/2 levels during penile flaccidity and detumescence were found to be higher in the systemic circulation than in the cavernosal blood. However, Becker [94] concluded that their data did not support speculations regarding the involvement of ET-1 in the pathophysiology of ED. El Melegy [95] found significantly greater mean plasma levels of ET-1 in the venous blood of patients with ED than in controls. They also found that patients with organic ED had significantly higher levels of ET-1 in both venous and cavernosal blood than had those with psychogenic ED, and suggested that ET-1 could be a clinical marker of diffuse endothelial disease manifested by ED.

Mumtaz [96] assessed the effect of ET-1 and its possible role in the a1-AR pathway during the erectile process using organ bath studies on rabbit CC smooth muscle. ET_A receptors were found to play a greater role than ET_B receptors in the ET-1-induced contraction. The a1-AR-dependent pathway did not involve ET_A or ET_B receptors. In a rat model of chronic cocaine administration, Kendirci [97] found significantly increased plasma big-ET-1 levels in the cocaine treatment group compared with control animals. In the penis, cocaine administration significantly increased ET_A receptor expression compared with saline controls, while ET_B receptor expression was not altered. Cocaine-treated rats showed also significantly decreased endothelial NOS (eNOS) expression and NO production. The authors concluded that cocaine administration significantly reduces erectile function in rats and that the pathophysiologic mechanisms likely involved include increased plasma big-ET-1 levels, increased penile ET_A receptor expression and reduced penile eNOS expression.

In addition, ETs may function as modulators of the contractile effect of other agents, e.g. NA. They may also act as long-term regulators of CC smooth muscle tone and modulate cellular proliferation and phenotypic expression. ET-1 has been hypothesized to be directly involved in end-organ damage in salt-sensitive forms of hypertension. In support of this hypothesis, Carmeiro [98] found that activation of the ET-1/ET_A pathway contributed to mineralocorticoid hypertension-associated ED. ET_A receptor blockade may thus represent an alternative therapeutic approach for ED associated with salt-sensitive hypertension and in pathological conditions where increased levels of ET-1 are present. Even if much available in vitro information suggests that ETs may be of importance for erectile physiology and pathophysiology, the role of the peptides in vivo is unclear [99]. So far, the only published pilot clinical study with selective ET_A receptor antagonists failed to show enhancement of erectile responses in men with mild-to-moderate ED [100].

d) Dopamine and Dopamine Receptors

The importance of dopamine and dopamine receptors in the CNS for penile erection is well established. However, the role of dopamine receptors in the CC and penile vessels is less certain. Hyun [101] found dopamine D1 and D2 receptor gene expression in rat CC. In situ hybridization signals for dopamine D1 and D2 receptor mRNAs were localized to CC and dorsal vessels, and Western blot analyses showed peripheral dopamine D1 and D2 receptor proteins. Immunohistochemically, peripheral dopamine D1 and D2 receptor proteins were detected in dorsal nerves, dorsal vessels and CC smooth muscle of the rat penile tissues. D’Emmanuele di Villa Bianca [102] demonstrated that both D1 and D2 receptors were expressed in the human CC, D1 receptors being two-fold more abundant than D2 and that both receptors were mainly localized on the smooth muscle cell component. They concluded that apomorphine had a peripheral relaxant direct effect as well as antiadrenergic activity, and that human CC possessed more D1-like (D1 and D5) than D2-like (D2, D3 and D4) receptors. Both D1- and D2-like receptors were mainly localized on smooth muscle cells and the relaxant activity was most probably mediated by D1-like receptors partially through NO release from endothelium.

Apomorphine may thus not only amplify sexual and copulatory behaviour but also, by a complementary role, amplify neurogenically mediated erections by acting in the periphery [103]. On the other hand, Matsumoto [104] investigated the role of peripheral
dopamine receptors for regulation of penile erection. They found that in the rat isolated CC, pre- and postjunctional effects of apomorphine appeared to involve dopamine D1- and D2-like receptors, as well as α-adrenoceptors. At relevant systemic doses of apomorphine, however, peripheral effects of the compound were unlikely to contribute to its proerectile effects in rats.

### e) Serotonin and Serotonin Receptors

Serotonin (5-hydroxytryptamine: 5-HT) pathways in the brain are known to be involved in the induction of penile erections in rats [61-63], and Kimura [105] presented evidence that the 5-HT<sub>2C</sub> receptor in lumbosacral spinal sites mediates not only dopamine–oxytocin–5-HT action but also melanocortin action on penile erections.

The importance of peripheral 5-HT receptors is less well established. Finberg and Vardi [106] demonstrated an in vivo 5-HT-mediated inhibitory action on penile erection in rats due to vasoconstriction of the cavernosal arteries. Also, Esen [107] showed that the in vitro 5-HT-mediated contractile response in human penile veins was augmented in patients with venoocclusive disease. The involvement of 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, and 5-HT<sub>2A</sub> receptors [108, 109] in contracting cavernosal smooth muscle was shown in animal studies. Furthermore, 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub> and 5-HT<sub>1C</sub> receptors were implicated in human erection [110, 111]. Lau [112] further confirmed that the peripheral 5-HT pathway may play a part in the erectile process via 5-HT<sub>2A</sub> receptor-mediated contractile and 5-HT<sub>1C</sub> receptor-mediated relaxant activities. It cannot be excluded that neurally released 5-HT is an important contractile neurotransmitter in the erectile process. If so, doxazosin, ketanserin, and 5-HT<sub>1A</sub> and 5-HT<sub>1C</sub> receptor antagonists may be useful as a form of combination therapy to treat ED.

### f) ATP, Adenosine and Adenosine Receptors

ATP and other purines were shown to decrease both basal and phenylephrine-stimulated tension in isolated rabbit CC preparations [113, 114]. It was suggested that ATP is a NANC transmitter in the CC, and that purinergic transmission may be an important component involved in the initiation and maintenance of penile erection [113]. However, none of the purines tested facilitated or inhibited the response of CC smooth muscle to electrical field stimulation, and therefore their role may be in the modulation of erection rather than acting as neurotransmitters [114]. ATP injected intracavernously in dogs was found to produce increases in intracavernous pressure and erection [115]. This effect, which was unaffected by atropine and hexamethonium, could be obtained without changes in systemic blood pressure. In addition, adenosine produced full erection on intracavernous administration [116].

The relaxant activity of ATP may be mediated either by its interaction with ATP receptors, or by adenosine generated through the endonucleotidase-mediated breakdown of ATP. Adenosine was suggested to act through stimulation of receptors belonging to the A<sub>2A</sub> subtype [117]. Filippi et al. [118] found that ATP acted as a potent and NO-independent relaxant agent of human and rabbit CC. They also showed that the ATP effect was partially attributable to the metabolic breakdown of ATP to adenosine but was also due to a direct stimulation of P2 receptors, seemingly different from the classical P2Y and P2X receptor subtypes. Shalev [119] showed that human CC strips can be relaxed by stimulation of P2Y purinceptors via NO release. This relaxation was mediated by an endothelium-dependent mechanism. They suggested that purines may be implicated in physiological erection in man. However, the roles of ATP or adenosine in the physiological mechanisms of erection still remain to be established [120 – 122].

Adenosine produces its effect on target cells by binding to four specific G-protein-coupled receptors: A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, and A<sub>3</sub>. Each receptor has a unique affinity for adenosine and a distinct cellular and tissue distribution. A<sub>1</sub> and A<sub>3</sub> receptors are coupled to adenylyl cyclase by the inhibitory G-protein subunit (G<sub>I</sub>) and hence serve to lower intracellular levels of cAMP. A<sub>2A</sub> and A<sub>2B</sub> adenosine receptors are commonly coupled to adenylyl cyclase by the stimulatory G-protein subunit (G<sub>S</sub>) and serve to increase intracellular cAMP [120]. As pointed out by Dai et al. [120], adenosine has several features making it an excellent candidate for contributing to normal and abnormal penile erection: it is a potent vasodilator with a very short half-life (<10 seconds), and it generates erection via cyclic nucleotide second messengers.

Adenosine-mediated cAMP induction activates protein kinase A and results in decreased calcium calmodulin-dependent myosin light chain phosphorylation and enhanced smooth muscle relaxation [124]. Studies in several animal species, including humans [125] showed that intracavernous injection of adenosine resulted in tumescence and penile erection [126, 127]. More recently, Tostes [128] presented data suggesting that adenosine-induced relaxation in mouse CC is mediated through activation of both A<sub>2B</sub> and A<sub>3</sub> adenosine receptors. Mice lacking adenosine deaminase (which is necessary for the breakdown of adenosine) showed priapic activity involving A<sub>2B</sub> receptors [129]. Consistent with these reports, a recent study demonstrated that ED in men in some cases may be due to endothelial A<sub>2B</sub> receptor dysfunction [130]. However, not all forms of ED are associated with impaired adenosine signaling. For example, Carneiro et al. [122] showed that adenosine actions are preserved in ED seen in obese and Type II diabetic da/db mice, suggesting that increased CC responses to adrenergic nerve stimulation are not
due to impaired negative modulation of sympathetic neurotransmission by adenosine in this diabetic model.

**g) Prostanoids and Prostanoid Receptors**

Human CC tissue has the ability to synthesise various prostanoids and the additional ability to metabolize them locally [131 - 133]. The production of prostanoids can be modulated by oxygen tension and suppressed by hypoxia. Corresponding to the five primary active prostanoid metabolites (PGD$_2$, PGE$_2$, PGF$_2$, PGI$_2$, and thromboxane A$_2$ (TXA$_2$)), there are five major groups of receptors which mediate their effects—the DP, EP, FP, IP, and TP receptors. cDNAs encoding representatives of each of these groups of receptors have been cloned, including several subtypes of EP receptors.

Penile tissues may contain most of these groups of receptors; however, their role in penile physiology is still far from being established [131-133]. Prostanoids may be involved in contraction of erectile tissues via PGF$_{2\alpha}$ and TXA$_2$, stimulating thromboxane (TX) and EP receptors and initiating phosphoinositide turnover, as well as in relaxation via PGE$_1$ and PGE$_2$, stimulating EP receptors (EP2/EP4) and initiating an increase in the intracellular concentration of cAMP [134 – 136]. Prostanoids may also be involved in the inhibition of platelet aggregation and white cell adhesion, and there is evidence suggesting that prostanoids and transforming growth factor-β$_1$ (TGFβ$_1$) may have a role in the modulation of collagen synthesis and in the regulation of fibrosis of the corpus cavernosum [137].

Brugger [138] characterized the pharmacological and physiological activity of novel subtype-selective EP and DP receptor agonists using isolated human and rabbit penile cavernosal tissue in organ baths and in vivo measurements of intracavernosal pressure in rats and rabbits. They found no consistent correlation between the pharmacological profile (receptor binding and second messenger assays) of the EP agonists and their effect on cavernosal tissue tone. However, they found that a potent DP1-selective agonist, AS702224, caused penile erection. They concluded that the DP1 receptor mediates relaxation in human cavernosal tissue and stimulates pro-erectile responses also in both rat and rabbit.

**h) Endocannabinoids**

Little information exists concerning the peripheral effect of cannabinoids on CC tissue. Ghasemii [139] investigated the effect of the endogenous cannabinoid anandamide on the NANC relaxant responses to electrical field stimulation in isolated rat CC. They showed that anandamide has a potentiating effect on NANC-mediated relaxation of rat CC through both CB1 and vanilloid receptors. Furthermore, they demonstrated that the NO-mediated component of the NANC relaxant responses to electrical stimulation is involved in this enhancement. The same group studied the effect of biliary cirrhosis on NANC-mediated relaxation of rat CC and the possible roles of endocannabinoid and NO systems in this model [140, 141]. NANC-mediated relaxation was enhanced in CC strips from cirrhotic animals. Anandamide potentiated the relaxations in both groups. Either AM251 (CB1 receptor antagonist) or capsazepine (TRPV1 receptor antagonist), but not AM630 (CB2 receptor antagonist), prevented the enhanced relaxations of cirrhotic strips. Both the non-selective NOS inhibitor, L-NAME, and the selective neuronal NOS (nNOS) inhibitor, L-NPA, inhibited relaxations in both groups, but cirrhotic groups were more resistant to the inhibitory effects of these agents. Relaxations to sodium nitroprusside (NO donor) were similar in tissues from the two groups. The authors concluded that cirrhosis potentiates the neurogenic relaxation of rat CC probably via the NO pathway and involving cannabinoid CB1 and TRPV1 receptors.

Western blotting of CC tissues in this and other studies demonstrated the existence of CB1 receptors in CC strips of rat and rhesus monkey [142]. In contrast to rat CC tissue, relaxant responses to electrical stimulation were not altered in the presence of anandamide at 10 nM- 30 μM in monkey CC strips. Further studies are needed to elucidate the role of the endocannabinoid system in erectile tissue.

**i) Nitric Oxide and the Guanylate Cyclase/cGMP Pathway**

It is widely accepted that NO plays an important role in the relaxation of the CC smooth muscle and vasculature (143 - 146). In vitro, several investigators have shown that both ACh- and neuronally-mediated relaxation in animal and human corpus cavernosum involves the release of NO, or a NO-like substance (143). Both the nerves (nNOS) and the endothelium (eNOS) of the corpus cavernosum may be the source of NO, the former initiating erection, and the latter providing sustained maximal erection (147 - 149). The relative contribution of the different forms of NOS to erection has not been definitely established. However, more than one isoform of nNOS may be involved (148).

Mice lacking both eNOS and nNOS have erections, show normal mating behaviour, and respond with erection to electrical stimulation of the cavernous nerves (150, 151, 148). Surprisingly, isolated corporal tissue from both wild-type and NOS-deleted animals have demonstrated similar responses to electrical stimulation. However, Hurt et al. (146) showed that alternatively spliced forms of nNOS are major mediators of penile erection.

cGMP signals via different receptors in eukaryotic cells, including ion channels, phosphodiesterases,
and protein kinases. At present, the molecular targets which are activated by cGMP in order to execute the relaxation of penile smooth muscle are not known. Two different cGMP-dependent protein kinases (cGK I and II) have been identified in mammals. Inactivation of cGKI in mice abolishes both NO/cGMP-dependent relaxation of vascular and intestinal smooth muscle and the inhibition of platelet aggregation, causing hypertension, intestinal dysmotility, and abnormal hemostasis (152). Sadeghipour et al. (153) suggested that lithium, by interfering with the NO pathway in both endothelium and nitroergic nerve, can result in impairment of both the endothelium- and NANC-mediated relaxation of rat CC.

Male cGKI-deficient mice seem to have very low reproductive capability, likely due to the markedly reduced ability of their CC tissues to relax in response to NO, whether it is neuronally or endothelially released or exogenously administered (154). Analysis of the NO/cGMP-induced relaxation clearly shows that cGKI is the major mediator of the cGMP signaling cascade in murine CC tissue. Its absence cannot be compensated for by the cAMP signaling cascade (154). Taken together, these findings suggest that activation of cGKI is a key step in the signal cascade leading to penile erection.

Bivalacqua et al. investigated the expression of cGMP-dependent protein kinase (PKG)1α and PKG1b in the CC and evaluated the effect of adenoviral gene transfer of PKG1a to the erectile compartment on erectile function in a rat model of diabetes (155). They found PKG1a and PKG1b activities to be reduced in the erectile tissue of the diabetic rat. Gene transfer of PKG1α to the penis restored PKG activity and erectile function in vivo in diabetic rats. They concluded that gene therapy procedures targeting PKG1α might be an interesting future therapeutic approach to overcome diabetic ED resistant to oral pharmacotherapy.

Angulo et al. evaluated the influence of protein kinase C (PKC) activity on penile smooth muscle tone in tissues from diabetic and non-diabetic men with ED (156). They found that overactivity of PKC in diabetes is responsible for enhanced contraction and reduced endothelium-dependent relaxation of human CC smooth muscle. Thus, the authors concluded that such alterations can result in ED.

**j) Other Gaseous Mediators**

Carbon monoxide (CO) and hydrogen sulfide (H₂S) are together with NO considered to be the principal peripheral pro-erectile gasotransmitters that are released chiefly by cholinergic nerves and the sinusoidal endothelium to relax corporal smooth muscle through the cGMP pathway.

A significant, positive effect of the hemoxygenase (HO)/ CO system on penile erection has been reported in several studies, and its potential roles as molecular target in treatment of erectile dysfunction was reviewed by Shamloul (157). He noted that none of the studies examined the role of HO/CO system in aging animals; aging being considered the most important risk factor for ED. Furthermore, only one study tested the role of HO/CO system in erectile function. The author concluded that the HO/CO system may have an important role in many male sexual functions including penile erection, but that further studies are needed to precisely delineate the extent to which the HO/CO system plays a role in the physiology and pathophysiology of male sexual dysfunctions.

**k) Phosphodiesterases**

Phosphodiesterases (PDE) have been shown to be relevant for the erectile response by affecting cGMP and cAMP signaling in the penis. Specifically, their role is to degrade cyclic nucleotide second messenger products, thereby limiting their mode of action which result in CC tissue relaxation. The most prominently described PDE, PDE5, is well recognized as a primary pharmacologic target, and orally administered PDE5 inhibitors have indeed been successfully used for the treatment of ED (158). New concepts surrounding PDE5 biology as it relates to erectile function have centered on alternative mechanisms beyond direct pharmacologic inactivation for temporary erectogenesis (159). Scientific studies have suggested that this target could be applied for the treatment of various erectile disorders. The role of PDE5 is influenced by its gene regulation, and cyclic nucleotide-inducible promoters as well as enhancers precede the 3 PDE5A isoform mRNAs present in human penile CC (160). The inducibility of PDE5A promoters by cyclic nucleotides, as would be the case with increased cGMP levels in the penis resulting from the use of PDE5 inhibitors, offers a potential basis by which PDE5 expression and activity can be increased. Androgenic influences may also affect PDE5 function in the penis (161, 162), but the effect may be indirectly mediated by the influence of androgens on NOS function, which possibly induces cGMP production. These insights indicate that regulatory factors of PDE5 expression and activity in the penis critically determines the biological role of the enzyme.

**l) The RhoA/Rho-kinase Pathway**

A major mechanism of the calcium sensitization of smooth muscle contraction is through the inhibition of the smooth muscle myosin phosphatase (MLCP). The resulting myosin phosphorylation and subsequent smooth-muscle contraction therefore occurs without a change in sarcoplasmic calcium concentration. Several studies have revealed important roles for the small GTPase RhoA and its
The RhoA/Rho-kinase-mediated calcium sensitization is important for regulation of smooth muscle contraction, increased RhoA/Rho-kinase activity may lead to abnormal contractility of the corpora cavernosa. Evidence has been presented that elevated RhoA/Rho-kinase activity contributes to the pathogenesis of diseases such as diabetes and hypertension, and possibly to other conditions associated with ED, such as hypogonadism and aging. Several studies have suggested that NO inhibits RhoA/Rho-kinase activity, but the detailed mechanisms by which this regulation occurs are yet to be determined.

Vignozzi et al. (169) investigated the effect of testosterone on RhoA/Rho-kinase signaling in diabetes and found that overexpression of RhoA/Rho-kinase signaling contributes to diabetes-related ED. Moreover, treating hypogonadism associated with diabetes may maintain erectile function also by normalizing RhoA/Rho-kinase pathway upregulation.

One of the proposed mechanisms responsible for diabetes-related ED is overactivity of RhoA/Rho-kinase signaling, as seen in experimental models of diabetes. Morelli et al. (170) investigated whether the statin, atorvastatin, ameliorated diabetes-related ED. Streptozotocin-induced (8 weeks) diabetic rats and alloxan-induced (8 weeks) diabetic rabbits received atorvastatin (5 mg/kg daily) for the last 2 weeks. In both diabetic models, atorvastatin did not affect glycemia, lipid plasma levels, and the hypogonadal state. In diabetic rats, atorvastatin ameliorated the erectile response to electrical stimulation of the cavernous nerve and normalized sildenafil’s effect on erectile function. In penile tissue from diabetic animals, atorvastatin completely restored the diabetes-induced hypersensitivity to Y-27632 and prevented RhoA membrane translocation/activation. The authors concluded that atorvastatin improved diabetes-related ED and restored sildenafil responsiveness, most probably by inhibiting RhoA/Rho-kinase signaling. Gao et al. (171) suggested that impaired erectile function with aging in Sprague-Dawley rats is associated with the imbalance between nNOS and Rho-kinase activity and that the Rho-kinase inhibitor, Y-27632, could improve the erectile function in old Sprague-Dawley rats through adjusting this imbalance.

It has been shown that the Rho/Rho kinase calcium sensitizing pathway has been implicated in the pathogenesis of ED as well as systemic atherosclerosis. Park et al. (172) investigated whether chronic treatment with an oral Rho kinase inhibitor, fasudil, could prevent the development of both vasculogenic ED and pelvic atherosclerosis in a rat model. They found that the Rho/Rho kinase pathway is substantially involved in the development of ED and pelvic atherosclerosis, both of which could be prevented by chronic treatment with fasudil, and suggested that Rho-kinase might be considered a novel target for the prevention of vasculogenic ED.

Theoretically, suppression of an increased RhoA/Rho-kinase activity is an attractive therapeutic principle in ED. However, the ubiquitous occurrence of the Rho/Rho-kinase pathway limits the use of Rho-kinase inhibitors. If regulators of RhoA/Rho-kinase uniquely expressed in penile tissue can be demonstrated, they may be targets for drugs. This will potentially lead to the development of new therapeutic agents for the treatment of ED. Demir et al. (173) investigated the relationship of adrenergic responses in CC tissues in the presence of bladder outlet obstruction (BOO) using the α₁-AR receptor antagonist, doxazosin, and the Rho-kinase inhibitor, Y-27632. The contractility of human CC was increased in the presence of BOO; Doxazosin and Y-27632 generated effective CC smooth muscle relaxation in the presence of BOO. Doxazosin and Y-27632 may therefore be alternatives for the treatment of ED associated with benign prostatic hyperplasia.

### III. GROWTH FACTOR TARGETS FOR ED

#### 1. INTRODUCTION

The management of sexual disorders is not limited to traditional pharmacotherapy, in reference to drugs administered with targeted actions involving molecular mediators and their signaling mechanisms. Clinical therapeutics in this field will most certainly
exploit a growing understanding of the roles of diverse biological constituents involved in the sexual response. These constituents can be characterized across tissular, cellular and molecular levels, and they have relevance with respect to homeostatic, proliferative and regulatory requirements of sexual organs. In the penis, for example, the biology of growth factors has suggested alternative approaches to manage ED. Growth factor interventions for this organ refer to “targeting” the biologic properties of its cellular components, including nerves, endothelium and smooth muscle, either to facilitate mechanisms involved in the erectile response or to revitalize penile erectile tissues toward a functionally intact level in the face of injury or disease. In this subsection, we describe growth factor therapy applying the ED paradigm as a likely direction for therapeutics in sexual medicine.

2. NEUROMODULATION

Neuromodulatory therapy for ED implies a treatment strategy that is specific for the neurogenic loss of erectile function, arising from neurological disease, pelvic surgery and other conditions disturbing the neurological mediation of penile erection. The role of growth factors for neuromodulatory treatment has origins in the scientific disciplines of neurogenesis and neural development as well for prevention of neuronal cell death, with a purported basis to facilitate or augment the endogenous recovery of injured nerve tissue. Often used terms characterizing this general area of study are neuroprotection, neuroregeneration and neurotrophism. Particular emphasis for the application of neuromodulatory therapy in sexual medicine owes to the interest in preserving erectile function in men undergoing treatments for prostate cancer and other pelvic malignancies in which ED regularly occurs as a consequence of surgically traumatized cavernous nerves (174, 175).

Neurotrophins (neurotrophic factors) are secreted products both of the end organ for nerve terminations and Schwann cells, glial cells of peripheral nerves. Their source is generally restricted to Schwann cells following peripheral nerve injury, and upon release they target the nerve cell body and support survival of the nerve and stimulate its axonal regeneration. Neurotrophins interact with specific plasma membrane receptors in nerve cells activating Akt (protein kinase B) and/or mitogen activated protein kinases (e.g., ERK, JNK and p38), which regulate downstream effectors in neuronal proliferation and survival pathways. The range of their effects includes neuronal proliferation, differentiation, and changes in cell motility, structure and phenotype.

Neurotrophic molecules of particular interest in neuromodulatory applications for the penis include both classic neurotrophins as well as atypical neurotrophic factors. In experimental rat models of cavernous nerve grafting, nerve growth factor (NGF) and acidic fibroblast growth factor (FGF) enhance nerve function recovery in the penis and facilitate electrophysiologically induced erectile responses (176, 177). Basic FGF, insulin-like growth factor (IGF)-1 and transforming growth factor-β have been prominently localized in rat corporal tissue and associated with neurite outgrowth-promoting activity (178, 179). Brain-derived neurotrophic factor (BDNF) has shown particular importance as a neurotrophic factor for the penis based on its potent penile nerve recovery effects after adeno-associated virus transfer in a rat model of cavernous nerve injury (180). Recent in vitro and in vivo evidence has pointed to the important role of the JAK/STAT signaling pathway in mediating the effects of BDNF-induced functional recovery (181 - 183).

Additional interest has turned recently to glial cell-derived neurotrophic factors (GDNF) such as neurturin, persephin and artemin for neuromodulatory objectives in the penis. Prominent among these is the agent neurturin, again based on studies involving parasympathetic nerve regeneration in vitro and erection recovery in vivo using the cavernous nerve injured rat model (184, 185). GDNF delivered using a herpes simplex virus vector has been further shown to promote erection recovery in the animal model of cavernous nerve injury (186).

The atypical neurotrophin vascular endothelial growth factor (VEGF) has interestingly caused intrapenile nerve growth, besides having an angiogenic potential, in a rat model of traumatic arteriogenic ED (187). IGF-1 and IGF binding protein-3 complex regenerate penile nerve fibers and promote erection recovery in the rat model of cavernous nerve injury (188). Sonic hedgehog (SHH), a smooth muscle protein involved in penile development but also a neurotrophin secreted by Schwann cells, has been implicated in cavernous nerve regeneration in rats and may particularly serve to limit apoptotic effects in cavernous smooth muscle (189). Growth differentiation factor-5, a member of the TGF-β superfamily and a tissue developmental regulator like SHH, has been found to exert neurotrophic erection recovery effects in cavernous nerve injured rats (190).

The discovery of immunophilins in nerve tissue that operate as specialized receptors for neuroprotection and neuroregeneration has led to their investigation as a basis for therapy for conditions ranging from neurodegenerative disorders to peripheral nerve injury (191, 192). Excitement has surrounded the development and study of ligands specific for immunophilins, such as the immunosuppressants FK506 and rapamycin and particularly their non-immunosuppressive derivatives (e.g., GPI1046, FK1706), for this purpose. Basic scientific work has suggested that their modes of action involve anti-apoptosis, anti-oxidation and cellular repair.
the CC to include increasing endothelial cell content (193). This field of investigation has been brought to conditions of penile neuropathy associated with cavernous nerve injury both experimentally induced in animal models and clinically following radical prostatectomy (193 - 195, 185). Although erectile function recovery effects have not yet been observed at the clinical level unlike that shown preclinically, it remains of interest to explore further the possible utility of this treatment for clinical indications.

The cytokine hormone erythropoietin has been shown recently to have impressive neurotrophic effects for penile nerve function preservation. In both animal models of cavernous nerve injury and in men undergoing radical prostatectomy who were involved in a small, non-blinded clinical trial, the hormone exerted potent protective effects on erectile function (196, 197). The basis for this effect is understood to engage cell survival and anti-apoptotic mechanisms and possibly involve JAK/STAT signaling. Additional trials are warranted to evaluate the possible use of this therapy at the clinical level.

Stimulatory conditions for neurotrophic effects in the penis are also suggested as clever approaches to protect cavernosal tissue against risk for impairment. For instance, hyperbaric oxygen therapy promoted erection recovery in a rat model of cavernous nerve injury, with an effect that preserves cavernosal smooth muscle content and apparently involves heightened NGF and endothelial NOS function (198).

3. ANGIOGENESIS AND VASCULOPROTECTION

Investigational efforts have been given to understanding the functional and structural biology of the cavernosal tissue and penile vasculature and establishing ways to preserve and restore these tissue components for ED management. The notion to develop this scientific area is hardly trivial and attempts to address frequent pathogenic etiologies for ED of vasculogenic origin including hypercholesterolemia and atherosclerosis.

Great interest has been given to the potential application of angiogenic cytokines to promote erectile function. VEGF, a direct-acting specific endothelial cell mitogen and angiogenic factor, has been most significantly studied in relationship to genital vasculature. Splice variants for this cytokine have been verified in both rat and human cavernosal tissue (199, 200), and their expressions are downregulated in the corpus cavernosum of hypercholesterolemic rats and rabbits (201 - 203). In animal models of vasculogenic ED, intracavernous delivery of VEGF, by way of direct protein infusion or gene transfer, has effectively restored erectile function (9, 187, 201, 204). In line with effects of VEGF shown in other vascular systems, erectogenic responses were associated with multiple mechanisms operating in the CC to include increasing endothelial cell content (187, 201, 205) and causing both eNOS upregulation (7) and direct activation by Akt phosphorylation (9). Basic FGF has also been shown to exert angiogenic effects while also directly stimulating VEGF function in cavernosal tissue of the hypercholesterolemic rabbit (206, 207). Similarly, angiopoietin-1 has been demonstrated to have erectogenic effects and stimulate both angiogenesis and eNOS function in the CC of the hypercholesterolemic rat (202). These observations suggest an advantageous role for therapeutic angiogenesis in the treatment if not prevention of vasculogenic ED.

Targeting cytokine regulation in the penis has received additional attention as a strategy to treat vasculogenic ED. Interest has turned to pro-inflammatory cytokines, well described mediators of endothelial dysfunction. One such cytokine is tumor necrosis factor-alpha (TNF-α), which has been implicated in many cardiovascular diseases (e.g., hypertension, diabetes mellitus, metabolic syndrome) and is elevated in patients with ED (with or without cardiovascular disease). The suppression of eNOS expression by TNF-α constitutes a mechanism for its effect. As a direct investigation into this area, Carneiro et al studied erection responses and molecular mechanisms operating at the penile level in genetically engineered mice lacking the TNF-α gene (208). These mice exhibited improved erections in vivo and in vitro (i.e., increased NO-dependent cavernosal tissue relaxation and diminished sympathetically mediated effects) in association with increased protein expressions of both neuronal and endothelial NOS enzymes in CC tissue compared with control animals (208). This information suggests that anti-TNF-α therapies may be effective in treating forms of ED associated with endothelial dysfunction.

Besides therapeutic angiogenesis, other approaches are considered for preserving the morphology and function of the CC. Antihypertensive therapies represent an approach for vascular remodeling, interventions that may change the phenotype of “hypertensive" vessels toward decreased medial wall thickness (209). The changes are possibly associated with vascular smooth muscle cell apoptosis or rearrangement, changes in the extracellular matrix composition, or alterations in signaling pathways involved in vascular remodeling (209). The renin-angiotensin system may be particularly relevant for this concept, and angiotensin type 1 receptor antagonists have effectively been used to preserve erectile function experimentally in animal models of erectile dysfunction (210 - 214) as well as clinically in men with ED (215 - 217).
IV. REGENERATIVE MEDICINE AND GENE THERAPY FOR ED

1. INTRODUCTION

There has been a rather remarkable (re)evolution of therapies for the treatment of erectile dysfunction in the past 10-12 years. The goal of this section is to review potential therapies related to the application of stem cells, tissue engineering and gene therapy for the treatment of erectile dysfunction. While the first two provide the foundation for regenerative medicine, in one sense, all of these technologies serve as components of, or pathways to, regenerative medicine (Figure 5). Simply stated, regenerative medicine is the repair or replacement of damaged cells, tissues and organs. The goal is to restore native tissue and organ viability and function, in this instance, erectile capacity and sexual function. The regenerative nature of stem cell therapy and tissue engineering approaches are quite obvious, and clearly gene therapy techniques can be used to further improve the utility of both.

In this scenario, these technologies have rather recently generated great interest in the basic research and clinical communities. Table 1 summarizes the published literature. As illustrated, by far, the most widely studied of these technologies for the treatment of erectile dysfunction is gene transfer. Nonetheless, the purpose of this report is to provide an overview of the basic concepts and findings associated with each of these technologies. Clearly each topic could serve as subject matter for an entire chapter itself, and so the interested reader is referred to more detailed reviews of the subject matter in each instance below.

2. GENE THERAPY FOR ERECTILE DYSFUNCTION.

Gene therapy, or gene transfer, refers to the cellular incorporation of genes to mitigate or reverse a

Figure 5. Schematic depiction of potential future treatment strategies for erectile dysfunction. In this scenario, a diversity of regenerative and gene therapy technologies can be developed to treat a spectrum in the severity of erectile dysfunction, ranging from mild and moderate disease through complete end organ failure (i.e., lack of significant viable erectile tissue). Note that nanotechnologies are likely to play an important role as a drug and cell delivery vehicle for improvements to both regenerative and gene therapies.
disease process. Traditionally, gene therapy has been applied to the treatment of a life threatening disease relying on genomic integration with viral vectors in target cell populations (218). Despite early tragedy and disappointment, a recent editorial in the New England Journal of Medicine, notes that the tide may be turning (218). More recently, gene therapy has been pursued for the treatment of a wide range of disorders, including erectile dysfunction. In fact, the recent completion of the first Phase I gene transfer trial for erectile dysfunction (219) has started a new conversation concerning the potential application of gene transfer to diseases/disorders that have substantial impact on quality of life. As noted by Dr. Arthur Caplan (220), erectile dysfunction can be considered a serious medical problem as judged by a variety of relevant criteria. Moreover, since current treatment options are not effective in all patients, one can certainly make a strong case that gene therapy represents an ethical course of research for the treatment of erectile dysfunction (220).

The first preclinical publications on the potential applicability of gene therapy for the treatment of erectile dysfunction appeared in 1997 (221 - 223). Since then numerous research teams have confirmed the viability of this treatment modality, and examples of the numerous strategies employed to date are summarized in Table 2, and have been recently reviewed by several experts (224 - 226). One recent report has even noted that the preclinical studies of gene transfer for erectile dysfunction may even be useful for improved understanding of the pathophysiological basis of the disease process (227). The strategies thus far employed have interrogated numerous distinct molecular targets in several physiologically relevant erectile pathways, but again, as summarized in Table 1, the distinct strategies applied thus far can be grouped according to which cell type provides the primary mode of action. Not surprisingly, all of the gene transfer/therapy strategies used thus far affect either: 1) nerves, 2) smooth muscle cells, or 3) endothelial cells. However, because of the nonspecific mode of administration (i.e., intracavernous injection) as well as the lack of specificity of most of the vectors used, one cannot unequivocally rule out the possibility of involvement of more than one cell type in the observed response.

### Table 1. Summary of Medline-listed publications

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<th>Text word strategy</th>
<th>Number of hits</th>
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<tr>
<td>Gene transfer and erectile dysfunction</td>
<td>166</td>
</tr>
<tr>
<td>Stem cell therapy and erectile dysfunction</td>
<td>37</td>
</tr>
<tr>
<td>Tissue engineering and erectile dysfunction</td>
<td>28</td>
</tr>
</tbody>
</table>

#### a) Endothelial Cells

The presence of erectile dysfunction (ED) correlates highly in men with hypercholesterolemia, cardiovascular disease, hypertension, and diabetes mellitus (228). A common thread among these conditions is the putative presence of endothelial dysfunction, defined as a pathological state of the vasculature with compromised endothelial responsiveness to vasodilator mediators, or conversely, an increase in sensitivity to vasoconstrictors. Because ED generally precedes or presents concurrently with cardiovascular risk factors, and furthermore, because cardiovascular disease has been clearly associated with endothelial dysfunction, it is logical to conclude that ED may result from endothelial dysfunction of the penile vasculature (229 - 232). As a result, several gene therapy strategies have been employed to manipulate this cell and enhance the effects generated to treat the disease condition, and many of these studies have been recently reviewed (233). In short, these strategies have centered around modulation of expression of NOS isoforms, SOD and most recently HO-1. In all cases the goal is the same, that is, to increase cGMP levels/NO bioavailability.

#### b) Vascular Function

While not strictly an index of endothelial cell health or dysfunction, an insufficient vascular supply is thought to be responsible, at least in part, for the etiology of men with erectile dysfunction. While it seems that in many cases, sufficient corporal smooth muscle relaxation (i.e., intracavernous injections) can overcome this deficit, there is nonetheless a rational basis for expecting that an increased blood flow will aid recovery of erectile function/capacity. In this regard, the concept here is to use angiogenesis to increase the vascularity of the penis and provide an increased blood flow component to the erectile process. While the number of patients whose erectile dysfunction is solely related to decreased vascularity may be small, a technique that could produce more subtle increases in vascularity might prove to be prophylactic. In fact, VEGF gene transfer techniques are currently being applied to the treatment of other ischemic cardiovascular diseases such as myocardial ischemia (234). The direct intracorporal injection of VEGF in a rat model of vascular
With respect to K channel gene transfer, it is based on K channel gene transfer (see below). The ultimate distinguishing feature among these approaches is the advent of human clinical trials. The preclinical success of gene transfer targeting smooth muscle has been nothing short of spectacular. In short, these initial studies provide proof of concept that increasing the magnitude of the stimulus for erection can be accomplished via manipulation of neuronal innervation density. Such a possibility has been previously suggested on both theoretical and practical grounds (223), and would present a major step forward (186, 249). In fact, Kato et al. (186, 250) used gene transfer with herpes simplex virus vector (HSV) expressing glial cell line-derived neurotrophic factors (GDNF or neurturin) in rats where the cavernous nerve was bilaterally injured using a ‘gutless’ (i.e., replication incompetent) Ad vector, as well as plasmids (247). In addition, this group has also evaluated the utility of pSilencer2.1-U6-PIN-shRNA gene therapy (PIN; protein inhibitor of nNOS), and concluded that it was more effective than the antisense PIN mRNA in ameliorating ED in the aged rat. Regardless, the implication is that PIN is indeed a physiological inhibitor of nNOS and nitrergic neurotransmission in the penis (248). In all cases the therapeutic strategy is the same, that is, to increase the bioavailability of NO following erectile stimulation.

In addition to overexpression of NOS in existing nerves, others have tried gene transfer with neurotrophic factors. The goal here is to increase the number and/or function of nerves, and thereby increase the stimulus for erection. Obviously, this approach is of specific interest when addressing neuropathic changes that accompany age, diabetes or radical prostate surgery, for example. Thus Lue and colleagues (180) examined the ability of brain derived neurotrophic factor (BDNF) gene therapy to restore the cavernous nerve-stimulated ICP response in a rat model of neurogenic impotence. In short, these initial studies provide proof of concept that increasing the magnitude of the stimulus for erection can be accomplished via manipulation of neuronal innervation density. Such a possibility has been previously suggested on both theoretical and practical grounds (223), and would present a major step forward (186, 249). In fact, Kato et al. (186, 250) used gene transfer with herpes simplex virus vector (HSV) expressing glial cell line-derived neurotrophic factors (GDNF or neurturin) in rats where the cavernous nerve was bilaterally injured using a clamp and dry ice. Four weeks after nerve injury, treated rats displayed significant recovery of erectile function compared to rats treated with control vector or untreated rats.

e) Clinical Trials

The ultimate goal of all of these approaches is to apply the findings to improve the treatment of ED in humans. In this regard, the first human clinical trial of gene transfer for the treatment of ED has been completed (219). In this seminal dose-escalation safety study, sponsored by Ion Channel Innovations, LLC (see www.ionchannelinnovations.com for
details) eleven patients with moderate to severe erectile dysfunction (ED) were given a single-dose corpus cavernosum injection of hMaxi-K, a “naked” DNA plasmid carrying the human cDNA encoding hSlo (for human slow-poke), the gene for the alpha, or pore-forming, subunit of the human smooth muscle Maxi-K channel (in a pVAX expression vector). More specifically, 3 patients each were given 500, 1000, and 5000 µg, and two patients were given 7500 µg, of hMaxi-K and followed for 6 months. The primary endpoint of this phase I study was safety. Importantly, no serious adverse events or dose-related adverse events attributed to gene transfer were observed for any patient at any dose during any study visit. Moreover, no clinically significant changes from baseline were seen in physical evaluations (general or genitourinary), hematology, chemistry, and hormone analyses. There were no cardiac events, as determined by repeated electrocardiograms, and no plasmid was detected in the semen of patients at any time after the injections. In addition, secondary efficacy endpoints were measured using the International Index of Erectile Function (IIEF) scale, with patient responses validated by partner responses. In this regard, one patient at each of the two highest doses of hMaxi-K (i.e., 5000 and 7500 µg doses) had apparently sustained improvements in erectile function (EF) as indicated by improved IIEF-EF domain scores over the length of the study. In fact, these patients reported EF category improvements that were highly clinically significant and maintained throughout the 24 weeks of study. While efficacy conclusions clearly cannot be drawn from the results of a phase I trial without a control group, these initial safety data are very encouraging. Moreover, the preliminary indications of potential effectiveness suggest that hMaxi-K gene transfer may be a viable approach to the treatment of ED. Clearly further clinical investigation is both required and justified. Nonetheless, these exciting data represent a major step toward one day making gene transfer a treatment option for ED.

3. STEM CELL THERAPY FOR ERECTILE DYSFUNCTION

Cellular therapy for the repair of damaged tissues and organs represents the entry point technology for regenerative medicine (see Figure 5). That is, in addition to technologies built around genetic modification of endogenous cells (to restore physiologically relevant aspects of cellular, tissue and organ function), another possibility is the (re-)implantation/introduction of cells into the corpus cavernosum, where the goal is to essentially “re-seed” or “repopulate” the penis with the requisite parenchymal cells for normal tissue/organ function. In theory, this could be accomplished by either systemic or intracorporal injection, but in light of the specialized anatomy and external location of the penis, direct injection is the currently preferred route of cellular delivery. Assuming there is sufficient viable tissue and vascularity remaining, (i.e., moderate erectile dysfunction; see Figure 1) to support the regenerative process then this approach provides a tractable therapeutic option.

Wessells and William (251) were the first to demonstrate the feasibility of utilizing autologous transplantation of endothelial cells into the corpus cavernosum of the rat for this purpose. Certainly, the use of autologous cells would be most beneficial, but in some cases, there may not be sufficient erectile tissue for this purpose. Thus, a considerable amount of effort has been devoted to identifying alternative cell sources (Table 2). More specifically, in addition to the injection of differentiated cell populations, one can also utilize stem or progenitor cells. Stem cells, by definition, retain both their clonogenic capacity (i.e., ability for self renewal) as well as their potential for multilineage differentiation (i.e., ability to differentiate into distinct cell types; Rookmaaker et al., 252). As recently pointed out (232, 233), stem cell therapy for ED is still a relatively young field of research, albeit a quite promising one. Not surprisingly then, there are only a handful of publications reporting original preclinical work with stem cell therapies. Nonetheless, the extant preclinical work summarized in Table 3 bodes well for the potential utility of cellular therapy for erectile dysfunction, and the interested reader is referred to these publications for additional details.

4. TISSUE ENGINEERING FOR ERECTILE DYSFUNCTION

At the other end of the regenerative medicine technology spectrum is tissue engineering. The basic concept is to use biocompatible, biodegradable scaffolds, either with or without cells, to repair rather extensively damaged tissues and organs. The concept of tissue engineering in urology has received considerable recent attention (253 - 256). Tissue engineering is required when the end organ damage is extensive, and thus, requires replacement for restoration and maintenance of function-rather than modulation. In a seemingly ever-aging population, regardless of the precisely etiology for the onset of erectile dysfunction, it is clear that if the duration of organic disease is sufficiently long, traditional pharmacotherapies will eventually fail. The latter provides the rationale for pursuing tissue engineering strategies for the treatment of erectile dysfunction (257).

In this scenario, the use of acellular scaffolds has shown value in preclinical studies for tunica patch repair (258) as well as cavernous nerve regeneration (259). In addition, a series of publications has shown the plausibility of using tissue engineering for phallic reconstruction and formation and reconstitution of
Table 2. Summary of published literature for preclinical gene therapy studies in rats

<table>
<thead>
<tr>
<th>Vector used</th>
<th>Gene target</th>
<th>Cell Target</th>
<th>Physiological end points</th>
<th>Duration(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus[11]</td>
<td>eNOS</td>
<td>Endothelial</td>
<td>Increased ICP to NS, Ach and Zapranist</td>
<td>1 day</td>
</tr>
<tr>
<td>Adenovirus[10]</td>
<td>eNOS</td>
<td>Endothelial</td>
<td>Increased ICP to NS</td>
<td>5 days</td>
</tr>
<tr>
<td>Adenovirus[23]</td>
<td>eNOS+Sildenafil</td>
<td>Endothelial</td>
<td>Increased ICP to NS</td>
<td>1-2 days</td>
</tr>
<tr>
<td>Adenovirus[39]</td>
<td>eNOS+Mesenchymal stem cells</td>
<td>Endothelial</td>
<td>Increased ICP to NS</td>
<td>21 days</td>
</tr>
<tr>
<td>Adenovirus[33]</td>
<td>VEGF</td>
<td>Endothelial</td>
<td>Increased ICP to NS</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Adenovirus[34] cDNA/Liposome (Aziz, 2009)</td>
<td>Ang1+VEGF165</td>
<td>Endothelial</td>
<td>Increased ICP to NS</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Adenovirus[25]</td>
<td>SOD</td>
<td>Endothelial</td>
<td>Increased SOD activity and cGMP levels</td>
<td>1 day</td>
</tr>
<tr>
<td>Adeno-associated virus [31]</td>
<td>VEGF+AAV-BDNF</td>
<td>Endothelial</td>
<td>Increased ICP to NS</td>
<td>4 months</td>
</tr>
<tr>
<td>Adeno-associated virus[8]</td>
<td>BDNF</td>
<td>Neuronal</td>
<td>Increased ICP to NS</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Herpes simplex[53] (Kato et al., 2009)</td>
<td>GDNF</td>
<td>Neuronal</td>
<td>Increased ICP/BP to NS</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Herpes simplex[54]</td>
<td>NT3</td>
<td>Neuronal</td>
<td>Increased ICP to NS</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Adenovirus[13]</td>
<td>pNOS</td>
<td>Neuronal</td>
<td>Increased ICP to NS</td>
<td>≤18 days</td>
</tr>
<tr>
<td>Plasmid [13]</td>
<td>pNOS</td>
<td>Neuronal</td>
<td>Increased ICP to NS</td>
<td>≤18 days</td>
</tr>
<tr>
<td>Adeno-associated virus[12]</td>
<td>Rho A</td>
<td>Muscle</td>
<td>Increased resting ICP</td>
<td>1 week</td>
</tr>
<tr>
<td>Adenovirus[9]</td>
<td>CGRP</td>
<td>Muscle</td>
<td>Increased ICP to NS</td>
<td>5 days</td>
</tr>
<tr>
<td>Naked DNA pc DNA 3.1[2, 4, 45, 49, 50]</td>
<td>hSlo</td>
<td>Muscle</td>
<td>Increased ICP to NS</td>
<td>≥3-4 months(^b)</td>
</tr>
<tr>
<td>cDNA[45, 64]</td>
<td>K(_{ATP}) channel</td>
<td>Muscle</td>
<td>Increased ICP/BP</td>
<td>1 week</td>
</tr>
<tr>
<td>cDNA[40]</td>
<td>VIP</td>
<td>Muscle</td>
<td>Increased ICP to NS</td>
<td>≥ 2 weeks</td>
</tr>
<tr>
<td>Antisense oligonucleotides[7]</td>
<td>PDE V</td>
<td>Muscle</td>
<td>Increased cGMP in cultured corporal smooth muscle cells</td>
<td>≤1-6 h</td>
</tr>
<tr>
<td>Adenovirus[5]</td>
<td>iNOS</td>
<td>Muscle</td>
<td>Increased ICP to NS</td>
<td>At least 10 days</td>
</tr>
<tr>
<td>Adenovirus[14]</td>
<td>iNOS</td>
<td>Muscle</td>
<td>Increased ICP to NS</td>
<td>2 days</td>
</tr>
</tbody>
</table>

ICP denotes intracavernous pressure response; NS: nerve stimulation; Ach: acetylcholine; BDNF: brain-derived neurotrophic factor; CGRP: calcitonin gene-related peptide. HO-1; heme oxygenase-1. \(^a\)Duration of effect refers to the latest time point at which a physiologically significant increase in the ICP response was measured. \(^b\)The most recent data from our group indicates that the physiological effect on ICP lasts for up to 6 months in the aged rat model, and up to 4 months in an experimentally diabetic rat model. Also note that an increased ICP to NS refers to a statistically significant increase over that observed in an untreated age-matched control rat. In general, the responses observed in the gene therapy treated rats was similar to that observed in young animals.
corporal tissue both in vitro and in vivo (260 - 264). With respect to the former, engineered cartilage rods were made via the combination of autologous chondrocytes suspended in biodegradable polymers. These structures were implanted as engineered penile prostheses, and when retrieved possessed the histological and biomechanical characteristics of cartilage (260 - 262). With respect to the latter, taken together, these experiments demonstrate the feasibility of using autologous donor cells for corporal tissue reconstruction, and moreover, illustrate that human corporal smooth muscle and endothelial cells seeded on biodegradable scaffolds formed vascularized cavernosal tissue when implanted in vivo (262 - 264). In a rabbit model, this approach, that is, autologous penile corpora cavernosa replacement was sufficient to support mating activity by three months postoperatively (265). Development of methods to further enhance cellular content, and thus function, of these engineered constructs are currently ongoing (266).

5. COMBINATION THERAPY FOR ERECTILE DYSFUNCTION

As one views the horizon for novel treatments for erectile dysfunction, it is clear that all of the technologies discussed thus far can be used not only individually, but likely also in combination (again, refer to Figure 1 for details). For example, in applying the regenerative technologies, one can envision that recapitulating aspects of normal erectile developmental biology with sonic hedgehog might also be useful (267 – 268). Certainly, the regulatory hurdles will be greater for combination therapies, but nonetheless, it is important to evaluate the possibilities in preclinical studies. Furthermore, it corresponds to intuition that combination therapies would be more likely to succeed in the case of severe erectile dysfunction. Undoubtedly, this field of research will continue to evolve, and the enabling tools and technologies available to the investigator (i.e., nanotechnologies for sustained and controlled gene, growth factor or drug delivery) will only further increase in sophistication.

V. PHARMACOLOGIC TARGETS FOR EJACULATORY DISORDERS

1. INTRODUCTION

Ejaculatory dysfunction may be caused by any problem in this series of events, including premature ejaculation (PE), retarded ejaculation, anejaculation, retrograde ejaculation and painful ejaculation. However, PE is the most common type of ejaculatory dysfunction. As such, PE will be the main paradigm applied for this subsection.

Studies on the etiology and pathophysiology of PE critically depend on research animal models, which are very important to investigate the anatomy, physiology, cell biology, biochemistry and pharmacology of PE and to develop new therapies for PE. However, experimental animal models of PE have not been developed to investigate the etiology, pathophysiology and pharmacological mechanism of drug therapy on PE yet. The problem in researching the etiopathogenesis of PE and developing a therapy for PE is that it is very difficult to create a standard animal model of PE. Most of our current understanding of the neurobiology of the sexual and ejaculatory function has been derived from animal studies using rats or rabbits with normal sexual behavior (56). Spinal somatosensory evoked potentials and bulbocavernosus reflex in rabbits were used for evaluating the efficacy of the topical agent SS-cream (270 - 272). Olivier (273, 274) and Pattij (275) established an animal model of PE and delayed ejaculation research using male Wistar rats. Fast and slow ejaculatory rats were distinguished based on the number of ejaculations during 30-minute tests, each presenting almost 10% at both ends of the Gaussian distribution. Similar to the situation with humans, intravaginal ejaculatory latency time (IELT) distribution is positively skewed with regard to basal ejaculatory performance in a normal population of rats. However, standard guidelines applying animal models for PE research still needs to be developed.

In general, at present, various biological and psychological theories have been proposed to explain the cause of PE. Most of these theories are not evidence-based and are speculative at best. The psychological theory emphasizes the impact of early experience and sexual conditioning, anxiety, sexual technique, the frequency of sexual activity and other psychodynamic conditions. The biogenic theory relates to evolutionary theories, the sensitivity of the penis, central neurotransmitter levels and receptor sensitivity, a certain degree of arousability, the speed of ejaculation reflex and sex hormone levels.

2. PHARMACOLOGICAL TREATMENTS

Pharmacological modulation of the ejaculatory threshold provides a novel and refreshing approach to the treatment of PE and is distinct from the psychosexual and behavioral treatment model. Current and widely accepted pharmacological treatment options include anti-depressive agents, topical desensitizing agents, PDE5 inhibitors and alpha-receptor blockers.

a) 5-Hydroxytryptamine

Several studies using male rats have shown that serotonin (5-hydroxytryptamine [5-HT]) and various serotonin receptors are involved in the ejaculation process. Activation of 5-HT2c receptors can delay ejaculation, while activation of 5-HT1a receptors
speed-up ejaculation. PE has been attributed, in part, to decreased central serotonergic neurotransmission, 5-HT\(_{2C}\) receptor hypersensitivity, and/or 5-HT\(_{1A}\) receptor hypersensitivity (275-277). Thus, 5-HT\(_{2C}\) receptor agonists, such as selective serotonin reuptake inhibitors (SSRI) and serotonergic TCAs, should theoretically work for PE.

5-HT transporters blockade, similar to acute administration of SSRIs, has been demonstrated to increase 5-HT levels in the synaptic space and the space around neuronal cells (278). Increasing 5-HT levels activates 5-HT\(_{1A}\) autoreceptors, resulting in a lower 5-HT release into the synaptic cleft within minutes (278 - 281). A higher 5-HT concentration will increase activation of presynaptic 5-HT\(_{1B}\) autoreceptors that by itself will reduce the 5-HT release. In physiological conditions, the net effect of the acute SSRIs administration is only minor or no increase in the 5-HT neurotransmission and mild or no stimulation with all the postsynaptic 5-HT receptors (279-281). Based on these data, it is predicted that on-demand SSRI treatment does not acutely cause stimulation of the 5-HT post-synaptic receptors; therefore, there is hardly any of the 5-HT increase in the synapse and little or no synaptic stimulation of 5-HT receptors. If postsynaptic 5-HT receptors have little or no activation, clinically relevant ejaculation delay will not occur (283, 284). Therefore, the development of some novel SSRIs for acute administration in PE treatment is needed.

In contrast, chronic administration of currently available SSRIs induce delayed ejaculation by a different mechanism. The ongoing blockade of 5-HT results in a persistent increase of 5-HT levels in the synaptic spaces around cells. As opposed to acute administration, this leads to desensitization of the 5-HT\(_{1A}\) autoreceptors in a few weeks (285) and also possible desensitization of 5-HT\(_{1B}\) autoreceptors (285), which therefore causes less inhibition of 5-HT release into the synapse. The net effect of chronic administration is that more 5-HT is released into the synapse, enhancing 5-HT neurotransmission more strongly, and consequently stronger activation of the 5-HT receptor compared with acute SSRIs administration (283, 284, 286, 287). These data suggested that the daily treatment of SSRI will stimulate 5-HT post-synaptic receptors and therefore lead to clinically significant ejaculation delay after 1-2 weeks (286).

b) Noradrenaline

Clomipramine is a tricyclic antidepressant that inhibits the uptake of noradrenaline and 5-HT by adrenergic and 5-HT neurons (288).

Tramadol is a registered central analgesic agent, which has been used for many years, and its safety is widely accepted. The mode of action of tramadol is not fully understood. From animal experiments, there are at least two different mechanisms: one enantiomer exerts a major weak μ-opioid effect, while the other inhibits norepinephrine and serotonin reuptake, activating descending monoaminergic inhibitory pathways (289 – 293). Inhibiting reuptake of norepinephrine and serotonin may represent its effect of ejaculation delay (293). However, the action of 5-HT\(_{1A}\) and 5-HT\(_{2C}\) induced by tramadol requires further investigation.

c) Phosphodiesterase Type 5

Some experiments have shown a relationship between ejaculatory function and PDE5 function. Mancina and colleagues demonstrated the expression of PDE5 in human and rabbit vas deferens muscle (294). Kriegsfeld and colleagues reported the role of endothelial NOS on sexual function by observing abnormalities in ejaculatory function in endothelial NOS gene knockout mice. The effect was proposed to be associated with reduced sympathetic nervous system activity (295). Based on these findings, PDE5 inhibitors have been suggested in the management of patients with ED and concomitant PE (296, 297).

d) α1-Adrenoceptors

It is known that ejaculation is controlled by the sympathetic nervous system; therefore, a hypothesis was proposed that α-blockers might also be effective in the treatment of PE. Some animal studies have demonstrated that the stimulation of hypogastric nerve can reduce the pressure of the vas deferens and the seminal vesicle (298).

e) Hypoaesthesia

One of the proposed etiologies of PE is hypersensitivity of the penis. Thus, one of the goals of PE treatment is to reduce the sensory perception of the penis. The basic principle for the use of topical agents has traditionally been based on penile hypersensitivity in PE patients (299 - 301). The topical drugs for PE treatment that are currently available include the SS cream, lidocaine and prilocaine cream, and lidocaine spray (297).

The SS-cream (CJ Co Ltd, Seoul, Korea), developed at Yong-Dong Severance Hospital in Korea, is made with the extracts from nine natural products. A novel formulation, named ‘Renewal SS-cream’, is a new local agent composed of two main components of the original SS-cream. However, so far, only the results of animal studies have been published. The renewed SS-cream delays the latency of spinal somatosensory evoked potential more effectively than the original SS-Cream in rabbits (270 - 272, 297).

f) Oxytocin

Immunohistochemical studies have revealed the local synthesis of oxytocin and its synthesis-
associated protein, neurophysin I, in epithelial cells of the epididymis\(^{[132]}\). Therefore, the use of oxytocin as a potential therapeutic agent in the treatment of PE has been under investigation (302). Interventions at other points in this pathophysiologic pathway are also under investigation (303, 304). Dietary deficiencies, such as low magnesium intake, may prove to play a limited role (305).

VI. CENTRAL NON-HORMONAL AND HORMONAL TARGETS FOR FSD

Women with female sexual dysfunction secondary to low sexual interest, reduced sexual arousal or impaired or muted orgasm may be considered to have: 1) under-activity of the excitatory system regulating critical central nervous system structures involved in desire, arousal or orgasm, 2) over-activity of the inhibitory system, or 3) some combination of the two where, in the end, functional central inhibition is the more prominent action (10, 306 - 309). In women with low sexual interest, arousal and/or orgasm, reduced sexual activity is secondary, in general, to a combination of psychologic and physiologic factors (10, 306 - 310). As it concerns the physiologic, organic factors, basic science knowledge regarding the neurochemical contribution to inhibition and excitation is increasing. It is hoped that one day, in addition to time-honored psychologic strategies, novel pharmacologic treatments (307, 308, 310 - 317) can be available to help reverse either the underactive excitatory neurochemical system or the overactive inhibitory neurochemical system or both so that functional sexual excitation and, in the end, sexual satisfaction of the woman, improves.

An understanding of the neurochemicals involved in sexual inhibition and excitation is required when looking at future treatment targets. Sexual inhibition involves such neurochemicals as serotonin (318 - 322), endocannabinoids (322 - 325) and opiates (326 - 330). Conceptually, pharmacologic agents that inhibit the synthesis, release or receptor binding of brain inhibitor neurochemicals will increase sexual excitation. The most prominent and well-studied brain inhibitor neurochemical strongly linked to sexual inhibition is serotonin. Pharmacologic treatments that stimulate serotonin activity decrease sexual desire, while treatments that inhibit serotonin action increase sexual desire (318 - 322). Endocannabinoid and opiate activation, similar to serotonin release, act to decrease sexual desire and diminish orgasmic capacity (322 - 325). Antagonists to these neurochemicals will increase sexual activity.

Sexual excitation involves such neurochemicals as oxytocin (331 - 335), noradrenaline (336 - 338), dopamine (339 - 342), and melanocortins (343 - 345). Conceptually, pharmacologic agents that activate the synthesis, release or receptor binding of brain excitatory neurochemicals will increase sexual excitation. Oxytocin is a well-investigated sexual facilitator neurochemical that acts to stimulate sexual behavior, especially orgasm, when delivered centrally (331 – 335). Another brain neurochemical that facilitates sexual interest is noradrenaline, an alpha–1 adrenergic agonist. In appropriate levels centrally, unrelated to levels consistent with panic or apprehension, alpha –1 adrenergic agonist is associated with increased sexual behavior (336 – 338). An alpha–2 receptor blocker, such as yohimbine (346-347), prevents pre-synaptic endogenous noradrenaline inhibitory feedback, and thus results in increased noradrenaline levels. Agents such as yohimbine facilitate sexual interest, arousal and orgasmic capabilities (346-347). Dopamine agonists are the most well-known sexual neurochemical facilitators. Such agents are typically used for Parkinson’s disease where they have been recognized for years to be associated with increases in sexual interest. On the other hand, agents that are dopamine receptor antagonists have been shown to block sexual facilitation and result in lowered sexual interest, arousal and orgasm (339 - 342). Finally, other facilitator neurochemicals are melanocortin agonists that have been reported to stimulate sexual arousal and sexual interest in women with sexual dysfunction following intranasal and subcutaneous administration (343 - 345).

Sex steroid hormones are also involved in sexual desire, arousal and orgasm. Sex steroids such as testosterone (348 - 351), 17–beta estradiol (352 – 357) and progesterone (358) act at the molecular level to direct the synthesis of multiple proteins such as enzymes and receptors for the various facilitory neurochemical systems including oxytocin, noradrenaline, dopamine, and melanocortins. Sex steroid hormones bind to specific androgen, estrogen and progestin hormone receptor complexes in the cytoplasm that form transcriptional agents in the nucleus, and lead to the synthesis of different neurotransmitter proteins and transmitter receptor proteins. The overall effect of sex steroid hormones is to provide the protein biochemical machinery to enable a state in which sexual stimulation is likely to result in sexual desire, arousal and orgasm (348 – 358).

Non-hormonal centrally acting agents that have been investigated and may play a future role in the treatment of hypoactive sexual desire disorder in women include bremaelanotide (308, 311) and fibanserin (312-317). Bremelanotide is a melanocortin agonist that increases sexual interest by increasing dopamine release in the medial pre-optic area mPOA. Subsequent stimulation of downstream dopamine
ventral tegmental area outputs facilitates critical dopamine outputs in the mesolimbic area that form relevant and crucial neuronal circuits in the overall dopamine sexual excitatory system. Government regulatory agency approval of bremelanotide in the United States is currently delayed based on safety data. There is an increase in systolic blood pressure in some patients requiring additional clinical studies (308, 311).

Flibanserin is a serotonin antagonist that lowers central serotonin levels via two positive actions. The first is to diminish serotonin release (serotonin 1A agonism) and the second is to inhibit binding to the serotonin 2A receptor (serotonin 2A antagonism) involved in inhibitory cortical outflow. Furthermore, flibanserin increases dopamine and noradrenalin levels. In the end, this mixed serotonin 1A agonist and serotonin 2A antagonist both reduces inhibitory serotonergic function and increases excitatory dopamine and noradrennergic function. Flibanserin does not appear to be associated with addiction or dependence, as flibanserin does not have direct action on dopamine receptors or dopamine reuptake mechanisms. In addition flibanserin does not directly effect the opioid system so there is limited opportunity for excessive sexual desire with drug administration (312 – 317).

In summary, the current state of knowledge is that sexual activity may involve, in part, central sexual activation of various dopamine pathways in the medial pre-optic area and nucleus accumbens that focus attention to sexual-based motivation stimuli and sexual-based motor patterns (306, 307). Inhibition of sexual activity may involve, in part, central sexual activation of various inhibitory neurochemicals that feedback to multiple levels of the excitatory dopamine pathway. In general, the end result of neurochemical inhibition of sexual activity is stronger than that for sexual excitation (306, 307). The outcome of reduced excitation or excessive inhibition of central reflexes is low sexual interest, arousal and/or orgasm (306, 307). As our knowledge of the neurochemical interactions in the brain increases, novel non-hormonal and hormonal methods of central extracellular, intracellular, and molecular sorting are being realized in different regions, especially as they pertain to regulation of sexual reflexes. In women with distress from low sexual activity who seek medical/psychologic intervention, it is hoped that safe and effective non-hormonal and hormonal pharmacologic strategies, along with traditional sex therapy strategies, can one day be developed to reduce excessive central neurochemical inhibition and/or to increase central neurochemical excitation to result in improved patient satisfaction with sexual activity (306, 307).

**Current Status and Future Trends of Functional MRI for Female Sexual Dysfunction**

Female sexual arousal response is a neurovascular event that is elicited by various sexual stimulations, such as visual, auditory, olfactory or tactile input. Physiological measures for the assessment of sexual arousal in women include central components, as well as peripheral genital components. Recent innovative functional MRI (fMRI) studies are capable of measuring CNS correlates of sexual arousal. The principle use of fMRI is based on changing cerebral blood flow when neurons become active. The brain regions of neuronal activity show localized increase in blood flow, which changes the ratio of oxyhemoglobin/deoxyhemoglobin in cerebral tissue and result in MRI signal changes (359). The functional neuroanatomy of sexual arousal has been investigated using 1.5 or 3 Tesla fMRI with BOLD technique in women with or without sexual dysfunction (Table 3). Park et al (360) reported the first study by evaluating cerebral activation areas associated with female sexual arousal response. Karama et al (361) found that

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**Table 3. Summary of published preclinical findings for stem cell therapy for erectile dysfunction**

<table>
<thead>
<tr>
<th>Stem cell source</th>
<th>Measured Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDSCs (Kim et al., 2006; Nolazco et al., 2007)</td>
<td>Increased ICP responses due to muscle content, evidence of neural protection/recovery in rats</td>
</tr>
<tr>
<td>NESC (Bochinski et al., 2004)</td>
<td>Increased ICP responses and evidence of neural protection/recovery</td>
</tr>
<tr>
<td>HNCSCs (Song et al., 2007)</td>
<td>Identification of human endothelial and smooth muscle cells in rat corpora</td>
</tr>
<tr>
<td>FBSC Fetal Brain Stem Cells (Song et al., 2008)</td>
<td>Differentiation into corporal smooth muscle cells</td>
</tr>
<tr>
<td>MSCs (Bivalacqua et al., 2007)</td>
<td>Increased ICP responses, differentiation into smooth muscle and endothelial cells</td>
</tr>
<tr>
<td>EPCs (Strong et al., 2008)</td>
<td>Provided evidence for the potential of this cell source for therapy for ED</td>
</tr>
<tr>
<td>ADSC (Lin et al., 2008; 2009)</td>
<td>Provided evidence for the potential of this cell source for therapy for ED</td>
</tr>
</tbody>
</table>

*Where: MDSCs denotes muscle derived stem cells; NESC denotes neural embryonic stem cells; HNCSCs denotes human neural crest stem cells; FBSC denotes fetal brain stem cells; EPCs denotes endothelial progenitor cells; ADSC denotes adipose derived stem cells.*
there were many similar areas of brain activation in both male and female subjects. The differences between genders were in the activation areas of the thalamus and hypothalamus.

Hormone influences CNS arousal response in menopausal women. Murphy et al (362) suggested that aging is associated with a decrease of glucose metabolism in the brain; including frontal, temporal and parietal lobes. The activation pattern of regional cerebral blood flow attenuated in prefrontal cortical structures during a hypoestrogenic state (363). Jeong et al (364) reported that brain activation ratios of menopausal women were generally less than those of premenopausal women (Figure 6). Archer et al (365) reported that agonadal serum hormone levels result in decreased brain activation patterns in postmenopausal women during erotic stimulation. Administration of both estradiol and testosterone increases limbic system activation.

Depression is closely related with sexual dysfunction. Yang et al (366) reported that depressive women had lower activity in the brain areas of the hypothalamus, septal area, anterior cingulated gyrus and parahippocampal gyrus. Sexual desire disorder is the most commonly reported sexual complaint in women. Arnow et al (367) reported that women with no history of sexual dysfunction (NHSD) demonstrated a significantly greater activation in the bilateral entorhinal cortex than women with hypoactive sexual desire disorder (HSDD). In contrast, HSDD females showed a higher activation than NHSD in the medial frontal gyrus, right inferior frontal gyrus and bilateral putamen. Interestingly, peripheral sexual response was not significantly associated with brain activation patterns, which was presumed to have a weak relationship between the genital and subjective arousal responses in women.

The effect of centrally acting medication can be measured by a fMRI. One of the future potential roles of fMRI techniques is to evaluate the central effect of medications for the treatment of female sexual dysfunction as well as to define possible anatomic sites of its action in the brain. Van Wingen et al (368) investigated whether nasally applied testosterone rapidly increases amygdale reactivity in healthy, naturally cycling, middle-aged women. They found that a single nasal testosterone administration increases amygdale reactivity in middle-aged women to young adulthood level. Centrally acting medication such as bremelanotide, apomorphine will be a good candidate to elucidate the activation areas of the brain using fMRI (308, 369).

For the future perspectives of fMRI studies, high resolution fMRI will provide an ideal tool to investigate functional neuroanatomy of subcortical structures in erotic and emotional processing (370). The MRI-based diffusion tensor imaging (371), white matter fiber tractogram (372), and electroencephalogram (373) will be helpful to obtain additional information on neural connectivity and electrical potentials.

**Summary**

Since 1973, with the advent of surgical treatments for biologic forms of erectile dysfunction, such as, penile prosthesis insertion and microvascular arterial bypass surgery, there have been realized numerous advances in basic science and clinical research in biologic focused sexual medicine. Such investigations have led to an increasingly profound understanding of the underlying molecular biological factors and mechanisms governing both male and female sexual function. Ongoing scientific investigation in sexual medicine is mandatory to both increase and enhance our knowledge in all areas of male and female sexual function. Such knowledge will set the groundwork for the next line of treatments for the various male and female sexual dysfunctions.

The goal of this committee was to present current scientific, state of the art, evidence based knowledge of the major cellular and molecular targets of biologic systems responsible for sexual function. With such information as a background, the committee was charged with emphasizing the most innovative and exciting developments in the field of biologic-focused sexual medicine in such areas of pharmacotherapy, growth factor therapy, gene therapy, stem and cell-based therapies, regenerative medicine and others. It is hoped that current knowledge and future research will translate into future safe and effective biologic therapies for various sexual medicine disorders of desire, arousal, and orgasm. Disorders of sexual pain will be discussed in different committees. Future psychologic therapies will be discussed in other committees.
Figure 6. Typical axial and coronal fMR images activated by sexual visual stimulation with erotic video film in premenopausal(a) and menopausal(b) women.
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Committee 12

Standards for Clinical Trials in Male Sexual Dysfunctions

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Standards for Clinical Trials in Male Sexual Dysfunctions

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I. INTRODUCTION

Male sexual dysfunctions symptoms are highly prevalent and must be considered as the most frequently reported health complaints of men.[1-7]. Based on the literature the most prevalent and therefore most important male sexual disorders are:

Erectile dysfunction (ED)
Premature ejaculation (PE)
Delayed/absent ejaculation
Libido disorders/loss of desire

With the exception of lifelong PE which has shown a consistent prevalence rate of between 18 and 25% in several surveys across all age groups between 18 and 65 years, all male sexual dysfunctions/diseases are age dependent with profoundly increasing prevalence rates from the 5th decade on [1-12]. For all male sexual dysfunctions their significantly negative impact on life quality and satisfaction with sexual life as well as on a broad range of psychosocial domains and partnership issues is well documented [1-14]

Besides the above, well defined male sexual dysfunctions, which are reported in epidemiological studies and surveys, the following diseases/pathological conditions are also associated with a clear negative impact on sexual life and satisfaction and therefore were/are subject to medical treatment and development of new therapeutic strategies being investigated in clinical trials:

Peyronie’s disease
Late Onset Hypogonadism (LOH)

Peyronie’s disease is a fibrotic disorder of the cavernous bodies of the penis originating in the tunica albuginea and the septum penis resulting in penile deformities and penile shrinking. The etiology of this disease is not well understood. It may be associated with contractions of the palmar (M.Dypuytren) and plantar (M.Ledderhose) tendons and afflicts between 3% and 8% of the entire male population [15]. It is quite often associated with erectile dysfunction and results in a considerable subset of patients in the inability for vaginal penetration either to the extent of penile deformity and/or the severity of associated ED.

Late Onset Hypogonadism is the decrease of testosterone levels below 3 – 3.5 ng/ml, depending on the definition used, associated with clinical symptoms of hypogonadism. LOH may be prevalent in up to 40% of males above the age of 45 [16]. Sexual symptoms of LOH may be libido-, erectile and ejaculatory dysfunctions depending on the T-levels measured.

Because there is a substantial body of evidence that all the above male sexual dysfunctions show a clear impact not only on the sexuality but also on the psyche and general well-being of the males, afflicted by these disorders, there is a great medical need for the development of new efficacious and safe treatment options either as medications or other conservative options or even as surgical procedures.

Since the previous 2 International Consultations on Sexual Medicine a substantial number of new validated questionnaires were developed and used to investigate the change in patient reported outcomes (PRO’s) after therapy for certain male sexual dysfunctions. Until now validated questionnaires were developed, used and published for investigating the outcome of clinical trials in ED, PE and LOH. Two further new questionnaires are developed and currently undergoing validation process in Peyronie’s disease and LOH.
The current chapter on “Standards for Clinical Trials in Male Sexual Dysfunctions” critically reviews the published literature in this field with special focus on the study designs and study endpoints used. Recommendations are also provided for the future regarding the development and assessment of new therapeutic options in this field.

II. DESIGN OF CLINICAL TRIALS IN MALE SEXUAL DYSFUNCTIONS.

1. GENERAL CONSIDERATIONS

a) Impact of the Sexual Partner

The evaluation of therapy for Male Sexual Dysfunctions (MSD) distinguishes itself from clinical trials in other medical conditions in so far that in general the interaction of 2 human beings is involved – the male afflicted by the sexual dysfunction and his sexual partner either hetero- or homosexual. This is in contrast to many other diseases/dysfunctions requiring the development of new therapy where the impact on the sufferer is the key index. In the design of studies in MSD it is therefore essential that the influence of the sexual partner is considered and should not be underestimated both in terms of the efficacy and the acceptance of the medication/treatment under consideration. There is no doubt that the willingness of the respective sexual partner to accept the participation of the patient in such a clinical trial can play an important role regarding the outcome, personal perception of the treatment and discontinuation rates. Unwilling partners who, for whatever the reason, are negative towards a new treatment aimed at improving the sexual function/performance of the patient can exert a negative or even discouraging influence on the partner and thereby his perception of the efficacy and tolerance of the treatment in question.

Moreover large epidemiological studies have provided evidence that a considerable number of women are suffering from sexual dysfunctions too which of course may have an impact on both their willingness to engage in sexual activities and the level of the sexual life as such in a partnership[3-6].

All of the above has to be considered regarding the design, selection of primary and secondary endpoints and the overall assessment of the study drug/treatment under consideration.

Therefore it is strongly recommended that at least all phase III trials in male sexual dysfunction are also considering study endpoints for the sexual partner in the format of validated patient reported outcomes (PROs) / questionnaires/assessment tools). In addition, the males participating in clinical trials for sexual dysfunction should in the trial protocol at least be strongly encouraged that they communicate the trial design at home with their regular partner. Ideally, the trial should include a requirement for informed partner consent. However, it is recognized that under these conditions recruitment for such trials becomes much more difficult considerably expanding the recruitment phase and trial duration.

As a minimum it is recommended that all participants should at least verbally inform their partners. Preferably a signed partner consent form should be mandated, to ensure the accuracy of data recording.

Recommendation 1 (Grade B)

All clinical trials in male sexual dysfunction should consider the involvement of the sexual partner at least by verbal communication thru the study participant.

All clinical trials which consider active involvement of the sexual partner, i.e. collection of partner reported outcomes a signed partner consent should be mandated to ensure maximally possible accuracy of data recording.

b) Study Duration

In contrast to many other dysfunctions/diseases such as hypertension, diabetes or CAD sexual dysfunctions become only interpretable when assessed over a few weeks; sexual activity occurs on average once to three times a week and can be intermittent. Clinical trials in male sexual dysfunctions have to consider this very special situation which is unique in the clinical research setting and must therefore allow a reasonable time frame for investigating the changes in the sexual dysfunction under investigation and yet if possible record data from each sexual encounter.

It is recommended that phase IIb and phase III in male sexual dysfunction should include at least a 3 month treatment period to give the couple the opportunity for reasonably numerous sexual attempts to ensure that the data recorded is representative of their normal (pre-dysfunction) at home sexual activity.

The treatment phase must be preceded by a treatment-free run in period of at least 4 weeks, or even better 6-8 weeks treatment free run-in period to achieve a consistent baseline.

Because many couples who are confronted with moderate to severe male sexual dysfunctions for a longer time have often given up any sexual activities for longer periods of time, even for years, it is important that in such relationships the protocols should not force couples to adopt an unnatural sexual frequency pattern.
Recommendation 2: (Grade A)

All clinical at home phase IIb/III trials in MSD should consider

a, at least a 4 , preferable 6-8 weeks medication free run-in period to give those patients/couples, who have given up sexual activities for a longer time, an adequate time period to re-familiarize with their sexual life under natural basic conditions enabling them to collect correct baseline data regarding the severity of the dysfunction under consideration.

b, at least a 3 months medicated treatment phase following the medication free run in period to provide a reasonable time period for collecting efficacy and safety data of the investigational drug.

c) Study populations

As sexual performance patterns and sexual perceptions may differ markedly between nations, cultures and religions it is recommended by the committee that once a certain treatment/medication is considered for world-wide approval/launch the respective clinical trials should consider at least the major populations.

The same recommendation applies for different sexual orientations. In clinical trials for male sexual dysfunctions in theory one phase III clinical trial should be conducted in a homosexual population which accounts for about 7 % of male sexual orientations.

Recommendation 3 (Grade C)

Clinical trials in MSD should consider

a, possible differences regarding sexual habits among different cultures and countries, i.e. that at least the world-wide most representative cultures should be considered in a clinical research program of any investigational drug.

b, not only heterosexual but also homosexual populations

d) Study designs for clinical trials in male sexual dysfunctions

The only acceptable study design for a new drug for MSD, as for other diseases is in randomized, double-blind, placebo-controlled format.

In general after a certain drug has been identified in the preclinical setting to have the potential for the treatment of a certain (sexual) dysfunction this drug has to undergo a well established clinical phase I-III/IV research program according to the requests/rules of the regulatory authorities, which may vary with respect to study endpoints, numbers of patients and populations being investigated. To expedite eventual regulatory approval all pharmaceutical companies are in regular contact with the authorities to obtain up to date guidance. To help with this process, the FDA has created a Guidance for Industry in 2006 [17]

Recommendation 4 (Grade A)

All clinical trials in MSD regarding a new investigational drug/treatment must follow where ever feasible a Randomized, double-blind, placebo-controlled study design

All clinical trials in MSD regarding the investigation of any treatment either conservative or invasive should consider at least a randomization of the study population under investigation to avoid any undesirable bias

III. RATIONALE AND DESIGN OF PHASE I TO IV CLINICAL TRIALS IN SEXUAL MEDICINE

Drug development in male sexual dysfunction requires a carefully phased approach. In this process, safety, tolerability and pharmacokinetics of a novel compound are studied early in development (Phase I, conducted in healthy volunteers), preliminary efficacy and safety at a range of doses are studied next in the Phase II. Commonly phase II stage subdivides in Phase Ila and Phase Ilib trials. Phase Ila represents a proof of concept stage to investigate in small patient populations, suffering from the sexual dysfunction under consideration,
whether the drug shows significant efficacy against placebo. Afterwards one or two Phase IIb dose finding studies are conducted in an at home setting in larger patient groups with the typical patient/sexual dysfunction profile at which the drug is aimed for approval. Ideally in Phase IIb trials those doses are identified which show both a statistically significant efficacy against placebo and on the other hand a tolerable safety profile. Clinical efficacy and safety are confirmed fairly late in the Phase III stage in which the most common special study populations (for example diabetic or hypertensive patients etc.) are investigated with the doses identified at the Phase IIb program, just prior to marketing approval. Studies in special populations, observational safety studies, and studies for novel clinical uses may be conducted either during this process (where appropriate) or after initial marketing of a product (Phase IV).

1. PHASE I

In Phase I, a new drug or treatment is tested in a small group of people for the first time to evaluate its safety, to determine a safe initial dosage range for subsequent efficacy studies, and to identify commonly occurring side effects. Since these studies are often the first in humans, particular care is spent in the design to ensure patient and/or volunteer safety. The most important decisions in the protocol design are: rationale for the study, objectives of the study, design of the study to meet the objectives, selection of dose and dosing frequency, recognition of all potential risks, monitoring for those risks, and maintaining adequate precautions to manage those risks.

The earliest studies of a new molecular entity are usually single and multiple-dose safety, tolerability and pharmacokinetic (PK) investigations. These tend to be conducted in healthy young volunteers, followed by the same studies in older (age-matched) volunteers. In some cases the studies can be in patient volunteers. The starting dose is selected using the results of pre-clinical (animal or in vivo) toxicology, safety pharmacology and toxicokinetic studies. One might also use the results of non-clinical in vitro studies (such as receptor binding studies) and other non-clinical evidence to select a starting dose. This dose is usually many times lower than the toxic dose and the No-Observed-Adverse-Effect Level dose (NOAEL) in animals. It is common to "escalate" the dose in single-dose Phase I trials. One may escalate the dose in the same cohort of patients or one may select a new cohort for each dose escalation step. Dose is usually escalated in multiple of two (e.g. 1x, 2x, 4x 8x 16x) until a "maximally tolerated dose" (MTD) is reached.

Phase I dose-rising studies are often conducted totally in-hospital or in a clinical research centre because the clinical adverse events associated with the compound are yet to be fully delineated and because a major objective of these studies is to identify (or to safely "prompt") these side effects. Safety assessments are monitored at frequent and regular intervals and these may include clinical adverse events, vital signs, ECGs, clinical serum and urine chemistries, and other special safety assessments (e.g. injection or other application site monitoring, visual effects monitoring, pain assessments, sedation scores, etc.)

Phase I studies also routinely test the pharmacokinetics of a compound; that is, the concentrations of the compound and its metabolites in the plasma. This requires blood sampling at regular intervals to determine the maximum plasma concentration ($C_{max}$), time to maximum concentration ($T_{max}$), the average concentration ($C_{avg}$), area-under-the-concentration time curve (AUC), and elimination half-life ($T_{1/2}$). These parameters, are determined both after single doses and after multiple doses, in younger and in older patients, after eating and while fasting, after various dose strengths, and after various dosing frequencies. In these early studies, it is not uncommon to seek out the metabolic pathways for the compound in order to gain insight into future problems with specific drug interactions or the need to lower the dose in special populations (e.g., those with renal or hepatic impairment or the elderly). However, such analyses in sub-populations are often carried out later in the drug development program.

The importance of understanding the pharmacokinetics of the compound and the body's handling of the compound cannot be overemphasized in the study of drugs intended to treat sexual dysfunction.

In Phase I, it may also be possible to conduct some preliminary efficacy assessments, but only if these do not interfere with the primary reasons for doing the study: to assess safety, tolerability and PK. These may be carried out in patient volunteers. There is a cautionary note in that whatever "efficacy" measurements are made, the accrual of safety data should not be compromised. In ED, where preliminary efficacy may be assessed through a visual sexual stimulation test (VSS) using Rigiscan device, such efficacy procedures may confound the more critical safety assessments. The same could be true from the use of the SAM device in the assessment of ejaculation latency. One should avoid the tendency to try to answer too many questions in one Phase I or Phase II study. In other research areas, such as the study of medication for benign prostatic hyperplasia (BPH), a simple urine flowmetry examination may not confound safety assessment.
2. PHASE II.

In Phase II trials, the study drug or treatment is given to a larger group of people (anywhere from several dozen to several hundred persons) in order to characterize its preliminary efficacy and to provide additional safety data.

The key objective of the Phase II program is to explore a wide range of doses so as to define accurately the lowest effective dose, the dose(s) to be carried into larger Phase III trials, the maximally tolerated dose and the dose(s) showing obtrusive side effects. In essence this is the definition of therapeutic ratio or benefit: risk ratio.

This determination is key in sexual dysfunction, where both PE and ED are considered “lifestyle” indications and where there will be limited acceptability for a poor therapeutic ratio. For development of drugs for the treatment of sexual dysfunction, Phase II is a key phase, in part because the Phase III programs are usually very large and costly and dose-ranging in Phase III is unwieldy. Also, toxicities and preliminary efficacy that are identified in Phase II tend to predict those that will be seen in Phase III. Therefore, the Phase II estimates can be used to predict Phase III outcomes, to plan Phase III trials designs, and to focus attention on the most important clinical safety and clinical pharmacology concerns. The information from phase II is invariably used to determine the powering (patient numbers) for the pivotal phase III studies.

In Phase II, actual patients with the clinical condition (as opposed to healthy volunteers or “subjects”) almost invariably serve as the study population. One would particularly like to determine clinical benefit and safety in selected high-risk or treatment-resistant groups in Phase II. Early evidence of efficacy and safety in these “more difficult to treat” groups often bodes well for efficacy and safety in the broader Phase III population and may expedite a decision to move the program forward.

In Phase II, it may also be appropriate to explore particular safety issues in a small number of highly monitored patients; these issues might include: drug interactions, use in selected populations, selected organ-system risks (e.g. eye, liver, cardiovascular, neurological), local toxicities, or other drug-specific matters.

The endpoints in Phase II efficacy trials are usually similar to those in Phase III but may include such “pharmacodynamic” parameters as Rigiscan-monitored percent rigidity, or duration of time for maintaining a certain degree of rigidity. Such endpoints are often referred to as “surrogates” i.e. indirect indices of clinical benefit. Also, shortened versions of classical endpoints (modified sexual history diaries, patient-reported outcomes measure, and quality-of-life questionnaires) or shorter treatment periods, may be used to lessen the overall time, effort and financial burden of the individual Phase II program. Since these trials generally do not serve as the “pivotal” evidence for safety and effectiveness, novel endpoints may be explored at the discretion of the investigator or pharmaceutical company, preferably in consultation with the regulatory authorities.

Trial design in Phase II is not unlike Phase III, except perhaps for the use of shorter treatment intervals and greater use of crossover designs. It is possible to conduct smaller Phase II trials (Phase IIa) or much larger Phase II trials (Phase IIb) which resemble Phase 3 trials in their scope. Phase II studies may be designed according to the two-stage designs of Simon [18,19]. These are based upon deciding between “acceptable” and “unacceptable” response proportions. If the response proportion is high, i.e. “acceptable”, then the treatment will be considered for further study. If the response proportion is low then the treatment will not be considered for further study. Often these studies recruit in the region of 25-50 patients with about 15-25 in the first stage and the remainder in the second stage. If the proportion of patients in the first stage responding to the therapy is sufficiently low as to make it highly unlikely that the proportion of patients responding is at the acceptable level then the study is terminated early. This means that potentially poor treatments are stopped early. If the proportion of patients in the first stage responding to the therapy is sufficiently high then the second stage subjects are recruited and a decision made at the end of the study. As Phase II studies often have a small number of patients, it is generally best to use exact statistical methods to analyze them: e.g. StatXact or LogXact [20]. However, several web-based power calculation services are now routinely available and these have aided in satisfactory clinical trial design and data analysis.

It is possible to design Phase II trials taking into account both toxicity and treatment response; for example, using the methodology of Bryant and Day [21]. When using the methodology, the sample sized will be larger because one must take into consideration two variables: safety and efficacy. Such designs also have a mechanism for stopping the study should toxicity prove to be high or treatment response be less than adequate.

3. PHASE III

Phase III trials provide the bulk of the “substantial evidence” towards regulatory approval of a compound and correspondingly are often referred to as pivotal.

In sexual dysfunction, at least two such trials are usually conducted. These must be adequate and well-controlled. All Phase III trials in sexual dysfunction should be randomized, double-blinded and placebo-
controlled. In general, they tend to use parallel, fixed-dose arms, but are not limited to such designs. In fact, crossover designs or mixed crossover-parallel designs (where crossover treatment periods are built into a parallel randomization) are possible. However, if a crossover design is employed, one must take into consideration the possible bias of carryover effects or sequence effects in the design and analysis of the trial. Most regulatory authorities prefer parallel arm to crossover design studies at phase III.

The Phase III trial duration must be long enough to predict efficacy over a reasonable duration of use, but not so long as to cause excessive dropout in the placebo arm. The treatment period in most ED trials has been traditionally 12 weeks in duration and this would seem to be a realistic period of assessment of ejaculatory function in PE studies. There must be some form of a baseline period to allow for screening and baseline (prerandomization) assessments of efficacy. During the baseline period, a certain number of attempts at sexual intercourse should be made and in order for a given patient to be eligible for continued participation, a certain percentage of these should be failures. These baseline periods tend to be treatment-free, but some studies have used a single-blind placebo to estimate treatment compliance. The controlled treatment period is usually followed by an open-label extension study for the purpose of collecting longer-term safety data.

The population in Phase III must be as broad as reasonable safety permits, such that anyone who might receive the drug after marketing was at least eligible to receive treatment in Phase III. It may not be possible to conduct distinct subgroup analyses for each of these patient types, but that should not prevent this “open enrolment” policy. One might exclude those patients at the highest risk of adverse events, such as someone who has recently suffered significant major illness, e.g. a stroke, a myocardial infarction, or life-threatening arrhythmias. One might exclude patients with substantially reduced drug clearance such as those with significant renal or hepatic diseases.

Of the greatest importance in Phase III trials is the choice of a reliable, validated and sensitive primary efficacy endpoint (or endpoints) and the proper analysis of these. In ED, a tri-partite primary endpoint has been used with successful regulatory and clinical outcome: the Erectile function (EF) domain of the International Index of Erectile function (IIEF) and Questions #2 and #3 of the Sexual Encounter Profile (SEP) diary [22,23]. The later two questions refer to the per-attempt, diary-documented success in inserting the penis into the vagina and in maintaining the erection until satisfactory completion of sexual intercourse. We have found the use of these three endpoints to yield easy-to-interpret results and to provide reliable, reproducible clinical data. Also, we have found that using all three of these endpoints is sensitive to small drug treatment effects but does not exaggerate such effects.

In PE, likewise co-primary endpoints are used and data are presented as a composite of single event records particularly IELT and domains from validated patient reported outcomes (PROs)

Additional information relevant to Phase III outcomes for ED and PE may be found in the Patient Population and Outcomes Assessments sections below.

4. PHASE IV

Phase IV studies are those conducted following marketing approval or conducted as a condition of approval. They may be requested specifically by a regulatory agency, or may be conducted voluntarily. There are many reasons to conduct a Phase IV study.

a) Pharmaco-Vigilence Database

In addition all regulatory authorities require that a pharmaco-vigilence database is set up to record all clinical side effects post approval. Some of these reasons include the following:

• To assess better safety and efficacy in a specific subgroup.
• To assess better a particular safety concern that does not preclude approval.
• To monitor for a potential risk.
• To assess the efficacy and safety of a novel clinical use of an already approved product.
• To compare the efficacy and/or safety of two approved products.
• To interpret better the impact on overall quality-of-life.
• To assess longer-term safety in controlled trials.
• To assess patient or physician understanding of product labelling, or compliance with labelled instructions.

Other factors that may warrant a Phase IV study include health-related economic issues, such as drug costs, overall drug benefit for overall cost, or comparative costs. Such studies relating to healthcare economics are mandated in the EU.

In sexual dysfunction, conducting of post approval Phase IV studies is not unusual. However, because the acceptability of drug risk is fairly low in perceived lifestyle indications, although in the medical domain they are generally recognized diseases, some regulatory agencies may request that specific potential drug safety issues (for example, selected
relevant drug interactions) be studied prior to marketing approval. In all situations, phase IV studies intended for marketing claims must be designed as carefully and must be analyzed as rigorously as Phase III studies.

b) Drug Interaction and Special Population Studies

In developing a novel drug for erectile dysfunction, it is of utmost importance that the interaction potential of that novel compound with other clinically relevant compounds undergoes investigations. We are now fully aware that the sexual dysfunction population is a largely varied group, with many middle-aged and older males who have co-morbid medical conditions and who take concomitant medications. We are also now aware that compounds for sexual dysfunction are pharmacologically potent medications which can have adverse effects if taken with other substances. While not all concomitantly administered medications can (or should) be investigated, the most relevant potential interactions ought to be assessed.

For example, if it is known that a given drug has a potential effect upon the metabolism or excretion of the investigational sexual dysfunction drug, this may be assessed by a controlled drug-drug interaction study. An example of this would be a drug that inhibits a cytochrome P450 liver iso-enzyme that is critical to the metabolism of the particular ED or PE drug (e.g. the inhibitory effect of ketoconazole on the 3A4 iso-enzyme may affect the metabolism of the PDE5 inhibitors). Or, if the investigational drug itself affects the CYP450 iso-enzymes then particular drug-drug interaction trials may be appropriate. These types of studies are called "pharmacokinetic drug interaction" studies. They seek to determine the effect of a given drug upon the bodily exposure of the other drug, and vice versa. Blood concentrations of parent drug and the major metabolite(s) are the endpoints of interest. Safety endpoints such as vital signs and electrocardiograms may also be assessed concurrently in these studies.

Another type of critical drug interaction study is the "pharmacodynamic study". When two drugs have an interaction potential not related to pharmacokinetic interaction, but when their combined effects are still clinically relevant (for example, lowering of the blood pressure or increase in the heart rate), then a pharmacodynamic trial may be appropriate. Some relevant situations include the interaction between PDE5 inhibitors and nitrate-containing medications, or the interaction between a PDEI for ED and selected anti-hypertensive medications, alpha-adrenoceptor antagonists, or with alcohol. The endpoints of greatest interest in these trials are by definition "pharmacodynamic" endpoints and these can include vital signs, effects on cognition or sedation, or effects on other bodily signs or symptoms.

Finally, given the importance of the pharmacokinetics of the compound and the knowledge that sexual dysfunction (particularly ED) patients are often aged, and often have co-morbid conditions that may limit renal or hepatic function, it is crucial to understand the safety of the compound in special populations such as the aged, the renal impaired, or those with hepatic insufficiency. Other special population studies may also be appropriate and careful consideration is required in each particular circumstance.

Recommendation 5 (Grade A/B)

1. General: The requirements for all phases of clinical development of novel drugs in erectile dysfunction are well established and in the public domain and on web-sites for regulatory authorities. These should be adhered to, to ensure adequate benefit-risk ratio is identified.

2. trials at each phase have a different purpose and each phase helps investigators and/or the pharmaceutical industry to answer a different set of questions.

3. The earliest studies of a new molecular entity are usually single and multiple-dose safety, tolerability and pharmacokinetic investigations.

4. The critical objective of the Phase II program is to explore a wide range of doses so as to capture the lowest effective dose, the dose to be carried into larger Phase III trials, the maximally tolerated dose and the toxic dose(s). Surrogate endpoints are often used at this stage.

5. It is recommended that several endpoints are used as primary indices and these are derived from validated questionnaires.

6. Phase III trials provide the bulk of the "substantial evidence" towards regulatory approval of a compound. Endpoints must be relevant to the disease condition in the patient and usually involve PROs.

7. Phase IV studies are those conducted following marketing approval. They may be requested specifically by a regulatory agency, or may be conducted voluntarily. There are many reasons to conduct a Phase IV. Studies in specific populations can be required as part of the phase IV program.

8. Pharmacokinetic and pharmacodynamic drug-drug interaction studies and studies in special populations are critical to the overall understanding of the safety and efficacy of a given drug for sexual dysfunction. While each particular drug may require different studies, and careful consideration is necessary in each situation, it is assumed that almost all drug development programs in sexual dysfunction will require at least some of these types of investigations.
In PE the track for global drug approval (registration) has not yet been established. However, the early stage (phases I/II) should be similar to that from ED.

Likewise it is recommended that phase III in PE should be similar to ED in that 2 double-blind placebo-controlled studies are conducted with an open-label extension giving an exposure of at least 1 year to at least 100 patients.

**IV. CLINICAL TRIALS ON ERECTILE DYSFUNCTION**

1. **SPECIAL CONSIDERATIONS FOR CLINICAL TRIALS IN ERECTILE DYSFUNCTION**

   **a) Study populations - Key-inclusion Criteria**

   In general the overwhelming majority of all clinical trials conducted in this indication have required the following criteria for enrollment:

   1st: Chronic erectile dysfunction for at least 3 months (in many trials 6 months)
   
   2nd: Stable partner in a heterosexual relationship for at least (3)/6 months
   
   3rd: Willingness to participate in the trial and comply with the key requests of the trial:

   To maintain regular sexual activities over the whole course of the trial with a mean frequency of sexual activities of at least once per week
   
   To give up any other erectile function enhancing treatment including hormonal (testosterone) replacement therapy with study entrance
   
   To complete the patient’s diaries where applicable
   
   To present at the scheduled visits and return all study drug material (drug accountability)

   **b) Key Efficacy Endpoints - ED Severity**

   The presence of chronic erectile dysfunction is ensured during the treatment free run in phase mostly by means of the following assessment tools:

   **1) **SEXUAL ENCOUNTER PROFILE (SEP) **QUESTIONS 2 AND 3**
   
   **2) INTERNATIONAL INDEX FOR ERECTILE FUNCTION - ERECTILE FUNCTION DOMAIN (IIEF-EF) [22,23]**

   The Sexual Encounter Profile (SEP) is a 5 item questionnaire which is completed after each sexual intercourse attempt and contains the following questions:

   1. Were you able to achieve at least some erection (some enlargement of the penis)?
   
   2. Were you able to insert your penis into your partner’s vagina?
   
   3. Did your erection last long enough for you to have successful intercourse?
   
   4. Were you satisfied with the hardness of your erection?
   
   5. Were you satisfied overall with this sexual experience?

   Many clinical trials for male erectile dysfunction used the SEP 2/3 data as the main entrance criteria requesting that in at least 50 % of the requested sexual intercourse attempts (usually at least 1 attempt per week, i.e. at least 4 attempts within 4 weeks, were key for considering of randomization) either question 2 and/or 3 were answered with no.

   The International Index of Erectile Function (IIEF) is a 15 items comprising validated questionnaire which was developed with the financial support of the pharmaceutical industry (here Pfizer Incorp. New York, US) for the sildenafil clinical research development program [22,23]. Later on the IIEF-EF domain, comprising questions 1-5 and 15 served as the basic standard tool for categorization of the severity of the erectile dysfunction as was subjectively reported/felt by the patients included in clinical trials.

   The IIEF-EF domain was used until now in all clinical trials for a variety of new ED medications which were considered for market development.

   **Per definition the data of the IIEF-EF reflect the patients’ memory recall of their sexual experience during the past 4 weeks.**

   The maximum score which can be reached in the IIEF-EF domain is 30 and the categorization of the severity of ED according to the IIEF-EF domain is as follows:

   **Severe ED:** Score 1-10
   
   **Moderate ED:** Score 11-17
   
   **Mild ED:** Score 18-25
   
   **No ED/normal function:** Score 26-30

   Per definition do all patients with an IIEF-EF domain score < 26 suffer from any kind of erectile dysfunction and were therefore generally allowed to be involved in the majority of clinical ED trials.

   Some trials in the past restricted the inclusion criteria to a certain IIEF-EF score below and above which patients were not allowed to be recruited and some ED trials randomized patients according to the IIEF-EF severity at baseline, i.e. to assign patients with mild, moderate and severe ED per random to a certain treatment arm.
In many ED trials the final IIEF-EF domain score and/or its change from baseline was used as primary or secondary endpoint.

Another quite often used endpoint in clinical trials is the number/percentage of patients reaching a normal IIEF-EF score at study end indicating normal erectile function.

It has been proven in several clinical studies that the ED severity as assessed by the IIEF-EF score does not at all correspond with the underlying ED – etiology, i.e that the IIEF-EF ED categorization does not allow any conclusions regarding the assignment of the ED cause in terms of organic – mixed – psychogenic ED.

Thus the IIEF cannot substitute any diagnostic work-up aimed at identifying the underlying ED etiology.

c) Further study endpoints used as primary or secondary endpoints were:

Global Assessment Question (GAQ):

Has the treatment you have been taking over the past four weeks improved your erections?

O yes   O no

(Please compare to your erections before your participation in this study)

Patient Global Confidence Question:

Over the past 4 weeks, to what extent did your level of sexual functioning affect your self-confidence?

O (1) significantly lowered my self-confidence
O (2) moderately lowered my self-confidence
O (3) did not affect my self-confidence
O (4) moderately raised my self-confidence
O (5) significantly raised my self-confidence

Both the GAQ and the Global Confidence Question represent relatively weak efficacy end points and are not recommended to be used as primary efficacy endpoints

d) Further Validated Questionnaires Used as Efficacy Endpoints in ED Trials:

1) EDITS: Erectile Dysfunction Inventory of Treatment Satisfaction:

The EDITS was developed with the financial support from Pfizer Inc. New York, US (manufacturer of Sildenafil – Viagra®) and underwent the common study drug

<table>
<thead>
<tr>
<th>Study drug (highest dose)</th>
<th>Mean IIEF-EF score</th>
<th>IIEF-EF≥26 (normal erectile function in %)</th>
<th>SEP 2 (%) (Vaginal possible) penetration</th>
<th>SEP 3 (%) (Completion of intercourse)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil (n=6659 and 2667) [24-26]</td>
<td>20 - 22.3</td>
<td>Not reported</td>
<td>No distinction between SEP 2 and SEP3</td>
<td>57-66</td>
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<tr>
<td>Placebo</td>
<td>10.4-11.8</td>
<td></td>
<td></td>
<td>21 - 25</td>
</tr>
<tr>
<td>Tadalafil, n=2102 [27]</td>
<td>21.1-23.6, 23.9, 25.2</td>
<td>46.4-56.1, 59</td>
<td>Not reported</td>
<td>75</td>
</tr>
<tr>
<td>N = 1112 [28]</td>
<td></td>
<td>70.9</td>
<td></td>
<td>59.5 - 69.6</td>
</tr>
<tr>
<td>Placebo [27-29]</td>
<td>13.0-15.9, 15.1, 17.2</td>
<td>6.3-13.1, 11.0</td>
<td>Not reported</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23.5</td>
<td></td>
<td>56.1</td>
</tr>
<tr>
<td>Vardenafil n= 762 [30]</td>
<td>21.4-21.8, 22.8</td>
<td>39.5-78.6</td>
<td>80.5-81.1</td>
<td>64.5-66.7</td>
</tr>
<tr>
<td>n = 601 [31]</td>
<td></td>
<td>Not rep.</td>
<td>Not rep.</td>
<td>74.6</td>
</tr>
<tr>
<td>Placebo [30,31]</td>
<td>15.0, 15.6</td>
<td>4.0-21.4</td>
<td>51.7-51.9</td>
<td>32.2-32.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not rep.</td>
<td>Not rep.</td>
<td>39.5</td>
</tr>
<tr>
<td>Lodenafil, n=72 [32]</td>
<td>22.8</td>
<td>Not rep.</td>
<td>89.6</td>
<td>74.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>12.6</td>
<td></td>
<td>71.0</td>
<td>23.3</td>
</tr>
<tr>
<td>Udenafil ,n=167 [33]</td>
<td>24.2</td>
<td>48.1</td>
<td>92.4</td>
<td>75.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>13.3</td>
<td>3.7</td>
<td>53.4</td>
<td>15.4</td>
</tr>
<tr>
<td>Mirodenafil, n= 223 [34]</td>
<td>25.7</td>
<td>62.3</td>
<td>91.9</td>
<td>73.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>17.0</td>
<td>17.3</td>
<td>60.6</td>
<td>26.8</td>
</tr>
</tbody>
</table>

Table 1: Results of oral drug phase II/III trials for Erectile Dysfunction (ED): Range in key efficacy endpoints in non selective broad- spectrum ED populations.

Number of study patients reported in the table refer to the whole study populations (active + placebo).

Integrated analyses of sildenafil trials reported “successful sexual intercourse attempts” not distinguishing between successful penetration (SEP2) and maintenance of erection up to completion of sexual intercourse (SEP 3)
validation process to assess satisfaction with medical treatments for erectile dysfunction and comprises a patient (11 items) and a partner (5 items) part. Test-retest reliability for the patient EDITS was 0.98 and for the partner EDITS 0.83. [35]. EDITS was used in several clinical trials with PDE 5 inhibitors. All items are scored from 0 (no satisfaction or dissatisfaction) to 4 (high satisfaction) and inally the mean satisfaction score was calculated and multiplied by 25 so that EDITS scores could range from a low of 0 (extremely low treatment satisfaction) to a high of 100 (extremely high satisfaction).

2) PAIRS: PSYCHOLOGICAL AND INTERPERSONAL RELATIONSHIP SCALES:

Pairs was developed and validated with the financial support by Eli Lilly and Company, Indianapolis, US (manufacturer of Tadalafil - Cialis®) to measure sexual self-confidence, spontaneity, and time concerns associated with ED and its treatment [36]. Later on a 15-item short version of Pairs was introduced [37]. Because the items contained in Pairs were obviously linked to the pharmacokinetic profile of Tadalafil with its longer half-life time this tool was exclusively used in clinical trials with Tadalafil and not accepted by the other PDE 5 inhibitor companies.

3) SEAR: SELF-ESTEEM AND RELATIONSHIP QUESTIONNAIRE:

Sear was developed and validated with the financial support of Pfizer Incorp., New York, US (Manufacturer of Sildenafil – Viagra®), to evaluate treatment responsiveness to sildenafil in ED patients. There are two domains: Sexual relationship (8 items) and conidence (6 items), the latter comprising two domains with sexual relationship (4 items) and overall relationship (2 items) subscales [38].

4) TSS: THE TREATMENT SATISFACTION SCALE:

This scale was developed and validated with the financial support by Bayer Healthcare, Germany (manufacturer of Vardenail – Levitra®) and comprises six scales: “satisfaction with medication”, “ease with erection”, “satisfaction with erectile function”, “pleasure from sexual activity”, “satisfaction with orgasm” and either “sexual conidence” for patients and “conidence in completion” for partners [39]. The TSS was used in clinical vardenail trials.

5) EQS: ERECTION QUALITY SCALE:

The EQS was developed and validated to investigate the erection quality and was supported by an unrestricted fund from Bayer Pharmaceutical Corp. and GlaxoSmithKline (manufacturer of Vardenail-Levitra®) [40]. With its 15 questions only related to erection it is comprehensive and was therefore rarely used in clinical trials.

6) EHS: ERECTION HARDNESS SCORE:

The EHS is a single-item, patient reported outcome...
(PRO) for scoring erection hardness and was financially supported by Pfizer Incorp., New York, US (manufacturer of Sildenafil – Viagra®) [41,]:

EHS: How would you rate the hardness of your erection?

0 Penis does not enlarge
1 Penis is larger but not hard
2 Penis is hard but not hard enough for penetration
3 Penis is hard enough for penetration but not completely hard
4 Penis is completely hard and fully rigid

7) QEQ: Quality of Erection Questionnaire:

The QEQ has been developed and validated with the financial support from Pfizer Incorp., New York, US (manufacturer of Sildenafil – Viagra®). It comprises 6 questions related to erection quality and duration with the sum of responses to all items being transformed onto a 0 – 100 scale with 100 as the highest possible score [42]

8) Proposals for PROs Used in Clinical Trials with in ED:

The need for a reliable patient reported outcome is obvious and now mandated by the regulatory authorities. In ED, historically the IIEF-EF domain score has been used and was considered as the standard efficacy PRO tool to assess the efficacy of any new drug under consideration for approval to treat ED and all the other validated PRO’s served as additional secondary efficacy endpoints to demonstrate further details on the features of a certain drug.

There is no question that the IIEF has shortcomings and may therefore deserve changes and improvements. It should be remembered in the design of new PROs that of paramount importance for patient and partner is the capability to induce a hard erection for a sufficiently long time to allow satisfactory sexual activities. Therefore the ED PROs should predominantly focus on:

A. completion of sexual intercourse/activities
B. rigidity/hardness of erection
C. self-confidence to engage in sexual activities.
D. impact of the new drug on patient’s personality/ quality of life
E. impact of the new drug on relation-/partnership-issues

The major problem with many of the PRO’s, focusing on all these items, is that all were funded by always only one pharmaceutical company and may have therefore considerable biases directed towards the product of that pharmaceutical company.

These shortcomings can only be overcome by the development of a new completely neutral PRO-tool aimed at capturing all the important items, mentioned above, and developed by a neutral committee of experts with an unrestricted fund of all drug producers in this field. Only when (or if) this happens will we have a neutral PRO tool for ED-trials capturing all the important items.

Recommendation 6 (Grade A)

For clinical trials with a new investigational drug in ED (Grade A)

a, Study populations - Key inclusion/exclusion criteria:

Only patients with a well-established, permanent chronic ED for at least 3, preferably 6 months, living in a stable partnership at least 3, preferably 6 months should be considered.

Patients must be willing to comply with the key requests of the trial i.e. to maintain regular sexual activities over the whole course of the trial with a mean frequency of sexual activities of at least once per week, must give up any other erectile function enhancing treatment, including hormonal (testosterone) replacement therapy with study entrance.

Patients with concomitant risk factors/diseases which may raise safety concerns because of the pharmacodynamic or pharmacokinetic profile of the study drug under consideration must be excluded.

b. Assignment of ED etiology

Assignment of the underlying ED etiology in terms of psychogenic, organic or mixed psychogenic-organic etiology is only justified and therefore recommended where specific etiology-oriented diagnostic investigations such as hormone parameters and intracavernosal injection test combined with penile duplex/color doppler are part of the study protocol.

Otherwise assignment of ED etiology must be considered arbitrary and unreliable

c. Assignment of ED severity

As long as there is no other more sensitive validated tool available ED-severity should be categorized according to the IIEF-EF Score.

d. Study endpoints (primary/secondary)

As long as no other more sensitive and more specific new validated questionnaires are available both the IIEF-EF score and SEP data are recommended for primary efficacy endpoints.
Because IIEF-EF is missing a key efficacy parameter in ED trials, i.e. erection hardness, it is strongly recommended to use in addition a validated erection hardness scale/score.

Regarding SEP data the committee recommends to use as study endpoints SEP 3 (ability to complete sexual intercourse) and SEP 4 (satisfaction with erection hardness) and not SEP 2.

Regarding assessment of other efficacy parameters such as effects on psyche, self-confidence, partnership and life quality the use of validated questionnaires is recommended which contain a patient and partner version like EDITS, TSS and SEAR.

e. Safety data

Established and recommended objective safety data are lab-exams, ECG recordings and blood pressure monitoring which have to be determined on a regular basis in phase II/III pivotal trials. It is highly recommended that at least in the early clinical research stage blood pressure and ECG recordings are conducted in conjunction with the study drug intake for 2-3 hours to investigate the direct impact of the study drug on these vital parameters.

It is recommended that adverse event (AE) data collection in conjunction with the study drug use is managed by means of an at home documentation considering a time frame of 24 h after study drug intake and using a Likert-like intensity/severity scale.

2. SPECIAL CONSIDERATIONS FOR COMPARATOR ED DRUG TRIALS

The arrival of three effective but similar PDE5 inhibitors in the marketplace has prompted the pharmaceutical industry to conduct comparator studies to determine patient or partner preference. Such preference studies are controversial particularly when designed by pharmaceutical companies.

The 2007 European Association of Urology Guidelines [43] stress the importance of patient education emphasizing the fact that all available PDE5 Inhibitors have similar effectiveness, claiming that ‘the patient will choose the final drug after his own personal experience’. The acknowledgement that the ED patient and his partner play an important role in therapeutic decisions has fuelled interest in the concept of patient preference and the need to determine the drug that most patients and partner prefer. From a clinical viewpoint, it seems logical that comparisons of existing PDE-inhibitors will be made as such evaluations might allow patients and physicians to choose a compound giving an optimal profile for their particular needs.

a) Methodological Aspects

Several preference studies have been conducted in the last few years, either by independent investigators or sponsored by the respective drug company eager to show any advantages of the own product. Unfortunately, the majority of these studies have shown serious design and methodological flaws limiting their clinical value and reliability. J Mulhall emphasized that patient preference studies differ from the classical efficacy and safety studies regarding study design and study endpoints [44,45].

The major limitations of published preference studies are biased drug instructions, compromising the blinding process or even conditioning patients’/couples’ preference, comparison of non-equivalent doses, inadequate wash-out intervals between treatment periods, lack of standardized preference assessments, differences in patient demographics, and lack of robust statistics [46].

The absence of a well-designed and validated questionnaire to evaluate adequately all aspects of patients’ and partners’ preference is a major issue. An extreme example is that in some studies only a single question reading ‘Which treatment did you prefer?’ is used as an index.

Recommendation 7 (Grade A)

Comparator trials in ED should consider the following rules:

a. randomized, double-blind, crossover study-design with adequate wash-out phases in between
b. no pre-selection of patients to avoid any bias suitable to favor one study drug
c. equivalent maximum doses of each study drug
d. equivalent treatment periods for each study drug
e. adequate and equivalent wash-out phases

3. SPECIAL CONSIDERATIONS FOR ED TRIALS WITH TOPICAL, TRANSURETHRAL AND INJECTABLE VASOACTIVE DRUGS

In ED trials with topical agents, transurethral or injectable vasoactive drugs the same criteria regarding study designs and endpoints should be employed as for oral drugs. The only exception is that in self-injection (intra-cavernosal) trials a placebo arm may be not considered appropriate by some ethical review committees due to the somewhat invasive nature of the procedure.

For topical agents only with prostaglandin E1 (alprostadil) have placebo-controlled trials with reasonable numbers of patients been published.
Equally only a limited number of adequately controlled trials on transurethral and intracavernosal applications of alprostadil as MUSE® or alprostadil alfadex or sterile powder have been published [48,50-52]

In addition to oral drug-trials trials with locally administered ED drugs should consider:

- Ease of application
- Acceptance rates
- Prolonged erections/priapism
- Local complications such as burning, fibrosis, infection
- Long-term use

4. SPECIAL CONSIDERATIONS FOR ED TRIALS WITH VACUUM-DEVICES

Reliable date on long-term use and acceptance is relatively limited and frequently concern the Osbon ErecAid device [53] Trials with vacuum devices should follow the same recommendations as described for the other ED treatments regarding the endpoints and questionnaires. In addition because of the special mode of application trials with vacuum devices should consider

- Ease of application
- General acceptance of application mode by both the patient and the partner
- Local complications
- Long-term use discontinuation rate
- Mechanical failure rates

5. SPECIAL CONSIDERATIONS FOR ED TRIALS WITH PENILE IMPLANTS

There is general agreement that penile implants represent the last step/resort in the treatment cascade of erectile dysfunction [54-55] Because penile prosthetic surgery is the most invasive treatment option for ED prospective trials have to follow special rules regarding potential study populations. In addition because from the operational point of view there are generally speaking 3 different device options: semi-rigid, 2 piece inflatable and 3 piece inflatable implants the general question raises whether it is reasonable to conduct prospective trials in this field only with a certain type of implant (inflatable, semi-rigid) or to consider all types of implant in the same trial and to leave the choice to the participating patient.

Considering the numbers of penile implants being inserted per year with only about 30,000-40,000 per year world-wide [54] it is understandable that prospective trials in this field are difficult and cumbersome to conduct. These problems regarding prospective trials in penile prosthetic surgery have become obvious in one of the very few prospective trials which have been published in this field with a reasonable number of patients[56]: In this prospective multicenter trial with the inflatable Mentor alpha one prosthesis only 54 % (234/434) of the patients were willing to fill a patient questionnaire after a mean follow-up of 22 months. The overwhelming majority of penile implants today are 3 piece inflatable prostheses amounting to more than 80 % of all inserted implants. In an review of the most experienced institute the long-term survival rate of inflatable penile implants comprising altogether 14 different inflatables (n=2,384) 10-years revision free survival rates were 68,5 % and 15-years revision free survival rates were 59,7 % [57].

These figures make clear that regarding potential prospective trials in penile prosthetic surgery should ideally comprise a time frame of between 10-15 years similar to prospective trials in prospective prostate cancer trials.

With these data in mind the challenges of prospective trials in this field are obvious.

In general prospective trials in penile prosthetic surgery must therefore consider 2 different parts:

- **Mid-term trials** ideally with a mean follow-up of at least 2 years evaluating the following topics:
  - Short-term mechanical failure rates (cylinders, pump, and reservoir)
  - Surgical failure rates (infection, mal-insertion such as Concorde phenomenon, bulging etc.)
  - Patients' and partners’ acceptance rates
  - Patients and partners’ satisfaction rates regarding the implant function and sexual life as such
  - Ease of device operation
  - Penile length and penile shape
  - Effects of penile implant surgery on partnership, self-esteem etc.
  - Regular use rates of the penile implant
  - Additional use of other ED treatments such as PDE 5 inhibitors, MUSE, others

- **Long-term trials**
  - With the primary outcome revision free survival after 5, 10 and even 15 years in addition to the above mentioned topics.
  - **Prospective trials in penile prosthetic surgery** should only consider experienced surgeons/institutes with a reasonable number of procedures per year.
  - In the previously mentioned multicenter trial the request was > 20 implants per year which seems a reasonable number in this field.
Unfortunately there is no validated questionnaire available in the public domain which considers all the special items linked to penile implants.

6. SEXUAL FUNCTION (REHABILITATION) ASSESSMENT AFTER PELVIC SURGERY

After the introduction by Walsh and Donker 1982 Nerve-Sparing Radical Prostatectomy (NSRP) has become world-wide the procedure of choice to preserve erectile function postoperatively provided location and volume of PCA is not speaking against that procedure. Although the majority of all radical prostatectomies either performed as open or as laparoscopic/Robotic procedure is eager to preserve the cavernosal nerves incidence of post operative ED is still high and recovery of erectile function does not occur in the majority of cases without medical support even after bilateral nerve sparing prostatectomy (BNSP)

In the current era of early PCA detection, where increasingly many young, sexually active men are undergoing this surgical procedure, the importance of preservation of erectile function becomes even more crucial. To improve postoperative outcome of curative prostate cancer treatment the concept of penile rehabilitation was first introduced by Montorsi 1997 [58]. The rationale of penile rehabilitation is to prevent cavernous tissue and function damage, which inevitably occurs after cavernosal nerve injury.

Following the idea of Montorsi’s research group Mulhall further developed this concept, showing in a non randomized study with 132 patients not responding after prostatectomy to on demand sildenafil, that a pharmacologic penile rehabilitation protocol (sildenafil and alprostadil) resulted in higher rates of spontaneous functional erections [59].

Recently, PDE-5-inhibitors have been studied for their use in penile rehabilitation, either on demand, given at night or daily. [60-63] Unfortunately there is considerable heterogeneity among these studies and the scientific evidence available today that penile rehabilitation therapy works is still limited. Table 3 summarized the most relevant clinical trials dealing with penile rehabilitation published today.

Some of these studies provided limited evidence that early penile rehabilitation strategies with PDE 5 inhibitors may be superior to wait and see strategy [60,62,63].

Recently Montorsi et all [64] published a multinational prospective randomized, double blind, double–dummy study in a huge population of 628 patients after NSRP, conducted only in so-called centers of excellence, with normal preoperative erectile function (IIEF-EF score ≥ 26). Erectile function and sexual intercourse completion rates improved significantly in both treatment arms compared to placebo during the initial double-blind period. But the results clearly show that nightly dosing with vardenafil did not have any effect beyond that of on demand use. Following a washout phase for 2 months with placebo, IIEF-EF scores ≥ 22 were achieved in 28.9%, 24.1%, and 29.1% of patients who were prior to this 2 months wash-out phase on placebo, vardenafil nightly, and vardenafil on demand, respectively, showing no statistically significant difference among the 3 different treatment arms . The advantage of the vardenafil treatment arms over placebo was not persistent in the open-label phase. Although this is currently the most comprehensive prospective study dealing with penile rehabilitation therapy after BNSP unfortunately due to a mayor study design flaw this study could not answer the question whether daily PDE 5 inhibitor therapy, dosed adequately according to the pharmacokinetic profile of the study drug, may be superior to an on demand regimen. Regarding the short half life of vardenafil with about 4 hours daily vardenafil should have been dosed three times per day to guarantee a steady drug exposure and not once as it was the case in this trial.

a) Methodological Problems in Trials for Penile Rehabilitation Therapy After Curative Treatment (Surgery, Brachytherapy, External Radiation) for Prostate Cancer

At present all the published data except one on this subject did only focus on restoration of erectile function and completely ignored the high frequency of other sexual dysfunctions which occur especially after prostatectomy. Just recently at the annual congress of the European Association of Urology 2009 in Stockholm a multidimensional scale for the assessment of sexuality after radical prostatectomy was introduced showing that [65]:

- 75.4% of 53 consecutive patients after RRP used ED treatments 82% i.c. injections and only 10 % PDE 5 inhibitors

- 53% reported lower sexual desire and 79% a decrease of sexual activities

- 41.5% reported loss of orgasm (!!) , another 38% decreased orgasmic intensity

- 21% reported loss of urine during orgasm

- 59% reported lower sexual satisfaction of the partners

- 82% reported loss of masculinity

- 55% reported loss of self-esteem

These data make clear that prostatectomy exerts a profound negative impact on all sexual functions even on self-esteem and masculinity. Until now in all the published studies only erectile dysfunction was
considered disregarding that prostate removal shows a much broader spectrum of negative consequences on sexual functions and psychological features.

Considering these new data and our personal experiences, prospective trials for sexual rehabilitation therapy must consider the following domains:

**Erectile function**

**Ejaculatory/orgasmic function/intensity**

**Incontinence problems during sexual activities**

**Penile length/shape problems**

**Sexual satisfaction**

**Impact on psyche and life quality**

**Impact on partnership and partner’s satisfaction**

**Recommendation 8 (Grade B)**

Sexual (Penile) Rehabilitation Trials After Pelvic Surgery/Radiation Therapy Should

- be conducted timely after the procedure, i.e. 2-4 weeks afterwards
- be conducted in homogenous, well defined study populations (BNSP, UNSP or NNSP, cystectomy, brachytherapy other)
- last for a reasonable period of time (6-12-24 months – at least 12 months study duration is recommended).
- be followed by a 2 months wash-out phase (placebo or no treatment) to assess IIEF-EF and SEP data afterwards
- consider the pharmacokinetic profile of the study drug regarding the frequency of dosing if daily dosing trials are considered: short acting drugs must be dosed 2-3x/day, long-acting once a day.
- consider age and relevant preexisting co-morbidities which may interfere with the study outcome
- be conducted only in those couples/patients who were regularly sexually active before the intervention in question and wished to continue.
- should consider in one arm combination therapy regimens such as PDE 5 inhibitor with injection- or intraurethral therapy

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Design</th>
<th>Agent used</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montorsi et al. [58]</td>
<td>30</td>
<td>Prospective, randomized trial</td>
<td>PGE1 3/week vs. no treatment</td>
<td>Increased spontaneous erections</td>
<td>No preoperative EF data, small number of patients, short follow-up</td>
</tr>
<tr>
<td>Mulhall et al. [59]</td>
<td>132</td>
<td>Prospective, nonrandomized study</td>
<td>Trimix or bimix 3/week vs. no treatment or as needed</td>
<td>Higher rates of spontaneous erections. Increased % of patients having intercourse and response to sildenafil</td>
<td>No placebo arm, dropouts not included</td>
</tr>
<tr>
<td>Gallo et all [66]</td>
<td>40</td>
<td>Prospective nonrandomized study</td>
<td>Vardenafil 20 mg on demand 6 month</td>
<td>Statistical significant in IIEF EF compared to baseline</td>
<td>No control group no definition of on demand treatment</td>
</tr>
<tr>
<td>Barnowsky et al. [63]</td>
<td>43</td>
<td>Prospective, randomized controlled</td>
<td>Low dose of Sildenafil daily</td>
<td>Treatment group improved recovery of EF (86% versus 66% placebo) and higher spontaneous erection rates</td>
<td>Small number of patients, no placebo, only included patients with preserved EF post-operatively</td>
</tr>
<tr>
<td>Padma-Nathan et al. [60]</td>
<td>76</td>
<td>Randomized, double-blind, placebo-controlled study</td>
<td>Nightly sildenafil vs. placebo</td>
<td>Nightly sildenafil increased return of spontaneous erections</td>
<td>Relative low number of patients weakens the strength of the results.</td>
</tr>
<tr>
<td>McCullough et al. [62]</td>
<td>54</td>
<td>Prospective, randomized, placebo controlled</td>
<td>Nightly sildenafil vs. placebo</td>
<td>Nightly sildenafil improved nocturnal erections, higher return of rigidity vs placebo</td>
<td>Small number of patients, nocturnal tumescence data do not necessarily correlate with erection during intercourse</td>
</tr>
<tr>
<td>Montorsi et al. [64]</td>
<td>628</td>
<td>Randomized, placebo-controlled, double-blind, double-dummy, multicentre study</td>
<td>Vardenafil administered either nightly or on-demand vs. placebo</td>
<td>Nightly vardenafil did not have any effect beyond that of on demand use. As-needed vardenafil showed greater efficacy than placebo (45% vs. 24% SEP3)</td>
<td>The largest randomized placebo controlled study</td>
</tr>
</tbody>
</table>
7. GENE THERAPY TRIALS IN ERECTILE DYSFUNCTION

The bar to conduct clinical gene transfer trials for ED has been set quite high because of the well publicized deaths of 18 years old Jessie Gelsinger in 1999, two children in Paris who developed leukemia after treatment to modify stem cells with a retroviral vector for leukemia and a 36 year old woman, Jolee Mohr, who was transferred with adeno-associated viral vector for chronic painful rheumatoid arthritis.[67-69] Most of the approximately 800 gene transfer trials have been conducted in people with diseases in which there are few other alternatives or are potentially fatal such as cancers, end stage ischemic disease, or for a genetic, immutable disease. The stigma related to those aforementioned deaths has made the conducting of a clinical transfer trial for the indication of ED dificult. Particularly as some assume that ED is not a significant enough problem to warrant the risk or that it is no longer considered a problem as the problem is considered “managed by the PDE5 inhibitors”

In the United States all gene transfer trials submissions are reviewed by the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA). CBER has recognized the following:

1) ED is a significant problem that both adversely effects the quality of life of the patient and his sexual partner,
2) That the pursuit of therapy may unmask an underlying life-threatening illness, and
3) that there is room for improvement above currently available therapies.

In addition to FDA each application is also reviewed in an advisory capacity by the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH). The NIH established the RAC on October 7, 1974 in response to public concerns regarding the safety of manipulating genetic material through the use of recombinant DNA techniques.

Important considerations regarding gene therapy trials in ED or other dysfunctions in Sexual Medicine include the following:

- The plasmid should be manufactured under good manufacturing process conditions (GMP) by a licensed production company. That process insures that the product is what it is supposed to be in terms of
  1. gene structure
  2. plasmid size
  3. gene restriction mapping
  4. plasmid stability,
  5. host strain purity,
  6. no toxic contaminants,
  7. guaranteed sterility.

The GMP process is a lengthy multistep process.

- The final product must be tested and shown to have a physiological effect before transfer into humans is allowed.
- It must use a vector that does not have a high incidence of allergy in the population (for example use of a kanamycin resistance gene rather than a penicillin resistance gene in the manufacturing process).

IND Approval

Extensive pre-clinical Information is vital for IND approval. Some of the major points include

- Proof of efficacy that demonstrate activity of the transferred gene
- Duration of action in the organ or tissue of interest
- Biodistribution of the gene after transfer

For this point 42 organs and fluids of the animal model are evaluated for untoward effects after transfer.

- Duration of activity of the stored product.

Institutional Review Board (IRB) Approval

Once IND approval is granted no study in humans can be conducted without (IRB) approval. That is true whether studies are done in academic institutions or in private practice offices or centers designed for trial. However, the IRB may be either based at an institution or independent. In the case of ICI’s ED trial the institutional IRB would not approve the trial because of concerns of conflict of interest, but a private IRB, comprised of many of the same reviewers did approve the trial. To allow total neutrality in both accruing participants or analyzing data the sponsor or developer of the product should not have any direct role in the trial. [70]

Informed consent

The issue of proper informed consent has received the most intense scrutiny in the lay press, in scientific journals, and by biomedical ethicists.[71,72] This component of the process is particularly important for a trial using gene transfer done for a non-fatal disease. In addition to the specific additional recommendations for Informed Consents for gene therapy trials (compared to ordinary drug trials), added layers of protection for the participant must be included.

In addition to independent IRB approval the protocol
must also be approved by a separate Institutional Biosafety Committee (IBC). The charge of the IBC includes:

1. Review of ALL research proposals involving recombinant DNA.
2. Conducting periodic review to ensure compliance
3. Proscribing emergency plans covering accidental spills and personnel contamination by recombinant agents, as developed and recommended by the Biosafety Office.
4. Reporting significant problems or violations of the NIH Guidelines

Other specific issues related to gene transfer include:

- The FDA has great concern that the gene should not be transmitted by sperm thus placing progeny at some unspecified risk. Thus all men and their partners in separate informed consents in the trial agreed that condoms would be used during the duration of the trial.
- Semen specimens are requested at the visits during the trial
- Men could only be admitted to the trial with moderate to severe ED who had failed, or were unwilling to continue using other modes of therapy
- Participants were willing to have an autopsy should they succumb during the trial
- Initially the participants agreed to 15 year follow-up after transfer. That was later modified to 18 months after plasmid transfer as opposed to viral vector transfer.

Phase 2 and 3 trials will include the added element of a placebo group, multiple dosing of the gene and use of transfer into specific subgroups as for drug trials. Safety data and any (including lack of) efficacy accrued in phase 2 trials should be reviewed with the participant.

Efficacy and duration of effectiveness after transfer as a byproduct of the phase 1 trial are similar to those employed in the drug trials for ED listed in this chapter.

At present only one gene transfer phase 1 trial for ED has been successfully conducted and published using gene transfer of potassium channels to treat smooth muscle diseases(73,74)

**Recommendation 9 (Grade A)**

For clinical trials with a gene transfer in ED

**a. Study populations - Key inclusion/exclusion criteria:**

Only patients with a well-established, permanent chronic ED for at least 6 months, living in a stable partnership at least 6 months should be considered.

Participants must be willing to comply with the key requests of the trial i.e. to maintain regular sexual activities over the whole course of the trial with a mean frequency of sexual activities of at least once per week, must give up any other erectile function enhancing treatment, with study entrance.

Participants who are capable of ejaculation must be willing to use condoms during coitus (until it is proven that the gene does not transfer to semen)

Participants must be willing to be followed for 18 months post-trial for plasmid transfer and 15 years if viral vectors are used.

Participants must be willing to give permission for autopsy in the event of death post transfer during follow up period.

Participants and partner should be explicitly told that they should not expect cure from transfer by an independent counselor while obtain informed consent.

Participants with concomitant risk factors/diseases which may raise safety concerns because of the profile of the study gene under consideration must be excluded

**b. Assignment of ED severity**

As long as there is no other more sensitive validated tool available ED-severity should be categorized according to the IIEF-EF Score. For Phase I and Phase II trials participants should be in the moderate to severe range. For Phase III after long-term safety has been demonstrated the participants can be extended to mild to severe ED

**c. Study endpoints**

For Phase I safety is the primary study outcome. Sequential increase in dose should be used and before proceeding to the next highest dose an independent Data Safety Monitoring Board must review the collected data and agree that the next cohort can commence.

For Phase II and Phase III trials both safety and efficacy should be followed. The primary study outcome will be the change from baseline or last observation carried forward of IIEF-EF and SEP at 12 weeks after transfer.

As long as no other more sensitive and more specific new validated questionnaires are available both the IIEF-EF score and SEP data are recommended for primary efficacy endpoints.

Because IIEF-EF is missing a key efficacy parameter in ED trials, i.e. erection hardness, it is strongly recommended to use in addition a validated erection hardness scale/score.
Regarding SEP data the committee recommends using as study endpoints SEP 3 (ability to complete sexual intercourse) and SEP 4 (satisfaction with erection hardness) and not SEP 2.

d. Safety data

Established and recommended objective safety data are lab-exams, semen evaluations for gene, exam of penis at regular intervals, ECG recordings and blood pressure monitoring. It is highly recommended that at least in the phase I and II blood pressure and ECG recordings are conducted in conjunction with the transfer for 2-3 hours.

V. PATIENT REPORTED OUTCOME (PRO)

1. PRO VALIDATION PROCESS SHOWN ON OCCASION OF IPE DEVELOPMENT

The following represents the background on the need for PROs and the validation procedure. This is described in detail for the IPE, one of the more recently developed PROs.(75) This does not indicate that the committee has any preference for the IPE over any other validated PRO but the only is illustrative of the validation exercise.

Although IELT is an objective measure of ejaculatory function it does not address the impact of therapy on the patients’ well-being and confidence in their sexual performance, which are important markers of treatment benefit. This can be measured by the use of patient-reported outcome (PRO) questionnaires. A PRO is a measurement of any aspect of a patient’s health status that comes directly from the patient, without the interpretation of the patient’s responses by a physician or anyone else. In clinical trials, a PRO instrument can be used to measure the impact of an intervention on one or more aspects of patients’ health status, hereafter referred to as PRO concepts, ranging from the purely symptomatic (response of a headache) to more complex concepts (e.g., ability to carry out activities of daily living), to extremely complex concepts such as quality of life, which is widely understood to be a multidomain concept with physical, psychological, and social components. Data generated by a PRO instrument can provide evidence of a treatment benefit from the patient perspective. For this data to be meaningful, however, there should be evidence that the PRO instrument effectively measures the particular concept that is studied. Generally, findings measured by PRO instruments may be used to support claims in approved product labeling if the claims are derived from adequate and well-controlled investigations that use PRO instruments that reliably and validly measure the specific concepts at issue. The glossary defines many of the terms used in this guidance. In particular, the term instrument refers to the actual questions or items contained in a questionnaire or interview schedule along with all the additional information and documentation that supports the use of these items in producing a PRO measure (e.g., interviewer training and instructions, scoring and interpretation manual). The term conceptual framework refers to how items are grouped according to sub-concepts or domains (e.g., the item walking without help may be grouped with another item, walking with difficulty, within the domain of ambulation, and ambulation may be further grouped into the concept of physical ability).

In the context of studies in sexual dysfunction, a PRO is a measurement of any aspect of a patient’s health status that comes directly from the patient, without the interpretation of the patient’s responses by a physician or anyone else, and therefore uniquely provides evidence of treatment benefit from the patient perspective. Guidance from the regulatory authorities indicates that both objective and PRO methods are required to document improvements in sexual function [17]. For data to be interpreted and evaluated by the regulatory authorities, the PROs used must be both validated and relevant to patients.

The 10-item IPE questionnaire (Table 4) is divided into three domains, i.e. ejaculatory control (four questions), sexual satisfaction (four questions) and distress (two questions), each answered on a 6-point scale. The maximum possible scores for control and satisfaction are 20 points (most control/satisfaction) and the maximum score for distress is 10 points (least distressed).

The stages of the validation exercise for the IPE are summarized in Table 5. Ultimately any instrument must be capable of detecting change and defining or identifying minimally clinically important differences (MCIDs, Table 6).
Table 4: IPE Individual Questions.

All questions relate to the past 4 weeks with graded responses:

- How often did you have control?
- How much confidence did you have?
- How often was intercourse satisfactory?
- How satisfied were you with your sense of control?
- How satisfied were you with the length of intercourse?
- How satisfied are you with your sex life?
- How satisfied have you been with your sexual relationship with your partner?
- How much pleasure has sexual intercourse given you?
- How distressed were you by how long you lasted before ejaculation?
- How distressed have you been about your control over ejaculation?

Table 5: Stages in IPE PRO validation.

Develop initial questionnaire

- Interviews with Althof & Rosen: 17 item questionnaire
- Assess measurement properties
- Four domains identified via factor analysis
- One domain found dropped
- Good reliability (internal consistency and test-retest reliability) and validity (convergent and known-groups)

Modify questionnaire

- Qualitative interviews with PE patients: question refinement; no new concerns raised
- FDA requested modifications to some questions: cognitive debrief with PE patients; small refinements
- Current version: 10 items, 3 domains (control, satisfaction & distress)

Reliability and validity retested and found to be good

- Internal consistency (Cronbach’s α >0.7)
- Test-retest reliability (ICC >0.7)
- Correlation with IELT >0.6 for all domains
- Discriminates between PE and normal men

Table 6: Final requirements for validation.

Ability to Detect Change

- Change versus changes in global rating of change
- Change versus changes in premature ejaculation profile (PEP)
- Change versus changes in IELT

Minimum clinically important difference (MCID)

- Anchor based
- Small improvement in global rating
- One category improvement in PEP
- Distribution based
- 0.5x SD

Recommendation 10. (Grade A)

PROs have been developed for several urological conditions such as stress incontinence, OAB, BPH and ED. Almost all regulatory authorities require the use of validated PROs in phase III pivotal studies and the validation exercise is described on their websites.

It is recommended in phase III that either a validated PRO is used or if not available that the validation procedure explained on regulatory authority websites is adhered to rigorously.

VI. CLINICAL TRIALS IN PREMATURE EJACULATION (PE)

1. DEFINITION OF PE

Premature ejaculation represents one of the most common male sexual disorders with prevalence rates between 18 and 25% depending on the definition used.

Until recently 5 different definitions for PE were in use:

International Classification of Diseases 10th Edition (ICD-10) [76]
Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) [77]
American Urological Association (AUA) Guidelines [78]
European Association of Urology (EAU) guidelines [79]
2nd International Consultation on Sexual Dysfunctions/World Health Organization (ICSD/WHO) 2004 [80]

The major shortcoming of all these definitions was that they were all authority based rather than...
evidence based and were not supported from controlled clinical and/or epidemiological studies, a fact which raised criticism in the literature [81]

To address this obvious lack of a generally acknowledged definition of PE which establishes the basis for both diagnosis and treatment of PE and clinical trials for PE, the International Society for Sexual Medicine (ISSM) convened an ad-hoc steering committee on PE 2007. The members were the world-wide leading experts in PE, identified through peer reviewed publications in this field, and were responsible for constructing a new evidence based definition of PE. Based on an extensive literature review of the last decades, the committee formulated the following new definition for lifelong PE [82];

Lifelong PE is defined as a male sexual dysfunction characterized by

- Ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration; and
- Inability to delay ejaculation on all or nearly all vaginal penetrations; and
- Negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy

The restriction of the Intravaginal Ejaculation Latency Time (IELT) to about one minute is supported by several epidemiological studies using stop-watch measured IELT’s in men with lifelong PE and those with normal PE, serving as controls[9,83]: According to these studies about 90 % of patients with lifelong PE ejaculated within 1 min. after vaginal penetration with 80 % of them showing an IELT within 30 sec. whereas the median IELT of an unselected normal population, comprising 500 heterosexual couples, was 5.4 min [81]. In the US observational study with a total of 1.587 subjects, among them 207 subjects with PE according to the DSM-IV criteria, the median IELT in men with PE was 1.8 min. as compared to a median IELT of 7.3 min. in non-PE men [9]. In this study 26 % of PE men showed an IELT< 1min., 52 % < 2 min.,35 % between 2-5 min. and 13 % between 5-25 min. In the non-PE population in 6 % of all men the measured IELT was < 2 min.

With these data in mind the defined IELT of about 1 min. in the new ISSM PE definition sets a strict criterion for defining PE.

In addition to the IELT as an objective indicator, the following parameters were identified as being particularly significant for the diagnosis of PE:

Lack of control over ejaculation/inability to delay ejaculation

PE-related negative consequences such as distress, bother, frustration.

These assessment measures which turned out to be sensitive for the definition of PE were elaborated in two different validated PRO-based questionnaires. One of these questionnaires (Index of Premature Ejaculation) was developed with the financial support of Pfizer Incorp.;US [75] and the other one (Premature Ejaculation Profile (PEP) with the financial support of Johnson & Johnson,US and was used in the Dapoxetine clinical research program [84].

There is an increasing evidence in the literature that lifelong PE has an underlying neurobiological and/or genetic and thus a more organic than psychogenic etiology [85,86].

In contrast to lifelong PE acquired PE can have a variety of contributory risk factors such as Erectile Dysfunction (ED), prostatitis or thyroid disorders [87].

Regarding these differences between lifelong and acquired PE the ad hoc committee on PE 2007 decided that at that time there are insufficient published objective data to support an evidence based definition on acquired PE.

In an 2nd attempt to reach a consensus for an evidence based definition on acquired PE in a joint meeting of the ISSM and the European Academy of Andrology (EAA), which was held once more under the auspices of the ISSM Standards Committee at 2nd July 2008 in Hamburg the committee came to the following position statement:

- Acquired PE is a sub-type of premature ejaculation characterized by

  - a substantial decrease in time-to-ejaculation compared to a man’s previous sexual experience,
  - the inability to delay ejaculation on all or nearly all vaginal penetrations, and
  - negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy 1

1 The third construct required for PE definition, i.e, temporal range of IELT. Further clinical research is required to obtain IELT and PRO-data for acquired PE.

2. CLINICAL TRIALS FOR PE STUDY DESIGNS AND OUTCOME MEASURES

Based on the published literature regarding PE it is generally acknowledged that PE causes considerable psychological burden both for the patients and the partners and their relationship [88]. In this regard there is general agreement both in the medical domain and within the regulatory authorities that PE has to be considered a pathological condition/ dysfunction rather than a lifestyle issue and that it is worth to consider new treatments for alleviation of this dysfunction.
Considering all the different clinical trials conducted in men with PE and which has been published in peer reviewed journals only a few of them met more or less the new criteria for the definition of PE, i.e. IELT of about one minute, PROs such as lack of control over ejaculation/inability to delay ejaculation and distress/bother related to PE, and were conducted as randomized, placebo-controlled, double-blind trials [89].

3. DAPOXETINE CLINICAL TRIAL PROGRAM

Dapoxetine is a new serotonin transporter inhibitor with a short T MAX and a short T ½ which has been developed for on demand use in premature ejaculation. The drug is meanwhile approved and launched across several European countries.

a) PROs Used in Clinical trial Program

1) Premature Ejaculation Program (PEP)

2) Clinical Global Impression of Change (CGI-C):

Compared to the start of the study, would you describe your premature ejaculation problem as:
- 3 much worse
- 2 worse
- 0 no change
- 1 slightly better
- 2 better
- 3 much better

The world-wide Dapoxetine clinical trials program used world-wide the same study design:

US-trials [90,91]

Men ≥ 18 years and living in a stable monogamous heterosexual relationship for ≥ 6 months with PE according to the DSM-IV criteria for ≥ 6 months (in the US trials IELT was neither reported nor assessed)

European/Canada/South America/South Africa 22 countries trial [92]

Men ≥ 18 years and living in a stable monogamous heterosexual relationship for ≥ 6 months PE according to the DSM-IVTR criteria for ≥ 6 months

Moderate PE-related distress or interpersonal difficulty

Measured IELT of ≤ 2 min. in ≥ 75 % of valuable events (at least 4 requested) during a 4 –wk screening/baseline run in phase.

No relevant ED as assessed by an IIEF-EF score of ≥ 21

Study endpoints used in the Dapoxetine program:

US-trials

Changes in the Premature Ejaculation Profile (PEP) [84] Assessment of treatment/drug-related adverse events

European/Canada/South America/South Africa 22 countries trial [92]

Stopwatch measured IELT

PRO measures including the Premature Ejaculation Profile (PEP, 84) and the Clinical Global Impression of Change (CGI)

In this regard a composite PRO definition of clinically relevant benefit was applied based on the percentage of patients achieving an increase of greater than or equal to two categories in control and a decrease of greater than or equal to one category in distress at week 12 and week 24. In addition other secondary endpoints were the percentages of men with a decrease of greater than or equal to one category in distress or an increase of greater than or equal to one category in satisfaction.

Table 7: The Premature Ejaculation Profile [84]
Fig. 2: Study design of the European/Canada/South America/South Africa 22 countries trial [92]

Fig. 3: Dapoxetine clinical trials: mean IELT by study and treatment at endpoint [90-94]

Fig. 4: Dapoxetine clinical trials (pooled data) Drug-related adverse events [90-94]
b) Outcome of Dapoxetine Trials

The relevant efficacy and safety data of the Dapoxetine trials are summarized in fig. 2-5 and may lay the reference basis for other drugs under consideration for PE treatment. Regarding patients with lifelong or acquired PE the pooled data did not show any statistical significance in terms of efficacy and safety.

4. TOPICAL EUTECTIC MIXTURE FOR PREMATURE EJACULATION (TEMPE - PSD502) CLINICAL PROGRAM

PSD502 is a topical agent designed specifically for treating PE and consists of a metered-dose aerosol formulation of lidocaine and prilocaine dissolved in a non-chlorofluorocarbon propellant, which also acts as a solvent, forming a eutectic-like mixture [95,98]. Uniquely the desensitizing agents in this non-aqueous formulation can penetrate the poorly keratinized modified mucosa of the glans penis, but not the fully keratinized skin of the penile shaft, enabling a localized desensitizing effect [95,97]. The efficacy of PSD502 in PE has been tested in two previously published clinical trials [96,98]. In both of these studies, patients were selected according to the subjective Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) definition of PE which does not include a time element [96,98].

In the phase III multicentre, multinational study in all, 300 men with PE, were randomized from 31 centres in the UK (37), Czech Republic (121), Hungary (21) and Poland (121). Men aged >18 years, in stable heterosexual, monogamous relationships, and with lifelong PE diagnosed according to both the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (text revision) criteria and the ISSM definition, consented (together with their partners) to enter the baseline period of the study. Patients who documented an IELT of ≤1 min with two or more of the first three sexual encounters during the 4-week baseline period were randomized, in a 2:1 ratio, to receive double-blind treatment with PSD502 (three actuations of spray each containing 7.5 mg lidocaine and 2.5 mg prilocaine applied 5 min before intercourse) or placebo for 3 months. Patients completed Index of Premature ejaculation (IPE-75) questionnaire at entry and at monthly clinic visits, and recorded stopwatch-timed IELT during each sexual encounter. Patients rated the quality of their orgasms on a 5-point scale at baseline and at the end of the treatment period, and rated the study medication on a 4-point scale. The flow of patients through the screening, baseline and double-blind phases of the study is shown in fig. 5. At entry to baseline, the PSD502 groups had similar overall demographics and PE history. All patients except three (in the PSD502 group) were Caucasian and the mean age was 35 years in both groups (SD 9.6 and 11.2, PSD502 and placebo). Overall, 95% of patients in both groups had lifelong PE and a similar proportion of men in both groups were uncircumcised (94% and 93% in the PSD502 and placebo groups respectively). A similar proportion of patients in each group had used previous treatments for PE, the most common being SSRIs or other oral antidepressants, which had been previously used by ≈25% of patients in both groups.

The Index of Premature Ejaculation (IPE-75) Individual questions (all questions relate to the past 4 weeks with graded responses):

- How often did you have control?
- How much confidence did you have?
- How often was intercourse satisfactory?
- How satisfied were you with your sense of control?
- How satisfied were you with the length of intercourse?
- How satisfied are you with your sex life?
- How satisfied have you been with your sexual relationship with your partner?
- How much pleasure has sexual intercourse given you?
- How distressed were you by how long you lasted before ejaculation?
- How distressed have you been about your control over ejaculation?

The geometric mean (range) IELT over the 3-month treatment period increased from a baseline of 0.6 min in both groups to 3.8 (0.3-57.8) and 1.1 (0-15.0) min in the PSD502 and placebo groups, respectively. Adjusting for treatment-group imbalances, this represents a 6.3-fold and 1.7-fold increase in adjusted geometric means. There were significantly greater increases in the scores for the IPE domains of ejaculatory control and sexual satisfaction in the PSD502 group than in the placebo group, with a mean 7.0 (SEM 0.59)-point difference between treatments in change from baseline to the IPE domain for ejaculatory control and a 5.9 (SEM 0.57)-point difference in change from baseline in the IPE domain for sexual satisfaction (both P < 0.001). This was supported by improvements in all secondary endpoints. At the end of the treatment period 66% of patients rated PSD502 as ‘good’ or ‘excellent’.

PSD502 was well tolerated and no systemic adverse events were reported. Localized treatment-related adverse events were reported by 2.6% and 3.1% of patients and partners, respectively.
5. CONCLUSIONS ON CLINICAL TRIALS IN PE

a) Observational Trials in PE:

The purpose of observational trials is to provide reliable and representative data of a certain health condition/disorder in certain nations/cultures.

Regarding the new developments in the field of PE observational studies should make use of the new ISSM PE definition [82] and the new validated PRO measures developed for investigation of PE [75,84]. Observational trials in PE usually provide prevalence data with a representative cross-section analysis of the population/cohort in question.

Because there is a substantial body of evidence that PE exerts also a great negative impact on the partnership and on partners’ sexual life experience and satisfaction it is explicitly recommended by the committee that partner data of PE patients are also collected in these studies by means of validated PROs. Wherever possible observational studies in PE should follow a prospective trial design [98,99,100].

b) Interventional (Drug) Studies in PE

In the future drug trials should follow a standardized trial design which follows the rules of all trials: prospective, randomized, placebo-controlled and double blind.

Similar to ED trials PE trials should allow the enrolled couples adequate time periods both for the run-in phases, in which the baseline data regarding the severity of PE are generated, and for the treatment phases in which the change from baseline data is investigated.

The non medicated run-in phases should last between 4 and 6 weeks and the treatment phases at least 3 months.

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Fig. 5 Study-Design of the TEMPE - PSD502 study

Figure 6: Geometric Mean IELT at baseline and over the 3 month treatment period: ITT population [98]

Figure 7: Change from baseline to month 3 in adjusted mean IPE scores [98]
Measured IELT must be considered as a standard regarding primary study endpoints in PE trials and PRO’s with validated measures, containing questions addressing control over ejaculation and distress/bother related to PE, as standard for secondary endpoints. In this regard the PEP seems currently to be the most appropriate and widely used one PRO measure for PE.

Data collection is managed both by home diaries, recording each single sexual event (IELT recording) and at the scheduled visits, where the different PROs are recorded as well as treatment related adverse events.

For all new PE drug trials at least one flexible dose study design should be considered in the phase III program. Such a flexible dose study design, starting with the minimally effective dose as identified during the phase II program, will provide more realistic data for the broad spectrum market use especially as for the frequency and severity of drug-related AE’s and usually mirrors the later labeling recommendations. A flexible dose study design finally also generates more reliable data on how many patients are satisfied with lower doses.

Unfortunately in the Dapoxetine clinical program flexible dose study designs were not considered.

Finally for all new drug trials designs in PE it is recommendable to consider one treatment arm either in the phase IIB or phase III trials with the standard dose of this drug which has been approved for PE and is considered as the current standard medication in this indication.

Recommendations 11 (Grade A)

Clinical Trials in Premature Ejaculation Should Consider the Following Items:

a. Key inclusion and endpoint parameter is the measured IELT

b. Although the new ISSM definition for lifelong PE sets an IELT cut off point of 1 minute the committee recommends also consideration of patients with IELT cut-off points of 2 and between 2-5 min. provided there is evidence by history taking and/or PRO’s that the patients/couples show psychological distress

c. PE patients should be randomized according to the respective IELT cut-off values considered in the trial

d. PE trials should enroll reasonable numbers of both patients with lifelong and acquired PE to ensure collection of reliable data for both patient populations

e. One trial in a population with ante portal ejaculation is encouraged

f. At least one trial in an investigational drug development program should consider a well-defined population suffering from a combination of ED and PE

g. Validated PRO’s specifically developed for PE trials such as IPE or PEP should be used as study endpoints in addition to IELT

h. Evaluation of validated partner reported outcomes (available in PEP) is encouraged.

VII. PEYRONIE’S DISEASE (PD)

1. INTRODUCTION

Peyronie’s disease (PD) is an acquired fibrotic disorder of the tunica albuginea and the septum penis which affects between 3% and 8.9% of all men >18 years depending on the populations investigated [15,101-103]. Although the etiology of Peyronie’s disease is not well understood many facts speak for a multifactorial etiology of this disease with genetic factors (in between 10 and 30% Peyronie’s disease is associated with the autosomal dominant passed fibrosis of the palms: Dupuytren’s contracture, Paget’s disease of the bones and in some per cent with fibrosis of the plants: Ledderhose’s contracture), microtrauma (in some patients Peyronie’s disease manifests after latent or obvious penile fracture) and an increase in the concentration of Transforming Growth Factor (TGF) – β1 in cell cultures of the fibrotic plaques [15]. The course of Peyronie’s disease is usually progressive in many cases commencing with a painful nodule/plaque frequently at the dorsal(upper) surface of the tunica albuginea of the cavernous bodies spreading into the septum penis, sometimes at the lateral and rarely at the ventral (lower) surface of the tunica albuginea. Quite often the course of Peyronie’s disease is characterized by phases more than by a stable progression whereby nodules and deformities can change their location and direction.[101,102]

Pain with erectile state of the penis is a characteristic feature of early Peyronie’s disease and usually disappears in nearly all patients with or without treatment within 3-18 months. But pain is not present in all cases and may be absent in up to more than 80% [103,104].

The cumulative manifestation ages for Peyronie’s disease are between 45 and 65 years.

2. THE DIFFERENT PHASES OF PEYRONIE’S DISEASE

Usually 3 phases of Peyronie’s disease can be distinguished:

Acute inflammatory phase often associated with painful erections and manifestation of a “soft” nodule/plaque and onset of penile curvature
Fibrotic/calcifying phase with hard plaques characterized by ultrasonography as clearly hyper-echoic lesions without or with (calcified plaques) echoes.[Fig.7-10,103] At this phase of Peyronie's disease patients may develop considerable deformities of the penis either as notching and circumferential hourglass defects with or without penile curvature or as rapidly increasing penile curvatures up to more than 90 degrees making sexual intercourse impossible. In the majority of the patients the direction of the penile deviation is dorsal (upward) often associated with a lateral component either to the left or to the right side. Rarely Peyronie's disease plaques manifest at the ventral(lower)surface of the cavernous bodies causing a downward (ventrally) directed curvature[105] Regardless of the direction and the extent of the penile deviation at this stage of the disease the patients are complaining of a marked shrinking of the penis, often associated with a considerable narrowing of the cavernous bodies distal to the curvature. Many patients are complaining of a considerable, "join-like" instability of the distal part of the penis causing them to say that the distal part of the penis is not able to get firm.

During both the first and the second phase of the disease new nodules /plaques and changes in the degree and direction of penile curvature is not uncommon.

Terminal (stable) stage of the disease: This is characterized by the fact that no changes within the last 12 months occurred, i.e that this stage has to be considered as the final stage of Peyronie's disease with a high likelihood that no new nodules/ deviations will occur. At this stage of the disease severe deviations may remain either with calcified plaques or not and may require surgical corrections once sexual intercourse is severely impaired. This final stage of the disease is also characterized by a considerable shrinkage of the penis which may account for loss of penis' length of up to 4-6 cm in the erect stage.

Especially in the first inflammatory and also in the fibrotic, not yet calcified phase spontaneous regression ("healing") may occur without treatment. The spontaneous/natural healing rate of Peyronie's disease is observed in between 10 and 15 % of all cases.

Fig. 7: Hypo-echoic not well confined plaque in the dorsal tunica albuginea in acute Peyronie's disease

Fig.8: Three hyper-echoic plaques in the septum penis with moderate acoustic echoes 6 months after onset of the disease

Fig. 9 : Proximal and distal plaques in the septum penis in the same patient 9 months after onset of disease

Fig. 10: End stage of Peyronie's disease with calcified plaque on the dorsal tunica albuginea and 90 degree deviation
According to a mono-center prospective observational study of Peyronie’s disease course in 246 men after 1 year without treatment the situation was as follows: 12 % improved, 40 % remained stable and 48 % worsened [106]

3. PEYRONIE’S DISEASE AND ED

Peyronie’s disease is frequently combined with Erectile Dysfunction (ED) with incidence-rates in the literature ranking between 36 % and 100% (101-108). In many of these patients the etiology of ED is vasculogenic, i.e. either arteriogenic or veno-occlusive or both, proven by intracavernosal injection test combined with penile duplex/color Doppler sonography [107,108].

4. THERAPEUTIC STRATEGIES IN PEYRONIE’S DISEASE

Typical nonsurgical treatments for Peyronie’s disease are oral drug therapies including para-aminobenzoate (Potaba), vitamin E, colchicine, tamoxifen, propol, acetyl-L-carnitine and propionyl-L-carnitine and intralesionally injected drugs such as verapamil, interferon-alpha2a, collagenase, cortisone, hyaluronidase and superoxide dismutase [107].

In a survey analyzing the US urologist practice patterns in the management of Peyronie’s disease with a response rate of 24 % the following treatments/strategies were applied [108]:

Vitamin E 70 %, wait and see 32 %, potaba 20 %, colchicine 12 %, verapamil injections 7 %, verapamil gel 10%. Surgery was performed by 57 % of the respondents.

Other in the literature reported treatments for Peyronie’s disease are extracorporeal shock wave and radiation therapy. Some of the above mentioned treatment options were investigated in mono-or multicenter trials with the majority of them exhibiting considerable flaws in the study designs especially due to the fact that Peyronie’s disease predominantly represents a disease in phases rather than with a stable course and there is no validated PRO measure capturing all the different features of Peyronie’s disease. In addition until now there is no general agreement on objective measures which should be used in clinical trials.

5. GENERAL CONSIDERATION FOR TRIALS IN PEYRONIE’S DISEASE:

The real difficulties regarding trials in Peyronie’s disease are the facts that the course of this disease is usually subdivided in phases and that there is a variety of features which are characteristic for this disease but not necessarily all being present in the same patient.

Regarding the different stages of Peyronie’s disease clinical trials have clearly to define the study population according to the disease’s phase.

Regarding the different features of Peyronie’s disease clinical trials should capture all these different features of Peyronie’s disease by means of appropriate subjective PROs and objective measures.

Until now there is no validated PRO measure available for Peyronie’s disease although one has been developed and is currently undergoing validation process for the ongoing Xiaflex (combination of collagenases which has to be injected into the plaque-developed by Auxilium Pharmaceuticals,US) phase II/III program [109].

a) Domains/Items to be Considered for PRO’s in Peyronie’s Disease

According to the different phases and characteristics of Peyronie’s disease a valid and reliable PRO measure capturing the most important changes after treatment must consider the following items:

Penile shape (deviation, notch, hourglass deformity)
Penile size (length and circumference)
Penile stability during erection (in many Peyronie’s patients penile instability occurs because of pseudo-joint formation at the site of angulations)
Penile pain
Sexual intercourse possible related to degree of deviation
Sexual intercourse possible related to erectile function
Erectile function (hardness/rigidity of erection)
Ejaculatory/orgasmic function/feelings
Impact of Peyronie’s disease on patients’ psyche and mood
Distress/bother related to Peyronie’s disease
Satisfaction with treatment modalities (oral injections, surgery etc.)
Satisfaction with treatment outcome
Body image/physical appearance
Life quality
Clinical Global Impression of Change

Especially changes in patients’ psyche/mood should be given a broad space in PRO because it is proven that many Peyronie patients may develop depressive symptoms [110,111].

Because Peyronie’s disease frequently has a
negative impact on the sexual performance and sexual relationship a PRO measure for partners must also be considered for trials in Peyronie’s disease.

b) Objective Measures to be Considered for Clinical Trials in Peyronie’s Disease:

Measurement of the stretched penis length

Documentation of the degree of penile curvature in the erect stage by intracavernosal injection test (alternatively self-documentation by means of auto-photography may be considered but it does not provide as reliable data as with in office testing)

Measurement of the penis circumference

Sonographic measurement of the plaque’s/plaques’ sizes

(this diagnostic tool provides only reliable data with clear echoic/calcified plaques but not with soft plaques during the early stage of Peyronie’s disease!!)

Because Peyronie’s disease shows a variety of clinical features it is mandatory that clinical trials are considering these different features, ie. that they should enroll reasonable numbers of patients showing certain main characteristics of Peyronie’s disease:

Measurable echoic but not calcified plaques

Measurable echoic and calcified plaques with acoustic shadow

Peyronie’s disease without penile curvature but only nodules/plaques

Peyronie’s disease with penile curvature between 10 and 60 degree

Peyronie’s disease with penile curvature between 60 and 100 degree

Peyronie’s disease with only notching and/or hourglass deformity.

Patients with/without ED

Only by stratification of the patient groups according to these main features of Peyronie’s disease reliable statements on the efficacy of a certain drug/treatment for the different characteristic manifestations of this disease may be possible.

Recommendation 12 (Grade B)

Considering the different phases, the potential for spontaneous healing, the completely different features of Peyronie’s Disease and the long-term course of this disease clinical trials should consider:

a. at least a 3 arm study design with a placebo, active and wait and see group the latter serving as control group.

b. study duration of at least 12 months, better 18 months

c. randomization according to the following parameters:

  - pain yes/no, plaque yes/no – clearly visible by sonography yes/not only notching-hour-glass deformity yes/not
  - penile bending yes/no – up to 60 and between 60 and 90 degrees penile shrinking/shortening yes/not combined with ED yes/not

d. PRO’s should consider the following domains:

  - Penile pain, penile shape, penile size (length and circumference) penile stability during erection sexual intercourse possible related to degree of deviation or related to ED
  - Erectile function (hardness/rigidity of erection)
  - Ejaculatory/orgasmic function/feelings
  - Impact of Peyronie’s disease on patients’ psyche and mood
  - Distress/bother related to Peyronie’s disease
  - Satisfaction with treatment modalities (oral injections, surgery etc.)
  - Satisfaction with treatment outcome
  - Body image/physical appearance
  - Life quality
  - Impact on psyche and mood

VIII. CLINICAL TRIALS IN TESTOSTERONE REPLACEMENT THERAPY FOR HYPOGONADISM

1. INTRODUCTION

Androgen deficiency in the elderly men and its substitution by testosterone replacement therapy, where clinical symptoms are evident, has become a topic of increasing interest and awareness. It is proven that from the age of 40 a continuous decline of total T and even more of free T occurs combined with a constant increase of sex hormone binding globulin (SHBG) (112,113). Many of these men develop clinical symptoms affecting general and sexual health.

The prevalence of so-called Late Onset Hypogonadism (LOH) clearly depends on the cut-off value used for normal T-serum levels: Based on the respective cut-off T-levels the incidence of hypogonadism in a population comprising 2.807 men
aged 25-85 and suffering from erectile dysfunction was as follows (114):

- T < 2.00 ng/ml: 7%
- T < 3.00 ng/ml: 23%
- T < 3.46 ng/ml: 34%
- T < 4.00 ng/ml: 48%

In a randomized selection of 130 out of 2650 GP practices where during a period of 2 weeks in all men > 45 years T-levels were measured between 8.00 and 12.00 am regardless of the complaints they were presenting 836/2162 (39%) have had T-levels < 3.0 ng/ml which meets the laboratory criteria of hypogonadism (115).

Hypogonadal T-levels are often associated with clinical symptoms / diseases such as fatigue, decline of vitality, loss of muscle strength and mass, osteoporosis and anemia or sexual dysfunctions such as erectile dysfunction, loss of libido and/or ejaculatory/ orgasmic dysfunctions which often improve with T-replacement therapy. Moreover several long-term observational studies have clearly shown that hypogonadism is linked to a higher cardiovascular and mortality risk (116-118). Although a variety of treatment options (T-gels, plasters, injections, pellets) are approved and available for treating hypogonadal men only limited data are available regarding the long-term safety of T-replacement therapy. The main obstacle for T-replacement therapy is the concern of imminent prostate cancer danger induced by exogenous T-substitution. Nearly all of the published studies regarding T-replacement therapy in hypogonadism have enrolled relatively small numbers of patients (mainly dozens and not hundreds or even thousands) with a limited follow-up. Thus no definite statements can be made with respect to PCA risk with T-replacement therapy. In a recent Medline supported review on this topic 197 publications relating to T-replacement therapy were identified but only 44 met inclusion criteria: 11 placebo-controlled, randomized studies; 29 non-placebo-controlled studies of men with no prostate cancer history; and 4 studies of hypogonadal men with history of prostate cancer (119).

In the 11 placebo-controlled, randomized studies, prostate cancer was detected in 7 of the 542 men treated with testosterone as monotherapy (1.3%) and 5 (1.5%) of the 333 men who received placebo. Prostate cancer incidences across studies varied from 0% for both the testosterone and the placebo groups in seven studies to 9.5% for the testosterone group and 21% for the placebo group in one study. Prostate cancer in testosterone-treated men was detected at as early as 3 months and in placebo-treated men at as early as 6 months. Gleason grades were reported for four testosterone-treated patients (two of grade 5, one of grade 6 and one of grade 7) and four placebo-treated subjects (all grade 6) (119).

Recommendations on the criteria for diagnosis, treatment and monitoring of late-onset hypogonadism were published recently (120):

According to these recommendations the definition of LOH is a clinical and biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum T-levels below the young healthy adult male reference range.

Symptoms which the committee identified to be often related to LOH are loss of libido, erectile dysfunction, decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, decreased vitality and depressed mood. But none of these symptoms are specific to low androgen levels.

Questionnaires such as the Aging Male Symptom Score (AMS), the Androgen Deficiency in Aging Men (ADAM) are not recommended for use as screening tools for hypogonadism because of their low specificity.

Regarding T-lab values total testosterone assessment should preferably be conducted in the morning between 7.00 and 11.00 am. A value of < 3.5 ng/ml (12 nmol/l) are in line with the diagnosis of LOH. T-levels above this value do not require T-substitution.

Regarding the assessment of treatment outcome (improvement of the clinical symptoms such as sexual dysfunctions) an interval of 3-6 months after initiation of T-replacement therapy is recommended. Considering prostate cancer risk under T-replacement therapy the committee concluded that there is currently no adequately powered and optimally designed long-term prostate disease data available to determine whether there is any prostate cancer risk from T-replacement therapy.

Prostate and blood (hematocrit, PSA) monitoring are recommended in 3-6 months intervals in the first year and at least annually thereafter.

Contraindications for T-replacement therapy considered by the committee are men with prostate and breast cancer, men with hematocrit > 52%, untreated obstructive sleep apnea and untreated severe congestive heart failure.

In a recently published study with 40 men and PSA values of between 2.5 and 4.0 ng/ml receiving a single intramuscular injection of 400 mg T-cypionate those men (18/40 - 45 %) with an increase of PSA of 0.9 ng/ml 4 weeks after T-injection showed prostate
cancer in the subsequent prostate biopsies whereas men with only a mild PSA increase of 0.3 ng/ml were cancer free (121)

Finally, debate has surfaced regarding the need for prostate biopsy in hypogonadal men prior to starting T replacement therapy. A study by Morgentaler et al (122) evaluated a total of 345 consecutive hypogonadal men with a PSA level of 4.0 ng/ml or less with digital rectal examination and prostate biopsy before initiating a program of testosterone replacement therapy. All men had low serum levels of total or free testosterone, defined as less than 300 and 1.5 ng/dl, respectively. Cancer was identified in 15.1%. The cancer detection rate was 5.6%, 17.5%, 26.4%, and 36.4% for a PSA level of 1.0 or less, 1.1 to 2.0, 2.1 to 3.0, and 3.1 to 4.0 ng/ml, respectively (P < 0.05). Cancer was detected in 26 (30.2%) of 86 men with a PSA level of 2.0 to 4.0 ng/ml. Cancer was detected in 21% of men with a testosterone level of 250 ng/dl or less compared with 12% of men with a testosterone level greater than 250 ng/dl (P = 0.04). Men with free testosterone levels of 1.0 ng/dl or less had a cancer rate of 20% compared with 12% for men with greater values (P = 0.04). The odds ratio of cancer detection for men in the lowest tertile compared with the highest tertile = 0.04). The odds ratio of cancer detection for men in the lowest tertile compared with the highest tertile was 2.15 (95% confidence interval 1.01 to 4.55) for total testosterone and 2.26 (95% confidence interval 1.07 to 4.78) for free testosterone. These data are controversial, but nonetheless might suggest the need for a preemptive prostate biopsy in certain men before starting T replacement.

The endocrine society guidelines (123) are presented for completion and suggest the follow up post inception of T replacement therapy: We recommend urological consultation if there is:

An increase in serum or plasma PSA concentration greater than 1.4 ng/ml within any 12-month period of testosterone treatment.

A PSA velocity of more than 0.4 ng/ml yr using the PSA level after 6 months of testosterone administration as the reference. PSA velocity should be used only if there are longitudinal PSA data for more than 2 yr.

Detection of a prostatic abnormality on digital rectal examination.

An American Urological Association (AUA) prostate symptom score of more than 19.

We recommend evaluation for symptoms and signs of formulation-specific adverse events at each visit

We recommend determining hematocrit at baseline, at 3 months, and then annually. If hematocrit is greater than 54%, stop therapy until hematocrit decreases to a safe level, evaluate the patient for hypoxia and sleep apnea, and reintiate therapy at a reduced dose.

These recommendations must be tempered against accepted urologic practice norms.

2. FINAL COMMENTS ON CLINICAL TRIALS FOR HYPOGONADISM

Regarding the current literature T-replacement therapy trials may be subdivided in:

a) Therapeutic T-replacement trials in men with clinical symptoms and proven hypogonadal T-levels (T< 3.5ng/ml or 12 nmol/l): in these men improvement of clinical symptoms may be expected in a time frame of 3 - 6 months or even later if muscle mass and strength, body composition and bone mineral density is considered provided that T-replacement is able to elevate the T serum levels within the normal range.

b) Preventive long-term T-replacement trials in asymptomatic men to evaluate the cardiovascular and mortality risk.

Regarding the increasing evidence in the past two years that hypogonadism is linked to a higher risk of major cardiovascular events and increased mortality, a long-term trial of T-replacement therapy in hypogonadal, asymptomatic men at risk (diabetics, coronary artery disease, metabolic syndrome) would make sense and would be desirable from the scientific point of view. Primary outcome of such a long-term trial with an untreated or placebo-treated control group would be major cardiovascular events (stroke, myocardial infarction) and mortality.
Recommendation 13 (Grade B)

1. The diagnosis of late–onset hypogonadism (LOH) is based on clinical symptoms combined with a morning total serum testosterone of less than < 350 ng/100 ml (12 nmol/l).

2. Currently, there are no accepted PRO instruments for either screening of hypogonadism or for follow up post starting T replacement therapy.

3. The risk of prostate cancer after starting and during long-term T-replacement is unknown, but thought to be low by expert opinion.

4. A serum PSA and hematocrit should be drawn within 3-6 months post starting T replacement therapy and thereafter in 6-12 months intervals depending on individual findings and risks.

5. The time course to determine T related benefits varies amongst the endpoints. While sexual function is thought to improve within 6 months post starting T replacement therapy, bone mineral density, muscle mass etc may require longer periods of time to see demonstrable effects.

6. An increase in serum or plasma PSA concentration greater than 1.4 ng/ml within any 12-month period of testosterone treatment, or a PSA velocity of more than 0.4 ng/ml/yr using the PSA level after 6 months of testosterone administration as the reference, should prompt a urologic evaluation and possible prostate biopsy.

7. If the hematocrit is greater than 54%, stop therapy until hematocrit decreases to a safe level, evaluate the patient for hypoxia and sleep apnea, and reinitiate therapy at a reduced dose.
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Committee 13

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Penile erection is initiated after central processing and integration of, e.g., tactile, visual, olfactory, and imaginative stimuli. Signals to the peripheral tissues involved are generated, and the final response is mediated by coordinated spinal activity in the autonomic pathways to the penis and in the somatic pathways to the perineal striated muscles. The central regulation of penile erection involves many transmitters and transmitter systems, the details of which are still incompletely known. Some of the anatomical areas of the brain that relate to sexual function have been defined, including the medial amygdala, medial preoptic area, paraventricular nucleus, the periaqueductal gray, and ventral tegmentum [1-3]. In rats, electrical stimulation of, e.g., the medial preoptic area [4], the paraventricular nucleus [5], or the hippocampal formation [6] can elicit an erectile response.

Spinally, there seems to be a network consisting of primary afferents from the genitals, spinal interneurons, and sympathetic, parasympathetic and somatic nuclei. This network appears capable of integrating information from the periphery and eliciting reflexive erections, and also to be the recipient of supraspinal information[7]. The degree of preservation of sensory function in the T11-L2 dermatomes could be used to determine the potential for psychogenic erectile responses in men with spinal cord injury[8].

The central mechanisms controlling erection include supraspinal as well as spinal pathways. The current knowledge about these mechanisms is largely based on experimental data from animals—mainly, rats.

Central dopaminergic neurons project to the medial preoptic area and the paraventricular nucleus [17]. Furthermore, dopaminergic neurons have been identified that travel from the caudal hypothalamus to innervate the autonomic and somatic nuclei in the lumbosacral spinal cord [18, 19]. Thus, dopamine can be expected to participate in the regulation of both the autonomic and somatic components of the penile reflexes.

Both the two major families of dopamine receptors, D1- (D1, D5) and D2-(D2, D3, D4) like receptors [20], have been associated with central erectile functions; however, the D2-like receptor subtype seems to have the predominating effect. The non-selective dopamine receptor agonist, apomorphine, when administered systemically to male rats, was found to induce penile erection [21], simultaneously producing yawning and seminal emission. Similarly, low-dose systemic administration of other dopamine agonists initiates erection [1]. The effects of these agonists can be attenuated by centrally-, but not peripherally-acting, dopamine receptor antagonists.

Injection of apomorphine into the medial preoptic area demonstrated that low levels of dopaminergic stimulation, via D1 receptors in particular, facilitated erections[22]. In contrast, dopaminergic antagonists injected into the medial preoptic area decreased the number of penile reflexes [23, 24]. In the paraventricular nucleus, similar experiments have established that D2- rather than D1- like receptors primarily facilitate erections [1].
The erection following paraventricular D2–like receptor stimulation apparently involves oxytocinergic neurotransmission. Dopaminergic neurons impinge on oxytocinergic cell bodies in the paraventricular nucleus [25, 26], and apomorphine-induced penile erection is prevented dose-dependently by oxytocin receptor antagonists [27], or by electrolytic lesions of the paraventricular nucleus that deplete the oxytocin content [28-30]. Conversely, injection of oxytocin into the paraventricular nucleus induced erections that were not attenuated by dopamine receptor blockade, suggesting that dopaminergic neurons activate oxytocinergic neurons in the paraventricular nucleus, and that released oxytocin then accounts for the erectile response. Melis et al. (2006) showed that penile erections in male rats induced by selective dopamine D4 agonists were reduced by selective dopamine D4 antagonists, voltage-dependent Ca2+-channel blockers, neuronal nitric oxide synthase inhibitors and oxytocin receptor antagonists given in the lateral ventricles, not in the paraventricular nucleus. Martino et al. [31] investigated central oxytocinergic and dopaminergic mechanisms regulating penile erection in conscious rats and concluded that pro-erectile activity mediated via D2-like (D4?) receptors may be dependent on supraspinal and spinal oxytocin receptors, and that oxytocin-mediated erection (supraspinal and spinal) requires basal D2-like (D4) receptor activation. The same group aimed to identify dopamine D4 receptor signal transduction pathways in vivo [32]. They showed that the selective dopamine D4 agonist PD168077 induced c-Fos expression and extracellular signal regulated kinase (ERK) phosphorylation in the paraventricular nucleus. The selective dopamine D4 receptor antagonist A-381393 blocked both c-Fos expression and ERK1/2 phosphorylation produced by PD168077. In addition, PD168077-induced ERK1/2 phosphorylation was prevented by SL327, an inhibitor of ERK1/2 phosphorylation. Interestingly, treatment with A-381393 alone significantly reduced the amount of Fos immunoreactivity as compared to basal expression observed in vehicle-treated controls. Dopamine D4 receptor and c-Fos coexpression in the paraventricular nucleus was observed using double immunohistochemical labeling, suggesting that PD168077-induced signaling may result from direct dopamine D4 receptor activation. The authors concluded that these results demonstrate functional dopamine D4 receptor expression and natural coupling in the paraventricular nucleus linked to signal transduction pathways that include immediate early gene and MAP kinase activation. Further, the ability of the selective dopamine D4 antagonist A-381393 alone to reduced c-Fos expression below control levels were interpreted to indicate the presence of a tonic dopamine D4 receptor activation under basal conditions in vivo.

Brioni et al. [33] reported that the dopamine D4 receptor plays a role in the regulation of penile function using a selective dopamine D4 receptor agonist, ABT-724, with no effect on dopamine D1, D2, D3, or D5 receptors. ABT-724 dose-dependently facilitated penile erection when given s.c. to conscious rats, an effect that was blocked by haloperidol and clozapine (acting centrally and peripherally) but not by domperidone (acting only peripherally). A proerectile effect was observed after intracerebroventricular (i.c.v.) but not intrathecal administration, suggesting a supraspinal site of action. The drug seemed to be without emetic effects in a ferret model of emesis [34], and it was suggested that ABT-724 could be useful for the treatment of erectile dysfunction (ED).

The same group identified a structurally distinct D(4)-selective agonist with superior oral bioavailability to ABT-724 for the potential treatment of erectile dysfunction. Optimization with the (N-oxy-2-pyridinyl)piperidine template led to the discovery of ABT-670, which exhibited excellent oral bioavailability in rat, dog, and monkey (68%, 85%, and 91%, respectively) with comparable efficacy, safety, and tolerability to ABT-724 [35].

Injection of apomorphine into the lumbosacral subarachnoid space was reported to impair ex copula (i.e., outside the context of copulation) penile reflexes, slow the rate of copulation, and decrease the number of intromissions preceding ejaculation [36, 37], suggesting an inhibitory effect on spinal erectile mechanisms. This is in contrast to recent findings showing that intrathecal injection of apomorphine in rats evokes erection in both normal animals and animals where the spinal cord has been transected [38, 39]. Most likely, stimulation of the dopaminergic system can produce erection both at supraspinal and spinal sites.

As mentioned above, systemically administered apomorphine enhances seminal emission. Pehek et al. [37] found that apomorphine injected into the paraventricular nucleus, but not in the MPoA, enhanced seminal emission. Recording of intracavernosal pressure in the non-anesthetized rat after systemic administration of apomorphine showed that the pressure response consisted of both smooth and striated muscle components [40]. This implies that systemically given apomorphine has effects not only on the sacral parasympathetic output, but also on somatic pathways.

IV. OXYTOCIN

Oxytocinergic spinal projections from the supraoptic and paraventricular nuclei of the hypothalamus are likely to influence the sacral autonomic outflow more than the somatic outflow [41, 42]. The finding that immunoreactive oxytocin-containing spinal neurons associate with sacral preganglionic neurons supports the idea that oxytocin has an important role in the autonomic spinal circuitry that mediates penile erection [43, 44].
Oxytocin is a potent inducer of penile erection when injected into the lateral cerebral ventricle, the paraventricular nucleus, or the hippocampus of laboratory animals; intrathecal oxytocin can also initiate an erection. These erections can be blocked by the administration of oxytocin antagonists given (i.c.v.) or (i.t.), or by electrolytic lesion of the paraventricular nucleus. Additionally, non-contact erections can be reduced by a selective oxytocin receptor antagonist administered into the lateral ventricles, which supports the view that oxytocin mediates this response [45].

Succu et al. (2007) analyzed the effect of pro-erectile dose of the selective dopamine D4-agonist PD-168077 and apomorphine, a mixed dopamine receptor agonist, injected into the paraventricular nucleus on the concentration of extra-cellular dopamine and its main metabolite DOPAC in the nucleus accumbens in male rats [46]. Both drugs induced penile erection episodes that were reduced to various extents by D2/D3 and D4 antagonists. The pro-erectile effect and the concomitant increase in dopamine and DOPAC concentration in the nucleus accumbens dialysate were almost completely abolished by the potent oxytocin receptor antagonist d(CH(2))[5]Tyr(Me)[2]-Orn[8]-vasotocin, given into the lateral ventricles. The authors concluded that stimulation of dopamine receptors (mainly of the D2 to D4 subtype) in the paraventricular nucleus induces the release of oxytocin in brain areas that influence the activity of mesolimbic dopaminergic neurons mediating the appetitive and reinforcing effects of sexual activity.

Oxytocin increases NO production in the paraventricular nucleus [13, 47], and NO synthase (NOS) inhibitors prevent penile erection and yawning in rats induced by oxytocin, and also by dopamine, excitatory amino acids, the 5-HT(2C) receptor agonist, m-chlorophenylpiperazine (m-CCP; 5-HT(2C) agonist, trazodone metabolite), and ACTH/α-MSH. Yawning is a phylogenetically old, stereotyped event that occurs alone or associated with stretching and/or penile erection in humans and animals under different conditions [48]. It has been suggested that NO acts as an intracellular rather than an intercellular modulator inside the paraventricular oxytocinergic neurons in which NO is formed to facilitate the expression of this phylogenetically old event by guanylate cyclase-independent mechanisms [48, 49]. It is likely that this involves the parvocellular neuron population within the nucleus [49].

Plasma oxytocin concentrations are known to be elevated following sexual stimulation in humans [1]; however, the relevance of the oxytocinergic pathway has never been established. This makes it of interest to explore the therapeutic potential of this system.

V. ACTH AND RELATED PEPTIDES

Administered i.c.v., the adrenocorticotropic (ACTH) and α-melanocyte stimulating hormones (α-MSH) are able to induce penile erection—along with grooming, stretching, and yawning [1, 2, 50]. These effects are most probably mediated via stimulation of melanocortin (MC) receptors, of which five different subtypes have been cloned and characterized [51, 52]. Alpha-MSH/ACTH seem to act in the hypothalamic periventricular region, and grooming, stretching and yawning, but not penile erection, was reported to be mediated by MC(3) receptors [50, 53]. It is unclear, however, what MC receptor subtype(s) can be linked to the erectile responses. For example, the MC(3) receptor is found in high density in the hypothalamus and limbic systems [30], regions known to be important for erectile functions. The site and mechanism of action responsible of αMSH/ACTH seem to be different from those involving dopamine or oxytocin [15].

Martin et al. [54] concluded that current evidence indicates that the MC(3) receptor subtype contributes to the proerectile effects observed with melanocortin pan-receptor agonists. However, the putative receptor subtypes, pathways and mechanisms implicated in mediating the proerectile effects of melanocortins remain to be fully elucidated.

Melanotan II, a synthetic analogue of α-MSH, when given subcutaneously, was shown to have pro-erectile effects in men with psychogenic impotence [55]. Still, the therapeutic potential of α-MSH analogues remains to be established [56–58].

VI. NITRIC OXIDE

Several investigators have shown that within the CNS, NO can modulate sexual behavior and penile erection [59–63]. NO may act in several discrete brain regions, e.g., in the medial preoptic area [62, 63] and the paraventricular nucleus [5, 53]. NO production increases in the paraventricular nucleus of male rats during non-contact penile erections and copulation, confirming that nitric oxide is a physiological mediator of penile erection at the level of the paraventricular nucleus [61].

As mentioned previously, injection of NOS inhibitors i.c.v. or in the paraventricular nucleus prevents penile erectile responses induced by dopamine agonists, oxytocin, and NMDA in rats. NO may also mediate the actions of ACTH/α-MSH and 5-HT(2C) agonists, which elicit erections when injected into the intraventricular system, according to mechanisms unrelated to oxytocinergic neurotransmission [60]. The inhibitory effect of NOS inhibitors was not observed when these compounds were injected concomitantly with L-arginine, the substrate for NO [60].

Zheng et al. examined the role of nitric oxide (NO) within the central nervous system component of the behavioral responses including erection in diabetic rats [64]. Four weeks after streptozotocin (STZ) and
vehicle injections, NMDA-induced erection, yawning, and stretch responses through the paraventricular nucleus were significantly blunted in diabetic compared with control rats. Examination of nNOS protein by Western blot analysis indicated a reduced amount of nNOS protein in the paraventricular nucleus of rats with diabetes compared with control rats. Furthermore, restoring nNOS within the paraventricular nucleus by gene transfer using adenoviral transfection significantly restored the erectile and yawning responses to NMDA in diabetic rats. The authors concluded that a blunted NO mechanism within the paraventricular nucleus may contribute to NMDA-induced erectile dysfunction observed in diabetes mellitus.

VII. EXCITATORY AMINO ACIDS

Microinjections of L-glutamate into the medial preoptic area elicits an increase in intracavernous pressure [4], and behavioral studies have shown that N-methyl-D-aspartate (NMDA) increases the number of penile erections when injected into the paraventricular nucleus [65-67]. Furthermore, NMDA, amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA), or trans-1-amino-1,3-cyclo-pentadecarboxylic acid (ACPD) increases intracavernosal pressures when injected into the paraventricular nucleus [68]. The effect of NMDA was prevented by intracebroventricular administration of an oxytocin antagonist [65]. The NO synthase signal transduction pathway is considered to mediate the effect of NMDA. Injection of the amino acid leads to an increased concentration of NO metabolites in the paraventricular nucleus [69], and the administration of NOS inhibitors into the paraventricular nucleus and intracebroventricularly, blocked the NMDA effect [65, 70].

VIII. SEROTONIN

Neurons containing serotonin (5-hydroxytryptamine, 5-HT) can be found in the medullary raphe nuclei and ventral medulla reticular formation, including the rostral nucleus paragigantocellularis, and bulbospinal neurons containing 5-HT project to the lumbar spinal cord in the rat and cat [1]. Some serotonergic fibers occur in close apposition with sacral preganglionic neurons and motoneurons, and synapses were demonstrated at the ultrastructural level [44]. These morphological findings support the involvement of 5-HT in both the supraspinal and spinal pharmacology of erection, with participation in both the sympathetic and parasympathetic outflow mechanisms.

In animals, 5-HT seems to exert a general inhibitory effect on male sexual behavior [71], although the amine may be inhibitory or facilitatory depending upon its action at different sites and at different 5-HT receptors within the central nervous system [72, 73]. This may explain conflicting reports of 5-HT agonists either enhancing or depressing sexual function. Yonezawa et al. [74] found that p-chloroamphetamine (PCA), an indirect serotonin (5-HT) agonist, elicited both penile erection and ejaculation simultaneously in anesthetized rats. It was suggested that these effects were mainly produced by the release of 5-HT as limited to the lower spinal cord and/or peripheral sites. The use of selective 5-HT receptor agonists and antagonists can reveal different components of male copulatory behavior [9].

Kimura et al. investigated the effects of the novel 5-HT2C receptor agonist YM348 on intracavernous pressure (ICP) in anesthetized rats [75]. YM348 induced penile erection and ICP increases, and was significantly inhibited by the selective 5-HT2C receptor antagonist SB242084. YM348 decreased the latency of but did not affect the quality of ICP (duration, peak pressure and area under the curve) even at the highest dose. The authors concluded that activation of the 5-HT2C receptor increased ICP and, as a result, induced penile erection.

5-HT2C receptors seem to mediate erectile responses [76], and stimulation of 5-HT2C receptors increased circulating oxytocin [77]. NOS inhibitors given i.c.v. prevents 5-HT2C-receptor-mediated erectile responses [60]. These findings suggest that both oxytocin and NO are involved in 5-HT2C-receptor mediated erections.

IX. NORADRENALINE

The information on noradrenergic mechanisms involved in the central neuromediation of penile erection is sparse; however, the current data suggest that increased noradrenergic activity stimulates, whereas decreased noradrenergic activity inhibits sexual function [7, 71, 78].

X. GAMMA-AMINO BUTYRIC ACID

Cumulative data resulting from investigations on the role of gamma-aminobutyric acid (GABA) in penile erection indicate that this neurotransmitter may function as an inhibitory modulator in the autonomic and somatic reflex pathways involved in penile erection [79]. Activation of GABA(A) receptors in the paraventricular nucleus reduced apomorphine-, N-methyl-D-aspartic acid- (NMDA-), and oxytocin-induced penile erection and yawning in male rats [79]. Dorfman et al. examined age-related changes of the GABA(B) receptor in the lumbar spinal cord of Sprague-Dawley rats of different ages using quantitative autoradiography [80]. GABA(B) receptor affinity showed significant age-dependent and regional increases. However, the GABA(B) receptor decrease in aged rats did not seem not to be related to the inhibitory function in penile erection.
XI. CANNABINOIDs

Administration of endogenous and exogenous cannabinoids was shown to be associated with changes in penile erection and modulation of male sexual behavior [81, 82]. The cannabinoid CB1 receptor antagonist SR 141716A was shown to potentiate the penile erection responses to apomorphine in rats [83]. Also, it was shown that cannabinoid CB1 receptors present in the paraventricular nucleus may influence erectile function and sexual activity possibly by modulating paraventricular oxytocinergic neurons mediating erectile function [84]. It was also demonstrated that SR 141716 induced penile erection by a mechanism involving excitatory amino acid neurotransmission causing activation of neuronal NO synthase in paraventricular oxytocinergic neurons [85].

XII. OPIOID PEPTIDES

Available information supports the hypothesis that opioid μ receptor stimulation centrally prevents penile erection by inhibiting mechanisms that converge upon central oxytocinergic neurotransmission [1]. In rats, morphine injected into the paraventricular nucleus prevents non-contact penile erections (i.e., when penile erection is induced in the male by the presence of an inaccessible receptive female), and impaired copulation. These morphine effects are apparently mediated by prevention of the increased nitric oxide production that occurs in the paraventricular nucleus during sexual activity [86]). Morphine also prevents apomorphine- oxytocin-, NMDA- and non-contact-induced penile erection and yawning by inhibiting NO synthase activity in the paraventricular nucleus [87-89].

XIII. PROLACTIN

Long-term hyperprolactinemia can depress sexual behavior, reduce sexual potency in men, and depress genital reflexes in rats [73, 90]. Acute and chronic central prolactin treatment in rats, however, may have stimulatory and inhibitory effects on male sexual behavior, respectively [91]. Correspondingly, striatal dopaminergic activity was shown to be increased and decreased by acute and five-day central prolactin treatment [91], supporting the view that the effects of prolactin are associated with changes in striatal dopaminergic activity. Prolactin has been shown to inhibit the dopaminergic incertohypothalamic pathway to the medial preoptic area [92].

In humans, it is still unclear whether the negative effects of hyperprolactinemia on erectile function are mediated centrally by way of reduction in sexual interest and sex drive [93], or through a direct effect of prolactin on corpus cavernosum smooth muscle contractility. In dogs, a direct effect on the corpus cavernosum was suggested [94]. In any case, the effect seems independent of circulating testosterone levels and gonadal axis function [95].

Paick et al. evaluated 261 men for anthropometry, hormone levels, metabolic profiles and lifestyle factors [96]. Erectile function was evaluated using the self-administered International Index of Erectile Function. Patients were classified into two groups based on the six-item erectile-function domain, as those with sexual activity and those without. The authors found a significant difference in mean prolactin level between patients with and without sexual activity. A higher prolactin level was associated with a greater likelihood of sexual inactivity. Thus, prolactin levels might play a role in sexual activity in men with ED.

XIV. SEXUAL HORMONES

Androgens, particularly testosterone, are necessary (though not sufficient) for sexual desire in men. They are essential in the maintenance of libido and have an important role in regulating erectile capacity [97-101]. In men with normal gonadal function, however, there is no correlation between circulating testosterone levels and measures of sexual interest, activity, or erectile function [102]. Following castration in the male (which may reduce plasma testosterone levels by 90% [103]), or other causes leading to a reduction in androgen levels, there is generally a decline in libido, and sometimes in erectile and ejaculatory functions. Testosterone administration restores sexual interest and associated sexual activity in hypogonadal or castrated adult men [104-106]. The testosterone dose-response relationships for sexual function and visuospatial cognition differ in older and young men, higher testosterone doses needed in the elderly for normal sexual functioning [100]. El-Sakka et al. (2006) assessed the pattern of age related testosterone depletion in patients with erectile dysfunction. They found a significant decrease in testosterone level throughout the 4-year follow up in patients with erectile dysfunction. Patients with decreasing testosterone were older than patients with a steady testosterone level.

When castration has been performed in humans, the resultant sexual function may range from a complete loss of libido to continued normal sexual activity. Thus, the role of androgens in erectile function is complex, and androgen deprivation may not always cause erectile impotence, either in man [107], or in rats [108].

Suzuki et al. studied the effects of castration and testosterone (T) replacement on ICP elicited with electrical stimulation of the medial preoptic area and cavernous nerve in male rats [109]. They measured the ICP during electrical stimulation of the medial preoptic area and cavernous nerve in castrated male rats with and without testosterone replace-
ment. The erectile response was expressed as the ICP/blood pressure (BP) ratio. The ICP/BP ratios during cavernous nerve stimulation of the animals at 2, 4, and 8 weeks after castration were significantly lower than those of the intact animals. However, the erectile responses were not eliminated. In contrast to these peripherally evoked responses, erectile responses elicited by electrical stimulation of the medial preoptic area were eliminated following castration. After testosterone replacement, both erectile responses were restored. The authors therefore concluded that testosterone plays important roles in both the central and peripheral neural pathways for the maintenance and restoration of erectile capacity.

In hypogonadal individuals, it is known that exogenous testosterone administration stimulates both sleep-related erections and erectile responses to visual erotic stimulation [110-112]. Serum testosterone levels, however, have to fall to well below the lower end of the normal laboratory range before nocturnal penile tumescence is impaired [113]. In healthy men, testosterone enhances sexual desire and the rigidity of nocturnal penile tumescence, and leads to more rigid spontaneous erections with longer duration [112, 114]. It is therefore possible that testosterone acts on the motor neurons that supply the striated muscles of the penis. Other reports suggested that the site of androgen action within the penile tissue might be on the pro-erectile postganglionic parasympathetic neurones [115]. Castration studies in rats revealed that testosterone deprivation might alter the dorsal nerve ultrastructure, as the diameter of both myelinated and unmyelinated axons appeared smaller as assessed by transmission electron microscopy [116]. Spontaneous nocturnal erections are androgen-dependent [101, 117]; they are impaired in states of androgen deficiency and restored with androgen replacement. Erections in response to visual erotic stimuli, on the other hand, are partly independent of androgens [117, 118]. They persist in hypogonadal men and are not altered by androgen replacement [110, 119]. Thus, there may be one androgen-dependent system in the brain subserving sexual arousability and sexual desire, and one androgen-independent system involving response to moving visual stimuli [101]. Yassin et al treated hypogonadal men with erectile dysfunction with intramuscular long-acting testosterone undecanoate [120]. In all patients, serum testosterone levels were restored to normal within 6-8 weeks. They found that restoring testosterone levels to normal in men with proven subnormal testosterone levels improves libido in most subjects, and erectile function in more than 50% of these men. It may take 12-24 weeks before the effects of testosterone become manifest. Further, in normal individuals, it has been shown that there is a relationship between bioavailable testosterone and the frequency, duration, and degree of nocturnal penile tumescence [114, 121]. Other studies performed in eugonadal men have shown that high testosterone may promote sexual arousal with no significant changes in sexual activity [122]. Several studies, however, suggest that testosterone replacement therapy in relatively modest deficiency states may improve erections in a minority of patients [118, 119, 123, 124].

Data from the Massachusetts Male Aging Study revealed the association between erectile dysfunction and total testosterone, bioavailable testosterone, sex hormone-binding globulin and luteinising hormone. The authors concluded that no association among total testosterone, bioavailable testosterone, sex hormone-binding globulin and erectile dysfunction was found. Testosterone levels were associated with a decrease in risk of erectile dysfunction only in men with increased luteinising hormone levels.

Sexual hormones can induce structural changes in the nervous system, including alterations in cell size and number, neural connectivity, and neural sprouting [125-128]. These changes, which may result in sex differences (sexual dimorphism), are obvious in most mammalian species during the prenatal or early postnatal periods. There is evidence, however, that brain regions containing sexual hormone-accumulating neurons in adult animals possess a considerable plasticity in response to sexual steroids, and that androgens have the potential to stimulate the growth of neuronal processes and remodel neural circuits also in the adult brain [129-131]. Naturally-occurring, socially-induced changes in androgen levels were not shown to induce morphological changes of the motoneurons of the spinal nucleus of the bulbocavernosus muscle [132].

The MPOA of rats and the spinal nucleus of the bulbocavernosus [1] are sexually dimorphic model systems that have been well investigated. In humans, the localization and morphology of neurons innervating the small, striated pelvic muscles correspond to that of Onuf’s nucleus X [133, 134]. This nucleus, similar to its rat homologue (the spinal nucleus of the bulbocavernosus), contains fewer motoneurons in the female than the male [135].

**XV. PERSPECTIVES**

Ongoing and future studies assessing the efficacy and tolerability of centrally acting agents for male sexual dysfunction will reveal the most promising targets. Based on current literature, clinical trials have shown benefits for some of the mediators which have been discussed above. Today, none of the available agents can be regarded as a major player in the practical treatment of ED. However, in the light of the relatively high rate of patients that do not respond to or do not tolerate phosphodiesterase-5-inhibitors, additional central pathways modulating sexual responses may be beneficial in the future.
XVI. CONCLUSION

The central regulation of the erectile process is still only partly known. Central transmitter systems, which seem to be dependent on androgens as well as NO, may be the targets of future drugs aimed at the treatment of ED. Increased knowledge of the central (and peripheral) changes associated with ED may lead to an increased understanding of these pathogenetic mechanisms and therefore new treatments and possibly even prevention of the disorder.

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B. REGULATION OF SMOOTH MUSCLE FUNCTION

N Kim and S Ückert

I. INTRODUCTION

The penile corpora cavernosa are highly specialized vascular structures that are morphologically adapted to their function of becoming engorged during sexual arousal. In addition, the network of resistance arterioles that carry blood to the corpora cavernosa plays an equally important role in determining the state of penile engorgement. In the non-aroused, flaccid state, the arterial and trabecular smooth muscle remain constricted, and the hemodynamic environment of the corpora cavernosa is similar to the venous circulation in terms of pressure, flow, and oxygen tension. There is low resistance to the drainage of blood from the cavernosal bodies, and this contributes to the maintenance of penile flaccidity.

The onset and maintenance of penile tumescence is initiated by central psychogenic and/or peripheral reflexogenic sensory stimuli, as described in greater detail in the previous sections. Both central and peripheral pathways stimulate sacral parasympathetic efferent nerve fibers, which ultimately cause the relaxation of the vascular smooth muscle in the resistance arterial bed and the trabeculae of the corpora cavernosa. These events result in a higher rate of blood flow into the penis, and greatly increase the compliance of the cavernosal bodies, enabling expansion and accommodation of the increased blood volume within the cavernosal lacunae. The increased blood flow also potentiates local vasodilation through endothelial shear stress-induced responses. During this early filling phase, the hemodynamic environment within the erectile tissues transitions into an arterial system, with respect to blood flow and oxygen tension. However, blood pressure remains low.

The rapid volume expansion of the erectile tissue leads to engagement of the veno-occlusive mechanism, reducing the outflow of blood. The restriction of blood drainage is accomplished by elongation and compression of the subtunical venules that are located between the corpora cavernosa and the tunica albuginea. Veno-occlusion enables the trapping of blood within the cavernosal sinusoids and causes the intracavernosal pressure to rise to systemic arterial levels. As the pressure gradient between the systemic arterial circulation and the intracavernosal vascular compartment is dissipated, blood flow decreases. Altogether, these events act in concert to achieve and maintain full tumescence and rigidity.

Thus, changes in smooth muscle tone are crucial for regulating erectile function. In that regard, continuing research to elucidate the myriad of mechanisms that regulates vascular smooth muscle cell (VSMC) contractility is essential in understanding erectile physiology. The basic paradigm of smooth muscle, endothelium and nerve interactions to influence vascular reactivity is universally acknowledged, but warrants more detailed consideration within the context of genital tissues. The next several sections describe the basic mechanisms that regulate VSMC contractility, including additional consideration of non-contractile responses in VSMCs. While much of the information specific to genital tissue vascular physiology is derived from studies on penile corpus cavernousum, findings from cardiovascular research will also be presented to gain further insight into VSMC function.

II. TISSUE STRUCTURE AND CELLULAR ORGANIZATION

The overall structure of the genital tissues and the manner in which the cellular constituents are organized have significant implications on understanding the mechanisms that regulate smooth muscle tone and genital organ function. The erectile tissues of the penis have trabeculated structures that are uniquely suited to their function of becoming engorged during sexual arousal. In penile corpus cavernosum, the trabecular smooth muscle constitutes approximately 40-50% of tissue cross-sectional area, as assessed by histomorphometric analysis [1,2]. Most of the remaining cavernosal tissue area is occupied by extracellular matrix, which provides a fibroelastic framework and consists predominantly of collagen types I, III, and IV, and elastin [3-6]. Collagen types V and XI are also synthesized by the cavernosal smooth muscle at detectable levels. Although smaller in number, endothelial cells and neurons play critical roles in maintaining and regulating VSMC tone.

This complex architecture is maintained by the active and dynamic expression of numerous growth factors. Well-established as a regulator of limb morphogenesis, sonic hedgehog (Shh) has also been identified in the penis [7,8]. Studies indicate that inhibition of Shh in the adult leads to rapid atrophy and disorganization of the corpus cavernosum [7,8], suggesting that Shh is a critical protein in the development and maintenance of penile cavernosal tissue structure. Regulation of the growth and patterning of multiple cell types by Shh has been demonstrated in the central nervous system, vasculature, and penile tissue [8-15]. Thus, it is likely that Shh maintains the integrity of smooth muscle, nerve and endothelium in the penis. Of note, Shh levels
are regulated by cavernosal nerve activity and administration of exogenous Shh can reduce apoptosis in cavernosal tissue of animals subjected to cavernosal nerve injury [9,16,17]. Participants of the Shh signaling pathway such as patched (transmembrane receptor for Shh), the homeotic gene Hoxa-10, and the bone morphogenic protein BMP-4 have all been shown to participate in post-natal penile tissue differentiation and structure maintenance. In addition, Shh has been shown to stimulate the expression of vascular endothelial growth factor (VEGF) and nitric oxide synthase (NOS) in the penis [8]. Numerous other growth factors are expressed in the penis and are also likely to play important roles in maintaining cavernosal tissue structure and function. However, most studies have examined the use of exogenous growth factors to promote tissue growth, rather than investigating the roles of endogenously produced growth factors.

1. NERVES

The autonomic nerve fibers that extend from the pelvic plexus into the vascular tissues of the genital organs maintain the “basal” unaroused state and could be considered the initiators of sexual arousal in the periphery. While nerve tracing and immunohistochemical studies in penile cavernosal tissue have identified the presence of neurons containing numerous neurotransmitters, only a select few have been studied and many remain inadequately characterized.

In penile corpus cavernosum, unmyelinated nerve varicosities with no associated Schwann cells are observed to be localized to perivascular spaces and distributed in the parenchyma [18-21]. Histochemical studies demonstrate that adrenergic, cholinergic, and non-adrenergic, non-cholinergic (NANC) nerve endings appear in close proximity to VSMCs to regulate smooth muscle tone in the trabeculae and the blood vessels. In some instances, nerve endings have been identified near the endothelial layer [19]. Studies using immunostaining and confocal microscopy indicate that various peptide neurotransmitters are co-localized in the same nerve endings [21]. Among those identified are vasoactive intestinal polypeptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP) and helospectin. Interestingly, more recent studies utilizing similar approaches have also demonstrated the co-localization of neuronal nitric oxide synthase (nNOS) and VIP with vesicular acetylcholine transporter (VAcHT), a marker for cholinergic neurons [22]. Each of these neurotransmitters has been shown to cause relaxation of isolated penile cavernosal tissue strips. In contrast, tyrosine hydroxylase, a marker for adrenergic nerves, was not associated with any of the other neurotransmitters examined. Thus, these data suggest that there may be a single class of parasympathetic nerves containing acetylcholine and the various NANC neurotransmitters. Alternatively, there may be a heterogeneous population of parasympathetic nerve fibers that contain various combinations of neurotransmitters that cause smooth muscle relaxation.

While the anatomical evidence is compelling, functional studies have revealed nerve interactions that cannot be discerned from histochemical studies alone. Neurotransmitter release and contractile experiments suggest that acetylcholine inhibits adrenergic nerve activity and stimulates NANC nerves through pre-junctional muscarinic receptors [19,23]. In addition, pre-junctional alpha-2 adrenergic receptors on adrenergic nerves inhibit neurotransmission and provide a self-regulating negative feedback loop for secreted norepinephrine.

It is important to note that not all NANC neurotransmitters initiate relaxation of smooth muscle. For example, neuropeptide Y has been shown to contract smooth muscle in the corpus cavernosum and in the circumflex veins of the penis [24]. In addition, with the exception of nitric oxide, the roles of NANC neurotransmitters as modulators of penile erection remain unclear due to inconsistent experimental findings and the lack of specific and effective antagonists.

2. ENDOTHELIUM

The endothelium consists of a monolayer of cells that forms a single, continuous surface lining the vascular compartment throughout the body. The total mass of the endothelium has been estimated to be 500 grams in the average adult human; the majority of which is contained in the pulmonary vasculature [25]. Much like skin, the endothelium may be considered a single organ with multiple functions and differential responses that are dependent upon both the systemic and local environments. Among other functions, a healthy endothelium serves to provide an anti-thrombotic, anti-inflammatory, and anti-atherogenic surface while also regulating vascular tone and permeability. The importance of endothelial regulation can be better appreciated by considering pathological states that share in common dysfunctional endothelium. Endothelium-dependent relaxation of blood vessels has been shown to be compromised in animal models of atherosclerosis, hypertension, diabetes, aging, smoking, and renal failure [25-28]. Thus, diseased or damaged endothelium has been proposed to be a major contributor to vascular insufficiency of genital tissues in men and women.

The endothelium produces many vasoactive compounds that can influence the contractile, trophic or synthetic function of vascular smooth muscle cells. Among the factors that cause relaxation are nitric oxide (NO), carbon monoxide (CO), endothelium-derived hyperpolarizing factor (EDHF), prostacyclin (PGI2), and endothelin (through ETB receptors).
Among the factors that cause contraction are endoperoxides, thromboxane A2, superoxide anions, and endothelin (through ETA receptors). One of the more novel mechanisms of regulating endothelial signaling involves changes in the number of caveolae on the surface of endothelial cells. Caveolae are invaginated microdomains of plasma membrane that are rich in endothelial nitric oxide synthase and the family of transmembrane structural proteins known as caveolins, as well as cholesterol, sphingolipids, and glycosylphosphatidylinositol-linked proteins. In addition, caveolae contain numerous other signaling proteins such as receptors with seven-transmembrane domains, G-proteins, adenylyl cyclase, phospholipase C, protein kinase C, calcium pumps, and calcium channels. Thus, these specialized signaling regions have been termed transductosomes [29].

Most cells possess the ability to respond to physical deformation through mechanotransduction pathways. By virtue of their location on the inner surface of blood vessels, endothelial cells possess the ability to sense shear stress across their apical surface. While the actual mechanisms of shear-induced signaling remain unknown, it has been hypothesized that shear causes changes in membrane fluidity by decreasing the density of phospholipid molecules within the cell membrane [30]. Independent of a specific membrane receptor protein, G-proteins may become activated due to their increased mobility within the more fluid phospholipid bilayer as shear stress is increased [30]. Such a change would be caused by a rapid increase in blood flow, as occurs during penile erection (Figure 1). Activation of G-proteins by shear stress may lead to receptor-independent activation of phospholipase C, triggering a rise in intracellular calcium and subsequent activation of endothelial NOS (eNOS). Alternatively, shear stress-induced G-protein activation could stimulate phosphatidylinositol 3-kinase (PI3K), which in turn phosphorylates Akt (also known as protein kinase B). Phosphorylated Akt is then able to phosphorylate eNOS, increasing its enzymatic activity in the absence of calcium. An interesting mechanism that has recently been defined is the activation PI3K through sphingosine 1-phosphate (S1P). S1P receptors have been demonstrated in penile corpus cavernosum and this may be an important pathway mediating prolonged calcium-independent activation of eNOS [31,32]. Increased shear stress can stimulate the production and secretion of numerous vasoactive factors from the endothelium, but it remains unclear as to how the cell differentially processes flow-induced shear stress to produce specific factors.

Figure 1. Activation of endothelium by shear stress. A) Receptor-independent activation of G-protein; B) Shear-induced NO synthesis by calcium-dependent mechanism; C) Shear-induced NO synthesis by calcium-independent mechanism; D) Receptor-mediated NO synthesis by calcium-independent mechanism.
3. VASCULAR SMOOTH MUSCLE

As a major constituent and primary effector of the vascular structures in the genitals, the vascular smooth muscle cell (VSMC) is highly adaptable and multi-functional. The two primary functions of VSMCs are contraction and synthesis/maintenance of extracellular matrix. In cell culture experiments, VSMCs have been characterized as having either "contractile" or "synthetic" functional phenotypes. However, these two categories are considered to be extremes that are manifested under in vitro conditions and it is likely that a range of intermediary phenotypes exist in any given tissue in vivo. Increasingly, protein and gene expression studies are illustrating the ability of VSMCs to alter their cellular phenotypes in response to changes in their environment [33,34]. In addition, studies by developmental biologists indicate that VSMCs in different vascular beds may arise from varying cellular lineages (multiple sources of progenitor cells) and can be recruited from different locations in the developing embryo [35]. Further, comparative studies of VSMCs have led investigators to speculate that lineage-specific differences in growth and transcriptional responses may persist beyond the early developmental period and into the adult organism [35]. It remains unclear as to what extent the observed heterogeneity of VSMCs is due to adaptation in altered cellular environments versus differences in lineage. The apparent mosaic nature of smooth muscle throughout the body may account for some of the diversity in responses found in different vascular tissues in health and disease. Nevertheless, most VSMCs in peripheral blood vessels are derived from the mesoderm and exhibit a set of common characteristics. This chapter describes the general mechanisms of signal transduction in smooth muscle cells that regulate contractility with particular regard to genital tissues. Additional consideration of non-contractile responses in VSMCs is also included. However, regulation of extracellular matrix by smooth muscle has been omitted, since it is addressed elsewhere. While much of the information specific to genital tissue vascular physiology is derived from studies on penile corpus cavernosum, findings from cardiovascular research will also be presented to gain insight into VSMC function in male genital tissues.

4. COORDINATED REGULATION OF VSMCs

The majority of VSMCs in blood vessels and in cavernosal tissues are not adjacent to or in direct contact with an endothelial cell or nerve terminus. However, the thickness of any arteriole or trabecular bundle is limited to several cell layers. Given this arrangement, intercellular communication for the purpose of regulating smooth muscle tone in a coordinated fashion can be accomplished by two general mechanisms: 1) extracellular diffusion of vasoactive and trophic factors released by endothelium, nerves and smooth muscle (paracrine and autocrine regulation), and 2) intracellular diffusion of second messengers from stimulated cells into adjacent cells by means of gap junctions. These mechanisms are not mutually exclusive and it is likely that they act in complementary fashion to propagate regulatory signals.

Extracellular diffusion of regulatory substances requires sufficient concentrations to be secreted near a population of effector cells. The magnitude of response would be determined by the number of cells that were directly stimulated by the secreted substance. In contrast, intracellular propagation of signals along multiple cells through gap junctions does not require every responding cell to be activated by the initial stimulus. A single cell may be stimulated by a secreted substance and generate second messengers that can diffuse into neighboring cells. In this mechanism, the magnitude of response would be directly proportional to the number of cells activated by the spread of intracellular messengers, rather than the number of cells directly stimulated by the secreted substance.

The structure and function of gap junctions in the vasculature have been studied for the past several decades. VSMCs and endothelial cells are known to form functional syncytia by virtue of junctional plaques in their plasma membranes [36,37]. These plaques contain hundreds to thousands of gap junction complexes. The diameters of plaques between VSMCs range from 0.2 to 0.5 μm, whereas those between endothelial cells have been observed to be up to twice as large [36]. The area of each junctional plaque may be important in determining the rate of signal propagation. Each gap junction channel is formed by the docking of two hemi-channels; each hemi-channel being contributed by an opposing cell. Hemi-channels are hexameric structures formed from connexins, a large family of proteins derived from multiple genes [38]. VSMCs have been shown to express connexin 40 (Cx40) and connexin 43 (Cx43), whereas endothelial cells express Cx37 in addition to Cx40 and Cx43 [36]. Connexin proteins apparently have relatively short half-lives with estimated cycling times of 1 – 5 hours [37]. This suggests that junctional plaques are highly dynamic structures that may have the ability to attenuate or potentiate smooth muscle responses.

While the role of most connexins have not been studied in genital tissues, the expression of Cx43 has been confirmed in smooth muscle and endothelial cells derived from human penile corpus cavernosum [36,37]. Further, functional and pharmacological studies, as well as theoretical modeling, suggest that gap junctions play an important role in signal propagation by virtue of their permeability to a wide array of intracellular molecules, including ions, inositol phosphates, cyclic monophosphates, nucleotide triphosphates, nucleotides, amino acids, glucose
and its metabolites, small RNAs, and small peptides [39-42]. Although it is likely that connexins are not uniformly permeable and do exert a level of specificity, the selectivity and relative permeability of different gap junctions to intracellular signaling molecules remains largely unknown and is the focus of more recent research efforts. It has been postulated that junctional permeability may change in response to elevated concentrations of specific ions or second messengers [40], but direct demonstration of this phenomenon is lacking.

In studies using non-genital tissues, junctional plaques between endothelial and smooth muscle cells have also been observed [43,44]. However, the presence of these “myoendothelial” gap junctions has not been studied in genital tissues and their significance remains unclear. Thus, gap junctions enable smooth muscle and endothelial cells to form a continuous network of functional units. These cellular networks can rapidly coordinate the response to various stimuli that may not be homogeneously distributed throughout the tissue.

### III. MECHANISM OF SMOOTH MUSCLE CONTRACTION

Multiple overlapping pathways regulate vascular smooth muscle tone. However, before any of these mechanisms can be discussed, it is essential to understand the basic mechanism by which smooth muscle cells generate force, which is ultimately determined by the interaction between myosin cross-bridges and actin filaments [45-47]. Numerous dense bodies consisting of α-actinin are distributed throughout the smooth muscle cell, either in the cytoplasm or associated with the plasma membrane. Analogous to the Z-disk structures in striated muscle, dense bodies provide points of anchorage for actin filaments and are themselves stabilized by a network of intermediate filaments that are composed of desmin and vimentin. Unlike striated muscle, the molecular contractile units of interdigitating actin (thin) and myosin (thick) filaments are not regularly aligned with one another and can be oriented in multiple directions.

Smooth muscle myosin is a large hexameric protein, consisting of 2 heavy chains and 4 light chains. The heavy chains are identical and have both globular and linear domains. The linear domains contain the C-termini and form coiled-coil structures that result in the “tail” of the myosin molecule, while the globular domains contain the N-termini and possess actin binding sites and ATPase catalytic activity. These globular heads of the myosin molecule form the cross-bridges of the contractile apparatus. The 4 light chains in myosin consist of 2 essential light chains that have a molecular weight of 17 kD each (ELC17) and 2 regulatory light chains that have a molecular weight of 20 kD each (MLC20). One essential and one regulatory light chain is associated with each globular head in myosin. In smooth muscle, myosin molecules self-associate into a side-polar arrangement in which the globular heads protrude in a linear array on 2 opposing sides of the thick filament [48]. On any given side, the globular heads are oriented in the same direction, but antiparallel to those on the opposite side. This is in contrast to skeletal muscle myosin, which has a bipolar helical arrangement in which the globular heads protrude in a helical pattern around the thick filament and are oriented in opposite directions on either side of the M-line within the sarcomere. Actin filaments are composed of two long strands of globular actin that intertwine into a double helical arrangement. While troponins are absent in smooth muscle, other regulatory proteins such as caldesmon and calponin are known to be associated with actin. The potential roles of these proteins will be discussed following a brief presentation of the cross-bridge cycle.

1. FORCE GENERATION IN VSMC – CENTRAL ROLE OF CALCIUM

The contractile response of the smooth muscle cell is tightly associated with the intracellular concentration of free calcium (Ca⁡²⁺). However, intracellular Ca⁡²⁺ regulates the contractile apparatus in an indirect manner through the regulatory protein calmodulin, which has the capacity to bind four calcium ions. Calcium-bound calmodulin undergoes a conformational change and thereby increases its affinity for myosin light chain kinase (MLCK) and activates it. Calmodulin-activated MLCK then phosphorylates the serine-19 residue of MLC20. In the presence of ATP, this phosphorylation enables actin to activate the myosin ATPase and initiates cross-bridge cycling. Crystal structure studies of myosin complexed to analogues of ATP and the ATP-ADP transition state suggest that a single power stroke can achieve approximately 10 nm of linear displacement [49].

Beginning with a state in which myosin cross-bridges are bound to actin with high affinity in the absence of ATP, one complete cycle consists of the following events (see Figure 2):

- Phosphorylation of MLC20 by Ca⁡²⁺-calmodulin-MLCK complex activates myosin’s ATPase.
- ATP binds the globular head of myosin and causes it to dissociate from the actin filament. This dissociation alters the cross-bridge angle to prepare for the power stroke.
- In this dissociated state, myosin hydrolyzes ATP and rebinds with actin in a low affinity state.
- Release of the hydrolyzed inorganic phosphate increases the affinity of myosin for actin and
generates the power stroke of the globular myosin head, shortening the contractile apparatus.

- Dissociation of ADP from myosin enables another molecule of ATP to bind the myosin cross-bridge and continue onto a second cycle.

This series of events continues until MLC20 is dephosphorylated by myosin light chain phosphatase (MLCP). Assuming that energy stores are not limiting, maintenance of high intracellular Ca\(^{2+}\) concentrations assures that MLCK remains active and perpetuates cross-bridge cycling.

**2. REGULATORY MOLECULES INFLUENCING THE CONTRACTILE APPARATUS**

**a) Myosin light chain phosphatase and Rho-kinase**

At any given level of intracellular Ca\(^{2+}\), the contractile apparatus may become further sensitized by the inhibition of MLCP, such that the rate of myosin dephosphorylation (inactivation) is reduced and the action of MLCK becomes more efficient. Thus, modulation of MLCP activity is thought to be important for regulating smooth muscle contraction. MLCP is a holoenzyme consisting of a type 1 phosphatase (PP1cδ), a myosin-targeting subunit (MYPT1 – also called MBS for myosin binding subunit), and a 20 kD subunit of unknown function [50,51]. The activity of MLCP can be modulated by a variety of factors. Two of the more well-recognized mechanisms involve both direct and indirect effects of Rho/Rho-kinase pathway. Rho proteins are small GTPases classified as a subgroup of the Ras superfamily and can be activated by the binding of agonists to G-protein coupled receptors [52]. Activated Rho can in turn activate Rho-kinase (also called ROK or ROCK), a serine/threonine kinase. Rho-kinase can then phosphorylate multiple substrates including MYPT1, the 17 kD protein kinase C-potentiated inhibitor protein (CPI-17), and MLC20 [52-54]. Phosphorylation of MYPT1 and CPI-17 results in the inhibition of PP1c phosphatase activity, whereas phosphorylation of MLC20 would stimulate activation.

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**Figure 2: Mechanism of smooth muscle contraction. Adapted from Kim NN, Vascular physiology of erectile function, In: Carson CC, Kirby RS, Goldstein I, Wyllie MG, editors, Textbook of Erectile Dysfunction, 2nd Edition. New York, USA: Informa Healthcare, 2009.**
of myosin. In genital smooth muscle, the RhoA/Rho-
kine pathway and its effects on MLCP have been
shown to play an important role in regulating smooth
muscle contractility in both male and female genital
smooth muscle [55-58], whereas the importance of
MLC20 phosphorylation by Rho-kinase remains
unclear. The presence of CPI-17 protein has
been detected in human and rabbit penile corpus
cavernosum [55], but its functional significance
remains to be determined.

b) Potential regulatory roles of actin-associ-
ated proteins in VSMCs

Inasmuch as myosin may be considered the mole-
cular motor that mediates contraction, experimental
evidence suggests that cross-bridge cycling rates
and tension development in smooth muscle are not
necessarily proportional to MLC20 phosphorylation
[46, 59]. These discrepancies are partially attributable
to the presence of other proteins associated with ac-
tin that may regulate myosin-actin interactions. In-
cluded in this list of proteins are caldesmon, calponin,
and tropomyosin. While much of the experimental
evidence regarding these actin-associated mole-
cules remains controversial, ignoring these potential
regulatory mechanisms reduces our understanding
of the contractile apparatus to an oversimplification.

Both caldesmon and calponin have the ability to bind
actin and myosin and can inhibit myosin ATPase ac-
tivity to suppress development of smooth muscle
tone [46, 59]. In some studies, binding of Ca2+-acti-
vated calmodulin to caldesmon or phosphorylation of
caldesmon by protein kinase C (PKC) or extracel-
ular regulated kinase 1 (ERK1) can antagonize the
inhibitory effect on myosin ATPase [59]. However,
whether caldesmon is a natural substrate for PKC or
ERK1 in the VSMC is subject to speculation. Interest-
ingly, calponin has been shown to bind desmin and
phospholipids, as well as ERK and PKC. Immuno-
precipitation studies demonstrate that calponin can
associate with ERK and PKC as a trimeric complex.
Additional evidence suggests that calponin binds the
regulatory domain of PKC and may facilitate its ac-
tivation. In other studies, ERK has been shown to
be activated at the cell surface by phosphorylation
events, which result in translocation of ERK to the
contractile filaments, where it phosphorylates calde-
smon and stimulates contraction [59].

Taken together, these data suggest that calponin
may facilitate agonist-induced signal transduction
by facilitating PKC activation in the plasma mem-
brane. Further, calponin may mediate the targeting
of ERK and PKC to the plasma membrane. Lastly,
tropomyosin is intimately associated with actin fil-
ments, forming a continuous strand made of coiled-
coil monomers. In the absence of troponins, smooth
muscle tropomyosin appears to participate in coop-
erative interactions between actin and myosin, as
well as with caldesmon. Thus, through changes in
their associations between actin and myosin and
other key signaling molecules, calponin, caldesmon
and tropomyosin may regulate cross-bridge cycling
and VSMC tone in a manner that could not be ac-
complished by calcium alone.

c) Latch – a unique characteristic of VSMC
contraction

A hallmark of smooth muscle function is its ability to
maintain tension for prolonged periods without a cor-
respondingly high consumption of energy. Thus, the
rate of ATP hydrolysis is not proportional to the num-
ber of myosin heads engaged in generating force.
This efficiency in maintenance of tone has been
termed the latch state and is critical for sustaining the
“basal” non-aroused state in genital tissues, which
requires the smooth muscle to remain contracted for
most of the time. The mechanism by which VSMCs
can achieve latch remains unknown. However, de-
creased MLC20 phosphorylation and low myosin
ATPase activity have been associated with latch
[47]. In addition, after attaining the latch state, mam-
nalian smooth muscle is not able to redevelop force
when cross-bridges are subjected to a quick re-
lease by the addition of ATP in the absence of Ca2+.
These data suggest that the latch state results from a
decrease in the rate of cross-bridge detachment from
the actin filament. Under normal physiological
conditions, ATP availability is not restricted and any
dephosphorylated myosin bound to actin in the high
affinity state would quickly bind ATP and dissociate
from the actin filament. Thus, this mechanism could
not account for a slow rate of cross-bridge detach-
ment. For these reasons, it has been proposed that
dephosphorylated myosin remains bound to actin
in the high affinity state while still binding ADP. This
type of interaction could also facilitate cooperative
attachment of non-phosphorylated myosin to actin
to help stabilize the latch state. Recently, it has been
proposed that calponin participates in the latch state
by simultaneously binding actin and myosin to sta-
bilize cross-bridge interactions and slow the rate of
detachment [60].

IV. SIGNAL TRANSDUCTION
PATHWAYS REGULATING VSMC
TONE

Pathways that regulate smooth muscle contractility
ultimately influence intracellular Ca2+ levels and/or
alter the calcium sensitivity of the contractile proteins
(Figures 3 & 4). Thus, vasoactive substances via
pharmacomechanical coupling and/or changes in
cell membrane potential via electromechanical
coupling can change intracellular Ca2+ concen-
trations, which regulate the contractile apparatus, as
described in the previous section. However, intracel-

lular Ca\textsuperscript{2+} concentrations need not change for contraction or relaxation to occur if the sensitivity of the contractile apparatus to Ca\textsuperscript{2+} is changed. This additional mode of Ca\textsuperscript{2+}-independent regulation can result in sensitization through inactivation of MLCP or desensitization through the inactivation of MLCK.

Both phosphatase and kinase activity can be inhibited by phosphorylation events (e.g. phosphorylation of MLCP by Rho-kinase). In light of these fundamental mechanisms that alter smooth muscle tone, the main signal transduction pathways that regulate intracellular Ca\textsuperscript{2+} levels and contractile apparatus sensitivity to Ca\textsuperscript{2+} will be summarized in the following sections.

1. PHARMACOMECHANICAL COUPLING

In general, most vasoactive substances exert their effects through intracellular signaling mechanisms that involve at least some aspect of pharmacomechanical coupling (contraction or relaxation in the absence of membrane potential changes). While an exhaustive review detailing the pharmacology of each vasoactive substance or class of receptors is beyond the scope of this chapter, several key pathways that regulate smooth muscle tone will be highlighted.

a) Pathways involving IP3, DAG and PKC

Vasoconstrictor agonists such as norepinephrine (\(\alpha\)-adrenergic receptors), endothelin-1 (ETA receptors), angiotensin II (AT\(_1\) receptors), prostaglandin F2\(\alpha\) (FP receptors) and thromboxane A\(_2\) (TP receptors) bind their respective receptors to activate G\(_q\), which in turn stimulates phospholipase C beta (PLC-\(\beta\)). This membrane bound enzyme hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP\(_2\)) to liberate inositol 1,4,5-trisphosphate (IP3) and 1,2-diacylglycerol (DAG). IP3 binds to specific receptors (IP3R) on the smooth endoplasmic reticulum (SER) to stimulate the release of Ca\textsuperscript{2+} from intracellular stores. IP3R’s act as Ca\textsuperscript{2+}-activated Ca\textsuperscript{2+} channels, similar to the ryanodine receptor. Binding of IP3 to these receptors not only activates the channel, but...
Also increases the sensitivity of the IP3R to Ca\(^{2+}\) and facilitates calcium-induced calcium release (CICR). It is likely that specialized regions of the SER containing IP3R's remain in close proximity to the plasma membrane, enhancing signaling efficiency through the maintenance of functional microdomains [61].

As Ca\(^{2+}\) efflux from the SER decreases the internal stores, free Ca\(^{2+}\) is recycled back into the SER by the SER Ca\(^{2+}\)-ATPase pump (SERCA). Since SERCA is not able to recycle Ca\(^{2+}\) with complete efficiency, store-operated channels (SOC's) in the plasma membrane enable entry of extracellular Ca\(^{2+}\) to replenish the internal stores (capacitative Ca\(^{2+}\) entry). The mechanism by which the SER regulates SOC's is not understood. However, it is clear that SOC's and SERCA function to prevent depletion of internal Ca\(^{2+}\) stores. Upon dissociation of agonists from their receptors, SERCA restores intracellular Ca\(^{2+}\) levels to the basal state and thereby is an important mechanism of signal termination. During prolonged periods of stimulation, SOC's may play a more important role in providing a source of Ca\(^{2+}\) for sustaining signal. It is interesting to note that very high levels of intracellular Ca\(^{2+}\) (near the micromolar range) can itself trigger desensitization of MLCK by activating Ca\(^{2+}\)-calmodulin-dependent kinase II (CaM kinase II). CaM kinase II has a significantly lower sensitivity to Ca\(^{2+}\) than MLCK and is activated only at higher Ca\(^{2+}\) concentrations. Once activated, CaM kinase II phosphorylates MLCK. This phosphorylation decreases the affinity of MLCK for Ca\(^{2+}\)-activated calmodulin and thereby reduces its kinase activity. Thus, strong stimuli that cause Ca\(^{2+}\) to rise to very high levels can trigger a feedback inhibition response.

DAG is also an important intracellular second messenger generated by PLC. DAG directly activates PKC, a family of isoenzymes that participate in diverse cellular functions and have the ability to translocate between the cytoplasm and the plasma membrane. With regard to smooth muscle tone, PKC can regulate ion channels or phosphorylate multiple substrates to facilitate contraction [46,62].

Figure 4. Signal transduction pathways regulating smooth muscle relaxation. Red arrows indicate association, binding and/or activation, whereas yellow arrows indicate inhibitory regulation. Indirect or putative interactions are indicated by dashed arrows. AM = actin-myosin contractile apparatus; BKCa = calcium-activated maxi-K+ channel; cAK = cAMP-dependent protein kinase; cGK = cGMP-dependent protein kinase; CaMK = calmodulin-dependent kinase; CO = carbon monoxide; HSP20 = 20 kilodalton heat shock protein; IP3R = IP3 receptor; IRAG = IP3R-associated cGK substrate; KATP = ATP-dependent K+ channel; MLCK = myosin light chain kinase; MLCP = myosin light chain phosphatase; NO = nitric oxide; PLmb = phospholamban; SER = smooth endoplasmic reticulum; SERCA = SER calcium ATPase. Adapted from Kim NN, Vascular physiology of erectile function. In: Carson CC, Kirby RS, Goldstein I, Wyllie MG, editors, Textbook of Erectile Dysfunction, 2nd Edition. New York, USA: Informa Healthcare, 2009.
these mechanisms are less well-defined, PKC may participate in activating the ERK signaling pathway to affect caldesmon function, as previously outlined in the section on actin-associated proteins. Through similar mechanisms, PKC may also mediate Ca\(^{2+}\)-independent contraction, since several of the PKC isoforms are insensitive to Ca\(^{2+}\) while still being activated by DAG. It is also interesting to note that PKC has been shown to inhibit Ca\(^{2+}\) channel activity and promote Ca\(^{2+}\) extrusion through the Na\(^{+}/Ca\(^{2+}\) exchanger; events that would decrease intracellular Ca\(^{2+}\) and cause VSMC relaxation [62]. Thus, while there are mechanistic aspects of PKC that are not fully understood, it seems likely that PKC causes contraction through Ca\(^{2+}\)-independent mechanisms.

An important distinction to note is the source of DAG. In addition to PIP2 hydrolysis by PLC-β, which generates IP3 and DAG, hydrolysis of phosphatidylinositol 4,5-bisphosphate (PI(4,5)P\(_2\)) by either a different isoform of PLC or the sequential action of phospholipase D (PLD) and phosphatidate phosphohydrolase (PA-PHA), produces DAG alone and does not result in the mobilization of intracellular Ca\(^{2+}\). It has been postulated that the rate of force development and the duration of contraction is related to the activation of different isoforms of phospholipid hydrolytic enzymes and PKC [62]. Thus, the rate and extent of DAG synthesis by the various phospholipases and the presence or absence of IP3 co-production may be correlated with the type of contractile response exhibited by the smooth muscle (e.g. short and transient vs. slowly developing and sustained). While PLD activity has been detected after exposure to norepinephrine, endothelin and angiotsensin II, the significance of this enzyme in mediating VSMC contraction is unclear. PLD activation may be a secondary response to strong activation of PKC as occurs experimentally with phorbol ester stimulation. It is also possible that PLD may play a more important role in mediating trophic, rather than tonic, effects. In VSMCs, termination of DAG/PKC signaling is accomplished predominantly by hydrolysis of DAG by lipases to yield free fatty acids and glycerol [62]. However, DAG can also be recycled to synthesize phospholipids and triacylglycerols.

Another mechanism of increasing intracellular Ca\(^{2+}\) is by permitting entry of extracellular Ca\(^{2+}\) through receptor-operated channels without a change in membrane potential [63]. Norepinephrine, endothelin, vasopressin and angiotensin II cause the opening of Ca\(^{2+}\)-permeable, nonselective cation channels. While these channels are termed “nonselective”, they do exhibit greater permeability to extracellular Ca\(^{2+}\) compared to other cations. In addition, their activity is not dependent on intracellular Ca\(^{2+}\) levels and can thus be distinguished from SOC’s. The activation of α1-adrenergic receptor by norepinephrine is a well-studied example of VSMC contraction mediated by receptor-operated channels. This process is independent on G-protein (Gq), PLC and DAG, but is independent of IP3 and PKC [63]. Yet, phosphorylation events are known to activate receptor-operated channels. MLCK inhibitors prevent nonselective cation current but the direct involvement of MLCK is inconsistent with other experimental data. Thus, it is likely that DAG activates another kinase that is similar to MLCK. Recent studies suggest that receptor-operated channels and store-operated channels share extensive homology and belong to the transient receptor potential channel (TRPC) family [64]. This family of channel proteins was first identified in the photoreceptors of Drosophila, where they mediate a sustained current in response to light activation of rhodopsin. To date, 7 mammalian homologues have been identified. Each channel consists of 4 subunits and each subunit has 6 transmembrane segments. The extent to which receptor-operated channels contribute to agonist-induced contraction, relative to mobilization of intracellular stores by IP3, remains unclear. However, antisense oligonucleotide studies in rat cerebral arteries suggest that downregulation of TRPC protein reduces reflex vasoconstriction in response to increased blood pressure [65].

Lastly, it is important to note that similar pathways regulating Ca\(^{2+}\) flux also occur in nerves and in endothelial cells. However, in these cell types, they usually stimulate the production of vasoactive factors that have Ca\(^{2+}\)-dependent synthetic enzymes. In intact tissues, these vasoactive compounds often cause relaxation of VSMCs even though they have the capability to directly stimulate smooth muscle to cause contraction (e.g. kinins and acetylcholine). Thus, the proximity of smooth muscle, endothelium and nerves in vascular tissues dictates that the net response of VSMC tone is dependent on the activation of specific receptor-mediated pathways and also the type of cell in which these pathways are primarily activated.

b) Pathways involving cyclic nucleotides

Generation of cyclic nucleotides (cGMP and cAMP) by guanylyl and adenylyl cyclases is a primary mode of mediating VSMC relaxation. Vasodilators such as VIP and prostaglandins E and D activate G-protein (Gs) coupled receptors that can stimulate plasma membrane associated adenylyl cyclase, whereas soluble (cytosolic) guanylyl cyclase can be directly activated by nitric oxide or carbon monoxide by binding to the heme moiety of the enzyme. Guanylyl cyclase activity is also present in the cytoplasmic domains of natriuretic peptide receptors. In penile cavernosal smooth muscle, C-type natriuretic peptide (CNP) receptor mRNA has been detected and CNP can stimulate cGMP accumulation and induce tissue relaxation [66,67]. However, the importance of membrane associated guanylyl cyclase in the normal function of genital tissue VSMC remains to be determined. Negative regulation of cyclic nucleotide
generation can facilitate contraction of VSMCs. The primary example is that of α2-adrenergic receptors, which act through Gi to inhibit adenyl cyclase.

Increased levels of intracellular cAMP and cGMP cause the activation of cAMP-dependent and cGMP-dependent protein kinases (cAK and cGK) [68-70]. Each cyclic nucleotide-dependent kinase can be activated by both cAMP and cGMP, although cross-activation requires approximately 10-fold higher concentrations of cyclic nucleotide [46]. Thus, in addition to specific activation, there is potential cross-activation of cAK (also called protein kinase A) and cGK (also called protein kinase G), which may be a mechanistic basis for signal cross-talk. However, while cAK and cGK may phosphorylate a number of common substrates, several lines of evidence indicate that the activation of cGK by cGMP and cAMP is the predominant mechanism by which cyclic nucleotides decrease intracellular Ca²⁺ to cause VSMC relaxation [46,71-74]. It should be noted that this does not rule out or diminish the participation of cAK-mediated pathways. For example, cAK (but not cGK) can inhibit Ca²⁺-calmodulin activation of MLCK through phosphorylation of MLCK [75]. Therefore, it is possible that cAK may play a more important role in Ca²⁺ desensitization of the contractile apparatus, rather than in reducing intracellular Ca²⁺ concentration. Nevertheless, as discussed below, it is likely that cyclic nucleotides provide redundant regulation of smooth muscle relaxation.

Cyclic GMP-dependent protein kinases are derived from 2 different genes that encode type I (cGKI) and type II (cGKII). Type I cGK is a dimer consisting of two identical subunits comprising a molecular mass of 156 kDa, and is widely distributed throughout the body. In smooth muscle, only cGK is expressed and exists as 2 splice variants (cGKIA and cGKIB). Type II cGK is a monomer of 86 kDa, and has limited tissue distribution, having been found only in intestinal epithelium, kidney and brain [76]. While specific roles of the 2 different cGKI isoforms are an area of continuing investigation, there is evidence that both isoforms differ considerably in their functional properties[77-79]. Immunoprecipitation studies in smooth muscle indicate that cGKIB is associated with IP3R and a 125 kD protein known as IP3R-associated cGKI (IRAG); both of which act as substrates for the kinase [80]. Phosphorylation of IP3R and IRAG decreases agonist-induced Ca²⁺ release from the SER. Recently, deletion mutation studies demonstrated that IRAG is a critical protein in mediating cGMP-dependent relaxation of smooth muscle [81]. In addition, cGKI is known to phosphorylate phospholamban, a small membrane-associated protein (6 kD homopentamer) that constitutively inhibits SERCA. Phosphorylation of phospholamban inactivates its inhibitory control of SERCA and increases Ca²⁺ re-uptake into the SER, where Ca²⁺ is bound by proteins such as calsequestrin and calreticulin. Interestingly, cAMP-mediated relaxation was unaffected by mutated, non-functional IRAG [81], whereas cAK can phosphorylate phospholamban to increase Ca²⁺ re-uptake [82]. Thus, the combined actions of cGKI and cAK can inhibit Ca²⁺ release from intracellular stores and also stimulate Ca²⁺ re-uptake.

Additional and perhaps equally important pharmacomechanical mechanisms by which cGMP and/or cGKI may cause relaxation involve activation of the plasma membrane Ca²⁺-ATPase pump, inhibition of IP3 generation, inhibition of Rho-kinase, stimulation of MLCP, and phosphorylation of heat shock proteins [71,76]. These mechanisms have been demonstrated in various cells, but their relevance to VSMCs in genital tissues has not been explicitly shown. The plasma membrane Ca²⁺-ATPase produces Ca²⁺ efflux independent of Na⁺ and its activity may be stimulated by cGMP directly or through intermediate enzymes/metabolites that are regulated by cGKI. PLC activity can also be inhibited by cGMP to reduce IP3 production. Some studies suggest that Rho-kinase and MLCP can both be phosphorylated by cGKI to antagonize Rho-kinase activity and stimulate MLCP. Since phosphorylation of MLCP by cGKI and Rho-kinase cause opposite effects on phosphatase activity, it is assumed that the phosphorylation sites are different. Lastly, the constitutively expressed 20 kD heat shock protein (HSP20) is associated with actin filaments and has been postulated to regulate smooth muscle contraction. Both cGK and cAK have the ability to phosphorylate HSP20, which presumably leads to desensitization of the contractile apparatus.

In the penis, immunostaining for cGKIα and cGKIβ has been observed within the smooth musculature and the endothelium of cavernous arteries and sinuses. Double-staining protocols revealed the co-localization of α-actin, cGMP, eNOS and cGKI isoforms, the expression of cGKI isoforms was confirmed by Western blot analyses [83]. Findings from in vitro functional studies are also in support of a significance of the cGKI in the control of human penile erectile tissue [84,85].

c) Phosphodiesterases

One of the main mechanisms by which cyclic nucleotide signaling is terminated is by the action of phosphodiesterases (PDEs), a heterogenous group of hydrolytic enzymes. PDEs are classified according to their preference or affinity for cAMP and/or cGMP, kinetic parameters of cyclic nucleotide hydrolysis, relative sensitivity to inhibition by various compounds, allosteric regulation by other molecules, and chromatographic behavior on anion exchange columns. PDEs share a catalytic domain of ~270 amino acids, an N-terminal regulatory domain responsible for binding cofactors, and a C-terminal domain of unknown function. Eleven families of PDE isoenzymes can be distinguished [86-91]. Some of these isoenzyme families contain more than one
gene (isogenes) and some genes are alternatively spliced so that more than 50 isoenzymes or variants have been described to date [92-95].

Thus far, 6 out of these 11 isoenzymes (PDE1, 2, 3, 4, 5 and 11) have been proven to be of pharmacological importance. Since the distribution and functional significance of PDE isoenzymes varies in different tissues, isoenzyme-selective inhibitors have the potential to exert specific effects on the target tissue. Although mammalian tissues express several members of PDE families or more than one variant of an individual family, there are numerous examples where an individual PDE is predominantly found in a specific location. Preferential expression of PDE5 in the corpus cavernosum and the cGMP-mediated relaxation of the cavernous smooth muscle during sexual stimulation have made inhibition of this enzyme by sildenafil, vardenafil and tadalafil a clinical benefit in the management of erectile dysfunction (ED). PDE5 was first detected as the major cGMP binding protein in lung and later characterized as a cGMP-binding cGMP-specific PDE. The purified protein is a homodimer of 99.6 kDa subunits and binds two zinc atoms per monomer (Kd ~0.5 mM) which are necessary for catalysis. PDE5 has two allosteric sites for cGMP binding (Kd ~1.3 and 3 mM). Occupancy of these sites is necessary for PDE5 phosphorylation which has been shown to occur in rat vascular smooth muscle cells via cPKG-dependent mechanisms. The amino acid residues comprising the active site of PDE5 have been examined by site directed mutagenesis studies and characterization of the mutant enzymes. Substitution of only four amino acids alters the cGMP selectivity of PDE5 toward cAMP by more than 100 fold. Within the active site, substitution of His643 and Asp754 (common to all PDEs) and His603, His607, His647, Glu672, and Asp714 produced marked changes in kcat while substitution of His643 and Asp754 (common to all PDEs) and His603, His607, His647, Glu672, and Asp714 produced marked changes in kcat while substitution of Tyr602 and Glu775 dramatically increased the Km (wildtype ~2 mM) without affecting the velocity of the enzyme.

Nevertheless, since PDEs form a biochemically and structurally diverse family of proteins, there might be more than one PDE isoenzyme or isogene serving as potential drug target in the treatment of ED. In the 1990s, the presence of PDE isoenzymes 2, 3, 4, and 5 was reported in cytosolic supernatants of human erectile tissue [96]. In addition, the expression of mRNA transcripts specifically encoding for 14 different human PDE isoenzymes and isoforms in human cavernous tissue was shown by means of RT-PCR and Northern Blot analysis: PDE1A, PDE1B, PDE1C, PDE2A and PDE10A, which hydrolyze both cyclic AMP and cyclic GMP; the cyclic AMP-specific PDE isoenzymes PDE3A, PDE4(A-D), PDE7A and PDE8A, and the cGMP-specific PDEs PDE5A and PDE9A [97].

The intracellular level of cAMP in human erectile tissue is mainly regulated by the cAMP-degrading PDE isoenzymes 3 and 4. Evidence for the presence of PDE 3 and 4 in human erectile tissue has been shown and messenger RNAs encoding for PDE3A, PDE4A-D, PDE7A and PDE8A, all of which are known to hydrolyze cAMP, were shown by means of RT-PCR and Northern blot analyses [97,98]. Results obtained in vitro suggest that PDE3 and PDE4 might be the predominant isoenzymes in the human corpus cavernosum) [97,99]. A significant role of PDE4 and cAMP in the control of human erectile tissues is further supported by the finding that immunoreactions specific for PDE4 and PDE4A were detected in cavernous endothelial and neuronal structures [84]. Interestingly, it has been shown that the reversion of tension mediated by an α1-adrenoceptor of isolated human corpus cavernosum induced by sildenafil and tadalafil were reversed by the protein kinase A inhibitor Rp-8-CPT-cAMPS, suggesting an involvement of cyclic AMP-mediated mechanisms in the action of PDE5 inhibitors. On the basis of these observations, an important complementary role might be considered for the adenylyl cyclase/cAMP/cAK pathway in the control of cavernous smooth muscle tone. This provides a rationale to further investigate the effects of selective PDE4-inhibitors, as well as compounds inhibiting both PDE5 and PDE4, in models for erectile dysfunction [100].

2. ELECTROMECHANICAL COUPLING – CONTRACTION AND RELAXATION PATHWAYS

Pathways that regulate VSMC tone and are associated with changes in membrane potential are defined as electromechanical coupling mechanisms. The primary electromechanical mechanism of contraction in VSMCs involves depolarization and the opening of voltage-gated L-type Ca\(^{2+}\) channels to allow influx of extracellular Ca\(^{2+}\). While VSMCs in genital tissues do not exhibit inherent autorhythmicity, they do exhibit cyclical phasic activity associated with changes in electrical signal. Most likely due to the release of paracrine and autocrine substances including neurotransmitters, this activity is inhibited by nifedipine, an L-type Ca\(^{2+}\) channel blocker [101]. Contractile responses caused by norepinephrine, endothelin-1 and angiotensin II are partly mediated by L-type Ca\(^{2+}\) channels [102-104]. Recent studies indicate that L-type Ca\(^{2+}\) channels can be activated by phosphatidylinositol 3,4,5-trisphosphate (PIP3) which is derived from PIP2 through the action of phosphoinositide 3-kinases (PI3K) [102]. PI3K’s are associated with the plasma membrane and can be activated by G-protein coupled receptors or tyrosine kinases.

Mobilization of intracellular Ca\(^{2+}\) through the IP3 pathway can also trigger noncapacitative entry of extracellular Ca\(^{2+}\). Ca\(^{2+}\)-activated nonspecific cation channels (distinct from receptor-operated channels) allow influx of extracellular Ca\(^{2+}\) along with Na+, K+, and Cl− ions.
which depolarizes the VSMC. This depolarization can activate L-type Ca\(^{2+}\) channels to further increase Ca\(^{2+}\) entry. In addition, the presence of Ca\(^{2+}\)-activated Cl- channels in penile corpus cavernosum suggests that Cl- influx may also play a role in depolarizing the VSMC [105]. Specific blockers of Cl- channels produce transient periods of penile tumescence and prolong neurogenic erection.

A major mechanism of VSMC relaxation is the activation of K\(^+\) channels. Activation of cGK and cAK has been associated with the opening of Ca\(^{2+}\)-activated maxi K\(^+\) (BK\(^{Ca}\)) channels in the plasma membrane, causing hyperpolarization. Various mechanisms involving direct and indirect phosphorylation/dephosphorylation events mediated by cGK or cAK have been postulated for the activation of BK\(^{Ca}\) channels in smooth muscle from different vascular beds. However, the precise mechanisms remain undefined. Hyperpolarization mediated by BK\(^{Ca}\) channels has been shown to be an important mechanism of NO-cGK-dependent relaxation in the cavernosal smooth muscle of the penis [106]. Some vasodilators that stimulate cAMP production have also been shown to activate ATP-sensitive K\(^+\) channels (K\(_{ATP}\)) in penile cavernosal tissue and resistance arteries [107,108]. Collectively, changes in membrane potential due to increased K\(^+\) efflux inactivates L-type Ca\(^{2+}\) channels to inhibit Ca\(^{2+}\) influx. NO may also cause VSMC hyperpolarization independent of cGMP and cGK. In aortic smooth muscle cells, NO has been shown to directly activate BK\(^{Ca}\) channels [109].

As its name suggests, BK\(^{Ca}\) channels are activated by Ca\(^{2+}\). When contractile pathways are activated and intracellular Ca\(^{2+}\) concentration is high, BK\(^{Ca}\) channels may provide negative feedback regulation. During the past decade, there has also been increasing evidence that transient, localized bursts of intracellular Ca\(^{2+}\) release or sparks in VSMCs can cause relaxation through BK\(^{Ca}\) channels [110,111]. These sparks are limited to microdomains of the SER that are situated just below regions of plasma membrane containing a collection of BK\(^{Ca}\) channels. The proximity of these Ca\(^{2+}\) release sites to the effector channels enables the local concentration of Ca\(^{2+}\) to become sufficiently high such that a hyperpolarization response is triggered without global changes in intracellular Ca\(^{2+}\). The K\(^+\) currents elicited by Ca\(^{2+}\) sparks have been referred to as spontaneous transient outward currents (STOCs). The regulation of Ca\(^{2+}\) sparks is not well understood, but nyladine receptors, which are also present on the SER of VSMCs are thought to play an important role in their generation. In both vascular and non-vascular smooth muscle cells, Ca\(^{2+}\) sparks have also been shown to activate Cl- channels to cause spontaneous transient inward currents (STICs) that depolarize the smooth muscle and lead to contraction [111]. In VSMCs of genital tissues, the regulatory role of Ca\(^{2+}\) sparks, STOCs and STICs remain to be studied.

## V. MAJOR REGULATORS OF PENILE CORPUS CAVERNOsum SMOOTH MUSCLE CONTRACTILITY

### 1. NITRIC OXIDE (NO)

NO is the primary mediator of NANC parasympathetic input and endothelium-dependent relaxation in the corpus cavernosum [19]. A highly reactive and unstable gas, NO can regulate a wide array of physiological functions in mammals. It is apparently synthesized on demand (with little or no storage) from the amino acid L-arginine and molecular oxygen by a family of enzymes known as NO synthases (NOS). Three distinct isoforms of NOS have been identified which were originally named after the tissues in which they were first described. Neuronal NOS (nNOS or type I) and endothelial NOS (eNOS or type III) are Ca\(^{2+}\)/calmodulin-dependent, constitutive isoforms. Inducible NOS (iNOS or type II) is a Ca\(^{2+}\)-independent isoform that is mainly expressed in macrophages and other tissues following an immunological stimulus [112]. After the gaseous transmitter has been released from nerve endings or the endothelium, NO can readily cross plasma membranes to enter target cells, such as the cavernosal smooth muscle cell. NO promotes the synthesis and accumulation of the second messenger molecule cGMP by the activation of the soluble guanylyl cyclase (sGC), which is the main intracellular receptor for NO. sGC is a heterodimeric protein that consists of an α- and β-subunit, both presenting a homologous domain constituting the catalytic center known to generate cGMP. The enzyme also contains a prosthetic heme attached to a histidine residue of the β-subunit, which is essentially required for the activation of the enzyme by NO. Although the binding of NO occurs in the β-subunit, both subunits are required for the stimulation of enzyme activity [113,114]. The activation of sGC is considered the most significant step in the signal transduction cascade which leads to a reduction in free cytosolic Ca\(^{2+}\) and, finally, penile erectile smooth muscle relaxation. However, NO has also been shown to interact directly with other cellular targets including receptors, ion channels and pumps, which may modulate smooth muscle cell contractility, independent of the cGMP pathway (115-117). Thus, in addition to guanylate cyclase, NO has other intracellular targets, which may play a role in the regulation of vascular smooth muscle contractility.

### 2. PROSTAGLANDINS

Prostanoids (eicosanoids, prostaglandins) are twenty-carbon derivatives produced by the action of cyclooxygenases on the common precursor arachidonic acid [118]. Prostanoids act locally and exert both trophic and tonic effects in an autocrine and paracrine manner. In the corpus cavernosum, prostanoids may play an important role...
in the regulation of extracellular matrix production. However, this discussion will limit its focus to the effects of prostanoids on smooth muscle contractility. The precise physiologic role of prostaglandins in penile erection remains poorly defined. In vitro, prostaglandins appear to be responsible for the rhythmic spontaneous contractile activity observed in isolated corpus cavernosum tissue [19,119]. In addition, the anti-platelet aggregating effects of PGI2 (prostacyclin) and NO, both released by the endothelium, may be important in preventing coagulation of blood, since blood flow within the cavernosal bodies is negligible during full penile tumescence.

The five primary active prostanoid compounds are the prostaglandins PGD2, PGE2, PGF2α, PGI2 and thromboxane A2 (TXA2) [119,120]. Isolated rabbit corpus cavernosum has been shown to synthesize PGE1, PGF2α, TXA2 and PGI2 while human corpus cavernosum smooth muscle cells in culture produce PGE2 and PGF2α [121,122]. The expression and/or activity of prostaglandin H synthase (PGHS1 and PGHS2) mRNA and protein has also been reported in rabbit corpus cavernosum and in cultured human corpus cavernosum smooth muscle cells [119,121-123]. It has been demonstrated that prostanoids can induce both relaxation and contraction in penile corpus cavernosum. In certain disease states, prostanoid imbalance may contribute to erectile dysfunction. For example, tissue levels of TXA2 are significantly increased in rabbits subjected to iliac artery endothelial injury and high cholesterol diet [124]. However, the clinical relevance of such findings remain controversial. PGE is the only endogenous prostaglandin that appears to elicit relaxation of human trabecular smooth muscle; the others causing constriction or having no effect on smooth muscle tone. Exogenous PGE2 and PGE1 relax isolated cavernosah tissue at submicromolar concentrations while PGE2 causes contraction at concentrations of 10μm or greater. The synthesis or pharmacologic action of PGD2 has not been examined in corpus cavernosum and the receptors for this prostanoid are localized primarily in the retina, brain, and small intestines, suggesting highly localized sites of action.

There are five major groups of prostanoid receptors termed DP, EP, FP, IP and TP which mediate the effects of PGD, PGE, PGF, PGI and thromboxane, respectively [118]. EP receptors have been most extensively studied and are further categorized into four pharmacologic subclasses (EP1, EP2, EP3, EP4). Several different isomers of the EP3 receptor have been identified and are found from alternative splicing of a single gene product. The multi-functional, dose-dependent effects of PGE2 may be explained by the coupling of EP receptor subtypes and isoforms to different second messenger systems. In general, the EP1, EP2, EP3 and EP4 receptors mediate smooth muscle contraction (by stimulating phosphatidylinositol hydrolysis or inhibiting adenylate cyclase, while EP2, EP3 and EP4 receptors mediate smooth muscle relaxation by coupling to Gs protein and stimulating adenylate cyclase to increase intracellular cAMP. In certain cases, the same isoform (e.g. EP3II receptor) has been reported to both increase intracellular cAMP possibly by a Gs-coupled mechanism and decrease cAMP via a pertussis toxin sensitive Gi-coupled mechanism, depending upon the density of receptors in the plasma membrane.

3. THE SPECIAL ROLE OF OXYGEN

Oxygen tension plays an active role in regulating penile erection [121,123,125]. Measurements of cavernosal blood PO2 in human volunteer subjects indicate that oxygen tensions change rapidly during the transition from the flaccid to the erect state. In the flaccid state, cavernosal blood PO2 is comparable to that in venous blood (~35 mm Hg). Following intracavernosal administration of papaverine and phentolamine to induce erection, cavernosal blood PO2 increases to arterial levels (~100 mm Hg), reaching 85% of the peak value within the first minute. Maintenance of constant oxygen tension is a critical imperative in most tissues of the body but the penis is the only organ which changes from venous to arterial oxygen tensions during the course of its normal function. This transition is the basis of a unique regulatory mechanism that takes advantage of key synthetic enzymes which utilize molecular oxygen as a co-substrate. NOS and prostaglandin synthase are two well-studied examples of a class of enzymes known as dioxygenases. At low oxygen tensions, measured in the flaccid state of the penis, the synthesis of nitric oxide is inhibited, preventing trabecular smooth muscle relaxation. This inhibition of nitric oxide synthesis is probably necessary for the maintenance of penile flaccidity. Following vasodilation of the resistance arteries, the increase in arterial flow raises oxygen tension. In the oxygen enhanced environment, autonomic dilator nerves and the endothelium are able to synthesize nitric oxide, mediating trabecular smooth muscle relaxation. The synthesis of prostanooids is similarly regulated in the flaccid versus the erect state [121-123]. Therefore, oxygen tension may regulate the types of vasoactive substances present in this vascular bed. For example, at low oxygen tensions, endothelin may predominate, while at high oxygen tension, nitric oxide as well as prostaglandins are made due to the requirement of oxygen for their synthesis.

4. VASOACTIVE INTESTINAL POLYPEPTIDE (VIP)

VIP-immunoreactive nerves are widely distributed throughout the genitourinary system [19,126]. Immunocytochemical detection of VIP indicates that the highest concentrations are found in the proxi-
mal penile corpus cavernosum. Isolated corpus cavernosum tissue from various species, including human, monkeys, rabbit and dog, exhibit relaxatory responses to VIP. VIP and NO synthase containing nerves are often co-localized in penile tissue [19]. The density and distribution of VIPergic nerves within the penis has led many to postulate that VIP, in addition to NO, is an important NANC neurotransmitter regulating penile erection. Along with the anatomical evidence, the role of endogenous VIP in mediating penile erection is further supported by the observations that anti-VIP antibodies and the VIP receptor antagonist VIP 10-28 inhibit nerve-mediated relaxation in isolated cavernosal tissue strips [19]. However, the role of VIP as a modulator of trabecular smooth muscle tone remains inconclusive since the effects of the peptide in vivo are not necessarily consistent with the in vitro findings. Intracavernosal administration of VIP in animals and humans has yielded varying results, ranging from no effect to partial turgence to full erection. Thus, while descriptive studies on the neuroanatomy and the observed relaxatory effects of VIP are supportive of its potential role in mediating or enhancing the onset and maintenance of penile erection, these responses are not well characterized and the physiologic mechanisms underlying its action have yet to be completely elucidated.

5. ENDOTHELIN

Endothelin-1 (ET-1), a member of the endothelin family of peptides, is one of the most potent vasoconstrictors yet described [127,128]. This peptide has also been shown to have growth factor activity, stimulating mitogenesis in fibroblasts, smooth muscle, and endothelial cells. In blood vessels, it is thought to act as a paracrine hormone in the endothelial control of vascular smooth muscle tone and structure of the blood vessel wall. Similar to nitric oxide, endothelin release from the intimal lining of blood vessels can be induced by shear stress. However, little is known about the physiological or cellular mechanisms which regulate its production in the penis. In human corpus cavernosum, ET-1 is synthesized by the endothelium and elicits strong, sustained contractions of corpus cavernosum smooth muscle [129,130]. Two major subtypes of endothelin receptors (ET\textsubscript{A} and ET\textsubscript{B}) have been characterized and cloned. Both receptor subtypes have been identified in penile corpus cavernosum. They are distributed on both the endothelium and the smooth muscle and are distinguished by their binding affinity for ET-3 [131]. Exogenous ET-1 or ET-2 causes equipotent contraction in isolated cavernosal tissue strips, whereas ET-3 induces much weaker contraction in corpus cavernosum. While the receptor binding affinity of ET-1 and ET-2 is not necessarily greater than that of other contractile factors, the rate of dissociation (k\textsubscript{d} = 2.4 \times 10^{-3} /h for ET-1) is significantly slower than many ligands [131]. This may account for the unique ability of endothelins to maintain long-lasting, sustained contraction in corpus cavernosum smooth muscle. Despite its action as a potent vasoconstrictor, the role of endogenous endothelin in penile cavernosal tissue has not been clearly defined. In animal models, acute administration of an endothelin receptor antagonist has potentiated erectile function, but this same antagonist has not proven to be beneficial in clinical studies [132]. It has been suggested that endothelin may also exert vasodilatory effects at low concentrations through a “super-high” affinity form of the ET\textsubscript{B} receptor. Although this vasodilatory role of endothelin in penile erection remains unclear, it has been demonstrated in the rat that ET-3 and submaximal doses of ET-1 increase intracavernosal pressure, potentially by stimulating NO production [133].

VI. SIGNAL TRANSDUCTION PATHWAYS REGULATING NON-CONTRACTILE RESPONSES IN VSMCS

Changes in VSMC growth and extracellular matrix production can have a profound impact on the function of genital tissues. The extracellular matrix itself is a dynamic structure that plays an important role in modulating cell morphology, movement, growth, differentiation and survival by regulating cell adhesion, cytoskeletal machinery and intracellular signaling. Given the perspectives on variations in VSMC phenotype that were summarized in the introduction of this chapter, it is possible that smooth muscle cells may transform from primarily contractile to primarily synthetic cells (or vice versa) in response to changes in their environment (e.g. chronic disease states or acute injury). Alternatively, there may be an inherently heterogeneous population of VSMCs in a given vascular tissue at any one time. In addition to growth factors and cytokines, vasoactive factors have also been shown to have trophic effects in the vasculature, suggesting that many of the same intracellular mediators that cause contraction or relaxation are also involved in trophic responses in VSMCs. While the overall integration of various stimuli and coordination of responses in a single cell is poorly understood, it is likely that the net response of any given VSMC is dependent upon the overall gene expression profile. Synthetic VSMCs are primarily characterized by a significantly decreased expression of contractile proteins. Thus, activation of signaling pathways that may have mediated tonic responses in contractile VSMCs can modulate cell growth or matrix production in a synthetic VSMC. Many of these pathways have been discussed in previous sections of this chapter, but the specific mechanisms regulating gene expression and cell growth remain, in large part, to be elucidated. For example, the NO-cGK pathway and its effects on gene expression is an area of active study. While
it appears that cGKI modulates the ERK pathway (also called mitogen-activated protein kinase or MAP kinase) to modulate proliferation and migration of VSMCs, the molecular targets of ERK that eventually control gene transcription have not been clearly defined [134].

Many growth factors stimulate cell surface receptors with intrinsic tyrosine kinase activity in their cytoplasmic domains. This tyrosine kinase activity is considered essential to regulating cell growth. Several of these receptors have been linked with the activation PLC-γ. Also, as mentioned in the previous section on pharmacomechanical coupling, PLD may be more important for mediating trophic responses than contractile responses. Some variations in responses to growth factors and vasoactive substances may be due to the different mechanisms of activation for different PLC isoforms. In addition to preferential activation of PLC-γ by tyrosine kinases, the β1 and β3 isoforms of PLC are activated by the αq subunit of Gq, whereas the β2 and β3 isoforms can be activated by the βγ subunits of Gi. As described in previous sections of this chapter, PLC activity gives rise to DAG and stimulation of PKC. Stimulation of PKC has been shown to have both proliferative and anti-proliferative effects to platelet-derived growth factor (PDGF), epidermal growth factor (EGF) and angiotensin II [62]. While the reasons for this variability remain unclear, it must be stressed that multiple isoforms of PKC exist and each isoform has numerous substrates. Aside from its effects on the contractile apparatus and ion channels, PKC has also been shown to modulate DNA synthesis, potentially through the phosphorylation of transcription factors [62]. Among the most intriguing of these is nucleolin, a multi-functional protein located primarily in the nucleolus. In addition to its activities as a regulator of ribosomal DNA transcription and ribosomal assembly, nucleolin has been shown to regulate DNA decondensation and act as a plasma membrane receptor and shuttling protein between the cell surface and the nucleus [135].

To date, it is widely accepted that several disorders of the male sexual response, such as male erectile dysfunction (ED) and orgasmic dysfunctions, can be therapeutically approached by influencing the function of the vascular and non-vascular smooth musculature of the genital tract. In order to achieve a pronounced drug effect without significant adverse events, especially on the cardiovascular system, a certain degree of tissue selectivity is mandatory. Selective intervention in intracellular pathways regulating smooth muscle tone has become a promising strategy to modulate tissue function.

VII. SUMMARY AND PERSPECTIVE

Although an impressive amount of knowledge has been accumulated regarding smooth muscle biology and vascular physiology, it is important to keep in mind that many questions still remain and are being actively investigated. While a central and enduring question has been how Ca²⁺ can elicit different responses within a given cell, it is becoming more apparent that unique spatial and temporal differences in intracellular Ca²⁺ flux play an important role in this regulation. Even in the well-established field of contractile proteins, novel findings are not uncommon. Future studies in genital tissue physiology will benefit from the application of knowledge gained from the fields of smooth muscle and vascular biology.

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C. DIABETES AND METABOLIC SYNDROME

K Chitaley and J S Paick

I. OVERVIEW

Diabetics are at increased risk for various maladies, including retinopathy, neuropathy, nephropathy and vascular disease. Prolonged, uncontrolled hyperglycemic insult results in altered signaling at the cellular level underlying the development and progression of these diseases. Erectile dysfunction (ED) is often characterized in part by insufficient non-adrenergic/non-cholinergic nerve stimulus, and/or an inability to dilate feeder arterioles of the penis resultant from vascular disease. As the diabetic population is susceptible to these changes, ED is indeed prevalent in this cohort. Although phosphodiesterase 5 (PDE5) inhibitors have revolutionized the field of ED treatment, these drugs are less effective in certain subsets of the population, including diabetics. Rendell et al. reported that 56% of patients with type II diabetes respond to PDE5, compared to 87% of non-diabetic patients[1]. Furthermore, Penson et al. found that the effects of treatment often decline over time in diabetics, as after 12 months of pharmacologic treatment, mean International Index of Erectile Function (IIEF) scores for type II diabetics reversed to baseline[2]. The remainder of this section will focus on epidemiological, clinical and basic science studies that have examined the prevalence, treatment and mechanisms underlying diabetic-ED. For the sake of this chapter, the work outlined will review mainly type 2 diabetic-ED and the metabolic syndrome (MetS), highlighting studies of type 1 diabetic-ED when relevant. Various reviews of valuable reference include: Hidalgo-Tamola et al.[3], Moore et al.[4], Vrentzos et al.[5], Musicki et al.[6] and DiSanto[7], amongst others.

II. EPIDEMIOLOGIC DATA

1. DIABETES MELLITUS

Diabetes mellitus is a common chronic disease, affecting 0.5-2% worldwide. In clinics that treat ED, the prevalence of diabetes as co-morbidity has remained at 20-25%, irrespective of whether the clinic is endocrine-based or andrology-based[8;9]. ED in diabetics is more common than retinopathy or nephropathy[10]. It was reported that up to 75% of men with diabetes have a lifetime risk of developing ED, much higher rates than 52% in men of ages 40-70 years in the Massachusetts Male Aging Study (MMAS)[11-13]. The prevalence of ED in diabetic patients was 40%, with a range of 27.5-75%[14]. This wide variation of the prevalence may be attributed to the heterogeneity of the studied population. Since the severity of ED was dependent on the duration of diabetes, glycemic control and the presence of complication, the prevalence of ED may be affected by the presence of above-mentioned factors[15]. Studies have revealed a prevalence of 49% rate of ED in patients with type 1 diabetes and 34% and 24% of severe and mild to moderate ED respectively, in patients with type 2 diabetes [16;17]. The onset of ED occurs at an earlier age in those with diabetes mellitus and presents within 10 years of the onset of diabetes in more than 50% of patients with any type of diabetes[18].

According to the MMAS, the prevalence of ED in diabetic men was three times higher than that of non-diabetic men. Giuliano et al.[19], evaluated the patients who sought medical care for hypertension and/or diabetes. Erectile function was assessed by IIEF-5. Of the 7689 patients, 2377 men had diabetes and ED was present in 71%. They found higher prevalence (77%) of ED in men with both hypertension and diabetes. The largest study of the prevalence of ED in men with diabetes was undertaken by Fedele and his colleagues[20]. Among the 9868 Italian men, the overall prevalence was 35.8%, and increased with age, such that it was 4.6% in men in their 20s and 45.5% in men older than 60 years.

2. METABOLIC SYNDROME

The prevalence of obesity has increased in the last decade. Comorbidities of obesity include type 2 diabetes mellitus, hypertension, and lipid abnormalities, all of which contribute to cardiovascular disease (CVD) and may be associated with endothelial dysfunction and oxidative stress[21]. Also, obesity significantly contributes to insulin resistance and impaired glucose tolerance and plays an important role in the pathophysiology of insulin resistance[22]. MetS, which is also called insulin resistance syndrome or syndrome X includes glucose intolerance, insulin resistance, obesity, dyslipidemia and hypertension. The MetS has been defined by several expert groups including World Health Organization (WHO)[23], National Cholesterol Education Program’s Adult Treatment Panel γ (NCEP:ATP γ)[24], European Group for the Study of Insulin Resistance[25] and International Diabetes Federation (IDF)[26]. All above-mentioned groups agree on the essential components of MetS but differ in the detail and criteria. At this time, a final definition is awaited.

Since the presence of the MetS independently indicates increased risk of cardiovascular disease,
which is closely correlated with ED, several epidemiological data have identified MetS as potential risk factors of ED. Grover et al.[27] evaluated the effect of various cardiovascular risk factors on ED in a primary care setting. ED was found in 49.4% according to a score of less than 26 on the IIEF EF domain in a cross-sectional survey of 3921 Canadian men. The presence of diabetes (odds ratio 3.13), undiagnosed hyperglycemia (odds ratio 1.46), impaired fasting glucose (odds ratio 1.26) and the presence of MetS (odds ratio 1.45) was identified as an independent risk factor for ED. Bansal and associates[28] evaluated the specific criteria in 154 consecutive consultations for ED. Three out of five criteria for MetS were met in 43% of men with ED, as compared to a reported 24% in a general population. Gunduz et al. [9] examined the prevalence of MetS in 79 patients with coronary artery disease and lipid metabolism disorder. ED was diagnosed in 59 (74.7%) patients. In 38 patients with MetS, all had ED. Although ED was not correlated with cholesterol levels, combination of hypercholesterolemia, hypertension and obesity (BMI>30) was found to be independent risk factor for ED. Conversely, Esposito et al.[30] looked at the prevalence of ED in men with the MetS and age and BMI matched control group. Higher prevalence of ED (26.7%) was found in MetS group than control group (13%). They also noted the prevalence of ED increased as did the number of components of the MetS. Similar relationship was revealed by Bai et al.[31]. They revealed increased risk of ED according to the accumulating number of metabolic abnormalities. ED severity was also correlated with the number of components of MetS. In a clinical study conducted by Demir et al.[32], 89 out of 268 patients, who constituted the MetS group, had a significantly decreased IIEF EF domain score, and EF domain score significantly decreased with the increasing number of metabolic risk factors. A similar finding was shown by Bansal et al.[28]. In an Austrian cohort of 2371 men, the prevalence of MetS was 33.8% and the presence of MetS was turned out to be associated with decreased IIEF-5 score in a multiple linear regression analysis. In addition, they found significant relationship between ED and MetS only in men with 50 years old or older. However this is not always the case, Paick et al.[33] did not find a significant relationship between ED severity and MetS parameters, except hypertension, in impotent men suggesting that the relationship between MetS and ED severity may not be cut, or may be selective for certain components. Could the presence of ED be the predictor of future MetS? Prospective data from MMAS revealed the importance of BMI and the presence of 1 or 2 conditions of MetS for future prediction of MetS[34]. In addition, they stated that ED was predictive of the MetS in men with BMI less than 25 with an adjusted relative risk of 2.1. Accumulating evidence indicated a certain relationship between testosterone and MetS and/or type 2 diabetes. Kaplan et al.[35] found an inverse relationship between mean baseline total T levels and number of NCEP-ATP III components expressed in 864 men (mean age 52 years). In large cross-sectional analysis, Laaksonen et al.[36] provided the evidence of declining T levels in MetS, suggesting an inverse relationship between total T levels and odds ratios for having MetS in 1,896 non-diabetic men. Similar results have been reported by Rodriguez et al.[37], in analysis of the Baltimore Longitudinal Study of Aging where men were followed for a mean of 5.8 years. They confirmed in a longitudinal study what others have found in cross-sectional studies, in that the prevalence of MetS increased with age, and that this was associated with lower androgen levels. They also found that lower total T levels, along with lower SHBG levels, predicted a higher incidence of the MetS.

III. CLINICAL FINDINGS

1. DIABETES MELLITUS

In 12% of type 1 diabetic men, ED was the first symptom of diabetes[38]. Men with diabetes suffer ED 5-10 years earlier than age-matched control subjects[15]. Almost 100% of patients with diabetic neuropathy will have ED[39]. The diabetic men with peripheral neuropathy are likely to have ED due to increased undiagnosed coexisting autonomic neuropathy. The prevalence of coronary artery disease (20%) and peripheral vascular disease (5%) among men with diabetes is far higher than in the general population. Pathologic changes in the cavernous arteries[40], ultrastructural changes in the cavernous smooth muscle[41], and impaired endothelium-dependent relaxation of the corporeal smooth muscle[42] have been noted in penile specimens from diabetic men with ED. Hirshkowitz and associates[43] reported that impotent men with diabetes have fewer sleep-related erections, shorter tumescence time, diminished penile rigidity, decreased heart rate response to deep breathing, and lower penile blood pressure than age-matched non-diabetic men. Current literatures support the idea that the presence of ED in diabetic patients could be the harbinger of fatal cardiovascular disease. Gazzaruso et al.[44] demonstrated that higher prevalence of ED in diabetic patients with silent coronary artery disease than those without any evidence of myocardial ischemia. The presence of ED was associated with more than 14 times higher risk for silent coronary artery disease in diabetic men. In the subsequent study, the same authors reported that ED was associated with higher major cardiovascular morbidity and mortality in diabetic patients with silent coronary artery disease[44]. This evidence indicates the presence of
ED in diabetic patients could predict the future major cardiovascular events.

What is the importance of glycemic control? Bodie et al.[45] assessed laboratory abnormalities for 3,547 men with ED and found that a large number of men presenting with a primary complaint of ED had elevated HbA1c levels. Also, HbA1c levels have been shown to increase with the severity of ED[46;47] and was found to be an independent predictor of the EF score in 78 men with diabetes type 2[15]. Thus, it is likely that adequate glycemic control could reverse ED. However, there have been conflicting results about the beneficial effects of strict glycemic control on the erectile function. Some studies reported improved erectile function following the reduction of HbA1c, while others reported no significant change despite the aggressive blood sugar control. Further well-designed prospective study will clarify this issue.

Hypogonadism is often associated with diabetic ED patients. Corona et al.[48] investigated the presence of hypogonadism in 1200 men with ED and 16% had diabetes mellitus. Hypogonadism was found in 24.5% of men with diabetes, versus 12.6% in the rest of the sample. The authors also found a relationship between the prevalence of hypogonadism in 1,027 diabetic and non-diabetic patients presenting with ED. With diabetics having a significantly greater prevalence of hypogonadism, especially in the sixth decade of life compared to non-diabetics, diabetics had a significantly increased prevalence of hypogonadism than did non-diabetics[49].

The PDE5 inhibitors have revolutionized the management of ED and oral drug therapy is currently first-line therapy for this condition. These agents act by potentiating the action of intracavernosal NO, thereby leading to a more sustained erection. It is often said that diabetic ED patients are difficult-to-treat population with current PDE5Is. There have been studies suggesting that T supplementation in human diabetics with ED receiving pharmacological treatment might be advantageous in the diabetic men in whom PDE5I given for ED do not work. Kalinchenko et al.[50] assessed diabetic ED patients and found that different baseline T levels in these patients determined a differential response to sildenafil. Responders typically had a total T value of 18.6±1.2nmol/L, while non-responders had a total value of 6.9±1.3 mmol/L. The authors found that co-administration of oral T with sildenafil reverses ED in those who showed insufficient response to sildenafil alone.

In addition to lower baseline T level, glycemic control was associated with the response to PDE5Is. Park et al.[51] found that uncontrolled diabetes was one of a predictors of a poor response to sildenafil in 162 consecutive elderly ED patients (mean age 64.1 yrs). Fonseca et al.[52] also showed that the efficacy of tadalafil treatment in 519 diabetic patients was a function of glycemic control. The authors found that though this treatment had a significant benefit in all HbA1c ranges, there was a downward trend of drug efficacy with increasing HbA1c values.

2. METABOLIC SYNDROME

MetS and increased waist-to-hip ratio have been associated with a higher proportion of moderate to severe ED in men older than 50 yr[53]. Conversely, ED may be predictive of MetS presence in men with a body mass index (BMI) of <25 kg/m[2.34] This interesting finding suggests that ED may be a warning sign for MetS in men otherwise considered at low cardiovascular risk.

Studies indicate the possible role of inflammation and endothelial dysfunction in the development of ED for patients with MetS. Men with MetS had an increased prevalence of ED, reduced endothelial function score, and higher circulating concentrations of hsCRP compared with men without metabolic disorders[30]. Another interesting study revealed higher circulating hsCRP levels in obese men with ED as compared to obese men without ED and erectile function score was negatively associated with BMI, waist-to-hip ratio, and hsCRP[54]. These 2 studies clearly showed the relationship between MetS, the inflammatory-endothelial activation and the prevalence of ED.

As mentioned earlier, low circulating androgen levels are clearly a risk factor for MetS and the reverse relationship is true as well. ED might occur as a possible consequence of hypogonadism and MetS. A recent study by Zhody et al.[55] elegantly related hypogonadism to ED and MetS by analyzing BMI measurements in 158 obese men. A significant statistical association was found between increasing BMI and the following parameters: systolic blood pressure, serum T, penile duplex parameters, TG, HDL, and LDL. With increasing BMI, the frequency of hypogonadism and ED increased, while total serum T showed a strong negative correlation. To assess the effect of BMI on vasculogenic ED, the authors examined this relationship in the absence of other risk factors and found that for a BMI<25, 3 out of 13 men (23.1%) had vasculogenic ED as compared to 32 out of 54 men (59.3%) with a BMI≥25.

What about the effect of testosterone treatment on MetS and ED? Makhida et al.[56] argued that hypogonadism is a central feature of the MetS and that testosterone treatment, in addition to restoring eugonadal hormone concentrations, is of a beneficial impact on the MetS itself, slowing the progression to diabetes and CVD. It is interesting that testosterone therapy might ameliorate components of the MetS and decrease cardiac risk because for many years testosterone was thought to be the factor that produced earlier cardiac disease in men versus women. A recent meta-analysis by Haddad et
al.[57] confirmed that T therapy does not carry any increased risks of cardiovascular events. In fact there is evidence to suggest that low T levels are associated with coronary artery disease [58]. As opposed to Maksida’s argument, Chen et al. [59] argued that although total T levels are inversely related to the likelihood of having MetS, it does not have a role in the development of type 2 diabetes. Moreover, Basu et al.[60] treated elderly men with T for 24 months, and did not observe any improvement in carbohydrate metabolism or insulin secretion and/or action. Therefore, despite the established relationship between hypogonadism and MetS, there is no consensus that T therapy will correct the components of MetS.

Can treating MetS improve ED? Currently, no direct pharmacologic therapy for MetS is available. In contrast, lifestyle change, including dietary changes and exercise leading to weight loss, are the cornerstones of therapy. Esposito et al.[61] assessed the effect of weight loss and increased physical activity on men with ED and endothelial dysfunction associated with obesity. BMI decreased significantly in the intervention group compared with usual-care controls. Weight loss was associated with a decrease in serum concentrations of interleukin-6 and CRP. Erectile function scores improved significantly with lifestyle intervention but remained stable in the control group. A significant proportion of men in the intervention group reported a return of normal sexual function. In multivariate analyses, changes in BMI, physical activity, and CRP were independently associated with improvement in erectile function. Thus, lifestyle changes are associated with improvement in sexual function in obese men with ED, while simultaneously improving endothelial function and markers of inflammation.

IV. BASIC SCIENCE MECHANISMS

The majority of basic science studies to date that examine mechanisms of diabetic-ED have done so using animal models of type 1 diabetes. Available studies outlining ED in animal models of type 2 diabetes and MetS have recently been reviewed[3]. An overview of these studies is outlined below.

1. NITRERIC DYSFUNCTION

Erection is activated by NO release from nNOS at NANC nerve terminals. Maintenance of cavernosal vasodilation is thought to occur through the activation of eNOS in endothelial cells, presumably in response to shear stress. Impaired vasodilatory signaling often results from NANC nerve dysfunction and/or endothelial dysfunction, leading to ED. Various studies in animal models of type 1 diabetic-ED support the presence of dysfunctional or altered dilatory signaling. Numerous studies have demonstrated streptozotocin-induced type 1 diabetic rodents and alloxan-induced type 1 diabetic rabbits to have impaired cavernosal relaxation to electrical field stimulation as well as decreased ICP following electrical cavernosal nerve stimulus, indicative of nitreric dysfunction[62-68]. However, although nitrergic dysfunction is established to play a key underlying role in type 1 diabetic-ED, the contribution of impaired nerve signaling to ED in the context of type 2 diabetest in animal models is unclear. In type 2 diabetic, BBZ/WOR mice, a trend toward decreased penile nNOS content was detected[69]. Using immunofluorescent staining, Kawano et al. demonstrated a decrease in nNOS in dorsal nerves in OLETF rats[70]. Similarly, Xie et al. found a decrease in penile nerve fiber nNOS staining evaluated nicotinamide adenine dinucleotide (NADPH)-diaphorase staining of corporal tissue, in high fat diet-fed mice[71]. Recent studies assessing cavernosal vasodilation in response to electrical field stimulus have demonstrated significantly decreased nitrergic-mediated relaxation in type 2 diabetic, db/db mice[72]. However, the extent of the impaired relaxant response was modest, leading the authors to question the true pathophysiologic relevance of this finding to the ED phenotype.

2. ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction is characterized by a decrease in NO bioavailability resulting from decreased endothelial nitric oxide synthase (eNOS) expression or activity, or increased NO scavenging. A study by Jesmin et al. demonstrated lower expression of penile eNOS protein and mRNA in OLETF rats[73]. Additional to decreases in eNOS expression, the activation of eNOS is itself a highly regulated process[6]. eNOS can be activated by hemodynamic stimuli, such as shear stress, as well as through protein signaling, such as that mediated by acetylcholine or vascular endothelial growth factor (VEGF). Both shear flow and VEGF signaling have been demonstrated to lead to eNOS phosphorylation on ser1177, an event associated with increased enzymatic activity. This phosphorylation event is mediated by the serine-threonine protein kinase Akt, and is thought to be relevant for penile erection[74]. In addition to phospho-regulation of eNOS, enzyme activity and subsequent NO production are also regulated by substrate concentration, co-factor availability and enzyme coupling. Although proper activation of eNOS is established to play a role in penile erection, the relevance of dysfunctional eNOS enzyme regulation remains relatively speculative in regards to diabetic-ED, and is reviewed by Musicci et al. [6]
strated attenuated relaxation to acetylcholine in cavernosal tissue from high fat diet-fed mice and Zucker obese-diabetic rats, respectively. Luttrell et al., found a similar impairment of endothelium-dependent dilation of penile tissue from another mouse model of type 2 diabetes, the db/db mouse. This mouse has a genetic mutation of the leptin receptor, resulting in the spontaneous development of hyperglycemia, obesity and insulin resistance by 2 months of age[72].

3. OXIDATIVE STRESS

Increased reactive oxygen species (ROS) and inflammation can result from prolonged hyperglycemia and may result in scavenging of NO. Chronic hyperglycemia induces free radical production through formation of advance glycation end-products (AGE), lipid peroxidation, polyol pathway activation, superoxide production and activation of protein kinase C[76]. AGE production can stimulate cytokine expression on monocytes and macrophages as well as upregulate endothelial adhesion molecules which induce vascular damage[77]. The resultant decrease in bioavailable NO is characteristic of endothelial dysfunction in conditions ranging from ED to atherosclerosis. Increased penile and serum AGE levels have been detected in STZ-induced rats. Further, treatment with a cross-link breaker, ALT-711, or aminoguanidine (which prevents AGE formation) attenuated the impairments in neurogenic and endothelial-mediated cavernosal relaxation in the type I diabetic mice[78;79]. Elevated ROS is also demonstrated in men with ED as well as in animal models of type 1 diabetes. Various studies have reported elevated superoxide in penile tissue from STZ-treated rodents and alloxan-treated rabbits. Further, impairments in acetylcholine and neurogenic-induced relaxation in these models was prevented with treatment with superoxide dismutase or a peroxynitrite decomposition catalyst, supporting a delirious role of oxidative stress in type I diabetic ED[80-82].

Despite evidence suggesting a role of elevated oxidative stress in ED associated with type I diabetes in men and animal models, data examining the role of oxidative stress in animal models of type 2 diabetes or MetS are scant. Decreased antioxidant levels may result in elevated ROS and oxidative stress in type 2 diabetic patients. Glutathione (GSH), an important cell antioxidant, acts as an electron donor to decrease ROS, as well as a cofactor for NOS-mediated NO synthesis. Depressed GSH levels may contribute to decreased NO synthesis. Kovanez et al. measured glutathione/glutathione disulphide (GSH/GSSG) ratio in Zucker diabetic fatty rats as an estimate of oxidative stress levels[83]. They found prolonged treatment with pioglitazone, a PPARg agonist said to have anti-inflammatory effects, to improve (although not normalize) the GSH/GSSH ratio[83], suggesting that glyemic stabilizing agents may have some additional benefit in decreasing damaging ROS agents.

Elevated plasma homocysteine levels are speculated to be a novel risk factor for the development of ED[84]. Homocysteine-induced vascular injury can occur through direct endothelial damage, impaired nitric oxide production, free radical formation, and platelet activation[85]. The exact mechanism in which hyperhomocysteinemia contributes to ED is unclear but appears to involve oxidative stress and superoxide formation. Jones et al. examined cavernosal vasoreactivity in rabbits made hyperhomocystenic by treatment with a methionine-supplemented diet. Cavernous from these rabbits demonstrated an impaired endothelium-dependent relaxation response to carbachol which was reversed by treatment with the superoxide scavenger, superoxide dismutase, or catalase[86].

4. CAVERNOSAL HYPERCONTRACTILITY

Increased contractile function of the cavernous can result from heightened sympathetic activation or potentiated intracellular contractile signaling of smooth muscle cells. Many animal models of diabetic-ED have pointed to cavernosal hypercontractility as a pertinent mechanism underlying the disease phenotype. A recent review extensively outlines potential pro-signaling pathways in the penile smooth muscle cell that may contribute to diabetic-ED[7].

A study by Carneiro et al. suggested the presence of increased sympathetic overactivity in type II diabetic-ED[87]. Contractility was measured in response to electrical field stimulation with the addition of inhibitors of NANC and parasympathetic nerves or to direct activation with phenylephrine[87]. Heightened contractility was detected in the db/db mouse in response to electrical field stimulation but not to phenylephrine, suggesting sympathetic overactivity as the cause. However, Luttrell et al., found increased contraction in cavernous from db/db mice in response to both sympathetic nerve activation with electrical field stimulation, as well as direct contractile activation with phenylephrine, when normalized to penile weight[72]. This study agrees that increased contractile signaling in present in db/db cavernousum, but suggest that this is mediated by penile smooth muscle, and not solely heightened sympathetic nerve activity.

Wingard et al. recently examined the mechanism underlying heightened contractile signaling in the type 2 diabetic rodent[75]. Using the Zucker obese diabetic rat, they detected potentiated cavernosal contraction to both phenylephrine and endothelin-1. They further delineated this increased contractile signaling to be due to overactivity of protein kinase C and Rho-kinase, two primary kinases mediating smooth muscle cell tone.

RhoA/Rho-kinase signaling promotes smooth muscle contraction through a calcium sensitizing mechanism, mediating contraction in response to adren-
ergic agonists and endothelin-1. The inhibition of Rho-kinase activity is sufficient to induce an erectile response in rodents, demonstrating the importance of this pathway in the maintenance of penile flaccidity[3]. Various studies have demonstrated increased RhoA/Rho-kinase expression and signaling in type 1 diabetic animals, as well as an enhanced sensitivity to Rho-kinase inhibition[88-90]. These data suggest that abhorrent elevations in RhoA/Rho-kinase signaling may contribute to diabetic-ED via an overly heightened smooth muscle tone. Other activators of smooth muscle contraction may be potentiated in diabetes as well[7], however, their exact contribution to the disease phenotype remains to be delineated.

5. VENO-OCCCLUSIVE DYSFUNCTION

The limiting of blood outflow through mechanical compression of the emissary veins against the tunica albuginea is essential for the maintenance of elevated corporal pressures and a rigid erection. Various studies in animal models of type 2 diabetes have suggested that a veno-occlusive disorder may underlie the ED phenotype. Kovanez et al. examined veno-occlusive function in the Zucker diabetic fatty rat by monitoring intracavernosal pressure changes during and following saline infusion[83]. They found the diabetic rats to have an inability to sustain adequate intracorporal pressure after the cessation of penile saline infusion, suggesting the presence of a veno-occlusive disorder. These studies have recently been validated in the db/db mouse model of type 2 diabetes[72]. The db/db mice demonstrated both an inability to sustain maximal intracorporal pressure in response to electrical stimulation of the cavernosal nerve, as well as an inability to sustain elevated pressures after cessation of exogenous saline infusion[72]. The study by Kovanez et al. further demonstrated that prolonged treatment with peroxisome proliferator-activated receptor γ (PPARγ) antagonist, pioglitazone, improved the veno-occlusive function in the diabetic fatty rats, suggesting a possible pathway for disease treatment[83].

Structural, matrix, or cellular content changes may underlie impaired veno-occlusive function. Various studies in animal models of type 2 diabetes have revealed altered cavernosal collagen expression and smooth muscle/collagen ratio[71;72;83]. Recently, elastin, an extracellular matrix component in sinusoids and the tunica albuginea, was reported to be decreased in the cavernosum of db/db mice[72]. Consistent with the reduced elastin content, decreased mRNA expression for tropoelastin, a precursor of elastin, and fibrillin-1, a scaffold protein, were also detected in cavernosum from db/db vs. control mice[72]. It is tempting to speculate that structural alterations in the tunica albuginea in type II diabetics may lead to altered distensibility of the corpora required for veno-occlusion and the maintenance of ICP.

Elevated levels of pro-apoptotic proteins such as caspase-3 and decreased expression of anti-apoptotic proteins such as Bcl-2, have been associated with decreased VEGF expression. This suggests that decreased VEGF in type 2 diabetic penile tissue may result in increased apoptosis and loss of erectile cells[73]. Jesmin et al. found decreased VEGF expression and increased expression of apoptotic markers in the Otsuka Long-Evans Fatty (OLETF) rat[73]. Decreases in cavernosal endothelium-dependent dilation, along with an abnormal endothelial cell number and smooth muscle/collagen ratio, have been observed in conjunction with lowered VEGF expression in the high cholesterol-diet fed mouse[91]. In this same model, Further, Xie et al. found treatment with basic fibroblast growth factor, to improve endothelium-dependent cavernosal vasoreactivity in a rabbit model of hypercholesterolemia[92]. Karaboga et al. found alterations in cavernosal smooth muscle actin in a rabbit model of chronic hypercholesterolemia to be irreversible, suggesting the potential importance of prevention, and not just treatment, strategies for erectile health[93].

V. CONCLUSIONS

The numbers of patients with type 2 diabetes and MetS continue to rise. It is clear that organic ED in these cohorts is underlined by multifaceted, complex mechanisms, involving nerve, vascular, and hormonal signaling at its core. Current pharmacologic treatments remain insufficient for these populations, and the need for improved therapeutics is evident. For example, combination therapies with PDE5 inhibitors and antioxidants or androgen replacement may be a promising. However, it is clear that more clinical and basic science studies are warranted.

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I. INTRODUCTION

Adequate vascular function is essential for erectile function. Vascular system is responsible for providing blood supply to the erectile tissue sufficient for allowing the corporo-veno-occlusive mechanism required for erection. Thus, any alteration of the vascular system may compromise erectile function. In 1940, the French surgeon René LeRiche associated the aorto-iliac obliteration with impotence when observed that a majority of patients, even young, with occlusive arterial disorders at the bifurcation of the aorta into the two major arterial trunks of the common iliac arteries presented “inability to keep a stable erection, the blood being insufficient to fill the spongious processes” [1,2]. The cause for erectile dysfunction in these patients can probably be ascribed to the presence of a flow limiting stenosis caused by atherosclerotic lesions in the large artery. This is associated with a reduced blood flow to corpus cavernosum during erection.

Although vascular disease in arteries supplying the penis obviously impedes erectile function by limiting blood flow, systemic vascular dysfunction is also intimately related to erectile dysfunction (ED). Cardiovascular disease shares with ED the same risk factors, namely hypertension, hypercholesterolemia, diabetes and smoking [3,4]. In addition, ED is highly prevalent in patients with cardiovascular diseases [5,6], suggesting that ED is another manifestation of vascular disease [7]. In fact, ED is actually considered a sentinel symptom of silent generalized cardiovascular disease.

II. ATHEROSCLEROSIS / VASCULAR ISCHEMIA AND ERECTILE DYSFUNCTION

There are a huge number of studies demonstrating the association of erectile dysfunction to systemic vascular diseases. On one hand, there is a high prevalence of erectile dysfunction in patients having, coronary artery disease (CAD) [8-10], peripheral arterial disease [11,12] and cerebrovascular disease [13,14]. In addition, the prevalence of ED seems to be increased as the severity of vascular disease augments. This is shown in a study where prevalence of ED was evaluated in 285 patients with CAD divided into groups depending on the burden of atherosclerotic lesions. Prevalence of ED was higher in patients with acute coronary syndrome presenting stenosis in more than one coronary vessel (55%) than that in patients having only one vessel affected (22%, not different to controls). The prevalence of ED was further elevated in patients with chronic coronary syndrome (65%) which is due to significant coronary stenosis frequently involving multiple arteries and sites [15]. In agreement with these observations, patients with significant lesions (a stenosis rate >50%) in two or more coronary arteries had worse erectile function, measured by using the Sexual Health Inventory for Men (SHIM) score, than patients with normal coronary arteries or single-vessel CAD, appearing SHIM score as an independent parameter to define the presence of significant lesions in two or more coronary arteries [16].

On the other hand, cardiovascular diseases are prevalent among patients with ED. In fact, early asymptomatic vascular disease has been detected in men complaining of ED. Coronary artery disease has been revealed in patients reporting ED without any other symptomatology of vascular disease. A prospective study in 50 patients with ED revealed that 19% of them presented silent, asymptomatic CAD, as detected by angiography [17]. Similar results had been previously obtained in 58 patients with ED. In this study, 24.1% of patients were diagnosed with symptomatic or asymptomatic ischemic heart disease, being peak systolic velocity in the cavernous artery a predictive factor of ischemic heart disease in ED patients [18]. ED has also associated to the presence of peripheral atherosclerotic lesions. Among 238 patients with ED, 66.4% presented atherosclerotic lesions, while among 52 age-matched patients without ED lesions were only present in 36.5% of them. An elevated prevalence of femoral (40.3% vs 11.5%) and carotid (25.2% vs 9.6%) plaques was also detected in ED patients [19]. These observations led to consider ED as an early manifestation of generalized vascular disease. ED symptoms were found to precede CAD symptoms in 58 to 67% of the patients [8]. In fact, in patients with chronic coronary syndrome complaining of ED, symptoms appeared prior to CAD detection in 93% of cases [15]. ED is manifested before other signs of vascular disease because penile artery diameter is smaller (1-2 mm) than the coronary (3-4 mm), carotid (5-7 mm) or femoral (6-8 mm) artery, then the symptoms caused by atherosclerosis in penile vasculature appear earlier [20,21]. A plaque with sufficient size to cause the blockage of blood flow through the penile artery and ED, would produce only 30-40% stenosis in arteries of larger diameter [22]. Thus, ED would be a sentinel symptom that warns of a probable underlying systemic vascular disease [23]. This consideration impacts the clinical management of patients presenting
with ED for prevention of potential life-threatening events, especially when other vascular risk factors are present.

The development of animal models of atherosclerosis has provided key evidences demonstrating the marked impact of atherosclerotic vascular disease on erectile function and proposing pathophysiological mechanisms. A rabbit model was firstly developed where atherosclerotic lesions were induced by balloon-deendothelialization of the iliac arteries and feeding a cholesterol- and triglyceride-rich diet. Most of animals (93%) having 50% or greater luminal occlusion of the iliofemoral arteries presented vasculogenic erectile dysfunction [24]. The erectile dysfunction in these animals can probably be ascribed to both a limited iliac blood flow and corporal veno-occlusive dysfunction due to a decreased expandability of the trabecular smooth muscle [25,26]. The authors have later demonstrated in the same animal model that chronic ischaemia provoked by stenosis of the proximal iliac artery is also associated with functional changes in the distal part of the penile vasculature such as decreased NOS activity, reduced endothelium-dependent and neurogenic NO-mediated relaxation in cavernosal tissue [27,28]. NO inhibits endothelial eicosanoid and superoxide production [29]. This observation may explain that in the rabbit model the impaired NO formation is associated also with increased production of contractile thromboxane and prostaglandin formation and potentiation of neurogenic contractions of the cavernosal smooth muscle [27,28]. Further studies demonstrated a time-dependent reduction of the expression of nNOS and eNOS in the cavernosal tissue from these animals, while a parallel increase of the expression of iNOS was also observed [30]. The above-mentioned studies, although extensive are concerned with the combined effect of hypercholesterolemia and ischaemia and do not allow to distinguish the influence of chronic ischaemia alone on the erectile apparatus. However, the reduced NOS activity has been confirmed in a rabbit model of cavernosal ischemia induced by surgical occlusion of iliac arteries [31]. In this model, decreased NOS activity was accompanied by impaired endothelium-dependent and neurogenic NO-mediated relaxation of ischemic cavernosal tissue. An elevation of the cavernosal content of endogenous inhibitors of NOS was proposed to be responsible for these effects [31].

On the other hand, a rabbit model where a long-term (80 weeks) but low-level (0.3%) cholesterol-enriched diet was administrated demonstrated the generation of atherosclerotic lesions without previous de-endothelialization of iliac arteries and the development of vasculogenic ED [32]. However, ED was only manifested in rabbits showing severe atherosclerosis but not in those presenting only moderate atherosclerosis. In fact a significant negative correlation between intima/media ratio of iliac arteries and erectile responses was observed [32]. The apolipoprotein E knockout mouse, a known experimental model of atherosclerosis, develops an impairment of erectile responses at 26 weeks of age (the first age evaluated) after receiving a Western type diet (0.15% cholesterol plus 42% milk fat) starting at 4 weeks of age. This reduction of erectile responses was accompanied of manifested atherosclerotic lesions in the aorta [33]. These mice, fed with 1.5% cholesterol diet, at earlier ages also show reduced endothelium-dependent and endothelium-independent relaxations, and impaired NO/cGMP pathway, while cavernosal tissue presented structural alterations [34].

As mentioned above, hyperlipidemia is a risk factor for ED. Association of ED to hyperlipidemia has been found in several clinical studies. In ED patients, a positive correlation between high LDL and cavernosal venous insufficiency was found [35]. When blood levels of different lipid fractions were determined in 943 patients with ED and 242 patients with no ED aged over 40 years, the incidence of abnormally elevated levels of LDL was significantly higher in patients with ED. There were no differences regarding total cholesterol, triglycerides or HDL but the incidence of hyperlipidemia, defined as more than one elevated lipid fraction, was also significantly higher in ED patients [36]. In a prospective study including 315 patients (215 with ED), logistic regression of data showed that low levels of HDL were predictive of ED, with no significant differences in triglycerides or LDL [37]. However, a case-control study with 100 patients in each arm, revealed a significant increase in total cholesterol and LDL in ED patients [38]. Hypercholesterolemia at baseline was also shown as a predictor of ED 25 years later in 570 patients included in the Rancho Bernardo Study [39], while high incidence of previously undiagnosed hypercholesterolemia (40%) and hypertriglyceridemia (28%) was observed among patients attending consultation for ED [40]. On the other hand, a pilot study showed that patients with pure hypertriglyceridemia displayed ED prevalence values (42.9%) higher than those obtained in men with normal cholesterol (24.2%) or even with pure LDL elevation (29.4%), although the low number of patients precluded a significant result [41]. In contrast, a survey of 1,899 men aged 30-79 in Boston area revealed the absence of association of untreated hyperlipidemia and ED [42]. In conclusion, although several evidences suggest an association of ED and dyslipidemia, there is no consistency in the involvement of the different lipid fractions, and a more precise analysis of this condition as independent risk factor for ED is still required [43].
With respect to a feasible pathophysiological mechanism, hypercholesterolemia appears to have an effect “per se” on the vasculature. Oxidized low density lipoproteins (ox-LDL) inhibit the endothelium-dependent NO-mediated relaxations in rabbit large arteries [44], but this does not appear to be the case in small systemic arteries [45] or the trabecular smooth muscle [46]. In the latter study the lipoproteins did not interfere with the NO/cGMP-pathway, but ox-LDL induced contractions [46], and these contractions are probably mediated through increases in intracellular inositol phosphate and calcium [47]. In contrast, chronic hypercholesterolemia reduces endothelium-dependent relaxations, but not the endothelium-independent relaxations in the corpus cavernosum [48-50]. In contrast to the endothelial NO/cGMP-pathway, the neuronal vasodilation does not appear affected in hypercholesterolemic rabbits [28]. The selective affection of the endothelial NO/cGMP-pathway in hypercholesterolemia could be ascribed to an increased superoxide production [50]. Superoxide could result from enhanced NADPH oxidase activity, since the inhibition of this enzyme improves endothelium-dependent relaxation of cavernosal tissue from rabbits fed with 1% cholesterol for 8 weeks [51]. L-arginine supplementation reverses the impairment of the endothelium-dependent relaxations [28], and this observation supports that increased endogenous production of NOS inhibitors contributes to endothelial dysfunction. In fact, increased plasma levels of asymmetric dimethyl arginine (ADMA), an endogenous inhibitor of NOS, has been detected in rats after 5 months of 2% cholesterol diet. At the same time, these rats displayed erectile dysfunction and systemic endothelial dysfunction [52]. Vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) are two key angiogenic factors which promote endothelial cell proliferation and are involved in the processes of endothelial repair and neovascularization after vascular injury. These growth factors also influence NO production. VEGF and VEGF receptor 2 (VEGFR-2) are downregulated in corporal tissue of rats eating a 4% cholesterol diet [53]. mRNA levels of VEGF were also reduced in rabbits fed with 1% cholesterol diet. This reduction preceded the impairment of endothelium-dependent relaxation [54]. The involvement of an unbalance of angiogenic factors in the pathophysiology of hyperlipidemia-induced ED was supported by the improvement of endothelial relaxation of cavernosal tissue from hypercholesterolemic rabbits after intracavernosal administration of VEGF and FGF-2 [55,56]. FGF-2 administration also induced the expression of VEGF as well as increased the expression of nNOS and the phosphorylation of eNOS at Ser 1177 (the most active form) [56]. Gene transfer of VEGF and angiopoietin-1 (other angiogenic factor) restored erectile responses in hypercholesterolemic rats, increasing eNOS phosphorylation and cGMP accumulation in cavernosal tissue [57].

These pathophysiological mechanisms suggest that hypercholesterolemia could alter the NO/cGMP pathway and induce endothelial dysfunction that would result in erectile dysfunction. However, since hypercholesterolemia is used for developing atherosclerosis in animal models, further studies must clarify if these mechanisms are specifically attributed to hypercholesterolemia or to ischemic vascular disease.

On the other hand, the pharmacological treatment of hyperlipidemia with statins was thought to be associated with an increased risk for erectile dysfunction [58,59]. However, in large study with 4444 patients with coronary heart disease treated with simvastatin or placebo for up to 6 years, the frequency of ED was not associated to the treatment with simvastatin [60]. Therefore, in patients treated with statins an underlying diseased vasculature rather than the drug appears the cause of erectile dysfunction. In fact, lipid-lowering therapy in hypercholesterolemic patients improves systemic endothelium-dependent vasodilatation probably due to an increased bioavailability of NO [61,62]. In nine patients with hypercholesterolemia as the only risk factor for ED, the correction of elevated cholesterol levels with atorvastatin improved erectile function [63], while in 25 patients with similar characteristics, combined administration of atorvastatin enhanced the IIEF score increase induced by sildenafil [64]. This suggests that the dysfunction of the endothelial NO/cGMP-pathway in hypercholesterolemia is reversible. However, atorvastatin has been reported to augments the number of patients recovering erectile function after prostatectomy which were also treated with sildenafil. Interestingly, these patients were not hyperlipidemic [65].

IV. HYPERTENSION AND ERECTILE DYSFUNCTION

Hypertension is an independent risk factor for development of erectile dysfunction [3,66,67]. In fact a high prevalence of hypertension has been found in ED patients. The analysis of a representative care claims database identifying 273,325 patients with ED in the US, revealed that the prevalence of hypertension in this ED population was as high as 41.6% [68]. In a further analysis, using a similar approach evaluating 285,436 men with ED and 1,584,230 men without ED, prevalence of hypertension in ED patients was more than twice the prevalence of hypertension in men without ED (41.2% vs 19.2%, respectively) [69]. Conversely, a high prevalence of ED is generally observed in hypertensive patient populations. Although, some former studies reported low presence of ED in hypertensive patients (14.4%) [70] and similar prevalences of ED in normotensive and hypertensive patients [71,72], the majority of the
evidences have revealed an elevated prevalence of ED in hypertensive men from different geographic areas [73-78].

However, hypertension is a risk factor not only for ED but also for cardiovascular disease. Then, the impact of hypertension on erectile function is contributed by the cardiovascular complications following hypertension, such as ischaemic heart disease and renal failure which are associated to even higher prevalence of ED [3,67,79]. Age, body mass index (BMI), hormonal profile, penile arterial flow, risk factors for arterial disease, and the presence of neurological and psychological abnormalities were evaluated in 32 consecutive hypertensive and 78 normotensive impotent men [80]. The overall analysis showed little differences between hypertensive and normotensive men with the exception that hypertensive men had marginally higher rate of ischaemic heart disease (P=0.06) and lower testosterone levels [80]. Other studies have also detected lower levels of serum testosterone in hypertensive patients [81,82], a fact that could be relevant to the development of ED in these patients. In fact, sexual activity correlated with testosterone levels in both hypertensive and normotensive patients [83].

The potential determinants for ED in hypertensive population have been investigated. In a sample of 358 patients with essential hypertension, ED was associated to older age, longer duration of hypertension and a more severe hypertension. ED was also related to the antihypertensive therapy [75]. Other revealed determinants for ED in hypertensive patients (52 with ED and 34 with normal erectile function) were the presence of subclinical atherosclerosis, the impairment of arterial function, systemic inflammation and higher levels of the endogenous inhibitor of eNOS asymmetric dimethylarginine (ADMA) as a possible marker of endothelial dysfunction [84].

Blood pressure control is tuned by key physiologic systems that act at central and peripheral levels and involve CNS pathways, hemodynamic processes, hormones, neurogenic factors and vascular factors. Hypertension likely results from alteration or disbalance of any of these processes. Since pathways controlling blood pressure are also key for erectile physiology, the alteration resulting in hypertension could also results in ED.

Experimentation with animal models of hypertension has brought light to the mechanisms related to ED in hypertension. Erectile function, evaluated by measuring intracavernosal pressure expressed as percentage of mean arterial pressure (MAP), which is the usual way to express erectile responses in animal models, was reported to be decreased in stroke prone-spontaneously hypertensive rats (SHR-SP) and DOCA-salt hypertensive rats, although the absolute increases in intracavernosal pressure did not appear very different [85,86]. Other studies showed ICP tracings that reveal moderately reduced ICP increases to cavernosal nerve stimulation in spontaneous hypertensive rats (SHR). These responses were markedly inhibited in SHR after normalization by MAP [87,88]. SHR also presented reduced endothelium-dependent relaxation and NO-donor-induced relaxation of cavernosal smooth muscle, being the impairment of endothelial relaxation mediated by prostanoïd products [87]. The longitudinal study of erectile responses in SHR rats showed that the reduction of ICP/MAP responses preceded the development of hypertension. This study also revealed that cavernosal endothelium-dependent and NO-donor-induced relaxations occurred before systemic vascular alterations were manifested [88]. This suggests that erectile tissue is at the front line of the development of endothelial dysfunction and would be an early target end organ.

Neurogenic relaxation of cavernosal tissue could also be affected by hypertension since these responses have been reported to be reduced in SHR. This impairment would involve not only a reduction of NO-mediated relaxation but also a reduced relaxation mediated by carbon monoxide neurotransmission [89]. Treatment of SHR with several anti-hypertensive agents improved neurogenic relaxations. Amlodipine enhanced NO-mediated relaxation and NO-derivatives and cGMP in cavernosal tissue after electrical field stimulation (EFS), while hydralazine potentiated CO-mediated relaxation [90]. However, both NO- and CO-mediated neurogenic relaxations were enhanced by treating SHR with the antioxidant, α-tocopherol. The antioxidant caused an increase of EFS-induced cGMP accumulation in cavernosal tissue but also produced an improvement of endothelium-dependent relaxation [91]. This suggests that oxidative stress may play a significant role in the alterations caused by hypertension on erectile function. In fact, an augmented production of superoxide anions could result from increased activity of NADPH-oxidase driven by angiotensin II [92].

In addition to these functional alterations of erectile physiology, it has been revealed that hypertension also induce structural modifications of erectile tissue. SHR show hyperproliferation of smooth muscle in cavernosal tissue and penile vasculature, which correlates with blood pressure values. Increased fibrosis was also observed [93]. Ultrastructural studies of cavernosal tissue of SHR also revealed mitochondrial damage in smooth muscle and endothelial cells and neurodegeneration [94]. Hypertension-induced alterations were improved after antagonism of type 1 angiotensin II receptors (AT1) [95,96]. AT1 blockade was also related with increased endothelial nitric oxide expression in sinusoidal endothelium [97]. In fact, the impact of hypertension on erectile structures is effectively prevented by long-term administration of sildenafil only when combined with an AT1 blocker. This combined treatment also improved
with more efficacy the endothelium-dependent relaxation of cavernosal tissue in SHR [98]. The interaction of PDE5 inhibition and the inhibition of renin angiotensin system has also been demonstrated in the renal vasculature of SHR [99]. Although the blockade of β1-adrenergic receptors with atenolol did not prevent hypertension-induced alterations of penile structures [95], other selective β1-blocker, nebivolol, reduced smooth muscle proliferation and collagen deposition in penile tissue of SHR and improved endothelial relaxation [100]. Nebivolol has been demonstrated to cause NO-dependent vasodilation [101] and augment NO production in corpus cavernosum in mice [102]. These results suggest that the alterations caused by hypertension in erectile structures of SHR would be related to increased angiotensin II and reduced NO availability, although confirmation in other models of hypertension should be required.

V. CIGARETTE SMOKING AND ERECTILE DYSFUNCTION

Among the risk factors shared by both cardiovascular disease and ED, cigarette smoking should also be considered. It has been clearly demonstrated that cigarette smoking is significantly and independently associated to coronary heart disease, including death [103-106]. In fact, the Framingham Heart study showed that cardiovascular mortality in men increased by 18% for each 10 cigarettes smoked daily, and smoking exerts a synergistic effect with other risk factors for favouring coronary artery disease [107]. On the other hand, cigarette smoking is also clearly related to ED. In the Massachusetts Male Aging Study (MMAS) smoking was not directly associated with ED but potentiated the likelihood of ED associated to other risk factors [3]. A follow-up of this study revealed that the smokers were more likely to have moderate or severe ED than non-smokers (OR 1.97) after adjusting by age and other covariates [72]. It was also revealed that passive smoking increased ED incidence [72]. Other studies showed both an increased prevalence of ED among smokers as well as a higher number of smokers among ED patients [11,108-110]. Although less markedly than active smokers, passive smokers seem to be at higher risk for ED than men not exposed to smoke, and the risk increases as the exposure increases [72,111]. However, since smoking is a determinant for vascular disease, its effects on ED could be due to the vascular damage. Although, some studies support this hypothesis [112,113] other studies suggest that smoking is associated to ED independently of cardiovascular disease [114,115]. In a large population of Chinese men without cardiovascular disease, smoking was still associated to ED [116].

These cross-sectional studies do not allow for establishing a causative effect of smoking in ED, however, a dose-response, i.e. the relative risk for ED increases as the number of cigarettes smoked increase, is shown in several studies [114-117]. The reversibility of the risk by removing the exposure to smoke is a key component in a possible causality. Some reports showed increased risk for ED in former smokers than in never smokers [114,118] although the relative risks trend to be lower than that in current smokers [108,112]. Erectile function improved in 25% of patients with ED 1 year after quitting tobacco smoking, while none of the men who continued smoking showed improved erectile function [119]. In fact, a significant improvement in nocturnal penile tumescence and rigidity was observed in 10 heavy smokers after 24 hours of smoking cessation [120]. These results are supported by recent demonstration of a significant improvement in penile end-diastolic velocity in 20 smoker patients with ED 24-36 hours after they ceased from smoking [121].

For considering that cigarette smoking may cause ED, plausible biological-pathophysiologic mechanisms should be provided. In this sense, smoking induces endothelial dysfunction. Cigarette smoking has been shown to induce an impairment of systemic endothelium-dependent vasodilation [122-124] and reduce NO biosynthesis [125]. The impact of smoking on vascular NO/cGMP pathway is supported by the reversion of acute smoking-induced endothelial dysfunction by sildenafil [126]. NO/cGMP pathway has shown to be affected also in cavernosal tissue. A reduction of penile NOS activity was observed after passive smoking in rats, although erectile responses were not reduced. In this study, decreased expression of penile nNOS was also reported while eNOS expression was unaffected [127]. These results are consistent with the significant reduction of nNOS, but not eNOS, expression in rabbit cavernosal tissue after administration of cigarette smoking extract in vitro. Cigarette smoking decreased NOS activity and cGMP content in cavernosal tissue, probably due to the induction of an elevated activity and expression of arginase together with an increase of the content of the endogenous NOS inhibitor, ADMA [128]. Cigarette extract has also been shown to inhibit neurogenic relaxation of mouse corpus cavernosum [129]. Mice exposed to cigarette smoke for 3 weeks presented a reduction of erectile responses to cavernosal stimulation or acetylcholine administration. While penile constitutive NOS and PKG activities were reduced, superoxide production and inducible NOS activity were increased leading to an elevated peroxinitrite generation [130]. Oral administration of a PDE5 inhibitor to smoke exposed mice augmented penile constitutive NOS activity while reduced inducible NOS activity and superoxide formation, then decreasing penile peroxinitrite. This resulted in improved erectile responses [130]. Thus, cigarette smoking would be related to down-regulation of NO/cGMP pathway in penile tissue, probably related to increased oxidative stress [129,130]. On the other
hand, acute nicotine administration caused a significant reduction of physiological erectile responses to erotic films in healthy non-smoker men [131], an effect that could be related to an increase of vascular constriction by stimulation of peripheral sympathetic nerves [132], although nicotine has been shown to alter vascular endothelium-dependent relaxation [133].

VI. PATHOPHYSIOLOGICAL MECHANISMS IN VASCULAR ERECTILE DYSFUNCTION

Arterial vasodilatation and relaxation of the corpora cavernosa play a pivotal role for penile erection, and therefore impaired neurogenic or endothelium-dependent relaxation of erectile smooth muscle will be expected to result in erectile dysfunction. The key mediator of penile smooth muscle relaxation is NO. As above described, vascular disease is clearly related to reduced availability of NO in erectile tissue, compromising the adequate smooth muscle relaxation and hence penile erection.

In addition to impaired relaxant pathways, an increase in production/activity of factors driving penile smooth muscle contraction would antagonize vascular and cavernosal relaxation and therefore would difficult erectile function. While the impairment of relaxation of penile smooth muscle is constantly found in association with vascular ED, the presence of augmented contraction is not a constant in this situation. However, evidences exist addressing this issue.

Finally, the continuous presence of vascular dysfunction would result in the alteration of vascular and cavernosal erectile structures hindering the arterial supply and the corporo-veno-occlusive mechanism.

1. INCREASED VASOCONSTRICTION

Enhanced basal and myogenic tone has been observed in arteries from hypertensive rats [134]. It is unclear whether enhanced myogenic constriction reflects a primary pathological defect contributing to the hypertensive state or a secondary adaptative process protecting the exchange vessels from elevated pressures [135]. Although, the role of myogenic tone in the penile vasculature for erection remains to be clarified [136], the increased vasoconstriction could contribute to decreased arterial inflow and erectile response in renal hypertensive rats.

Contractile activity of smooth muscle is triggered by intracellular calcium concentration increase but calcium sensitizing pathways allow the maintenance of contractile tone after the decay of calcium concentration. The RhoA/Rho kinase pathway plays an important role in calcium sensitization and tonic contraction of smooth muscle. Cardiovascular diseases are associated with an enhancement of RhoA/Rho kinase activity [137]. Hypercholesterolemia induces calcium sensitization of smooth muscle cells in humans and
Endothelin-1 (ET-1) is a potent endogenous vasoconstrictor released by endothelial cells. ET-1 induces contraction and proliferation of smooth muscle by acting on endothelin-A (ET$_A$) receptors. In contrast, endothelial ET$_A$ receptors promote NO synthesis and vasodilation. ET-1 levels are elevated in plasma from patients with atherosclerosis, hypertension and hypercholesterolemia [146-148]. Studies with ET$_A$ receptor antagonists suggest an increased activity of endogenous ET-1, at least in hypertensive patients, contributing to enhanced vascular resistance [149]. An increased activity/production of ET-1 could also antagonize erectile process. Patients with organic ED show higher venous and cavernosal ET-1 levels [150]. Enhanced responses to ET-1 in corpus cavernosum of DOCA-salt hypertensive mice have been reported [151] while in cavernosal tissue from DOCA-salt hypertensive rats the expression of ET$_A$ receptor was augmented, contractile responses to ET-1 were increased and relaxation caused by ET$_A$ activation was reduced [152]. A decrease in ET$_A$ receptors in cavernosal tissue from hypercholesterolemic rabbits was also detected [153]. Although these evidences would point to a pathophysiological role of ET-1 in vascular ED, preliminary evaluation of an ET$_A$ receptor antagonist on the treatment of ED yield no positive results [154].

Angiotensin II (Ang II) is the final effector of renin-angiotensin system (RAS). Exerts its actions via type 1 (AT1) and type 2 (AT2) receptors. AT1 receptors mediate smooth muscle contraction and proliferation. Both circulating and tissue Ang II are important modulators of vascular physiology. There is evidence of the existence of tissue RAS in the penis. Ang I and Ang II were detected in the human corpus cavernosum endothelial and smooth muscle cells [155]. AT1 receptors are expressed in rabbit cavernosal endothelium and smooth muscle [156] and Ang II causes contraction of human corpus cavernosum in vitro [157]. An elevation of Ang II levels as probably occurs in hypertension would negatively impact erectile tissue relaxation and erectile function. ACE expression has been shown to be up-regulated in rats with arteriogenic ED [158]. In fact, administration of an AT1 antagonist has been shown to improve erectile function in hypertensive patients with metabolic syndrome [159], although the long-term administration of an angiotensin-converting enzyme (ACE) inhibitor improved cavernosal perfusion in atherosclerotic ED patients but this improvement was not significantly different from placebo [160].

2. IMPAIRED NEUROGENIC VASODILATATION

Impaired neurogenic relaxation was observed in a rabbit model of cavernosal ischemia [31] while was unaffected in a rabbit model of hypercholesterolemia [28]. As mentioned above, NO and CO contribute to neurogenic relaxation of rat cavernosal tissue and both components are reduced in SHR [89]. Immunohistochemical and functional studies of isolated penile small arteries indicate that NO is the main neurotransmitter mediating these non-adrenergic non-cholinergic relaxations to electrical field stimulation [161-163]. In penile arteries from renal hypertensive rats (one-kidney, one-clip model) neurogenic relaxation of rat cavernosal tissue and corpus cavernosum of DOCA-salt hypertensive mice have been reported [151] while in cavernosal tissue from DOCA-salt hypertensive rats the expression of ET-1 precursor was augmented, contractile responses to ET-1 were increased and relaxation caused by ET$_A$ activation was reduced [152]. A decrease in ET$_A$ receptors in cavernosal tissue from hypercholesterolemic rabbits was also detected [153]. Although these evidences would point to a pathophysiological role of ET-1 in vascular ED, preliminary evaluation of an ET$_A$ receptor antagonist on the treatment of ED yield no positive results [154].

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3. ENDOTHELIAL DYSFUNCTION

Impaired endothelium-dependent vasodilation has been demonstrated in patients presenting cardiovascular risk factors and diseases (diabetes, hypertension, hyperlipidemia, hyperhomocysteinemia, smoking...) [165] and the presence of endothelial dysfunction in the coronary circulation of hypertensive patients can predict major cardiovascular events [166]. Coronary endothelial dysfunction has also been associated to the presence of ED in patients with early atherosclerosis but without obstructive coronary arterial disease [167]. Other studies
have demonstrated the association of systemic endothelial dysfunction to ED. These studies determine the endothelium-dependent flow-mediated dilation (FMD) of the brachial artery by measuring arterial diameter after reactive hyperemia using an ultrasound system. In the absence of CVD, 27 men without ED and 30 patients with ED were compared. FMD was significantly reduced in ED patients, although nitroglycerine (NTG)-induced dilation was also impaired [168]. Patients with vascular risk factors but no ED (n=40) had reduced FMD with respect to control subjects (n=25). However, when ED was present in addition to vascular risk factors (n=40), FMD was significantly further reduced. These patients also showed reduced NTG-induced dilation [169]. In 56 patients with ED of different severities but without CVD or other diseases, the impairment of FMD correlated to the severity of ED. The patients with severe ED presented more reduced FMD of the brachial artery [170]. Recently, using an especially adapted plethysmography system, endothelium-dependent dilation in the penis has been assessed. Among 59 patients without overt CVD, 40 had ED and the other 19 were taken as controls. Patients with ED had reduced basal penile blood flow and increased penile vascular resistance. Moreover, endothelium-dependent penile blood flow increases generated by reactive hyperemia were reduced in patients with ED. At the same time, endothelial function in the forearm vasculature was not significantly altered in ED patients [171].

In addition to the impairment of endothelium-dependent dilation, ED is also associated to other manifestations of endothelial dysfunction. In 141 analyzed patients, those patients with coronary artery disease showed increased levels of inflammatory and prothrombotic markers. However, patients with ED having or not coronary artery disease presented higher values than patients without ED [172].

4. PENILE STRUCTURAL ALTERATIONS

Objective reduction of smooth muscle cells has been demonstrated in patients with organic erectile dysfunction [173]. PGE1 and PGE2 formation is oxygen-dependent and increasing oxygen tension is associated with a rapid increase in unstimulated PGE2, followed by suppression of TGF-ß-induced fibrillar collagen synthesis in the rabbit and human corpus cavernosum and vice versa [174-176]. A decrease in cavernous trabecular smooth muscle and an increase in connective tissue are correlated...
with diffuse venous leakage and a failure of the venoocclusive mechanism, hence resulting in erectile dysfunction [26,177,178]. Therefore, arterial insufficiency followed by diminished oxygenation of corpus cavernosum, decreased PGE$_2$ production, and increased fibrosis play a role in erectile dysfunction [179]. Structural changes of the arterial and erectile tissue would result in increased resistance of the penile vasculature [180]. These structural alterations could contribute to the development of corporo-venoocclusive fail in hypertension. Thus, the increased vascular resistance in penile arteries and structural remodelling of cavernosal tissue would participate in the pathophysiology of vascular ED.

5. IN CONCLUSION

The presence of cardiovascular risk factors would cause functional impairments of penile vascular and cavernosal tissue, mainly affecting endothelium-dependent relaxation and also neurogenic relaxation. The endothelial dysfunction is probably accompanied by a reduced capacity of endothelial repair and regeneration associated to cardiovascular diseases, which exacerbates the functional impairment. This situation causes an alteration of penile vascular and cavernosal structures that also contributes to erectile failure. Reduced NO availability by enhanced ROS production or by NOS inhibition would be responsible for functional, and even structural anomalies, although other mechanisms such as increased vasoconstriction (ET-1, Ang II, Rho kinase) would participate in these alterations. Further research is required for evaluating the contribution of modified activity of hyperpolarizing factors and membrane ion channels in vascular ED. In addition, studies regarding the impact of cardiovascular disease on penile resistance arteries are still sparse.

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A range of studies suggest that erectile dysfunction (ED) is predominantly a vascular disorder caused by endothelial dysfunction [1-2]. It is notable that ED and cardiovascular diseases share considerable risk factors such as hypertension, hypercholesterolemia, diabetes, obesity, depression and cigarette smoking [3]. Given that ED has been there long before the first onset of cardiovascular diseases (CVD), ED may be an early clinical marker of subclinical systematic vascular disease and increased cardiovascular risks [4-6]. This recognition of ED as an early marker for cardiovascular disease may provide a good therapeutic opportunity for ED patients who have cardiovascular risk factors (CRFs) at an early stage. The bridge between ED and CVD is endothelial dysfunction which is a common pathophysiologic process of both conditions [6]. This chapter will discuss the important role of endothelial dysfunction in connecting ED with CVD. Moreover, this chapter involves the issues of endothelial dysfunction as a diagnostic and therapeutic standard for ED and CVD.

1. THE PREVALENT RATES OF CARDIOVASCULAR DISEASES OR CARDIOVASCULAR RISK FACTORS IN MEN WITH ED.

Massachusetts Male Aging Study [7] investigated the sexual quality of 1,290 healthy men aged between 40 and 70, and found that 52% of interviewees complained certain degrees of ED. This study reported age as a risk associated with the incidence of ED. Moreover, ED was connected closely with heart diseases, hypertension, diabetes and dyslipidemia. The results have attracted the attention that ED is likely to be a common condition in men with CVD or CRFs. Similarly, American/European Men’s Attitudes to Life Events and Sexuality (MALES) Study [8] showed that prevalent rates of CRFs such as diabetes and hypertension significantly increased in men with ED compared to those without. Brant A, et al. [9] has explored the association between ED and risk of coronary artery disease (CAD). 1402 community-dwelling men with regular sexual partners and without known CAD were screened biennially for the onset of ED and CVD. The incidence of CAD was significantly higher in men with ED than those without. In Kew-Kim Chew’s study [10], postal questionnaires were sent out randomly to 1,580 participants. The results showed that cardiovascular risks or diseases were more prevalent among aging participants with ED and severe ED.

2. THE INCIDENCE OF ED IN MEN HAVE CARDIOVASCULAR DISEASES OR WITH CARDIOVASCULAR RISK FACTORS.

Kloner RA, et al [11] carried out a Sexual Inventory through questionnaire and showed that 75% men with chronic stable coronary artery diseases had certain degrees of ED, among which the percentage of severe ED was 25%. This suggested that ED was a common condition in men with stable coronary disease. European and North, Central and South American participating MALES Study investigated the prevalence of ED in 27,839 men aged 20-75 [12] and demonstrated that ED was more prevalent among men with cardiovascular risk factors than those without. These CRFs included diabetes, hypertension, angina and high cholesterol. In Chew’s study [10], postal questionnaires were sent out randomly to age-stratified male population. ED was significantly more prevalent among participants with hypertension, ischemic heart diseases, stroke and peripheral arterial diseases.

These findings suggest that ED has tight connection with CVD and CRFs. Men with ED are more likely to have cardiovascular diseases or cardiovascular risks such as obesity, diabetes mellitus, hypertension, and dyslipidemia than those without. Accordingly, the prevalent rates of ED increase in men with cardiovascular diseases or cardiovascular risks [13].

Endothelium, producing several signaling molecules which have the effect of promoting vasodilation, inhibiting platelet aggregation and antibiosis, is a major regulator of vascular homeostasis [14]. Endothelial dysfunction, characterized by impairment of nitric oxide synthesis, altered anticoagulant, anti-inflammatory and vascular remodeling properties, could increase the permeability of vessels to plasma constituents (such as low-lipoproteins) and affect endothelium dependent vasodilatation. Endothelial dysfunction which contributes to the development of atherosclerosis [14] is a common characteristic of vascular diseases such as ED and CAD.
II. ENDOTHELIAL DYSFUNCTION AND CARDIOVASCULAR DISEASES

Atherogenesis, with endothelial dysfunction as its character, is the common pathophysiological basis of many CVD [15]. The process of atherogenesis can be divided into several steps. Endothelial dysfunction is the first stage of atherosclerosis during which patients have normal vascular imaging of vessel wall but abnormal vasodilation [16]. The last step of atherosclerosis is characterized by obstructive vascular changes, which would lead to symptomatic cardiovascular diseases. Endothelial dysfunction is also important at the late stage of atherosclerosis by changing compositions of plaque and influencing plaque stability [17]. Based on its important role in the development of atherogenesis, endothelial dysfunction could be crucial in diagnosis, treatment and prognosis of CAD. It has been found that endothelial dysfunction can be used to predict long-term coronary events in patients with or without symptomatic CAD [18]. Treatment of endothelial dysfunction associated cardiovascular risks or vascular conditions, such as hypertension, hypercholesterolemia and obesity have been proved to improve the prognosis of CAD [19].

III. ENDOTHELIAL DYSFUNCTION AND ED

Endothelial dysfunction, characterized with deficient synthesis, release, and activity of vasodilatation mediators from the vascular endothelium, would result in impaired ability to maintain penile erection, culminating in ED [20]. Recent studies suggest an intimate association between endothelial dysfunction and ED [21].

1. THE ROLE OF ENDOTHELIAL FUNCTION IN PHYSIOLOGY OF ERECTION

The penis consists of two corpus cavernosa and one corpus spongiosum that surrounds the urethra. The main blood supply of penis is from the dorsal and cavernous arteries, while venous return occurs mainly through superficial dorsal veins and deep dorsal vein. Erection tissue is characterized by abundant irregular sinusoids which connect with each other. There are plenty of trabecularms consisting of abundant smooth muscle fiber among the sinusoids. Actually, penis is a vascular organ, and penile erection is a vascular event.

Penile erection is a complex and coordinated process, which is the result of series of events involving sexual stimulation, neural conduction and endothelium responses. Vascular endothelium lining the cavernous sinus plays a key role in the physiology of erection through synthesis of vascoactive mediators, particularly NO. Briefly, responding to sexual stimulation, NO is released from vascular endothelium of corpus cavernosa as well as cavernous nerve terminals under the catalysis of eNOS (endothelial nitric oxide synthase, eNOS) and nNOS (neuronal nitric oxide synthase, nNOS). NO activates guanylyl cyclase in penile smooth muscle cells which increases the concentration of cyclic guanosine monophosphate (cGMP). The elevated concentration of cGMP results in relaxation of both arterial and trabecular smooth muscle cells which rises penile blood flow and enlarges the sinusoidal spaces. The process of erection is accomplished when the penile venous outflow are occluded as the intercavernous pressure rises [22].

2. THE ROLE OF ENDOTHELIAL DYSFUNCTION IN THE DEVELOPMENT OF ED

Erectile dysfunction in men is mostly vasculogenic [23, 24]. Endothelial dysfunction is a key process in the development of ED. Vascular cell adhesion molecule-1 (VCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1), endothelin-1 (ET-1) and P-selectin are markers of endothelial cell activation. Bocchio et al. [25] compared these circulating markers among patients with ED but without CRFs, patients with both ED and CRFs and healthy controls. This study demonstrated that markers of endothelial cell activation were significantly higher in patients with ED than those healthy subjects. Similarly, El傍 er et al. [26] investigated endothelial function in patients with ED, and found that patients with endothelial dysfunction had both significantly impaired erectile function evaluated by International Index of Erectile Function-5 (IIEF-5) and higher asymmetric dimethyl L-arginine (ADMA) plasma levels which is a marker of endothelial dysfunction. De Angelis L et al.[27] found that both blood pressure and platelet aggregation, which were both markers of endothelial function, were significantly reduced in men with ED compared with those without.

Similar with serum markers, physical assessment of endothelial function also changes in ED patients. Kaiser et al. [28] assessed vasodilation in patients with vasculogenic ED. Brachial artery flow-mediated dilation and vasodilation to nitroglycerin were significantly lower in patients with ED, compared to those in healthy controls. Similarly, Kaya et al. [29] demonstrated that endothelial-dependent brachial artery flow-mediated vasodilation and endothelial-independent vasodilation to nitroglycerin were lower in patients with ED than those without.

Endothelial dysfunction is a common character of vascular diseases including ED and CVD. It is believed that ED is one manifestation of systemic endothelial dysfunction. Patients with ED but no symptom of clinical cardiovascular diseases may have a peripheral vascular defect in endothelial-dependent
vasodilation. Therefore, it is easier to diagnose or evaluate the severity of ED condition through endothelial function assessment.

**IV. ED AND CVD: ED COULD BE A PREDICTOR OF CVD**

ED and cardiovascular disease have a common pathological basis—endothelial dysfunction. Furthermore ED and cardiovascular diseases share a lot of common risk factors. A good deal of data indicate that many patients with cardiovascular disease have symptoms of ED. Prostate Cancer Prevention Trial (PCPT) demonstrated that the onset of ED was a significant predictor of subsequent cardiovascular events [30]. ED is the most effective predictive factor for coronary artery disease in patients with diabetes [31]. The issue is whether ED can be an effective clinical predictor of cardiovascular diseases.

**1. EVIDENCES THAT ED PRECEDES CARDIOVASCULAR EVENTS**

It has been demonstrated that ED and CVD share common risk factors.

These risk factors are mainly asymptomatic at their early stages. Take coronary heart disease and type 2 diabetes for examples. Approximately 50% of men who suffered from coronary heart disease or died suddenly, showed no previous symptoms before death [32]. And type 2 diabetes cannot be diagnosed until 4-7 years after its initial onset [33]. Therefore, it is not easy to diagnose CVD or CFRs at an early stage. However, irreversible vascular damages probably have already existed for years before the occurrence of obvious symptom of CVD or CFRs [34]. ED as one manifestation of systemic vascular disease can be an ideal marker for diagnosis of CVD or CFRs at their early stages.

Various findings suggest that there is a close relationship between ED and CAD, and ED precedes cardiovascular events at least 2-3 years. Montorsi et al. [35] investigated the relationship between ED and acute coronary syndrome, and revealed that 99 patients out of 147 men presenting with acute coronary syndrome had experienced event ED approximately 3 years prior to the onset of acute coronary syndrome. The report of COBRA (association between erectile dysfunction and coronary artery disease) further proved this point. 93% of patients with a chronic ED syndrome complained ED symptoms before the onset of CVD with a mean interval of 24 months.

**2. MECHANISM THAT ED COULD BE A CLINICAL MARKER OF CVD**

A high prevalence of ED has been reported in men with CVD. The fact that ED and cardiovascular diseases share numbers of common risk factors, leads to the clinical consensus that most cases of ED are probably part of the spectrum of CVD [36]. The mechanisms that ED could be a clinical marker of CVD include vascular beds of corpus cavernosum, blood vessel sizes of dorsal artery and endothelial dysfunction.

**a) Vascular bed of corpus cavernosum**

Penis with relatively higher content of endothelium and smooth muscle than any other organs of the body is actually a vascular organ. It is more vulnerable to the changes of oxidative stress and systemic NO which is also the main etiological factor for systemic vascular diseases including CVD. Therefore, the penile vascular bed may be a sensitive indicator of systemic cardiovascular diseases [37].

**b) Blood vessels size of penis arteries**

Penile arteries, which are typically 1 to 2 mm in diameter, are narrower than the coronary arteries (3-4mm) [38], so that they are more vulnerable to the atherosclerosis and endothelial dysfunction. The blood flow of penis would be restricted sooner by the development of atherosclerosis process than those of heart and other organs [39, 40]. Relatively, it needs to form a greater plaque burden to restrict coronary blood flow and lead to heartstroke. Therefore, the atherosclerosis process may manifests as symptom of ED before the symptom of coronary artery disease. This artery size/lumen occlusion theory is the most common hypothesis adopted to explain the reason why ED occurs before clinical cardiovascular diseases [41].

**c) Endothelial dysfunction**

The other mechanism connects between ED and CVD is endothelial dysfunction which is one of the earliest changes of the spectrum of atherosclerosis [42, 43]. Endothelial dysfunction is a manifestation of malfunction of vascular endothelial cells, which is caused by cardiovascular risks including hypertension, dyslipidemia, diabetes, cigarette smoking and other noxious factors such as inflammation and infection. Angina would not occur until occlusion of coronary artery formed by atherosclerosis. Functional ED caused by endothelial dependent/independent smooth muscle relaxation, probably occurs before the development of structural, occlusive penile arterial disease and also before the symptom of angina. Therefore, ED may be one of the first signs of systemic vascular diseases [44].

**3. CORRELATION BETWEEN SEVERITY OF ED AND EXTENT OF CVD**

As mentioned above, ED could be a predictor of silent CVD. This section will discuss the relationship between severity of ED and extent of CVD. In a questionnaire-based study of male patients with ischemic heart diseases, patients’ penile erection conditions (through IIEF-5) and numbers of vascular lesions (through angiography) were recorded.
Interestingly, patients with one-vessel disease had significantly better sexual life compared with patients with multi-vessel diseases [45]. Similarly, the Association between erectile function and coronary artery disease (COBRA) [46] demonstrated severe ED (IIEF-5 score <10) was evidently more frequent in patients with multi-vessel disease than those with one-vessel disease. ED usually precedes cardiovascular events at least 2-3 years. However the time intervals between the onset of ED and CVD in patients with single vessel disease were longer than those with multi-vessel disease [46].

These findings suggest that there is a close association between the severity degree of ED and of coronary artery atherosclerosis. That is, the severity of ED is correlated with the extent of CVD. Patients with severe ED are more likely to have multi-vessel CVD than those with mild or moderate ED. The severity degree of ED can reflect the degree of vessel atherosclerosis.

It is apparent that ED could be the effective clinical marker of CVD. The close association between ED and CVD illustrates the implication that once the diagnosis of ED is established, patients with ED should be recommended to undergo a full medical screening for CVD or CRFs, especially endothelial dysfunction. Then, how about the clinical assessment of endothelial functions?

V. ASSESSMENT OF ENDOTHELIAL DYSFUNCTION

Since ED can be a clinical marker of cardiovascular risks or silent cardiovascular diseases. Patients with ED are recommended to take an assessment of risk factors for cardiovascular risks. Risks like smoking, hypertension, dyslipidemia, diabetes, obesity and secondary lifestyle, should be identified by history taking, physical tests and appropriate laboratory tests.

Endothelial dysfunction is the first step of atherosclerosis generation [47], and can be demonstrated in patients with the cardiovascular risk factors [48, 49]. However, specific markers for endothelial dysfunctions are yet to be established.

1. PHYSIOLOGIC ASSESSMENT OF ENDOTHELIAL FUNCTION.

Endothelial function can be assessed through physiological methods such as Flow-mediated dilation of the brachial artery and Peripheral arterial tonometry measuring reactive hyperemia.

a) Flow-mediated dilation of the brachial artery

Flow-mediated dilation (FMD) of the brachial artery is the most popular assessment of endothelial function [50]. FMD-reflected endothelial function is relative to coronary endothelial function [51] and cardiovascular risk factors [52]. And many recent studies suggest that FDM also has association with ED. Chiurla et al. [53] demonstrated worse FMD in men with ED, as opposed to better FDM in men without ED. Kaiser et al. [28] has similar finding in 30 men with ED and without manifestation of CVD.

Briefly, patients’ arms is occluded with a blood pressure cuff for 5 minutes and subsequently released. Endothelium-dependent vasodilation can be quantified by ultrasound. The mechanism of this test is that arterial occlusion and subsequent release can lead to reactive hyperemia and local endothelial activation.

b) Peripheral arterial tonometry measuring reactive hyperemia.

Peripheral arterial tonometry measuring reactive hyperemia (RH-PAT) is a more recent method of assessing endothelial function. RH-PAT has been verified to correlate well with coronary endothelial function and has extensively relation to early CAD (coronary artery disease, CAD) [54-56]. Chouraqui P et al. [57] investigated RH-PAT in patients with myocardial ischemia, and found that RH-PAT results were significantly impaired in patients with exercise-induced myocardial ischemia.

RH-PAT is a 15-minute noninvasive assessment that can be performed in an office setting. Briefly, patients’ upper arm is occluded by a blood pressure cuff to induce reactive hyperemia. And endothelial function can be quantified by a finger probe to assess digital volume changes accompanying pulse waves [58]. Compared with FMD, RH-PAT has the same function in reflecting peripheral endothelial function [59]. And RH-PAT is particularly useful in reflecting cardiovascular risk factors such as diabetes [60, 61] and metabolic syndrome [62].

2. SERUM BIOMARKER OF ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction has been considered as a major cause of ED, even in patients without evidence of organic vascular disease. However, specific serum markers for endothelial dysfunction are yet to be established. Some serum markers that can be used to assess endothelial function are listed.

a) Endothelin-1 (ET-1)

ET-1, a vasoconstrictor and pro-inflammatory factor, is normally secreted from endothelial cells [63]. It has been verified that the blockade of ET-1 receptor leads to improved endothelial function which increases availability of NO. Therefore, ET-1 is a serum marker associated with endothelial dysfunction [64].

b) Asymmetrical dimethylarginine (ADMA)

ADMA is an analogue of L-arginine and a competitively inhibitor of NOS [65]. High plasma level of ADMA reflects impaired endothelial function [66]. Furthermore, it has been shown to be a predictor of
cardiovascular events. Therefore, ADMA is a link between ED and CVD [67].

c) C-reactive protein (CRP)

As an inflammatory factor, C-reactive protein (CRP) has extensively connection with endothelial dysfunction, cardiovascular events and ED [68, 69]. Elevated plasma CRP level has been found to significantly correlate with vascular ED diagnosed by penile Doppler [70]. CRP can be used to assess endothelial function.

d) Cellular adhesion

Markers of cellular adhesion, such as E-selection [71], intercellular adhesion molecule-1 (ICAM-1) [72, 73] and vascular cell adhesion molecule-1 (VCAM-1) [74] have been verified to have connection with endothelial dysfunction and increased risk of CVD.

e) Transforming Growth factor-beta 1

It is believed that the plasma level of Transforming Growth factor-beta 1 (TGF-beta 1) is a diagnostic indicator of vascular disease [75]. Seong et al. [76] investigated the plasma level of the TGF-beta 1 in 62 patients with ED, and demonstrated a significant elevation compared with the control group and a more significant elevation in patients with vasculogenic ED.

f) Endothelial dysfunction inductor protein (EDIP)

Lopez et al have investigated a peculiar protein called endothelial dysfunction inductor protein which can cause endothelial lesions when activated or upregulated [77]. EDIP reduces the expression of endothelial nitric oxide synthesis and shortens the messenger RNA’s half-life [78] through interaction with the endothelial nitric oxide synthesis (eNOS). EDIP can be detected in periphery blood mononuclear cells using Western-Blot technique.

g) Nitric oxide (NO) pathway

The role of NO in physiology of erection is well known. NO pathway can be a parameter for characterizing endothelial dysfunction. Levels of eNOS, guanylate cyclase, cGMP and phosphodiesterase type 5 (PDE5) in lymphocytes can be analyzed to evaluate endothelial function. Both eNOS and soluble guanylate cyclase levels are increased in ED patients, compared with healthy controls [77].

The severity of endothelial dysfunction has been demonstrated to be correlated with ED [79, 80]. And endothelial function was significantly worse in subjects with arteriogenic ED as demonstrated by penile Doppler than those with other forms of ED. Therefore, assessment of endothelial dysfunction may be considered as a routine test to diagnose arteriogenic ED compared to invasive penile Doppler. Furthermore, screening endothelial dysfunction in the ED population is necessary in assessing cardiovascular risk [81].

VI. STRATEGIES TO IMPROVE ENDOTHELIAL FUNCTION AND PREVENT CARDIOVASCULAR EVENT IN MEN WITH ED

There is an interval between the onset of ED and CVD. This leading time provides an opportunity for early diagnosis and treatment of cardiovascular risk factors.

Here are some suggestions for patients with cardiovascular diseases or ED [44]:

1. ED should be a routine part of the cardiovascular history recording and systematic review in all men of 25 years and older regardless of their level of sexual function.

2. Men who are discovered to have ED must be thoroughly assessed for cardiovascular risk and occult systemic vascular disease.

3. Men with ED should be treated as if they already have vascular diseases. All men with cardiovascular risks should embark on lifestyle modification such as having healthy diet, doing exercise and quitting smoking.

1. CARDIOVASCULAR RISK REDUCTION IN PATIENTS WITH ED

There is no doubt that treatment of LDL cholesterol and hypertension reduces cardiovascular and cerebrovascular events in patients with cardiovascular risk factors. However, it is controversial that risk factors management could reduce the development or progression of ED. Maybe it is too late to reverse vascular damages that caused ED by the time when vascular damages have caused cardiovascular diseases [82]. But some studies suggest that the reduction of cardiovascular risks benefits patients with ED by improving the response to PDE5 inhibitors [83].

a) Blood pressure

The ideal blood pressure is < 140/90 mmHg for the general population and < 130/80 mmHg for patients with diabetes or chronic kidney diseases [84].

Hypertension is one of the common risk factors for cardiovascular diseases. However, ED is a frequent complication of hypertension management. There are evidences that the risk of ED is greater in patients who take specific classes of antihypertensive drugs including diuretics, methyldopa, clonidine, and beta-blocks than those take other antihypertensive drugs. Especially, the nonselective antihypertensive drugs have been found to have greater impacts on erectile function. Relatively, calcium-channel blockers and angiotensin converting enzyme inhibitors (ACEI) are reported to have less negative effects.
on sexual function [85]. Administration of ACEI in men with arterial ED demonstrated favorable effects for ED [86]. Similarly, another study showed that angiotensin II-receptor antagonist valsartan has some advantages for the quality of sexual life compared with beta-blocker carvedilol, despite their similar antihypertensive effects [87]. Therefore, it is important to ensure that the antihypertensive drugs have the lowest possible potential for causing ED in patients who are under anti-hypertension treatment. However, there is a contradiction between treatment for hypertension and the cause of ED. It is crucial to obtain the best balance between antihypertensive efficiency and the quality of sexual life.

**b) Cholesterol**

The ideal LDL (the bad cholesterol) goal is <100mg per 100ml in patients with known coronary disease and <70mg per 100ml in high-risk patients with coronary disease (such as acute coronary syndrome, multiple risk factors) [84]. HDL cholesterol (the good cholesterol): HDL is recommended to be > 40mg per 100ml.

Statins are regular drugs for reducing the plasma cholesterol level. In addition, it is well known that statins has beneficial effects such as improvement of endothelial function, decrease of inflammatory and thrombogenesis, and stabilization of atherosclerotic plaque. Recent studies indicate that statins have favorable effects on erectile dysfunction. This favorable effect of statins can be, at least partially, attributed to their action on the endothelial function through their anti-inflammatory properties [88]. A pilot study showed that atorvastatin may improve erectile function and patients’ responses to oral sildenafil [89].

c) Fasting blood sugar

American Diabetes Association considers a fasting blood sugar of 100 to 125mg per 100ml to be pre-diabetes and 126mg per 100ml or higher to be diabetes. Fasting blood glucose of ED patients with cardiovascular risks are recommended to be <100mg per 100ml [84].

d) Antioxidants

Production of oxygen-free radicals is considered to lead to endothelial dysfunction quenching endothelium-mediated NO-synthesis. Therefore, antioxidants which can seavenge oxygen-free radicals have been explored and applied as a possible therapy for endothelial dysfunction. Some studies revealed that a single dose of vitamin C has beneficial effect on endothelial function-mediated FMD in smokers and patients with CHD [90, 91]. Neunteuffl et al. [92] explored whether vitamin-E and lipid-lowering therapy have synergetic effects on improving endothelial function, and found that among hypercholesterolemic patients, improvement of endothelial function was significantly more apparent under statins and vitamin-E combined therapy than those under statin therapy alone. However, the long-term effect of antiveidants to improve endothelial function is still unclear.

### 3. SECONDARY LIFESTYLE

Patients under cardiovascular risks are recommended to stop smoking by attending a smoking cessation program that covers behavioral modification as well as various medicines to aid patients in quitting smoking [84].

Patients with stable cardiovascular disease are recommended to exercise (walking on a flat surface) for no more than 30 minutes a day 5 days a week, at least [84].

ED patients with high cholesterol and diabetes should be referred to professional dieticians.

### 4. PHOSPHODIESTERASE TYPE 5 INHIBITORS (PDE5I)

Phosphodiesterase-5 inhibitors have the first-line drugs for ED. It decreases breakdown of cyclic guanosine monophosphate in the smooth muscle cells, and enhances the downstream effects of NO [93]. PDE5I not only favorably improves erections, but also has beneficial effects on endothelial function [94]. It has been reported that daily administration of PDE5I can cure patients with ED through chronic activation of the eNOS pathway [95, 96]. Chronic administration of tadalafil for one month resulted in reduction of CRP, VCAM-1 and ET-1, which are important markers for endothelial dysfunction [97, 98]. Similar results were seen with sildenafil which is taken three times daily in men with type 2 diabetes mellitus [99, 100]. Several trials showed that chronic administration of tadalafil could increase mobilization of circulating endothelial progenitor cells (EPCs) and improve peripheral endothelial function measured by flow-mediated dilation of brachial artery [101, 102] in men with ED. PDE5-Is have a favorable effect on inflammatory activation due to increased activity of the NO-cyclic guanosine monophosphate axis (NOCGMP) [103]. In patients with cardiovascular risk factors, upregulation of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase and formation of superoxide would impact the function of endothelium. The mechanism of PDE5-I’s anti-inflammatory effects is to enhance the NO-cGMP pathway which also augments relaxation of smooth muscle cells [104].

This finding revealed that chronic administration of PDE5I is not only good for patients with ED, but also can improve systemic endothelial function. It seems that chronic PDE-5I therapy is required to achieve sustained improvement of endothelial dysfunction, which would be beneficial for patients with cardiovascular risks. On the basis of currently available evidence, it is likely that endothelial dysfunction and systemic cardiovascular pathology may be modulated by PDE5-I on a daily dosage.
VII. CONCLUSIONS:

Endothelial dysfunction is a key pathophysiologic process of both ED and CVD. Evidence has been accumulated that ED may be an independent predictor of future CV events in patients without onset of heart disease. According to this, each patient with ED should be considered as a cardiac patient until proven otherwise. Urologists should pay more attention to ED in each middle-aged man. And there is no need for patients to be embarrassed to talk about sexual dysfunction with their physicians. Once diagnosis of ED is established, patients with ED should undergo complete assessment to exclude the possibility of CVD or CRFs. Endothelial dysfunction is one of the most important markers to reflect one’s ED and CVD conditions. And strategies should be taken to improve endothelial function to repair ED and prevent cardiovascular events.

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F. DRUGS CAUSING ERECTILE DYSFUNCTION

Ulf Simonsen

I. INTRODUCTION

Erectile dysfunction is a common symptom amongst older men and will inevitably co-exist with other physical conditions prevalent in this population such as depression, diabetes and cardiovascular disease which are themselves risk factors for ED [1-3]. In addition sexual symptoms related to medication can involve a combination of complaints concerning sexual desire, arousal and orgasm rather than being concentrated on ED alone. Self-reported and questionnaire data concerning ED as a side effect of medication should therefore be interpreted with caution. In order to confidently establish a causative relationship three conditions should be satisfied: (1) There should be a higher prevalence of ED amongst men taking the drug calculated from data with placebo control and stratification for known risk factors of ED; (2) A greater prevalence of ED should also be found for the target drug compared to another drug with an equivalent therapeutic effect using data from a randomised controlled trial, again with allowance for confounding variables; (3) Finally, a credible physiological mechanism for the causation of ED by a particular drug should be postulated and proven by experimental studies. Animal models can be useful in this regard to generate hypotheses concerning the inhibitory action of prescribed drugs on erectile function by means of experiments on isolated cavernosal tissue or the effect on sexual behaviour in intact animals [4]. Concerning clinical effects, the occurrence of ED is rarely a primary end point in therapeutic trials and therefore the above conditions for proving a causative association are unlikely to be met in full. The difficulties of this approach are exemplified by longitudinal data from the Massachusetts Male Ageing Study (MMAS) showing that only non-thiazide diuretics and benzodiazepines, agents not previously strongly linked to ED, were independently associated with ED [5]. Despite the excellent design of this study, power was limited by the need for allowance of multiple confounding variables. Historically, review articles generally based opinion on uncontrolled data but the recent emergence of standardised methodology for systematic reviews and meta-analyses have increased the validity of our conclusions concerning the effect of drugs on sexual function.

II. CARDIOVASCULAR DRUGS AND ERECTILE FUNCTION

Erectile dysfunction and heart disease have common factors [2, 6], and therefore, patients with sexual dysfunction should always be examined for the presence of underlying cardiovascular disease and risk factors. However, comparing untreated and treated patients with heart disease or hypertension revealed that medication increases the relative risk for development of erectile dysfunction [5].

1. TREATMENT OF HYPERTENSION AND ERECTILE DYSFUNCTION

Current recommendations for treatment of hypertension suggest thiazide diuretics as first line, while angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 (AT1) receptor antagonists, calcium channel blockers, and beta-adrenoceptor antagonists are indicated as first line agents in specific high risk conditions (JNC7). Often two or more antihypertensive medications will be required to achieve goal BP <140/90 mm Hg (or <130/80 mm Hg in diabetic) hypertensive patients [7]. All drugs have ED listed as a potential side effect but well designed controlled clinical trials give conflicting results concerning causative relationships [8]. Animal studies do suggest possible mechanisms using in vitro and in vivo methodology [9].

a) Diuretics

This class of drug has been extensively studied following early trials which showed a high prevalence of self-reported ED. Possible mechanisms include decreased vascular resistance and lowered zinc levels leading to reduced androgen production although experimental animal data is lacking. Appropriate controlled studies with ED as an end-point give consistent results despite trends towards lower dosage schedules [10]. Older treatment regimens using higher doses of a thiazide showed a significant increase in ED compared to placebo [11]. Addition of a thiazide to existing treatment with propanolol or methyldopa also increased the prevalence of ED, whilst this effect did not occur when the thiazide was combined with an ACE inhibitor [12]. Data from a large UK trial showed that twice as many men taking thiazides for treatment of mild hypertension reported ED compared to those treated with propanolol or placebo, this being the commonest reason for withdrawal from the bendrofluazide arm of the study [13]. Similar findings were documented from the Treatment of Mild Hypertension Study (TOMHS) where the prevalence of ED at 2 years in men taking a low dose thiazide was twice that of both the placebo group and those on alternative agents [14]. Interestingly after 4 years of treatment prevalence of ED in the placebo group approached that of the thiazide group, a finding not fully explained by drop outs. It may be that thiazide therapy unmasks latent ED at an earlier stage rather
then being directly causal. A study comparing sexual side effects in hypertensive patients treated with a thiazide to those on placebo or atenolol also found a higher rate of ED in the thiazide group although the effect was ameliorated by weight loss [15]. It is interesting that treatment with non-thiazide diuretics was implicated as an independent factor for ED in the MMAS since these drugs have not been systematically assessed for unwanted sexual effects [5] although it is established that spironolactone has anti-androgenic properties. In addition they are infrequently used for hypertension alone. In summary it is likely that thiazide diuretics are associated with ED in men with hypertension, although this may represent unmasking of an existing problem and the effect can be reduced by lifestyle changes. The underlying pathophysiological mechanism is still unknown.

**b) β-Adrenoceptor antagonists**

Receptor studies show that only 10% of adrenoceptors in penile tissue are of the β-adrenoceptor subtype and activation leads to relaxation [4] and vasodilation of penile arteries [16]. This response is attenuated in vitro by non-selective drugs such as propranolol, possibly by blocking postjunctional β2 adrenoceptors [16, 17], but not by cardiac selective agents such as practolol and atenolol. However, direct cavernosal injection of propranolol in the intact animal has no effect. Depending on the lipophilicity of the beta-adrenoceptor antagonists (e.g. propranolol is hydrophilic while atenolol is hydrophobic) may also exert an inhibitory effect within the central nervous system, perhaps leading to lowered sex hormone levels [18]. Data from the MMAS confirmed higher usage of this class of medication amongst men with ED, although the significance of the association disappeared when confounding variables were taken into account. Interestingly cardiac selective blockers were the predominant type used by men in this study. Thus, the effect of β-adrenoceptor antagonists on erectile function to a large degree can be explained by their mechanisms of action, e.g. they are either general β-adrenoceptor antagonists, selective β1-adrenoceptor antagonists, or also possess vasodilatory properties (Figure 1). Non-selective drugs such as propranolol were associated with higher prevalence of ED compared to patients treated with placebo or ACE inhibitors [12, 13]. Later trials using agents with higher selectivity for the β1 adrenoceptor such as acebutolol have shown a substantial reduction in ED as a side effect with no difference being found against the placebo and ACE inhibitor groups [14]. This also applies to the use of selective β1-adrenoceptor antagonists in the prophylaxis of angina [19]. The clinical evidence therefore suggests that older non-selective drugs such as propranolol were associated with higher prevalence of ED but this effect is not seen with β1 selective adrenoceptor antagonists. The general β-adrenoceptor antagonists which also causes vasodilation by blocking α1-adrenoceptors, carvedilol and labetalol have in case of carvedilol in a cross-over study been reported to be associated with worsening in sexual function [20], while similar data are not existing for labetalol. Some of the recently introduced β1-adrenoceptor antagonists such as nebivolol have also vasodilatory effects mediated by release of nitric oxide. In cross-over studies nebivolol in contrast to the selective β1 adrenoceptor antagonists, metoprolol and atenolol, did not decrease sexual intercourse activity in hypertensive men, and may even have positive effects on erectile function [21, 22].

**c) α-Adrenoceptor drugs**

Animal studies have demonstrated a positive effect on erection for α-adrenoceptor antagonists, particularly those acting on the α1 adrenoceptor, by increasing or prolonging the relaxant response of cavernosal smooth muscle [23]. In addition, prejunctional α2-adrenoceptor activation modulates the release of nitric oxide, suggesting a putative vasodilatory role of α2-adrenoceptor antagonists [24]. Direct cavernosal injection of α1-adrenoceptor antagonists has been shown to cause erection in both experimental animals and humans, but this effect is not observed with drugs selective for α2-adrenoceptors [23]. In clinical trials drugs such as doxazosin used to treat hypertension [14] or lower urinary tract symptoms [25] are not associated with complaints of ED and indeed had lower rates than placebo groups. Drugs stimulatory to the α2 adrenoceptors such as clonidine result in diminished erectile function both clinically and experimentally by peripheral and central mechanisms [17, 23]. The centrally acting drug, methyldopa, has also been associated with ED in controlled trials compared with placebo and other antihypertensive agents [12] and may act by antagonising hypothalamic α2 adrenoceptors.

**d) Angiotensin Converting Enzyme (ACE) Inhibitors**

In addition to circulating angiotensin II, angiotensin converting enzyme (ACE) and chymase are expressed in erectile tissue, and functional as well as binding studies suggest angiotensin II induces contraction by activation of angiotensin II type 1 (AT1) receptors [8]. Moreover, angiotensin II increases during the detumescence phase in man [26]. However, experiments in normotensive rats suggested that the ACE inhibitor, captopril, does not cause any significant adverse effect on sexual function in awake rats [17], and enalapril may even improve erectile function in spontaneously hypertensive rats [27]. The contention is also supported by clinical studies of hypertension treatment comparing an ACE inhibitor with other agents and placebo. All three studies found either no difference compared to placebo or improved sexual function from baseline compared to other antihypertensive drugs [12, 14, 18, 28].
e) Angiotension II type 1 (AT1) receptor antagonist

In studies of hypertensive animals AT1 receptor antagonists e.g. losartan, valsartan, and candesartan reverse structural changes in the penile vasculature and appear to conserve erectile function [27, 29-31]. Moreover, in clinical cross-sectional studies AT1 receptor antagonists in contrast to other antihypertensive drugs even tend to improve erectile function [10], and in direct comparison with the β-adrenoreceptor antagonist carvedilol, valsartan has a beneficial effect on existing sexual dysfunction at baseline and have no adverse sexual effects during 12 months of treatment [20]. In case of losartan 3 month treatment was also reported to improve sexual function [32].

f) Calcium Channel blockers

Smooth muscle contraction requires increased cytosolic calcium derived from internal stores and extracellular fluid. It would therefore be anticipated that calcium channel blockers would have a permissive effect on penile erection but might inhibit bulbospongiosal contraction during ejaculation. This contention is supported by findings of in vitro studies which demonstrated a modest relaxant effect on isolated cavernosal smooth muscle [23] and penile arteries [33]. Clinical studies have demonstrated no adverse effect on erection and ejaculatory complaints seem short-lived [18]. In the TOMHS study there was no significant excess risk of ED in the amlopidine group compared to placebo-treated patients [14]. Another study also showed no increase in the prevalence of ED when hypertension was treated with diltiazem alone or in combination with an ACE inhibitor [34]. A comparative study of two calcium channel blockers showed that neither had any significant effect on sexual function although two patients withdrew from the nifedipine arm because of reduced libido [35].

g) Summary

Treatment of an asymptomatic abnormality such as mild to moderate hypertension requires agents with an acceptable side effect profile to minimise non-compliance. Despite lower dosage thiazide diuretic agents continue to be associated with higher rates of ED although this may be reduced by combination therapy and weight loss. There is no firm evidence to implicate other commonly used modern agents in the causation of ED although alpha-adrenoceptor antagonists and AT1 antagonists both tend to improve sexual function during treatment and may therefore be useful as antihypertensive therapy in men with pre-existing ED.

2. TREATMENT OF HEART DISEASE AND ERECTILE DYSFUNCTION

Erectile dysfunction is highly prevalent among patients with heart failure, because of neurohumeral changes, an imbalance of circulating vasomodulators, reduced cardiac capacity, depression, and potential adverse effects of heart failure medical treatment [36]. Thus, an array of drugs is applied for the treatment of heart disease. In most cases a multiple drug regimen is applied for conditions such as chronic heart failure, where patients are treated with diuretics for removal of surplus liquid, ACE inhibitors and/or AT1 receptor antagonists to cause peripheral vasodilation, digoxin as positive inotropic agent, antithrombotics, antiarrhythmics, anticoagulants, and hypolipidemic drugs. In addition, the aldosterone receptor antagonists, spironolactone and eplerenone, and β-adrenoceptor antagonists such as metoprolol, bisaprolol, carvedilol, and recently nebivolol have been found to enhance survival in patients suffering from heart failure [37-39]. Nitrates relieve pain, but they have not been shown to prolong survival in chronic heart failure unless they are taken in combination with the peripheral vasodilator, hydralazine [40]. Evidence regarding the effect on erectile function of most of these drugs is sparse [8], while there is some indications regarding the antidepressants often used in connection with heart failure (see below section III.2.).

a) Digoxin

Digoxin is indicated for treatment of atrial fibrillation and heart failure in functional stage III – IV according to the New York Heart Association (NYHA). However, digoxin has no life prolonging effect in patients with chronic heart failure, although it reduces the need for hospitalization [41]. In therapeutic concentrations (0.5 – 0.7 ng/ml) digoxin inhibits erectile function measured by visual sexual stimulation and by nocturnal penile tumescence in healthy volunteers [42]. The mechanism can probably by ascribed to the reported inhibitory effect of digitalis glycosides on NO-evoked vasodilation in isolated penile arteries [43] and corpus cavernosum strips [44]. In addition, a relation of digoxin to low plasma testosterone levels and decrease in sexual desire has been found [45]. Therefore, in the case of ED in patients treated with digoxin, they should consult a cardiologist to evaluate whether treatment with digoxin is necessary.

b) Anticoagulants, antithrombotics, and antiarrhythmics

The information regarding the effects of anticoagulants on erectile function is sparse. There are several case-reports suggesting heparin therapy is associated with priapism [46], and in a review of 121 cases of priapism, four of the patients were in treatment with heparin [47]. The prognosis for preservation of potency after treatment for priapism associated with heparin treatment is poor compared with the overall average with preserved erectile function in patients who have experienced priapism [47]. Treatment with the coumarin derivative, warfarin, was suggested to
be associated with an increased risk of ED in elderly men, but in this study only a few patients were actually treated with warfarin [48]. Therefore, although information regarding anticoagulants and erectile function is lacking, these drugs do not appear to impose a major risk for ED. The same appear to be the case for antithrombotic drugs evaluated over a six month period [49].

Regarding patients in treatment with antiarrhythmics and due to the risk of Q-T interval prolongation in the ECG vardenafil should not be given to patients in treatment with type 1 antiarrhythmics e.g. procainamide or type 3 antiarrhythmics e.g. sotalol and amidarone.

c) Lipid-lowering drugs (fibrates, statins)

Lipid-lowering therapy in hyperlipidemic patients with either fibrates [50, 51] and statins [52, 53] yield substantial health benefits such as diminished coronary events and deaths. High levels of total plasma cholesterol and low levels of high density lipoprotein are associated with an increased prevalence of ED [1, 54, 55]. However, ED was reported to be a frequent side-effect of treatment of hyperlipidaemic subjects using clofibrate [56] or gemfibrozyl [57]. In patients referred to a clinic for primary hyperlipidaemia an increased risk of ED was also observed in patients treated with one of four fibrate derivatives (fenofibrate, ciprofibrate, bezafibrate and gemfibrozyl) [58]. The mechanisms by which fibrates lower lipoprotein levels remain unclear, but they interact with peroxisome proliferator-activated receptors (PPARs) [59], which regulates gene transcription. In the liver activation of PPARα by clofibrate and gemfibrozyl stimulates liver microsomal esterification of estradiol and testosterone [60]. Further studies must show whether the latter mechanism of action is an explanation for the increased prevalence of ED reported in patients treated with fibrates.

In patients with hyperlipidemia and treated with statins such as simvastatin and pravastatin and referred to a clinic for primary hyperlipidaemia, an increased risk for ED was reported [55, 58]. Moreover, five patients with coronary artery disease developed ED one week after starting treatment with simvastatin, and sexual function was restored after stopping the treatment, but ED recurred when two of the patients were rechallenged [61]. No control patients were included in the latter study. In contrast, others in a cross-over study of 22 men with hypercholesterolemia randomized for placebo, simvastatin, or lovastatin, found an increase in nocturnal tumescence after 2 weeks, although the increase was not significant after 6 weeks treatment [62]. Evaluation of the frequency of ED reported in the Scandinavian simvastatin survival study, where 4444 patients with coronary heart disease were randomized to treatment with simvastatin or placebo for up to 6 y, ED was found in 28 placebo-treated patients with eight resolved cases, while ED was present in 37 simvastatin-treated patients with 14 resolved cases [63]. Therefore, so far in patients treated with simvastatin underlying diseased vasculature rather than the drug appears to be the cause of ED.

In contrast to simvastatin, positive effects on erectile function was reported for atorvastatin on erectile function: (1) Atorvastatin was reported to improve nocturnal penile activity in hyperlipidemic patients treated for 4 months [64]; (2) Atorvastatin combined with the angiotensin converting enzyme inhibitor, quinapril had positive effects on ED in men with established penile disease and suboptimal response to phosphodiesterase inhibitors [65]; (3) Atorvastatin improved the response to sildenafil [66]; (4) Combined treatment with atorvastatin and sildenafil had positive effects on ED in men undergoing prostatectomy with bilateral nerve sparing procedure [67]; (5) Atorvastatin had positive effects in patients with hyperlipidemia followed for 12 months [68]. These reported positive effects of atorvastatin, in contrast to simvastatin, on erectile function suggest that the effect of statins is not a class effect of statins. Moreover, in an observational prospective study it was reported that differences in dose, relative efficacy or relative lipophilicity of statin did not show correlation with changes in IIEF score over a 6 month period [49]. However, statins are structurally a heterogenous group of compounds and therefore, other mechanisms than the lipid lowering effects may have significance for the effect of a statin on erection e.g. (1) Atorvastatin, lovastatin, and simvastatin inhibit excretion of phosphodiesterase type 5 inhibitors by cytochrome CYP3A4, while fluvastatin and rosuvastatin inhibit metabolism of sildenafil by cytochrome CYP2C9; (2) The effect on endothelial cell calcium and vasodilatory effects of the different statins appear to differ markedly [69]; (3) Statins may improve erection by inhibition of Rho kinase as recently reported in rats with hypertension or diabetes and erectile dysfunction [70, 71].

d) Aldosteron receptor antagonists

Treatment with spironolactone and eplerenone increase survival in systolic chronic heart failure. In addition, to being an aldosteron receptor antagonists, spironolactone also blocks androgen receptors and that may explain why it is associated with sexual dysfunction. In contrast, the newer aldosteron receptor antagonist, eplerenone, is devoid of effects on sex hormone receptors.

3. SUMMARY

Heart disease and erectile dysfunction (ED) are two highly prevalent disorders that frequently occur concomitantly. Coronary artery disease, HF, and ED share several common risk factors, including diabetes mellitus, hypertension, smoking, and dys-
lipidemia. Additionally, the distinct physiologic sequelae of heart disease create unique organic and psychologic factors contributing to ED in this patient population. Standard HF therapy with beta-adrenoceptor antagonists, digoxin, and thiazide diuretics may worsen sexual dysfunction owing to medication side effects. The effect of statins on erectile function is controversial and may reflect that apart from the lipid-lowering effect, the effect of statins on erectile function is not a drug class effect, but can also be ascribed to other pleitropic effects such as Rho kinase inhibition and different effect on endothelial cell calcium. The aldosterone antagonist, spironolactone is associated with sexual dysfunction due to anti-androgenic properties, but this is not the case for eplerenone.

III. PSYCHOTROPIC MEDICATION

In common with drug treatment for cardiovascular disease, the underlying disorder for which psychotropic medication is being prescribed may be of more relevance than the resulting medication to any sexual dysfunction occurring during treatment. On the other hand neuronal receptor complexity and interrelation of pathways within the CNS make it inevitable that neurons and ganglia involved in sexual functioning will be acted upon by psychotropic drugs leading to functional changes that may be positive or negative. This distinction is illustrated by a comparative study which found that loss of sexual desire was common amongst non-medicated patients with schizophrenia whilst those on antipsychotic drugs had greater desire but increased erectile and ejaculatory disturbance [72]. Evidence of the mechanisms underlying these changes chiefly comes from laboratory study of animal models, particularly the rat. Clinical studies examining this issue tend to be of poor methodological quality and are hampered by the range of sexual symptoms encountered such as altered sexual desire, orgasmic dysfunction and ED. It is therefore difficult to give definitive statements concerning individual drugs.

1. ANTIPSYCHOTICS

Members of this class of drug have many effects within the CNS related to interaction with neuronal receptors and may also act peripherally. Their therapeutic effect is thought to relate to dopaminergic receptor blockade within the limbic and prefrontal areas of the brain. Their unwanted effects are due to alpha-adrenoceptor antagonism and anticholinergic properties together with antidopaminergic actions within the basal ganglia causing extrapyramidal side effects which commonly produce sexual symptoms [73]. The occurrence of extrapyramidal effects differentiates the older <typical> antipsychotics where they are frequent from the newer <atypical> antipsychotics where they are less common. This difference probably relates to variable affinities for particular classes of receptor [74] or avidity for particular areas of the cerebral cortex [75]. An additional effect of dopamine receptor blockade is hyperprolactinemia, which also alters sexual function by reducing dopamine release in permissive cerebral centres, is more common with older <typical> agents.

The results of animal experiments, chiefly in the rat, examining the role of CNS dopaminergic pathways in penile erection and copulatory behaviours has previously been reviewed [76]. It seems likely that D1 receptor activation in the medial pre-optic area (MPOA) of the hypothalamus facilitates erection through intermediary oxytocinergic and spinal cholinergic pathways. It is also possible that activation of D2 receptors in this area have the opposite effect [77]. Older agents such as haloperidol and flupenthixol have both been shown to reduce apomorphine-induced erections in experimental animals by means of D1 receptor antagonism [23]. In addition systemic administration of antipsychotic agents in the rabbit produced erection by a local non-dopaminergic action, possible involving antagonism of α1 adrenoceptors [78]. It can therefore be anticipated that the clinical effect of antipsychotics on sexual function will vary according to their affinity for particular receptors. This seems to be confirmed by reports in the literature of sexual dysfunctions ranging from ED to priapism [79].

In a non-randomised comparative study the prevalence of sexual dysfunction ranged from 40-70% [80]. Newer agents such as clozapine showed a lesser reduction in sexual desire although the group taking risperidone had the greatest decrease in frequency of erection. An earlier study found that thioridazine, an <atypical> agent caused ejaculatory problems rather than ED [81]. In summary, these agents have a credible mechanism of action, but their clinical effect is variable due to differing overall CNS effect. However, in case of sexual dysfunction a psychiatrist should be consulted to consider a switch from conventional to an atypical antipsychotic medication.

Summary

In summary, it is difficult to separate disease from drug effect and also difficult to obtaining reliable information from patients with psychotic illness. There is a paucity of controlled studies. Mainly older antipsychotic drugs results in decreased erection and anorgasmia, while newer anti-psychotics appear to have lower incidence of sexual dysfunction. Among newer anti-psychotics, risperidone appears to have the highest rate of sexual dysfunction, while there are insufficient data on aripiprazole and ziprasidone.

2. ANTIDEPRESSANTS

Depression by itself makes it difficult to separate effect of illness from additive effect of drugs, since
mood disorders may lead to lack of interest and emotional withdrawal from the sexual partner. Antidepressants can have numerous effects on sexual function including altered sexual desire, erection difficulties, and orgasm problems. The evidence has been summarized in a recent Cochrane review of fifteen randomised studies [82]. The main conclusion regarding co-medication to correct erectile dysfunction was an effect of sildenafil in three of the clinical trials, while the available evidence was insufficient regarding other strategies for correction of erectile dysfunction.

a) Tricyclic antidepressants

This drugs act by inhibiting the re-uptake of catecholamines in the CNS. Their sexual side effect profile is thought to relate to peripheral anticholinergic and beta adrenergic effects. It is also possible that they antagonise serotonin (5-HT) receptors. Animal studies needed to confirm these putative effects have not been performed. Controlled clinical studies suggest that orgasmic disorders in both sexes are most frequent, explaining the use of these drugs as inhibitors of ejaculation [83, 84]. Against this a case-control study showed no excess sexual dysfunction amongst patients taking a tricyclic antidepressants [85]. In summary these drugs most frequently cause orgasmic dysfunction for which the underlying mechanism is unclear.

b) Monoamine oxidase inhibitors

These drugs are now rarely used. In common with the tricyclic antidepressants they are associated with higher rates of orgasmic dysfunction in controlled trials [83], the nature of the central or peripheral mechanisms involved is uncertain.

c) Selective serotonin re-uptake inhibitors (SSRIs)

This represents the commonest class of drug currently used to treat depression. They inhibit the re-uptake of 5-HT (serotonin) into CNS neurones and can therefore produce stimulatory effects on various 5-HT receptors. It is estimated that up to 50% of patients taking these drugs experience a change in sexual function [86]. Possible mechanisms include stimulation of 5-HT2 and 5-HT3 receptors which may inhibit erogenous pathways within the spinal cord [87], decreased dopamine release in the medial preoptic area [88] and inhibition of both central and peripheral nitric oxide synthase. A controlled clinical study suggested that the improvement in sexual function resulting from alleviating clinical depression seen with SSRI treatment outweighed any negative effect of the drug [89]. Other placebo controlled randomised studies, however, did reveal increased sexual dysfunction, mainly anorgasmsia, in the SSRI treated group [90, 91]. Further studies have suggested that these adverse effects can be modified by co-treatment with other drugs such as sildenafil [73, 92, 93] or mianserin [94].

SSRIs differ in their ability to cause ED. A high incidence of ED has been observed in patients under treatment with the SSRI, paroxetine [95], while a lesser impact on sexual function has been reported in patients treated with the SSRI, citalopram [96]. This fact suggests that other mechanism(s) different from inhibition of serotonin reuptake could possibly account for ED associated to SSRI-treatment. This hypothesis is supported by the evidence that acute or chronic paroxetine, but not citalopram, caused ED in rats by inhibiting NO production [97]. Indeed, the inhibitory effects induced by acute paroxetine on erectile function in the rat can be prevented by inhibition of PDE5 with vardenafil [98]. On the other hand, venlafaxine a mixed inhibitor of serotonin and norepinephrine reuptake, produced ED in rats by increasing norepinephrine levels, since its inhibitory effects on erectile responses were prevented by phenolamine [99]. Thus, the ability to produce ED and the mechanism by which SSRIs cause ED may differ depending on the specific SSRI compound.

d) Other Antidepressants

Animal experiments suggest that stimulation of 5-HT1 receptors within the CNS helps modulate sexual function with the 5-HT1A sub-type increasing ejaculation and the 5-HT1C sub-type improving erection. This has a bearing on the use of recently developed antidepressant drugs such as mirtazapine and nefazodone which tend to have beneficial effects on sexual function possibly by activation of the 5-HT1c receptor which augments sexual response [100], although they may also antagonism at the 5-HT2C receptor [101]. The isolated reports of priapism seen with a prototype agent, trazadone, which has been shown to increase nocturnal erectile activity despite reducing REM sleep [102, 103] may be related to the 5-HT1C erogenic effect seen with its primary metabolite, m-chlorophenylpiperazine, in experimental animals [23].

e) Summary

It is difficult to separate the effect of illness from the additive effect of anti-depressant drug. SSRIs and venlafaxine may negatively affect all the steps of the male sexual response cycle (desire-arousal-excitement- оргasm). Bupropion, nefazodone, and mirtazapine have lower rates of sexual dysfunction than SSRIs. For men with anti-depressant-induced ED, the addition of sildenafil appears an effective strategy. Potentially promising strategies include also the addition of bupropion, tadalafil, and buspirone. There are insufficient randomised data assessing effect of dose reduction and e.g. drug holidays on sexual function in patients treated with anti-depressants.
3. ANXIOLYTICS

Although not previously associated with causation of ED, findings from the MMAS study implicate this class of drug in sexual problems reported by the male cohort [5]. Benzodiazepines are thought to act to potentiate the action of the neurotransmitter gamma amino butyric acid (GABA) in the reticular and limbic system but may also affect the serotonin and dopaminergic pathways. Experimental studies suggest that GABA-ergic drugs inhibit erection induced by apomorphine, a dopamine agonist [104]. Clinical correlates are scarce but a controlled study did demonstrate that a combination of lithium and benzodiazapine was associated with significantly higher rate of sexual dysfunction than treatment with lithium alone [105]. More recent anxiolytic agents such as bupropion, acting mainly by inhibiting dopamine reuptake, and buspirone which acts on 5-HT1A receptors are not associated with sexual side effects in placebo controlled trials [106] and can be used to alleviate sexual symptoms caused by other antidepressant medication [107].

4. ANTICONVULSANTS

Focal epileptic discharges from the temporal lobe may affect the function of the hypothalamic-pituitary axis, and hence the level of several hormones of importance for sexual function [108]. In addition, there are several case reports of anorgasmsia on gabapentin and carbamazepine as well as decreased libido on valproate [109, 110]. There are case reports of improved erectile function in patients switched to lamotrigine [110-112].

5. OPIATES

Long term intrathecal administration of opiates results in hypogonadotrophic hypogonadism and associated sexual dysfunction that can be restored with appropriate supplementation [113]. Administration of opioid antagonists to older men with ED however did not improve erectile function measured objectively by NPT monitoring [114]. Opioids do have a generalised depressant effect on sexual function when directly administered to the MPOA in rat brain but treatment with the opioid receptor antagonist, naloxone, had no sexual effect on healthy male volunteers [23].

6. ANTI-ANDROGENS

These drugs cause partial or near complete blockade of circulating androgens by inhibiting production or antagonism at the androgen receptor (AR). They will therefore have secondary effects on sexual function commensurate with the fall in circulating or tissue androgen levels. It is thought that in the adult androgens modify sexual behaviour chiefly by modulating sexual desire via AR within the CNS. The effects of androgen deficiency on sexual activity are variable within each individual ranging from complete loss to normal function. Experimental studies in humans suggest that spontaneous erections during REM sleep are androgen dependent whilst psychogenic erections in response to visual sexual stimulation are androgen independent [4]. An additional peripheral effect has been suggested from animal work which showed that castration decreased NOS activity within rat corpus cavernosum leading to reduced erectile activity. The addition of testosterone restored activity but this recovery was prevented by treatment with finasteride, suggesting that dihydrotestosterone may be the important androgen in peripheral sexual responses such as penile erection [115].

The anti-androgen with least effect on circulating testosterone is the 5 alpha reductase inhibitor, finasteride, which is used in the treatment of symptoms due to benign prostatic enlargement (BPE) and male pattern alopecia. In randomised placebo controlled studies of treatment with finasteride 5 mg daily for BPE approximately 5% of men complained of sexual symptoms of decreased desire and ED compared to 1% in the placebo group [116]. At the lower dose of 1 mg daily used to treat male pattern alopecia no excess sexual dysfunction was seen compared to placebo [117]. Given the animal work it seems possible that this effect is secondary to reduced availability of dihydrotestosterone in the penis.

More complete androgen ablation is achieved by competitive antagonism at the AR, so preventing transduction of response to circulating testosterone and dihydrotestosterone. Non-steroidal drugs such as flutamide and bicalutamide have relatively pure effects on the AR, whilst the steroidal anti-androgen, cyproterone acetate also has inhibitory effects on the hypothalamus. These drugs are used in the palliative treatment of locally advanced and metastatic prostate cancer either alone of in combination with a luteinising hormone releasing hormone (LHRH) agonist (complete androgen blockade). When used alone non-steroidal anti-androgens are associated with a rise in serum testosterone levels whilst combination with a LHRH agonist will reduce these to the castrate range. Again they can be expected to predominantly reduce sexual desire through a central action, an effect that occurs in up to 70% of men treated [118]. This unwanted effect is now becoming of more concern as such drugs are being used at an earlier stage of the disease.

When sexual activity in men being treated by castration or bicalutamide was compared in a small randomised trial no differences in self reported sexual activity or nocturnal penile tumescence were seen. In subsequent trials with larger sample size and longer duration, treatment with bicalutamide alone resulted in a lesser decrease in sexual desire [119]. In another large controlled trial treatment with either flutamide or cyproterone resulted in gradual loss of sexual desire in approximately 80% of men in both groups over a period of 2 - 6 years [120]. Even at a
low dose of 50 mg, bicalutamide therapy resulted in half the patients in one placebo controlled study suffering loss of erectile function [121].

The near complete androgen deprivation achieved by medical castration with LHRH agonists results in a profound loss of sexual desire which is usually accompanied by ED in controlled trials [122] This was objectively confirmed by nocturnal penile tumescence monitoring (NPT) before and after initiation of therapy in a small study [123]. These more recent findings make initial hopes that such drugs could be used to treat ED appear suspect [124].

In summary antiandrogen drugs produce the expected effects of sexual desire and erection commensurate with the degree of androgen ablation achieved.

7. MISCELLANEOUS DRUGS

Many other drugs are suggested as having sexual side effects, in particular that of ED in men, but these contentions are usually based on anecdotal case reports or post-marketing drug alerts rather than controlled trials.

a) Histamine H2 Receptor Antagonists

Cimetidine and ranitidine were previously widely prescribed for prophylaxis and treatment of peptic ulcer disease, their use has since declined as newer regimens have evolved but are increasingly available as <over the counter> medication. Case reports suggested that cimetidine was associated with ED and postulated mechanisms included anticholinergic effects and androgen inhibition. A single in vitro animal study suggested that histamine H2 receptor stimulation did cause cavernosal relaxation possibly via endothelial release of nitric oxide [23]. These reports have not been confirmed by well designed trials.

b). Retroviral Drugs

The need for evaluating sexual health in clinical trials where antiviral drugs are evaluated has recently been stressed [125]. Some studies have suggested that anti-retrovirals, in particular certain protease inhibitors e.g. ritonavir [126], may cause sexual problems or dysfunction [127-132], although this was not the case in a larger cross-sectional study [133]. The protease inhibitors are structurally very different and therefore, they may affect sexual function differently.

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Committee 14

Endocrine Aspects of Male Sexual Dysfunctions

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Hormones play an essential role in cellular dialog. Testosterone is the main hormone involved in the complex dialog between the brain and peripheral organs controlling male sexual function. Its presence is a prerequisite for erection in laboratory animals. Testosterone modulates multiple mechanisms involved in the erectile machinery, including expression of the enzymes that both initiate (Nitric Oxide Synthase) and terminate (Phosphodiesterase type V) erection. In addition it is essential for sexual motivation. Whether this well established animal data could be completely extrapolated to human erections is still a subject of controversy. Testosterone plays also a broader role in overall men’s health. Many recent studies have established strong associations of low testosterone with metabolic imbalances. These may partly result from the lowering effect of obesity on blood testosterone but low testosterone predicts diabetes and metabolic syndrome occurrence in lean men too. One example is the metabolic damage that follows androgen deprivation for treatment of prostate cancer. Likewise associations of low testosterone levels with cardiovascular disease and in some studies decreased longevity have been repeatedly reported and might be a consequence of the detrimental impact of low testosterone on metabolic functions. Low testosterone has also been reported to predict depression. However conflicting data do also exist: longitudinal studies do not support the predictive value of low blood testosterone for further cardiovascular events, and available interventional studies do not confirm a beneficial effect of testosterone therapy on depression of aging men (though they were of short duration). Prospective interventional studies of sufficient power and duration are therefore required before screening for testosterone deficiency and correcting it may be considered as preventive medicine as many data suggest.

The aim of this chapter is:
- To critically evaluate the peer reviewed scientific evidence supporting or refuting the role of androgens in men’s health and aging, especially including sexual health, psychic functions, metabolic balance and vascular health.
- To refine practical recommendations for testosterone deficiency screening, diagnosis and treatment, including a review of testosterone therapy safety, and guidelines for its follow-up
- To review the role of other hormonal and metabolic disturbances in male sexual dysfunctions, including those of estradiol, adrenal steroids, pro-opiomelanocortin derivatives, prolactin, growth hormone and thyroid hormones, and when justified to provide the reader with practical guidelines for screening for, diagnosing and treating such abnormalities.

This chapter has been drawn up in starting from two previous comprehensive reviews of the covered topics: the report of the committee “Endocrine Aspects of Men Sexual Dysfunctions” of the second consultation on Sexual Medicine held in Paris in July 2003 by Morales et al (1), and the chapter “Hormones, Metabolism, Aging and Men’s Health” of the book “Standard Practice in Sexual Medicine” published in 2006 by the Standard’s Committee of the International Society for Sexual Medicine (Buvat et al 2006, [2]). The readers may find more developments on the basic aspects of the corresponding topics in these reviews and in others mentioned in our chapter.
A. TESTOSTERONE

I. PHYSIOLOGICAL REMINDER

Levels of T are expressed either in pmol or nmol/L or in pg or ng/ml (1000 pg or pmol = respectively 1 ng or nmol. The conversion factors are nmol/L or pmol/L x 0.2884 = respectively ng/ml or pg/ml, and ng/ml or pg/ml x 3.467 = respectively nmol/L or pmol/L (Table I).

1. SECRETION, TRANSPORT,

Testosterone (T) is synthesized by an enzymatic sequence of steps from cholesterol within the Leydig cells. T biosynthesis involves 2 multi-functional cytochrome P450 complexes involving hydroxylations and side-chain cleavage together with 3 and 17 ß-hydroxysteroid dehydrogenases and ∆4,5 isomerase. Testicular T secretion is principally governed by luteinizing hormone (LH). T (and its androgenic metabolite, dihydrotestosterone (DHT), exert biological effects directly through binding to the androgen receptor and indirectly through aromatization of T to estradiol (E₂), which allows action via binding to the estrogen receptors (ERs).

T circulates in blood at concentrations above its aqueous solubility by binding to several plasma proteins, especially sex-hormone binding globulin (SHBG), with a single high-affinity androgen binding site. SHBG is secreted by the liver, so its circulating levels are particularly influenced by first-pass effects of oral drugs including sex steroids. Circulating SHBG (and thereby total T) are decreased by androgens and glucocorticoids or increased by estrogens and thyroxine. Other determinants of circulating SHBG levels are up-regulation by acute or chronic liver disease and androgen deficiency and down-regulation by obesity, insulin, and growth hormone (GH) deficiency. Under physiological conditions, 60-70% of circulating T is SHBG-bound with the remainder bound to lower-affinity, high capacity binding sites (albumin) and 1-2% remaining non-protein bound. According to the free hormone hypothesis (38-40), the “free” (non-protein-bound) fraction is capable of diffusing into the target cells and binding to its receptor. This is the most biologically active fraction while the loosely protein-bound T constitutes a larger “bioavailable” fraction of circulating T. Circulating T levels demonstrate a distinct diurnal rhythm. Diurnal patterns of morning peak T levels and nadir levels in afternoon are evident in younger men but this pattern is lost in some older men (3,4).

2. AGING AND TESTOSTERONE SECRETION

Plasma levels of total, bioavailable and free T fall with aging (4). Even though age itself impacts on the decline of plasma T over the lifetime (4), ill health, more than age itself, is a potent predictor of a decline in T levels in a man’s life (5,6). Chronic illness, a high body mass index (BMI) and a large waist circumference are related to a significant decrease in total, free and bioavailable T concentrations. Apparently healthy men have significantly higher

Table 1: Conversion factors for hormones

| - Testosterone          | 1 ng/dl = 100 ng/ml, 1 ng/ml = 1000 pg/ml, 1 nmol/l = 1000 pmol/l |
|                        | 1 nmol/l = 0.2884 ng/ml = 28.84 ng/dl                           |
|                        | 1 ng/dl = 0.03467 nmol/l ; 1 ng/ml = 3.467 nmol/l              |
|                        | 7 nmol/l # 200 ng/dl, 8 nmol/l = 231 ng/dl, 10 nmol/l = 288 ng/dl, |
|                        | 10,4 nmol/l = 300 ng/dl, 12 nmol/l = 346 ng/dl, 14 nmol/l = # 400 ng/dl |

| - Free testosterone    | 1 pg/ml = 3,467 pmol/l                                       |
|                        | 1 pmol/l = 0,2884 pg/ml                                    |

| - Estradiol            | 1 pg/ml = 3,671 pmol/l                                     |
|                        | 1 pmol/l = 0,2724 pg/ml                                    |

| - Prolactin            | 1 ng/ml = 20 mU/ml                                         |
median hormone concentrations at most time points than unhealthy men (7). The decline of plasma T begins in fact in the fourth decade. There is a constant percent change per year between ages of 39-70 years. Free T declines by 1.2%/year, and albumin-bound T by 1.0%/year. SHBG, the major serum carrier of T, increases by 1.2%/year, with the net effect that total serum T declines more slowly (0.4%/year) than the free or albumin-bound pools alone, so the total testosterone level is less accurate in older men.

3. PHYSIOLOGICAL EFFECTS OF TESTOSTERONE

a) effects on sexual function:

The testis is the key organ for male reproductive and sexual fitness. A T-based, gender-related, dichotomy is an essential condition for life perpetuation, allowing the male to be always ready to take advantage of sexual (and therefore reproductive) opportunities. In fact, while in women sex steroids substantially fluctuate as a function of ovarian cycles, in men T plasma levels are relatively constant and high, because of a continuous testicular production. In adult life, T is considered the hormonal fuel of sexual desire but it also regulates all the other steps of the male sexual response, including sexual excitation and orgasm/ejaculation. Androgen receptor (AR) is highly expressed in the brain, mainly in the hippocampus, cerebral cortex and hypothalamus, and in peripheral target tissues involved in excitation (pelvic floor muscles, penis) and ejaculation (epididymis, seminal vesicles, vas deferens and prostate). Low T is often associated with reduced sexual desire and nocturnal penile erections, while association with sex-induced erection is less evident. This is because T regulates not only cyclic Guanosine-Monophosphate (cGMP) formation, through nitric oxide synthase (NOS) stimulation, but also its catabolism, through phosphodiesterase-5 (PDE5) activity. The androgen-dependent PDE5 expression could explain the reduced effectiveness of PDE5 inhibitors (PDE5i) in the treatment of erectile dysfunction in hypogonadal patients. The main physiological action of T is therefore to timely adjust the erectile process as a function of sexual desire, therefore finalizing erections to sex. Accordingly, penile erection is not a random phenomenon but a discrete, timely adjusted event, consequent to sexual desire and arousal (2,8-10).

b) effects on other functions

The by consensus recognized signs and symptoms of Testosterone Deficiency (TD) include not only sexual dysfunction, but also depressed mood, decreased vitality, decreased lean and increased fat body mass, decreased bone mineral density and osteoporosis (11). TD has been recently considered one of the many adverse consequences of overweight and obesity. On the other hand, low T levels could contribute to the accumulation of excess fat, establishing a vicious cycle. Pathogenetic mechanisms linking hypogonadism with obesity and insulin resistance appear to be complex and often multi-directional. In fact, visceral obesity can probably be considered a relevant cause of hypogonadism (directly or through obesity-induced insulin resistance); at the same time, hypogonadism could be a cause of obesity and insulin resistance (2,10).

II. PATHOPHYSIOLOGICAL ASPECTS

1. CLASSIFICATION OF TESTOSTERONE DEFICIENCIES (FIGURE 1)

The classic taxonomy of TD includes defects of various nature and degree occurring at various levels of the hypothalamus-pituitary-testis axis. TD can be caused by an abnormality in the testicles (primary hypogonadism/TD), by a pituitary or hypothalamus failure (secondary hypogonadism/ TD) or by a combination of the two (mixed hypogonadism/TD). In addition a clinical TD could result from any impairment to T action because of

Figure 1: Characteristics of male hypogonadism/testosterone deficiency, reported according to the age of onset of the disease and the patient’s phenotype. Schematic prevalence in male population is also shown. Size of ellipsis reflects on abscissa (log scale): age of onset and on ordinates (log scale): incidence (right axis) or female to male phenotype (left axis, arbitrary unit). VEOH: very early onset hypogonadism/testosterone deficiency (red ellipsis), i.e. starting during foetal life for absence of testosterone formation or activity (examples are: Leydig cell hypoplasia type 2, complete androgen insensitivity or absence of 17β-hydroxysteroid dehydrogenase, yellow ellipsis) or impaired secretion or activity of GnRH (for causes see Table 1). EOH: early onset hypogonadism/testosterone deficiency (i.e. peri-pubertal onset, as in Klinefelter’s syndrome, blue ellipsis). LOH: late onset hypogonadism/testosterone deficiency, i.e. in adulthood or aging (also termed andropause, grey ellipsis). Adapted from Morelli et al 2007(12)
increased SHBG and decreased bioavailability or because of Androgen Receptor (AR) alterations. Causes of hypogonadism are listed in Table II. The nosography depicted in Table II retains a practical utility for treatment purpose. In fact, while patients with hypothalamic or pituitary causes of testis failure (secondary hypogonadism/TD) can be successfully treated with either gonadotropins/GnRH or T, for those affected by primary testicular failure (primary hypogonadism/TD), only T must be considered. However, this classification does not take into consideration symptoms. It is well known that both primary and secondary hypogonadism, if not treated, are characterized by symptoms and signs of different severity, according to the age of onset of testicular failure more than the cause of this failure. In the case of a very early onset hypogonadism (VEO), i.e. during early foetal life, symptoms can be dramatic, spanning from an almost complete female phenotype (complete androgen insensitivity or enzymatic defects blocking androgen synthesis) to various defects in virilization (micropenis, hypospadias, cryptorchidism), as in the case of impaired secretion or activity of gonadotropins or GnRH (Figure 1), (12). In the case of a peri-pubertal appearance of the hypogonadism (early onset hypogonadism/TD, EOH), because of milder central or peripheral defects (as in Klinefelter’s syndrome), there might be a delay in the onset of puberty with an overall eunuchoidal phenotype, including scant body hair, high-pitched voice, small testis, penis and prostate (Figure 1). On the other hand in the case of a post-pubertal onset hypogonadism/TD, due to any reason, symptoms will be relatively mild, insidious and difficult to be recognised. Generally speaking, however, the incidence of hypogonadism due to known aetiologies is not so frequent. EOH and, in particular; VEOH are often due to rather uncommon problems (although not so rare, spanning from 1:500 for Klinefelter’s syndrome to 1:100000 for complete androgen insensitivity syndrome). A more frequent form of post-pubertal TD is the so called age-related hypogonadism/TD (11) defined as late onset hypogonadism (LOH) or TD Syndrome (TDS), a condition affecting aging health with an unknown aetiology and natural history, which often results from a mixed contribution of testicular and hypothalamic-pituitary failure. In addition TD in adult life is often co-morbid to several often-present conditions as obesity, type 2 diabetes mellitus, use of medications and chronic illnesses. Whether TD is the cause or the consequence of these associated conditions is still a matter of intense debate.

2. THRESHOLD LEVELS FOR TESTOSTERONE ACTION AND THE IMPORTANCE OF RECEPTOR SENSITIVITY

A clear-cut threshold for TD has not been agreed upon. Rather, recent evidence demonstrates the prevalence of psychosomatic symptoms and metabolic risk factors gradually accumulates with decreasing androgen levels. Androgen-related loss of libido or vigor increases below T concentrations of 15 nmol/L, accumulation of visceral fat below concentrations of 12 nmol/L, whilst depression and type 2 diabetes mellitus (also in non-obese men) are augmented in men with T concentrations below 10 nmol/L (Figure 2). Erectile dysfunction has been identified as a composite pathology of metabolic risk factors, smoking and depression, and T concentrations contributed to that symptom only below 8 nmol/L (13).
Table II: Etiology of male hypogonadism. The typical hormonal pattern is reported in brackets. Note that conditions reported in italics are only characterized by impaired sperm production and not by abnormal testosterone synthesis and/or activity. KAL-1: anosmin or Kallmann protein; FGFR-1: fibroblastic growth factor receptor-1; PROK-2: prokineticin-2; PROKR-2: prokineticin-2 receptor, GnRH: gonadotrophin releasing hormone; GPR-54: g-protein-coupled receptor-54; DAX-1: dosage-sensitive sex reversal congenital adrenal hypoplasia critical region on the X chromosome-1; SF-1: steroidogenic factor-1; HESX1: HESX homeobox 1; PROP-1: prophet of Pit1, paired-like homeodomain transcription factor; LHSX3: LIM homeobox 3; GnRHR: gonadotrophin releasing hormone receptor; FSHR: follicle-stimulating hormone β-subunit; LHβ: luteinizing hormone β-subunit; STAR: steroidogenic acute regulatory protein; 3β-HSD: 3β-hydroxysteroid dehydrogenase; 17α-HSD: 17α-hydroxysteroid dehydrogenase; 17β-HSD: 17β-hydroxysteroid dehydrogenase; INSL3: insulin like-3 peptide; LGR8: leucine-rich repeat-containing, G protein-coupled receptor-8, or insulin like-3 peptide receptor; FSHR: Follicle-stimulating hormone receptor.

Synopsis:
1) Decreased testosterone production
   - Hypothalamic diseases (secondary or central hypogonadism)
   - Pituitary diseases (secondary or central hypogonadism)
   - Testicular diseases (primary hypogonadism)
2) Decreased testosterone bioactivity

1) Decreased testosterone production
   a) Hypothalamic diseases (secondary hypogonadism: ↓gonadotrophins, ↓testosterone)
      - Congenital
         i) Kallmann syndrome (including KAL 1, FGFR1, PROK2, PROKR2 mutations)
      ii) GnRH gene deletion
   III) Leptin and Leptin receptor mutation
   IV) GPR-54 mutation
   V) Prohormone convertase 1 mutation
   VI) DAX-1 mutation
   VII) SF-1 mutation
   VIII) Septo-optic dysplasia (including Hesx-1 mutation)

IX) Prader-Willi syndrome
X) Laurence-Moon syndrome
XI) Bardet-Biedl syndrome
   - Acquired
   I) Hypothalamic tumors
      - Germinomas and other germ tumors
      - Gliomas
      - Astrocytomas
      - Craniopharyngiomas
      - Meningioma
      - Metastases
   II) Infiltrative and infective disorders
      - Langerhans' histiocytosis
      - Sarcoïdosis and tuberculosis, syphilis
      - Fungal, parasites, viral
   III) Head trauma
   IV) Empty sella
   V) Vascular
   VI) Drugs
      - GnRH analogs (agonists and antagonists)
      - Estrogens
      - Anabolic steroids
      - Progestogens (including cyproterone acetate and spironolactone)

XII) X-irradiation

2) Decreased testosterone bioactivity
   a) Pituitary diseases (secondary hypogonadism: ↓gonadotrophins, ↓testosterone)
      - Congenital
         I) Multiple hormone deficiency (including Prop1, LHX3, DAX-1 mutations)
      II) GnRHR mutations
      III) FSHβ and LHβ mutations
      IV) Pituitary aplasia or hypoplasia
   V) Hemochromatosis
      - Acquired
      I) Pituitary tumors
         - Functional and non-functional adenomas
         - Craniopharyngiomas
         - Metastases
         - Hematologic malignancy
         - Rathke's cyst
      II) Infiltrative
         - Primary hypophysitis
         - Sarcoïdosis and tuberculosis, syphilis
         - Fungal, parasites, viral
      III) Head trauma
      IV) Empty sella
      V) Vascular
      VI) Drugs
         - GnRH analogs (agonists and antagonists)
         - Estrogens
         - Anabolic steroids
         - Progestogens (including cyproterone acetate and spironolactone)
   
   b) Testicular diseases (primary hypogonadism: ↑gonadotrophins ± ↓testosterone)
      - Congenital
         I) Klinefelter syndrome
      II) Defects of testosterone biosynthesis (STAR, 20-22 desmolase, 3β-HSD, 17α-HSD, 17-20 desmolase, 17β-HSD)
      III) Pure gonadal dysgenesis (46 XX and 46 XY)
      IV) Congenital anorchia
   V) Leydig cell hypoplasia (including type I and II for LH/HCG receptor mutations)

- Metabolic syndrome
- Cushing Disease
- Estrogens
- Anabolic steroids
- Progestogens (including cyproterone acetate and spironolactone)
- Functional disorders
- Nutritional
- Critical illness
- Excessive exercise (rare)
- Diabetes Mellitus
- Hyperprolactinaemia (prolactinoma, hypothyroidism, antidopaminergic and serotoninergic drug-induced, opiates-induced)
- Metabolic syndrome
- Cushing Disease

- Medical conditions characterized by impaired sperm production and not by abnormal testosterone synthesis and/or activity. KAL-1: anosmin or Kallmann protein; FGFR-1: fibroblastic growth factor receptor-1; PROK-2: prokineticin-2; PROKR-2: prokineticin-2 receptor, GnRH: gonadotrophin releasing hormone; GPR-54: g-protein-coupled receptor-54; DAX-1: dosage-sensitive sex reversal congenital adrenal hypoplasia critical region on the X chromosome-1; SF-1: steroidogenic factor-1; HESX1: HESX homeobox 1; PROP-1: prophet of Pit1, paired-like homeodomain transcription factor; LHSX3: LIM homeobox 3; GnRHR: gonadotrophin releasing hormone receptor; FSHR: follicle-stimulating hormone β-subunit; LHβ: luteinizing hormone β-subunit; STAR: steroidogenic acute regulatory protein; 3β-HSD: 3β-hydroxysteroid dehydrogenase; 17α-HSD: 17α-hydroxysteroid dehydrogenase; 17β-HSD: 17β-hydroxysteroid dehydrogenase; INSL3: insulin like-3 peptide; LGR8: leucine-rich repeat-containing, G protein-coupled receptor-8, or insulin like-3 peptide receptor; FSHR: Follicle-stimulating hormone receptor.
of onset of the disease. In a consecutive series of 1647 (mean age 52.4±13.1 years) male patients with sexual dysfunction (and therefore potentially with TD) it was found that parameters significantly associated with total and free T levels in the entire cohort were waist circumference and triglyceride levels, as well as an increased prevalence of metabolic syndrome (10). The prevalence of hypoactive sexual desire (HSD) decreased as a function of T only in the youngest (17-42 years old) age quartile, as well as the reported reduction in nocturnal erections. In the oldest age quartile it was reported an inverse relationship between T levels and the prevalence of severe erectile dysfunction (ED) and a positive relationship with intercourse frequency. Accordingly, in the oldest age quartile, subjects with higher T levels showed better penile flow at penile colour Doppler ultrasound, as well as a better lipid profile. An inverse association between somatized anxiety and T levels was observed only in the oldest age quartile. It is interesting to note that from this study (10) low testosterone was associated with sexual dysfunction more often in the oldest subjects.

### III. Metabolic Syndrome and Metabolism

Metabolic syndrome (MetS) is a clustering of conditions that increases the risk of type 2 diabetes mellitus (T2DM: a clinical condition characterized by high levels of sugar in the blood and insulin resistance) and cardiovascular disease. The MetS components involve abnormalities of glucose metabolism, body composition, blood pressure, HDL cholesterol, and triglycerides. There are several definitions of the MetS (see in Table III and Guay 2008 [15], and Corona et al. 2009 [10] for reviews), although "android obesity" - nowadays known as "central or visceral obesity" – and insulin resistance are generally considered the key elements of MetS (16). Term insulin resistance underscores the inability of insulin to promote normal homeostasis of glucose, i.e a higher-than-normal concentration of insulin in order to maintain normal glycaemia and appropriate glucose utilization.

Over the last few years, the association between insulin resistance, T2DM, MetS and TD has emerged as an issue in subjects both with (17-22) and without ED (23,24). The evidence, in fact, universally shows a strong relationship between TD and MetS, and its individual components (figure 3), both in cross-sectional and longitudinal studies. Cross sectional studies have demonstrated an association between low T concentrations and T2DM since the 1990s (studies reviewed in Ding et al., 2006 [25]). In addition, prospective studies have clearly demonstrated that a low T at baseline could predict the development of T2DM (6,26-28) or both T2DM and MetS (29, 30); see for review Corona et al., 2009 a et b, Traish et al., 2008 a et b (10, 22, 23, 31). Moreover, it has also been reported that T2DM and MetS at the baseline could predict the development of TD (32-34).
TD is characterized by hypertriglyceridaemia-waist phenotype (see in Corona et al., 2009 [10] for review). Elevated waistline and triglycerides are the factors, among MetS determinants, most closely associated with insulin resistance. Interestingly, a strong inverse relationship between SHBG-unbound testosterone and pulse pressure (PP) was recently reported (35). Pulse pressure is the arithmetic difference between systolic and diastolic blood pressure and reflects arterial stiffness, another marker of insulin resistance. Cross-sectional studies have also demonstrated that MetS is associated with an increased prevalence of sexual dysfunctions, essentially characterized by worse erectile function, due to impairment in penile blood flow (36-43).

For all these reasons, men with MetS should have a T level drawn and men with TD should be evaluated for components of MetS, as these may foreshadow both diabetes mellitus and cardiovascular disease.

The effect of T therapy (Tth) in TD subjects is still a controversial issue. According to two recent meta-analyses, Tth exerts only small and clinically negligible effects on lipid fractions and blood glucose, whatever the baseline T level (44, 45). In addition, Tth is unlikely to improve the age-associated deterioration in glucose tolerance commonly observed in elderly men. However, Tth seems to improve insulin sensitivity and glycemic control in hypogonadal men with T2D or MetS (46-50).

| Table III: Diagnostic Criteria for the Metabolic Syndrome in Men According to Various Definitions (reprinted with permission from Traish AM, Guay AT et al 2009 [22]) |
|-------------------------------------------------|---------------------------------|---------------------------------|
| Components of the MetS | WHO: Criteria #1 + 2 of the other 4 | NCEP–ATP III: ≥ 3 of 5 criteria | IDF: Criteria #2 + 2 of the other 4 |
| 1. Hyperglycemia Hyperinsulinemia | FBS ≥ 110 mg/dL (≥ 6.1 nmol/L) ↑ insulin or IR or T2DM | FBS ≥ 110 mg/dL (≥ 6.1 nmol/L) or T2DM | FBS ≥ 100 mg/dL or T2DM |
| 2. Increased Body Size | WHR > 0.90 WC ≥ 94 cm BMI ≥ 30.0 | WC ≥ 102 cm | WC ≥ 94 cm |
| 3. Triglycerides | ≥ 150 mg/dL (≥ 2.3 mmol/L) | ≥ 150 mg/dL (≥ 2.3 mmol/L) | ≥ 150 mg/dL (≥ 2.3 mmol/L) |
| 4. HDL Cholesterol | < 35 mg/dL (< 0.9 mmol/L) | < 40 mg/dL (< 1.03 mmol/L) | < 40 mg/dL (< 1.03 mmol/L) |
| 5. Blood Pressure | BP ≥ 140/90 mmHg or HTN on Rx | BP ≥ 130/85 mmHg or HTN on Rx | Systolic BP ≥ 130 mmHg Diastolic BP ≥ 85 mmHg or HTN on Rx |

Figure 3: Main correlations between hypogonadism and metabolic parameters leading to the Metabolic Syndrome (adapted from from Traish AM, et Guay AT 2009 [22]).
49), though this data has still to be confirmed with more controlled trials. Weight loss and exercise ameliorate not only glycaemic control and prevent T2DM but can also raise androgen levels, as found in some studies in obese men (50-54). However, negative studies have also been reported (55,56). Nonetheless, life-style modifications should be strongly encouraged in subjects with MetS, because it has been demonstrated that in a Finnish cohort followed longitudinally for 11 years, those having MetS at baseline but not at follow-up, did not retain a statistically significant risk of having hypogonadism (32).

Experimental studies in human and animal models have recently helped in understanding the vicious circle underlying the positive interaction between MetS and TD, which is summarized in Figure 4. AR is mostly expressed in visceral fat and negatively regulates differentiation of preadipocytes to mature adipocytes (57). In addition, androgens might decrease fat mass by regulating the differentiation of mesenchymal stem cells to adipocytes (58). In humans, T acutely inhibits oleic acid uptake in omental and retroperitoneal, but not subcutaneous, adipose tissue, acting through lipoprotein lipase (59). In a recent study involving 60 aging males, testosterone therapy for 1 year, in comparison with placebo, selectively reduced visceral fat accumulation without modifying total body composition, while increasing fat-free mass and skeletal muscle mass (60). Overall, these studies demonstrate that the androgenic milieu can affect visceral fat disposition and that this action is rapid and maintained over the long term.

Lin et al. (61) demonstrated that male but not female androgen receptor (AR) knockout (ARKO) mice are characterized by progressively reduced insulin sensitivity and impaired glucose tolerance with advanced age. In addition, recent evidence (62,63) demonstrated that the specific deletion of hepatic AR is associated with the development of insulin resistance and liver steatosis in male but not female mice, suggesting a different tissue-specific role of AR in males. A mixed (primary and secondary) TD could be then considered one of the many adverse consequences of overweight and obesity. Which molecule plays the major role in this vicious circle is still unknown but reasonable candidates are estrogens, insulin, leptin, TNFα or other adipokines. Insulin can directly signal with the hypothalamus by increasing GnRH synthesis and release (64). Accordingly, patients with T2DM showed a higher prevalence of hypogonadotropic hypogonadism (65,66) and in a mouse model of central depletion of the insulin receptor the phenotype recapitulates MetS and hypogonadotropic hypogonadism (67). Data from morbidly obese men indicate that LH levels and pulse amplitude were attenuated as compared to normal weight controls (68,69). Because P450 aromatase is highly expressed by fat tissue, obesity is considered a clinical condition characterized by a relative abundance of estrogens. In fact, increased aromatisation of androgens by fat stores increases estrogen levels, which, in turn, will decrease LH secretion for a negative feedback on both hypothalamus and pituitary. In a recent study it has been demonstrated that a weekly low

![Figure 4: Proposed interactions between increased visceral fat and hypogonadism](image-url)
dose (2.5 mg) of the aromatase inhibitor letrozole can restore testosterone levels and increase LH levels in severely obese hypogonadal men (70). Overall these experimental evidences indicate that an increased visceral fat and insulin resistance can decrease the activity of hypothalamic pituitary signalling to the testis. However there are data suggesting that also the testis itself could be less sensitive to gonadotrophin stimulation in MetS: Pitteloud et al (71,72) demonstrated that hCG-stimulated T levels are positively correlated with insulin sensitivity. Insulin itself is capable of stimulating T production and, simultaneously, of inhibiting SHBG concentration (73). Hence, insulin resistance associated with obesity could contribute to low testosterone levels seen in obese men, for a direct effect on the testis (71). Leptin, the adipocyte-derived adipokine product of the ob gene, circulates in plasma at concentrations that parallel the amount of fat reserves. Leptin receptors are present in testicular tissue and an excess of leptin circulating levels may contribute to the development of reduced androgens in male obesity (74,75). Obesity is characterized by an increase in circulating TNFα levels as a consequence of inflammatory cascade activation. Morales et al. (76) demonstrated that intratesticular TNFα delivery was associated with a blunted T response to the hCG stimulation, suggesting a possible contribution of this molecule in the obesity-associated-hypogonadism. In addition to a peripheral role, TNFα can also inhibit LH release acting at the pituitary or hypothalamic level (77). Pathogenetic mechanisms linking hypogonadism with obesity and insulin resistance appear to be complex and often multi-directional., Figure 4 summarizes the proposed interactions between obesity (increased visceral fat) and hypogonadism, based on the aforementioned evidence.

**IV. TESTOSTERONE AND CARDIOVASCULAR HEALTH:**

Coronary Heart Disease (CHD), the commonest cause of death worldwide, is more common in men than in women, which suggests an unfavourable effect of the male sex hormone testosterone on the cardiovascular system. Among over 30 cross-sectional studies which examined the possible associations between T levels and CHD (reviews in 10, 78-82), none found an association of high T levels with CHD. Conversely about half found lower T levels in the patients with CHD (78). Other cross-sectional studies found inverse correlations of T levels with aortic atherosclerosis (83), peripheral arterial disease (84), and Intima Media Thickness (IMT) (85-88) or plaque area in the carotid artery (88).

Seventeen prospective cohort or nested case controlled studies have also examined the relationship between T levels and cardiovascular morbidity and mortality. In 10 studies there was no correlation between baseline T levels and subsequent development of fatal or non fatal CHD, cerebro-vascular disease, or heart failure after adjustment for confounders, during observation periods of 5 to 31 years (88-97,99). Weak correlations of high androgen levels with cardiovascular mortality were observed in 1 study (98). Conversely 2 studies reported significant correlations between low baseline T levels and cardiovascular deaths (100,101), and 2 others between low baseline T and progression of carotid artery IMT (102) or between low T and an increased incidence of stroke or transitory ischemic events (103). However, 2 other prospective studies did not confirm the correlations with IMT progression (88), and with an increased risk of stroke (89). Lastly, the Caerphilly study found a positive association of the cortisol/testosterone ratio with CHD incidence and mortality (104).

**Taken together, these observational studies do not provide a consistent evidence of a relationship between circulating T and incident or existing CVD in men though T is often low in men with CVD in the cross-sectional studies.**

**Observation of men treated for prostate cancer with Androgen-Deprivation-Therapy (ADT)** may help to understand the effects of severe hypogonadism. Several prospective studies have shown that such men develop within 3 to 6 months increased fat mass and insulin resistance (105,106), while longer administration does not seem to result in further accumulation (107). Cross sectional studies after 12 months of ADT show an increased prevalence of T2DM and MetS (106,108-110). In addition ADT seems to be followed by an increase in CV morbidity (109) reaching 20% over 12 months (111) and mortality. At least where mortality is concerned, this effect seems very rapid, but shows no further increase with prolongation of ADT (112-114) and D’Amico et al (113) found no higher overall rate of fatal MIs in the long-term.

**Current available evidence suggests that T therapy in men over 45 years is not associated with an important increase in CV adverse events.** Two meta-analyses of RPCTs (45,115) found no significant difference between the T and placebo groups for all CV events, nor for each type of event, except an increase in hematocrit over 50% which was significantly more prevalent in the T group (115) (Table IV), and might augment the risk of thrombosis. However, many RPCTs included in the 2 meta-analyses enrolled only small numbers of men, often healthy, during short durations. Larger trials, measuring CV endpoints and enrolling men with CVD for longer durations, are needed to be sure of the CV consequences of T therapy in the medium and long terms.
Interventional studies have tested the effects of T in men with CHD. Acute administration reduced peripheral vascular resistance, cardiac afterload and increased cardiac index (116). Injecting supraphysiological doses of T into the left coronary artery led to a dose-dependent vasodilatation and increased coronary flow, but this effect was not observed with physiological doses (117). These effects were mediated by non genomic, endothelium-independent mechanisms. Acute administration of intravenous T also improved exercise tolerance and reduced the angina threshold in men with stable CHD/angina (117,118).

Chronic administration of low physiological doses of T has also been beneficial. Four RCTs (119-122) reported short-term improvements in ECG changes of CHD with respect to placebo, including longer exercise time to ischemia, after a maximum of 12 weeks of T supplementation. T therapy also substantially improved cardiac condition in 2 RCTs of men with heart failure (123,124). Direct effects of T on male vasculature could explain these acute and chronic findings.

T seems to exert mostly beneficial effects on classical cardiovascular risk factors. The favourable effects of exogenous T administration on body composition (increase in lean mass and decrease in fat mass, especially in visceral adiposity, associated with CV morbidity and mortality), have already been mentioned. These effects may contribute to the improvement in glycemic control and insulin sensitivity observed in some RCTs of T therapy in hypogonadal men with T2DM and hypogonadism (46,47). The effects of physiologic doses of TT on lipids and lipoproteins are negligible (44), except the possibility of a slight but significant decrease of both total, LDL and HDL cholesterol on IM injections of T esters, that may be explained by the higher levels of circulating T that these injections may induce (125). T therapy also decreases lipoprotein (a) (126), an independent risk factor for atherosclerotic diseases (78). With concerns to endogenous T, low T in men seems to be a component of the Metabolic Syndrome, characterized by obesity, T2DM, hypertension, hypertriglyceridemia, low HDL cholesterol and a procoagulatory and antifibrinolytic state (10,78).

The main hemostatic parameters associated with cardiovascular risk are fibrinogen, plasminogen activator inhibitor type 1 (PAI-1) and plasmin-alpha-2-antiplasmin complex (PAP) (78). T shifts the hemostatic balance towards decreased coagulation. Plasma levels of fibrinogen (127) and of the antifibrinolytic PAI-1 (128) are inversely correlated with levels of androgens in men. Hypogonadal men have low fibrinolytic activity, due to increased synthesis of PAI-1 (129). Intramuscular T significantly down-regulates fibrinolysis and the hemostatic turnover rate, as concentrations of PAP decrease markedly (130). However potentially detrimental effects of T on platelets have been suggested including increased expression of platelet thromboxane-A2 receptor and increased platelet aggregation response, leading to the recommendation of associating anti-platelet therapy with aspirin in patients with CHD taking exogenous T (80).

Data on the relationship between T and blood pressure are inconsistent. There is substantial evidence that androgens play a role in determining sex-specific blood pressure, which is higher in men, at higher risk of developing hypertension. Experimental data suggests that despite the decrease in vascular tone resulting from acute administration of T, the long-term net effect of androgens may be vasoconstriction, via up-regulation of thromboxane A2 expression, norepinephrine synthesis, angiotensin II expression and endothelin-1 action. Furthermore androgens promote vascular remodeling, and stimulate renal pro-hypertensive processes involving the renin-angiotensin-aldosterone system. Androgens seem

<table>
<thead>
<tr>
<th>Event</th>
<th>Testosterone Rate/1000 Patient/years</th>
<th>Placebo Rate/1000 Patient/years</th>
<th>Pooled Odd-Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit &gt; 50 %</td>
<td>64.5</td>
<td>2.8</td>
<td>3.67*</td>
<td>1.82, 7.51</td>
</tr>
<tr>
<td>Chest pain, ischemia</td>
<td>7.4</td>
<td>8.3</td>
<td>0.93</td>
<td>0.39, 2.26</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7.4</td>
<td>8.3</td>
<td>0.99</td>
<td>0.44, 2.26</td>
</tr>
<tr>
<td>Coronary procedure, CABG</td>
<td>3.7</td>
<td>13.9</td>
<td>0.79</td>
<td>0.35, 1.79</td>
</tr>
<tr>
<td>Atrial fibrillation or arrhythmia</td>
<td>9.2</td>
<td>2.8</td>
<td>1.22</td>
<td>0.53, 2.81</td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>5.5</td>
<td>11.1</td>
<td>0.86</td>
<td>0.38, 1.95</td>
</tr>
<tr>
<td>All cardiovascular events</td>
<td>33.2</td>
<td>44.3</td>
<td>1.14</td>
<td>0.59, 2.20</td>
</tr>
</tbody>
</table>

*Odd Ratio significantly different from placebo – CABG : Coronary Artery Bypass Graft

Table IV: Pooled Odd Ratios for adverse cardiovascular events of testosterone therapy (adapted from Calof et al 2005, 115)
also to promote oxidative stress in the kidney (131). However in population studies both systolic and diastolic blood pressures are inversely correlated with T levels (132). Men with prostate cancer undergoing ADT develop an elevated central artery pressure due to decreased arterial relaxation (133). Though T therapy has not been shown to affect blood pressure in RPCTs, low T levels have been shown to be associated with arterial stiffness (134,135). Pulse wave velocity, a measure of arterial stiffness, is ameliorated by normalization of T levels (135). There is therefore no contraindication to Tth in men being treated for hypertension.

**Sex steroid hormones may exert direct effects on the arterial wall** since the human vascular smooth muscle, endothelial cells, macrophages and platelets, contain receptors and converting enzymes needed for the genomic effects of T and estradiol (E2), and the local production of E2 (78).

Both beneficial and detrimental consequences may be expected from these effects (table V). Decreased **vascular responsiveness** is an early marker of atherosclerosis. This may be the result of endothelial dysfunction or of endothelium-independent disturbances in vascular smooth muscle. As a result decreased vasodilation and enhanced vasoconstriction can lead to vasospasm and angina. In addition endothelial dysfunction also contributes to coronary events by promoting plaque rupture and thrombosis (78). Akishita et al (136) found that low T is an independent determinant of endothelial dysfunction in men. T might especially be involved in endothelial repair since low T is associated with a low number of endothelial progenitor cells in young hypogonadal men (137), while T replacement is able to normalize their count (138). Sex steroid hormones and more especially T might in fact modulate most clinical and biochemical markers of endothelial dysfunction (139).

**Flow-mediated dilatation (FMD)** measured in the brachial artery is used to investigate endothelial-dependent arterial dilatation. In men with CHD, some short term studies of supra-physiologic doses of T increased FMD in brachial artery, which reflects increased nitric oxide release (140). Long term T therapy with physiological dose also improved NO mediated brachial artery vasodilatation in one study (141). Brachial artery reactivity correlates closely with coronary arterial endothelial dysfunction. These findings may therefore support the concept of T having a beneficial effect on coronary endothelial dysfunction (141). However more data support negative effects of T on vascular reactivity (79): for example FMD of brachial arteries is higher in androgen-deprived (142) and in hypogonadal patients (143). In the latter it is significantly reduced following T therapy. The sensitivity to T (CAG repeat polymorphism in the AR gene) is inversely associated with the endothelium-dependent and independent dilations of brachial arteries (144). High-dose androgens exert adverse effects on the endothelium-independent dilation in female to male transsexuals (145). The diversity of these effects may depend on differences in gender, concomitant diseases, mechanism of action, and dosage of T. **In conclusion T modulates vasoreactivity by both endothelium-dependent and –independent mechanisms, as well as by genomic and non-genomic modes of action.** Physiological concentrations appear to restrict vasodilation by activation of the AR. In contrast supraphysiological or pharmacological doses seem to potentiate vasodilation through non-genomic actions (78).

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**Table V: Dual Effects of Testosterone and Dihydrotestosterone in Atherogenesis, according to the cell type, the type of androgen, the type of exposure, and the transformation of T into DHT or into E2**

<table>
<thead>
<tr>
<th>Pro-atherogenic effects</th>
<th>Anti-atherogenic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ↓ HDL cholesterol</td>
<td>• ↓ visceral fat and ↑ lean mass</td>
</tr>
<tr>
<td>• ↓ NO release</td>
<td>• Insulin resistance</td>
</tr>
<tr>
<td>• ↑ platelet aggregation</td>
<td>• ↓ Lipoprotein (a)</td>
</tr>
<tr>
<td>• ↑ Expression of platelet thromboxane-A2</td>
<td>• Increase transfer of cholesterol esters from macrophages to HDLipoproteins</td>
</tr>
<tr>
<td>• ↑ Norepinephrine synthesis</td>
<td>• ↓ Fibrinogen</td>
</tr>
<tr>
<td>• ↑ Angiotensin II expression</td>
<td>• ↓ Plasminogen activator inhibitor type 1 (PAI-1)</td>
</tr>
<tr>
<td>• ↑ Endothelin-1 action</td>
<td>• ↓ Plasmin-α2-antiplasmin complex (PAP)</td>
</tr>
<tr>
<td>• ↓ Flow-mediated dilatation of arteries</td>
<td>• ↑ vasodilatation through non-genomic action (seems limited to supraphysiological concentrations)</td>
</tr>
<tr>
<td>• Increase expression of Vascular Cell Adhesion Molecule-1 (VCAM-1) through conversion into DHT</td>
<td>• Inhibit VCAM-1 m-RNA expression in endothelial cells through conversion into E2</td>
</tr>
<tr>
<td>• Enhance human endothelial cell apoptosis</td>
<td>• Promote endothelium repair</td>
</tr>
<tr>
<td>• Stimulate proliferation and migration of arterial wall smooth muscle cells (SMC)</td>
<td>• ↓ arterial wall stiffness</td>
</tr>
<tr>
<td>• Promote vascular remodeling and stimulate renin-angiotensin – aldosterone system</td>
<td></td>
</tr>
</tbody>
</table>

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Atherosclerosis involves monocyte adhesion to the vascular endothelium, followed by migration into the arterial wall to form foam cells. Such process requires cell adhesion molecules such as Vascular Cell Adhesion Molecule-1 (VCAM-1). Dihydrotestosterone (DHT), a non aromatizable androgen, increases the expression of the VCAM-1 gene in endothelial cells from human males (79,146). But in the same cells T inhibits VCAM-1 mRNA expression by its conversion to E2. By this latter mechanism T might have beneficial effects on the CV system (147,148). T enhances human endothelial cell apoptosis, another important cellular mechanism in atherogenesis, by a mechanism involving the AR, but not aromatization (79,149,150).

Proliferation and migration of arterial wall’s smooth muscle cells (SMCs) are important steps in the formation of neo-intima and stenoses. In the rat T and DHT stimulate this process while E2 inhibits it (79). In the human male T and DHT stimulate vascular SMC proteoglycan biosynthesis via the AR, suggesting a pro-atherogenic effect (151). In AR-positive vascular SMCs collected from human atherosclerotic aortas, T also markedly induces the human prostate overexpressed protein 1 gene which regulates proliferation of neo-intimal SMC, what suggests a role of T in aortic atherosclerosis (152). However endogenous T has also been shown to limit coronary neo-intima formation in male swine, what suggests a protective role of T in coronary vasculoproliferative diseases such as restenosis and atherosclerosis (153). This diversity of effects may result from gender and species specificities, as well as from the T doses, since for example DHT exerts a biphasic effect on DNA synthesis in human vascular SMC, i.e. stimulation at low concentrations and inhibition at high concentrations (154), or from predominant activation of either AR or aromatization dependent mechanisms.

Macrophages also play a key role in atherosclerosis by migrating into the arterial wall where they internalize exogenous lipids which transform them into foam cells forming the fatty streaks. DHT enhances this process since it increases lipid loading of male macrophages. Conversely T also increases transfer of cholesterol esters from macrophages to high-density lipoproteins (reverse cholesterol transport), which may retard the development of fatty streaks. T treatment of murine macrophages inhibits NO release, what could explain the platelet aggregation and thrombosis risk associated with androgen treatment by eliminating the anti-aggregatory effects of NO (79,81).

In conclusion many data, especially the inverse correlation of circulating T with most classical vascular risk factors, suggest the possibility of a detrimental effect of TD on cardiovascular health. However currently available results of the prospective longitudinal observational studies cannot definitely confirm the role of low T in atherosclerosis, since a positive association was found in only a minority of such studies. Androgens have been shown to both promote and suppress pro-atherogenic and pro-inflammatory effects on all cell types involved in atherosclerosis (table V). Given current evidence it would appear that androgen effects are dependent on cell type, dose, type of androgen, and type of exposure (81). A net effect of T on the arterial wall which would reduce or even delete the vascular benefit resulting from the improvement of the other vascular risk factors might explain the preceding discrepancy. More long term prospective epidemiological studies, as well as large scale, placebo-controlled, randomized trials of T therapy including vascular parameters among the primary end-points are urgently needed to resolve this issue.

V. ROLE OF TESTOSTERONE DEFICIENCY IN SEXUAL DYSFUNCTIONS AND EFFECTS OF TESTOSTERONE THERAPY

1. ERECTILE DYSFUNCTION:

a) Prevalence of testosterone deficiency in erectile dysfunction (155):  
Serum T was below 3 ng/ml (10.4 nmol/l) in 12% of 7000 men with ED compiled from 9 large series (including 4% of 944 men less than 50 years old and 14.7% of 4342 men more than 50 years old). The real prevalence may be lower because most of those men had a single T measurement, sometimes in the afternoon, while circulating T decreases after 11am in normal men, at least up to the age of 40. In one consecutive series of 1022 men with ED, the prevalence of TD, based on 2 consecutive values < 3ng/ml before 11am, was only 6.6%, including 4% before and 9% after 50 years old (156). The prevalence of marked TD (< 2 ng/ml, 7 nmol/l) was even lower: 1.8%, including 0.8% before 50 and 2.6% after 50 years old. In another consecutive series of 2794 men with ED aged 25-80 years, T measured only once, the most often between 07:00 AM and 02:00 PM was < 2 ng/ml in 7%, < 3 ng/ml in 23%, < 3.46 ng/ml in 33%, and < 4 ng/ml in 47% of men (157). Measuring FT or BT may find higher prevalence of low values (up to 37 and 24% respectively of ED patients aged more than 50 years). Among men with ED, the symptoms the most specific of associated TD are HSD, decrease of nocturnal erections, and absence of any erection (12).
b) Basic knowledge on the role of testosterone in erectile function:

1. ANIMAL STUDIES (reviews in Buvat et Bou Jaoude 2006, Traish et Guay 2006, Morelli et al 2007 [9,12,155]): Studies in rodents show that besides its well known effects on the brain centers of sexual function, especially the hypothalamic pre-optic area and arcuate nucleus, T plays a key role in the peripheral modulation of erectile function.

- Testosterone is required for maintenance of penile structure and functional integrity: Androgen suppression via castration results in profound structural changes in penile tissue: apoptosis of the penile cavernosal and spongiosal cells, loss of elastic fibers in the tunica albuginea and, in the corpora cavernosa, of smooth muscle fibers, an essential component of the penis, regulating detumescence and erection. Elastic and smooth muscle fibers are replaced by collagenous fibers, which may result in fibrosis. Alterations in dorsal nerve structure and endothelial morphology, and accumulation of adipocytes in the subcutaneous region of the corpus cavernosum that could impede blood outflow during sexual stimulation and contribute to venous leak are also observed. Thus androgens exert a direct effect on penile tissue, and androgen suppression produces a structural imbalance in the corpus cavernosum which may explain the veno-occlusive dysfunction and ED that occur in orchidectomized animals and are reversed by T administration.

- Testosterone modulates NOS and PDE5 expression in erectile tissue: The Nitric Oxide (NO)-cGMP pathway is critical for initiation and maintenance of erections. In animals, the expression of both the endothelial and neuronal NOS, and therefore the capacity for NO production, is regulated by androgens. Castration results in marked decrease in NOS activity and cGMP formation, through both NOS dependent and independent mechanisms, as well as in marked decrease in the erectile response to pelvic nerve stimulation. T administration normalizes NOS protein expression and activity and restores the erectile response. Therefore the NO-cGMP pathway is T-dependent in rodents.

On the other hand, cGMP, the key intracavernosal signal for the relaxation of the cavernosal smooth muscle and thus erection, is inactivated by the PDE5 present in the cavernous bodies. Following sexual stimulation, PDE5 Inhibitors (PDE5-I) reduce the hydrolysis of cGMP, and allow intracavernosal cGMP accumulation that enhances smooth muscle relaxation and improves the quality of erection. In rodents, castration reduces protein expression and activity of PDE5 and T treatment upregulates it (158,159). In addition, medical or surgical castration prevents the enhancing effect of PDE5I on erections induced by electrostimulation of the cavernous nerves. T seems required for proper functioning of PDE5-Is in animals.

- Critical threshold for the effect of T on erectile function: In castrated rats, erectile function is significantly and positively correlated with T plasma levels in a dose dependent manner, up to a critical threshold corresponding to only 10-12% of normal physiological concentrations ([160]. Above this level, there is no more correlation and erectile function is similar to that of intact animals.

2. STUDIES IN MEN (review in Buvat et Boujaoude [155]):

The effects observed in laboratory animals following a total suppression of T by castration may not be extrapolated without reservation to the consequences of the partial and often mild hypogonadism observed in most hypogonadal men with ED. All the more as men, unlike rats, produce dehydroepiandrosterone. Even in case of castration, this steroid may supply some testosterone following peripheral conversion. Until now the data supporting the importance of T for the intrapenile mechanisms of erection are less substantial in humans. However the expression of PDE5 is also T-dependent in our species (158).

- Sexual function of men with severe organic TD: Data accumulated in such men show that T is required for pubertal acquisition of gender characteristics, as well as adult sexual behaviour and functional capacity, including libido, ejaculation and spontaneous erections. Randomized Controlled Trials (RCTs) of T therapy have shown that sexual desire and arousal are T-dependent and represent the main impact of T on sexual function of men. The frequency of sexual activity and spontaneous erections (especially sleep related, ie morning and nocturnal) are also clearly T-dependent. The psychic erections (ie in response to erotic stimuli) were initially thought to be androgen independent but are in fact partly T-dependent. Ejaculations and orgasm are also partly T-dependent.

- Threshold levels for testosterone effects on sexual function: Trials of T therapy in hypogonadal patients have shown that in humans also, the effects of T upon sexual function are dose-dependent up to a certain serum level from which they are maximum. Below this threshold sexual function is suboptimal. This threshold level is close to the lower limit of the normal adult range. It is consistent within an individual (161,162), but markedly variable between individuals (161-163) and may be specific to each parameter of sexual function. For example, in a study by Kelleher et al the average T level from which they requested a new implantation was 2.6 ng/ml (or 10 nm/l), but the individual levels varied.
from less than 1 to 4.5 ng/ml (162). In another series of hypogonadal males on injectable T esters, the individual threshold level varied from 1.1 to 3.6 ng/ml (161). Overall, levels below 2 ng/ml (7 nmol/l) are in most cases associated with impairment of sexual function and levels below 1.4 to 2 ng/ml with diminished nocturnal erections ([164]. Conversely, from a ceiling level of maximum 4.5 ng/ml, the effect of T is maximum, and not enhanced with additional T supplementation. According to a study by Gray et al (165), the threshold level of the effects of T on sexual function may increase with aging. Lastly there is a grey zone, between 2 and 4.5 ng/ml, in which the impact of T on sexual activity may or may not be maximum according to the sensitivity to androgens of the individual.

- **Correlations between serum T concentrations and sexual function and dysfunction in population studies:** While most men referred for marked organic TD present with low sexual desire and ED, no study found any association between the TT level and the presence and severity of ED, especially in aging men (166-168). Some studies found significant associations of erectile function with FT (169,170) or BT (171) but these studies were not adjusted for age. In a better designed study, Schiavi et al (172) recorded nocturnal erections for 4 consecutive nights in 77 men 45-74 years old, and measured hormones every 20 min during the last night. They also found a significant association between BT, but not TT, and sexual desire and arousal, as well as with the nocturnal erections. But most of the correlations with BT, including those with erections, disappeared after adjustment for age. In such cross sectional studies, no association of T with erectile function persisted when the data were adjusted for age.

- **Impact of testosterone upon the penile mechanisms of erection:** For a long time the main sites of the T effects upon men's sexual function have been considered to be located in the brain. However there are androgen receptors in the human cavernous bodies, and some studies suggest T modulates the vascular mechanisms of erection in men too. Peak systolic velocity (PSV) of the cavernosal arteries, measured following intracavernosal injection of Alprostadil in men with ED, severe TD (T < 2 ng/ml), and no vascular co-morbidity, was significantly lower than the corresponding value of control men with psychogenic ED, and increased up to the range of the psychogenic group following 6 months of T therapy (173). In another study based on Color Duplex Ultrasound (CDU) of the cavernosal arteries, Aversa et al found a highly significant correlation of the resistive index with the serum value of FT ([174]. In a study of 20 arteriogenic ED patients with low normal T non responders to Sildenafil, T therapy significantly enhanced the accelerating effect of Sildenafil on PSV measured in the cavernosal arteries (175). Conversely, in a well designed RPCT by Rochira et al (176), 24 men with severe organic TD (mean age 35±12 years, T < 2 ng/ml, almost undetectable in most cases) and a same number of normal control men underwent Nocturnal Penile Tumescence and Rigidity Monitoring for 3 consecutive nights, with administration of 50 mg sildenafil or placebo at bed time on the third night. The men with TD were tested twice: at baseline and following T therapy for at least 6 months. In those men the single sildenafil administration restored normal sleep related erections to the same extent as 6 months of T therapy, suggesting a relative independence of the peripheral mechanisms of human erections from T. Therefore the few studies of the effects of T on the penile mechanisms of human erections have given inconsistent results.

c) **Effects of testosterone therapy in patients with ED and TD:**

Evaluation of these effects should help to clarify the role of TD in ED.

1. **Testosterone therapy alone:**

T therapy consistently restores erectile function in young patients with organic TD. A meta-analysis by Isidori et al (177) integrated 17 RCTs which had studied the effects of T therapy on male sexual function of men of any age. Sexual Dysfunction (SD) was not a criterion for inclusion. With respect to placebo, a significant but moderate improvement of all aspects of sexual function was observed in the studies of men with low and low normal mean T concentration at baseline (< 12 nmol/L, 3.46 ng/ml). The magnitude of the effect on erectile function (but not on libido) was inversely related to the baseline T concentration. The presence of risk factors for vasculogenic ED (diabetes, hypertension, hyperlipidemia), comorbidities, and shorter evaluation periods were associated with greater treatment effects. The effect of age was not studied in this meta-analysis.

- **T therapy seems less effective in the men whose TD is diagnosed at the occasion of an ED complaint.**

No controlled trial has been specifically devoted to such populations but a compilation of 8 observational studies including 258 such men with serum T < 3 ng/ml (10.4 nmol/l) found that TT definitely improved erectile function in only 36% (155). Such patients are mostly middle-aged or older and their TD is generally mild (serum T is below 2 ng/ml in less than 2% of men consulting for ED) (155). Their profile is different from that of the younger men with organic and often severe TD who constitute a substantial proportion of the populations studied in RCTs. Another meta-analysis of the effects of T therapy on sexual function included only trials devoted to men with SD at baseline (178). The results tend to confirm that the poor effects of T therapy in those men whose TD was diagnosed at the occasion of an ED complaint
may be linked to their higher age. Meta-analysis of the trials that enrolled participants with T levels < 3 ng/ml (10.4 nmol/l) at baseline showed a large and significant effect on libido and a moderate, non significant and inconsistent effect on erectile function. When the studies were subdivided according to men's age, the effect on erectile function proved to be large and significant in the 2 trials having included young patients, and very small and non significant in another 2 studies having included older patients (mean age > 50 years old).

- There are several potential reasons for the poorer effects of T therapy in older men with ED and TD compared with younger ones (155). In addition to the generally lower degree of TD in men consulting for ED, TD is the main cause of ED in the younger patients, while it is generally only one element of a multifactorial ED in the older ones. Vascular factors are predominant among the co-morbidities (156), and hamper the beneficial effects of T therapy since they are more prevalent in the patients not improved with this therapy (179). For that reason combined therapy with T and PDE5-I is often required in such men. PDE5-Is may correct the vascular factors, while T therapy may restore sexual desire, what cannot be done by PDE5-Is. In addition, it recently appeared that T therapy may be required for a PDE5-Is' full efficacy (see below). Other possible explanations for the above discrepancy involve the possibility of too early assessment of the effects of T therapy in certain trials: in a study of 22 hypogonadal ED patients of mean age 58 years treated with injections of T undecanoate, Yassin et Saad (180) observed that improvement of erectile function took longer than 6 weeks in 9 of the 12 markedly improved patients. In addition, the effects of T therapy may depend on the circulating T level that is achieved. This level may depend on the T formulation. In a non randomized prospective study comparing a T gel with injections of T undecanoate, Yassin et Saad (180) observed that mean age 60 years, Saad et al (181) observed on T undecanoate both higher mean T levels (5.3 vs 3.6 ng/ml with the T gel) and higher efficacy as shown by greater increases in the Erectile Function Domain (EFD) of the IIEF.

In an uncontrolled series of 12 men with corporal veno-occlusive dysfunction, considered as one of the most severe aetologies of ED, and low T, who were also treated with T undecanoate, the same authors reported a clinically significant improvement of erectile function associated with a disappearance of the signs of venous leakage at pharmacocavernosometry in 5/12 (179). They speculated on the possibility that veno-occlusive dysfunction of those patients resulted from adipocyte accumulation in penile sub-tunical area of the corpora cavernosa as has been observed in castrated rats. More data are requested to confirm this hypothesis, all the more that pharmaco-cavernosometry is not a totally reproducible investigation (182).

- Another putative explanation of the low success rate of T therapy in older men with ED and low circulating T is that in such patients the low T level may be a consequence rather than the cause of ED (see review in Buvat et al 2006). In two studies by Jannini et al (183) and Carosa et al (184) the low T level increased following successful non-hormonal ED therapies like psychotherapy, intracavernosal injections or PDE5-Is, while in the former study it did not change when such therapies failed. In such cases the reduction in T secretion was likely caused by reduced sexual activity (since this has been shown to stimulate T secretion) and by the stress and depression that often result from ED, through the well known negative impact of the two latter factors on the hypothalamic gonadotropic centers. In an additional study, Carosa et al (185) observed a reduction in the bioavailability of LH in ED patients, that could result from a spacing out of the LHRH pulses via a psychosomatic mechanism since it was also reversible with successful non-hormonal ED therapies.

- Lastly some authors also explain the modest efficacy of T therapy in older men with ED and low total T by the fact that TT may be a poor index of androgenicity. They think that only the bioavailable fractions of T should be taken into account to diagnose hypogonadism after 50 (9). This speculation was never confirmed as concerns the possible impact of T on sexual function. A study found that the success rate of T therapy in the ED patients with low levels of FT or BT was even poorer than that reported in those patients with low levels of TT, especially in the men who had low FT or BT and normal TT levels (155).

2. COMBINATION THERAPY WITH TESTOSTERONE AND PDE5 INHIBITOR IN CASE OF FAILURE OF T THERAPY ALONE

In an uncontrolled study, Greenstein et al (186) treated 48 patients with ED and TD (mean age 60.7y,TT < 4 ng/ml) with a T gel and obtained the unusually high success rate of 64% according to a score of the IIEF-EFD ≥ 26. The authors then combined Sildenafil with the T gel in the patients not improved with T therapy alone, ending in a 100% success rate.

3. COMBINATION THERAPY WITH TESTOSTERONE AND PDE5 INHIBITOR IN CASE OF FAILURE OF PDE5 INHIBITOR THERAPY ALONE

As detailed above, in rodents androgens modulate the expression of both NOS and PDE5, and the presence of androgens is a prerequisite for proper functioning of PDE5-I (9,12). PDE5 expression has been reported to be T-dependent in men too (158).
Several studies suggest that hypogonadism is a risk factor for reduced response to sildenafil in men too (review in Buvat et Bou Jaoudé [187]). Among the most significant ones, the mean TT level of diabetic men with ED was significantly lower in those who did not respond compared with those who responded properly to this PDE5-I (respectively 1.99 vs 5.36 ng/ml) (188). Following radiation therapy for prostate cancer Sildenafil efficacy was also lower in the patients with ED treated with androgen deprivation therapy compared with those without this treatment (189). In a study of 162 men with ED, TD (TT < 3 ng/ml) was one of the 3 significant predictors of poor response to sildenafil (OR 1.89, CI 1.12-3.16) (190). In men with ED and severe TD, Sildenafil failed to increase the erectile response to visual sexual stimulation and this effect was restored following T therapy for 6 months (173). Lastly, in the already mentioned study by Rochira et al where Sildenafil was able to restore the sleep-related erections with the same efficacy as T therapy, the effect of combining Sildenafil with T therapy was greater than the sum of each of these two therapies alone as concerns every parameter of nocturnal erections (176).

*Uncontrolled studies* reported a high prevalence (30 to 40%) of low to low-normal T levels in unselected or diabetic men with ED non responders to sildenafil or tadalafil (mean baseline TT 1.7 to 2.3 ng/ml in the corresponding studies) and a substantial improvement of the response to PDE5-Is in 37.5%-92% of these men following combination of T therapy with PDE5-I, while a short course of T therapy alone had only modest effects (review in [187]). A study suggested that the proportion of such patients improved by the combination with T therapy increased with the duration of T therapy (65% after 10 weeks vs 43% after only 4 weeks) (191).

*Three RPCTs support the speculation that TD hinders the effects of PDE5-Is on erectile function of men too.* In a small study, 20 patients with arteriogenic ED and both serum TT and FT in the lower quartile of normal range, who were non responders to 6 trials with 100 mg sildenafil, were randomized to T or placebo patches combined for 4 weeks while continuing with Sildenafil on demand (174). With respect to placebo, T therapy significantly increased the arterial inflow to cavernous bodies following Sildenafil administration, as well as the scores of the Erectile Function and the Satisfaction Domains of the IIEF. On the other hand Shabsigh et al studied 75 ED patients (mean age 58.5 years) with low to low normal TT (≤ 4 ng/ml), non responders to Sildenafil 100 mg (192). They were randomized to T or placebo gels combined with Sildenafil on demand for 12 weeks. After 4 weeks the mean increases in the scores of the Erectile Function, Orgasmic Function and Overall Satisfaction Domains of the IIEF, as well as the number of patients reporting that their gel improved their response to Sildenafil, were significantly greater in the T group (+ 4.4 vs + 2.1 in the placebo group with concern to the EFD). However the differences were no more significant at weeks 8 and 12, and this may be due to a too small cohort of patients. Lastly Buvat et al randomized 173 men with ED (mean age ≥ 45 years) and either TT ≤ 4 ng/ml or BT ≤ 1 ng/ml, non responders to tadalafil 10 mg once a day for 4 weeks, to receive a placebo gel or a T gel in addition to tadalafil. The EFD of the IIEF and the rate of successful intercourses increased somewhat more in the tadalafil + T gel group than in the tadalafil + placebo gel group, but the difference was statistically significant only in those patients with a T level at baseline below a certain threshold: 3ng/ml for TT, 0.6 ng/ml for BT, and 52 pg/ml for cFT (193).

*Other benefits of combining T therapy to PDE5-Is in men with low T have been reported in uncontrolled studies* (review in [187]): the first one is the improvement in sexual desire, often reduced when T is low, which may lead to withdrawal from PDE5-I therapy due to lack of motivation for sex. Theoretically PDE5-I therapy alone cannot improve sexual desire. However, as mentioned above in a study of 74 men with ED, 6 months of sildenafil, and even more of tadalafil therapy significantly increased the low normal mean serum testosterone level of 3.43 ng/ml to 4.7 ng/ml (184). But it has not been proven that such a small increase is sufficient to have a clinically significant effect on sexual desire, and 2 recent studies were unable to confirm an increase in T following 6 months of Sildenafil and 12 months of tadalafil (in Buvat et Bou Jaoudé [187]). Improvement in other symptoms of hypogonadism like reduced well-being has also been reported following combination therapy (187), but such an improvement, measured with the Aging Male Symptom scale, was also reported with sildenafil alone in a RPCT (194).

*d) significance of testosterone deficiency in erectile dysfunction:* T unquestionably plays a critical role in the control of erectile function of many animal species, including humans. Severe organic hypogonadism impairs every aspect of sexual function in young men, and its negative impact upon sexual function is eliminated by T therapy. However this is a rare finding in the men consulting for ED before the age of 50 years. For example only 0.8% of a consecutive series of 477 men less than 50 years old consulting for ED had a serum T < 2 ng/ml ([156]).

**1. The role of comorbidities:**
Fifteen per cent of the men aged more than 50 years who consult for ED prove to have a serum T repeat-
edly < 3 ng/ml (10.4 nmol/l) (155). The role played by TD in their ED is presently unclear. Only about one third have definite improvement on T therapy with regards to their erectile function. That may suggest that the low T level is not the real cause, or not the only cause of ED in every case. Hypogonadism is too often wrongly diagnosed, based on only one T measurement. A low result indicates a repeat measurement which will give a normal result in 30% of the cases (155). In addition, the majority of the ED patients aged more than 50 years who are found to have a low T level have only a mild or moderate hypogonadism, while the magnitude of the beneficial effect of T therapy on erectile function is inversely related to the baseline T concentration (177). In a consecutive series of 545 ED patients aged more than 50 years, 9% had a T level twice < 3 ng/ml, but only 2.6% (22% of the former) had a marked TD (T level twice < 2 ng/ml or 7 nmol/l) (156). In addition, ED is often multifactorial. In the preceding series, significant vascular factors such as obstruction of the penile arteries or veno-occlusive dysfunction were present in 42% of the patients with ED and TD ((156). In the diabetic men with ED, TD is associated with greater damage of penile arterial function (17). In older men with ED and TD, the prevalence of co-morbidities such as hypertension, hyperlipidemia and LUTS is more than twice higher in those whose erectile function is not improved following T therapy (179).

2. Testosterone deficiency may have itself contributed to the development of these comorbidities

As demonstrated by the frequent and significant association of TD with obesity and metabolic diseases: 58% of men with ED are obese, and in those men obesity is associated with lower levels of TT, BT and FT, as well as with a higher rate of penile arterial insufficiency according to penile CDU investigations (20). Many recent studies have confirmed the highly significant association of LOH with obesity (195-198) or increased waist circumference (199). Likewise, as already mentioned, TD is associated with insulin resistance, T2DM, and the MetS, a precursor state of cardiovascular disease, and with each of its components (15, 25, 200), especially in men with SDs (67). Hypogonadism predicts both T2DM and MetS in longitudinal studies, even in men lean at baseline (15), and in men with prostate cancer, androgen deprivation therapy induces rapidly IR, MetS and serious cardiovascular events (110). More details on these relationships are available in sections II.2.c. and II.2.d. One of the main reasons for the lack of improvement of erectile function following T therapy in the men with ED and TD may be that this treatment comes too late, when TD had already damaged the endothelium and the vascular bed, in part as a consequence of its detrimental effect on insulin resistance and the metabolic balance. A more direct evidence of the critical role of T in the ED of the men with TD is given by the T-dependence of the PDE5-Is' efficacy.

3. It is also possible that in certain cases low T is a consequence of reduced sexual activity or of the stress or the depression associated with ED rather than the cause of ED.

However the 2 uncontrolled studies by Jannini et al (183) and Carosa et al (184) which best support this hypothesis by reporting a significant increase of the T level of men with ED following improvement of erectile function with non hormonal therapies were not confirmed in subsequent studies following 6 months of sildenafil (194) nor 12 months of tadalafil (201). Lastly the association of ED and TD, which are both prevalent conditions does not imply a cause-effect relationship in every case.

2. Hypoactive Sexual Desire

A significant association of TT with the level of sexual desire has been reported in cross-sectional studies of aging urological outpatients (13,167) or of men with ED (12,184), and in a 17-year longitudinal evaluation of aging men (202). In a consecutive series of 1647 men with SD this association was significant only in the youngest age quartile (17-42 years old) (203). Such an association has also been reported with BT (167,202). However other parameters, especially ED (167), age, BMI, cigarette smoking and diabetes (202) interacted with T to determine HSD. In other cross sectional studies such associations were not confirmed, or disappeared after age adjustment (204). In addition the predictive value of low T for HSD was low in individual patients: The prevalence of HSD was of only 50% and 37% in men with TT < 2 and 3ng/ml, and 52 and 43% in those with BT < 1 and 1.2 ng/ml respectively. Two meta-analyses of RCTs (44,178), as well as other RCTs in older men with TD (60), or metabolic diseases (205), demonstrated a significant improvement of sexual desire following T therapy in populations of men with a mean T level < 3.46 ng/ml (12 nmol/l) at baseline. Therefore many studies support the association of low T level with low sexual desire, but suggest a multifactorial origin of this sexual dysfunction. In addition the prevalence of TD seems low in men consulting for isolated HSD (in a consecutive series of 73 patients with HSD and no other SD, TT was normal in every case) (206).
of TD suggesting that T may play a facilitating role in the control of the ejaculatory reflex. However in another consecutive series of 90 men consulting for retarded ejaculation or anorgasmia, only one had TD (206).

VI. ROLE OF TESTOSTERONE DEFICIENCY IN THE OTHER ASPECTS OF AGING

1. EPIDEMIOLOGY OF TESTOSTERONE DEFICIENCY IN AGING MEN:

As specified in section II.1.c, mean serum levels of TT gradually decline from the 40's, while SHBG increases, leading to an even greater decrease in serum BT and FT levels (4,208). However, there is great interindividual variability in T levels in aging men and not all older men will develop TD (209). Depending on what measurements and cut off values are used, the reported prevalence of TD in the aging male varies between 7% to 38.7% (Table VI). Measurements recorded in one longitudinal study revealed that approximately 12% of men aged 50–59 years, 19% of men aged 66–60 years, 28% of men 70–79 years and 49% of men ≥80 years have a low TT level. (94). TD is especially associated with health problems (210) and with obesity (20,195–197,199). In the 3200 aging men of the European Male Aging Study both preceding factors together with age and smoking were the 4 predictors of hypogonadism (198).

It is now recognized that only men who are found to have both low T level and relevant symptoms come within the indications of T therapy. In the MMAS study, 50% of the men with low T levels were asymptomatic (211). Table VII shows the prevalence and incidence of “symptomatic androgen deficiency” (SAD). Follow up over 15 years showed that the SAD was not a stable state, since after 8 years 55% of the men initially diagnosed as SAD had recovered a normal T level (212). The main correlates of SAD are by order of importance visceral obesity (waist circumference), health status and age (199).

The pathogenesis of TD in aging men involves 3 main mechanisms (4): 1. primary testicular changes with a diminished testicular secretory capacity due to decreasing Leydig cell mass and responsiveness to LH, whose serum level is often elevated in that case (208,213,214); 2. altered neuroendocrine regulation of the Leydig cells with apparent failure of the feedback mechanism on LH to fully compensate (213,214,215); 3. independent increase in SHBG binding capacity. Other mechanisms described in section II.2.c. (T and metabolism) may be involved in the many old men with TD who are obese. Further, changes in sensitivity to T leading to androgen resistance have been hypothesized (216,217). Age is associated with a decrease of concentration or down regulation of AR (4,216,217). Controlled trials of T therapy suggested that the threshold level of the effects of T on sexual function may increase with aging (165).

<table>
<thead>
<tr>
<th>References</th>
<th>Age Group</th>
<th>Threshold for hypogonadism</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>El-Sakka A et al 2005 (315) (Africa, Middle East) (Community based study in population with sexual dysfunction)</td>
<td>51.9 ± 12.2</td>
<td>TT (&lt;9.8 nmol/L)</td>
<td>15</td>
</tr>
<tr>
<td>Lin YC et al 2006 (316) (Asia, Taiwan) (Community based study)</td>
<td>40 - 80</td>
<td>Calculated FT (&lt; 0.023 nmol/L)</td>
<td>7 – 33</td>
</tr>
<tr>
<td>Wong SYS et al 2006 (317) (Asia, Hong Kong) (A community based cross sectional, cluster sampling study)</td>
<td>45 – 64</td>
<td>TT (&lt; 6.94 nmol/L)</td>
<td>8.2 – 16.8</td>
</tr>
<tr>
<td>Tan HM et al 2007a, 2007b (318,319) (Asia, Malaysia) (Randomized community based studies)</td>
<td>&gt; 40</td>
<td>TT(11.0 nmol/L)</td>
<td>19.1 18.5</td>
</tr>
<tr>
<td>Tancredi A et al 2004 (320) (Europe, UK) Community based study</td>
<td>50 – 70</td>
<td>FT (&lt; 0.24 nmol/L)</td>
<td>38.6</td>
</tr>
<tr>
<td>Yassin A et al 2007 (180) (Europe, Germany) (Community based study in population with erectile dysfunction)</td>
<td>mean age 56</td>
<td>TT (&lt; 12.0 nmol/L)</td>
<td>18.2</td>
</tr>
<tr>
<td>Abdo C 2007 (321) (Latin America, Brazil) (Community study in 19 Brazilian cities)</td>
<td>Not available</td>
<td>AMS Questionnaires</td>
<td>13.3</td>
</tr>
<tr>
<td>Araujo AB et al 2007 (327) (North America, USA) (Community based study, Symptomatic Androgen Deficiency)</td>
<td>30 – 79</td>
<td>TT (&lt; 10.4 nmol/L)</td>
<td>24</td>
</tr>
<tr>
<td>Mulligan et al 2006 (210) (North America, USA) (HIM Study, Men presenting to primary care office)</td>
<td>&gt; 45</td>
<td>TT (10.4 nmol/L)</td>
<td>38.7</td>
</tr>
</tbody>
</table>
Table VII: Prevalence and Incidence of “Symptomatic Androgen Deficiency” (SAD) according to age in the Massachusetts Male Aging Study (after Araujo et al 2004 [211]. Fifty per cent of men with low testosterone level were asymptomatic.

Table VIII: Signs and Symptoms shared by aging and hypogonadism, According to Morley et Perry 1997 [323] and Sternbach 1998 [324]

<table>
<thead>
<tr>
<th>Lean/muscle mass</th>
<th>↓ Muscle mass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>↓ Muscle strength</td>
</tr>
<tr>
<td></td>
<td>↓ Global performance</td>
</tr>
<tr>
<td>Fat mass</td>
<td>↑ Abdominal and visceral fat (“beer belly”)</td>
</tr>
<tr>
<td>Bone mass</td>
<td>↓ Bone mineral density</td>
</tr>
<tr>
<td></td>
<td>Back pain</td>
</tr>
<tr>
<td></td>
<td>↑ Risk of fractures (femoral neck, body of a vertebra, radius)</td>
</tr>
<tr>
<td></td>
<td>↓ Height</td>
</tr>
<tr>
<td>Metabolism and cardiovascular system</td>
<td>↑ Total and LDL cholesterol, ↓ HDL</td>
</tr>
<tr>
<td></td>
<td>↑ Cardiovascular risk? (atherosclerosis)</td>
</tr>
<tr>
<td></td>
<td>↑ Insulin resistance</td>
</tr>
<tr>
<td>Blood</td>
<td>↓ Erythropoietin</td>
</tr>
<tr>
<td></td>
<td>Anemia (fatigue, decreased performance)</td>
</tr>
<tr>
<td>Cognitive functions</td>
<td>↓ Spatial cognition and memory</td>
</tr>
<tr>
<td></td>
<td>Depressive mood</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
</tr>
<tr>
<td></td>
<td>Sleep disturbances</td>
</tr>
<tr>
<td>Sexual functions</td>
<td>↓ Sexual desire</td>
</tr>
<tr>
<td></td>
<td>↓ Sexual arousal</td>
</tr>
<tr>
<td></td>
<td>↓ Erections, ED</td>
</tr>
<tr>
<td></td>
<td>Retarded orgasm</td>
</tr>
<tr>
<td></td>
<td>Diminishing sperm production</td>
</tr>
<tr>
<td>Skin/hair</td>
<td>Atrophy (parchment skin)</td>
</tr>
<tr>
<td></td>
<td>↓ Secondary hair</td>
</tr>
<tr>
<td></td>
<td>Sweating, flushes</td>
</tr>
</tbody>
</table>
2. CORRELATION BETWEEN TESTOSTERONE LEVELS AND AGING SYMPTOMS

The symptoms of aging and of TD in men are similar (Table VIII). However, aging is also associated with a progressive decline in several other hormones like dehydroepiandrosterone (DHEA), thyroxine, melatonin, pregnenolone, DHT, androstenedione, IGF-1 and growth hormone (GH) (4) and in the efficiency of many essential biochemical regulations (i.e. the NO-cyclic GMP pathway). Thus many of the clinical manifestations may not be due to changes in T level.

The onset of these signs and symptoms varies and depends on many factors including the AR threshold level of the end organs. In hypogonadal men substituted with T pellets, the first symptoms which appear when pellets are exhausted are decreased libido and lack of vigor (162). This was confirmed by Zitmann et al (13) who showed in a population of aging men that the threshold level of circulating T below which the prevalence of a symptom is significantly increased with respect to the overall population differs according to the symptom (figure 2). In their study lack of libido and of vigor were the earliest symptoms manifested. The prevalence of lack of libido and of vigor in the population studied increased when the threshold of TT levels declined from normal to low levels. In addition the study of men on T pellets by Kelleher et al suggested an important inter-individual variability of the T threshold from which the symptoms of hypogonadism appear (162).

a) correlations with changes in body composition

Both aging and androgens have a significant impact on muscle mass and fat distribution. Several studies have confirmed an inverse correlation, independent of age, between abdominal fat mass and FT levels (218-220). These interrelations and their metabolic consequences are discussed in the section II.2.c (T and metabolism). Low FT has also been found to be associated with decreased muscle mass and muscle weakness in aging men (221). Loss of muscle mass seems a major cause of age associated decline in muscle strength (222).

Most studies support a moderate association of low T with physical decline of aging men. Serum T-levels, independent of age, were found to be positively correlated with isometric grip strength, leg extension (223) and overall muscle function (224). In 2 other cross-sectional studies low levels of TT and BT were associated with impaired mobility and low physical performance and muscle strength (225,226). In one of these studies, based on a MMAS sample, elevated levels of TT and BT (as well as of DHEA and DHEA-S) were associated with increased physical performance at a 7 items global physical performance test (but not at grip strength or chair stand tests) (227). But the correlation existed only up to certain critical concentrations (4.51 ng/ml for TT and 1.41 ng/ml for calculated BT). Levels beyond these critical concentrations, as might be achieved through exogenous supplementation, did not appear to confer additional benefits. A study of 20 men on ADT for PCAs found a significant decrease of hand grip strength and manual dexterity with respect to an age matched control group (227). Lastly 2 prospective cohort studies provided conflicting results. Orwoll et al (228) who studied a large cohort of 2587 men more than 65 years old, observed an association of lower T concentrations with reduced physical performance and an increased fall risk. Conversely in the study by Schaap et al, low levels of TT and FT were associated neither with 3 year decline in physical performance nor with 3 years decline in muscle strength (229), nor with an increased incidence of falls during the same period (225), perhaps because their cohort was smaller (constituted of 2 independent samples of 486 and 1071 men of mean age over 70).

In conclusion, and as confirmed by the results of the RPCTs of T therapy (see below), TD certainly contributes to increased fat mass, sarcopenia and decreased muscle strength of elder men, but these are probably multifactorial in origin. The decline in GH with age may also be involved since GH and T administrations have additive effects on these parameters (230,231).

b) Correlations with decrease in bone mineral density

Premature osteoporosis is seen in men with TD associated with Klinefelter syndrome, castration, HPRL, hypothalamic dysfunction and anorexia nervosa (213). Several large scale studies demonstrated that bone density in the radius, spine and hip are correlated with levels of bioavailable T, and even better correlated with bioavailable estradiol (213,232). The correlation between T levels, age and bone mineral density (BMD) have shown mixed results (208,209,213,214,233), but overall, in older men the prevalence of TD is twice higher in those with osteoporosis or rapid bone loss compared with the prevalence in men with normal BMD (234,235). However the prevalence of estradiol deficiency is even higher, and in a large group of 2447 men ≥ 65 years old, those with Total T or E2 deficiency were more likely to be osteoporotic (234). Possible mechanisms explaining the effects of diminished T on bone include reduction in estrogens produced by aromatization of androgens, reduction in calcitonin, and in osteoblast function (213,236,237). The respective responsibilities of the age-related fall in endogenous T and of the decline in endogenous estrogens have not been totally clarified. In a cross-sectional investigation of a large number of older men, though both T and estrogens were strongly related to BMD, both the posi-
tive relationships were independent from each other suggesting that the effect of T on BMD was not only a consequence of its aromatization in E2 (238).

The incidence of hip fractures among men over the age of 65 is 4-5/1000 (208). Many studies have demonstrated the association between minimal trauma hip fracture and low T level (239,240,241). TD is found in up to 20% of men with symptomatic vertebral fractures and 50% of elderly men with hip fractures (235). But data from the Framingham study suggest a predominant role of estrogens since in a cohort of 793 men followed for over 15 years, low T at baseline did not significantly increase risks for subsequent hip fracture while low estrogen did so. However men with low estrogen and T combined had the greatest risk of hip fracture (242).

**In conclusion** TD leads to osteoporosis and to a risk of hip fracture, in a large part, but not exclusively, due to a reduction in estrogens level.

**c) Correlations with decline in cognitive Function**

Correlational studies in young adults reliably implicate spatial cognition as the domain of cognitive function which is the most sensitive to T (243). In several, but not all, of these studies an inverted U-shaped relationship between T and this aspect of cognition was objectified. A large cross-sectional study of 40-80 years old men also found a curvilinear association between T and memory performance and processing capacity/speed, suggesting an optimal hormone level for particular cognitive tasks (244). In another cross-sectional study serum BT, but not TT, levels were associated with a lower risk of anamnestic mild cognitive impairment (245). Several longitudinal studies also suggest that in men the progressive decline of the bioavailable fractions of T with age is associated with the age-related declines in cognitive functions. Age-related decrease in BT has been found to predict decline in visual (246) and verbal (246,247) memories. In the Baltimore Longitudinal Study of Aging (BLSA), after an average follow-up of 10 years a high Free Testosterone Index (FTI) was associated with higher scores of visual and verbal memory, but not of verbal knowledge, general mental status or depressive symptoms (248). In another component of the same study eugonadal men proved to have a reduced rate of decline in visual memory with respect to men with TD, suggesting a possible beneficial effect of high circulating FT concentrations on specific domains of cognitive performance and cognitive decline in older men (94). In a neuroimaging study of a subsample of the BLSA, Positron Emission Tomography found that older men with higher FT had increased blood flow in the hippocampus bilaterally, while hippocampus is known to play a critical role in memory and possibly in spatial cognitive processing (243). However several cross-sectional studies did not confirm the association of age-related cognitive decline with low free or total T after adjustment for salient factors (249,250), or even observed association of high cFT with poorer performance at some cognitive tests (250).

The preceding data raise the issue of a **role of the age-related decline of T in the development of Alzheimer’s disease.** Several, but not all, cross sectional studies have reported lower concentrations of T in men diagnosed with this disease (243,245,251), but such studies may not determine the direction of causality. A prospective longitudinal study of 574 men with a mean age of 66.3 years at baseline, part of the BLSA, observed lower FT levels at 2, 5 and 10 years prior to the diagnosis of Alzheimer’s disease, and this suggests that the reduced T concentrations are unlikely the result of this pathology (252). This observation was not confirmed in another prospective cohort of 376 men, older than the preceding one (mean age 73 years at baseline), which was followed for only 4 years (253). Low FT may be responsible of the high circulating level of gonadotrophins found in Alzheimer’s disease (254). It has been speculated that gonadotrophins may have deleterious effects on brain function (251,255), since their elevated expression has been found to colocalize with neurons vulnerable to Alzheimer’s disease (254). In addition several studies have identified androgens as endogenous regulators of β amyloid protein, whose accumulation, inhibited by T, is widely believed to be the critical initiating step in the pathogenesis of Alzheimer’s disease (251).

**In conclusion** several studies are supporting low T, and, even more, low BT or FT levels, as risk factors for age-related selective losses in cognitive function, or for Alzheimer’s disease, but other studies are conflicting, and presently it is not possible to conclude unequivocally that T physiologically enhances brain and cognitive functions.

**d) Correlations with mood:**

Age-related decline in T levels is associated with a number of non-specific symptoms, including depressive symptoms. The relationship between depressive symptoms and T levels is confounded by numerous factors including medical illness, obesity, smoking, alcohol use, stress, and is thus complex. Studies have not consistently supported an integral role of reduced T levels in major depressive disorder, although T levels may often be reduced in men with treatment-refractory depression, and in older men with dysthymia (256,257). Several cross-sectional studies found especially significant associations of low TT or FT with overt depression in men with ED (OR for depression 1.9, [258]) or with other sexual dysfunctions (66), in middle aged men with long term depression (259), and in men over the age of 70 (2 studies reporting an increased rate of depression in the men with T levels in the lower quartile [260], or lower quintile [261] ) but others did not (262). Seidman et al (263) also reported a significant association between depression and AR gene CAG
repeat length in 1000 men aged 48-79 years. This association was not confirmed in another study of 2 smaller samples of men with median age 75.3 years (262). Lastly a prospective cohort study of 758 men > 50 years old by Shores et al (264) also found that low T levels (≤ 2.5 ng/ml) were associated with an earlier onset by about 2 years and greater incidence at 2 years of depressive illness (adjusted hazard ratio 2.1, CI 1.3-3.2).

In conclusion some studies support the possibility of an association between low T levels and mood but other data are conflicting and more studies are required for confirmation of the association and determination of the direction of the possible causality. There may be vulnerable subpopulations in whom TD contributes to depression but chronic depressive illness may also lead to hypogonadism.

e) Correlation with Metabolic and Cardiovascular Functions

The relationships between TD and these functions have been dealt with in sections III and IV of this chapter.

f) Correlations with Lower Urinary Tract Symptoms (LUTS)

Some uncontrolled studies have reported gradual improvements of the International Prostate Symptoms Score (IPSS) following long term T therapy in men with TD, metabolic syndrome and/or ED (see review in Yassin et al 2008 [265]). This has led to the speculation that lower T levels contribute to the exacerbation of Lower Urinary Tract Symptoms (LUTS) (266,267). In one study T therapy significantly increased bladder capacity and compliance and decreased detrusor pressure at maximal flow (268). Androgen deprivation has been shown in many laboratory studies to inhibit smooth muscle differentiation resulting in poorer relaxation of smooth muscle of the prostatic urethra and bladder (269,270). Other studies have implicated the role of T in maintaining normal autonomic reflex activity in the pelvis and bladder detrusor function through the Rho-kinase/endothelin and nitric oxide pathways (271,272). However no consistent correlation has been found between circulating T levels and LUTS in several studies (265). Therefore RPCTs of T therapy focusing on a beneficial effect on LUTS as primary end-point are required before confirming any possible association of TD with LUTS.

g) Correlations with changes in General Health, Quality of Life

Numerous studies have reported a relationship of lower T levels with poorer general well being and quality of life as reported in the Short-Form SF-12 Health Survey questionnaire, particularly the physical health index (273-275). Lower T levels are predictive of anemia which results in poorer overall health (276,277), especially in type 2 diabetic patients (adjusted OR for anemia 1.7, CI 1.1-2.8 for a TT level < 10 nmol/l, [278]). TD may be involved in frailty, a clinical syndrome characterised by reduced physiologic reserve affecting multiple organ systems and associated with increased risk of falls, fractures, hospitalisation and death (246,279). Frailty is multifactorial with aging, comorbidity, sarcopenia, and endocrine immune dysfunction contributing to the condition. The probable contribution of TD in this syndrome has raised the hope that T therapy could be beneficial to frail men.

3. EFFECTS OF TESTOSTERONE THERAPY IN AGING MEN

The following review has been almost exclusively based on the results of the randomized, placebo-controlled trials of T therapy, and their meta-analyses. The heterogeneity of the RCTs included in the review has to be emphasized. They differed in the serum T level chosen as inclusion criterion, the T preparations that were used, the duration of therapy, which was often short (> 6 months in only a minority of the trials) and the number of patients (8 to 406, but > 40 in only a minority). In addition many studies were insufficiently powered to demonstrate the absence of efficacy.

a) Body Composition and muscle strength

In a meta-analysis of 17 RPCTs of T therapy in middle-aged men by Isidori et al (44), an average of 9 months of T treatment resulted in a significant reduction of 1.6kg (CI: 2.5-0.6, P < 0.001) in total body fat which corresponds to -6.2% (9.2-3.3%) of initial percentage body fat. Active treatment also produced an increase of fat free mass by +1.6kg (CI: 0.6-2.6, P < 0.001) which corresponds to an increase of +2.7% (1.1-4.4) over initial percentage of lean body mass. Overall body weight was unchanged (44). The effects of TRT on muscle strength were heterogeneous, showing a tendency towards improvement only at the leg/knee extension and handgrip of the dominant arm.

In another meta-analysis which included 11 high quality RPCTs of the effects of T therapy on muscle strength of men 65 years old and older, Ottenbacher et al (280) found a mean g-index adjusted for sample size of 0.53, what amounts to a medium treatment effect. The elimination of a single study by Ferrando et al (281) markedly reduced the overall treatment effect (mean g-index 0.23 instead of 0.53). This 6 months study was the only investigation in which T was injected at weekly intervals, and the dosage size of 0.53, what amounts to a medium treatment effect. The elimination of a single study by Ferrando et al (281) markedly reduced the overall treatment effect (mean g-index 0.23 instead of 0.53). This 6 months study was the only investigation in which T was injected at weekly intervals, and the dosage...
In conclusion T therapy consistently results in limited but significant changes in body composition including reduction in fat mass of about 1.6 kg in average and increase in lean mass of also about 1.6 kg. No significant change seems to occur after 6 months. However improvement in muscle strength is less consistent and found in only about half of the studies with a trend to significance in meta-analyses. Improvement in global physical function (timed stair climbing, timed walking) has been reported in a limited number of studies, but does not appear to be convincing.

b) Bone Mineral Density (BMD)

The meta-analysis by Isidori et al (44) included 5 RPCTs of at least 12 months duration of the effects of T therapy on bone of middle-aged and older men. T improved BMD at the lumbar spine by 3.7% (CI 1.0-6.4%) compared to placebo but not at the femoral neck, and produced a consistent reduction in bone resorption markers, with no significant effect on bone formation markers. The highest effect was found with T esters. In one of the largest and longest studies (36 months), the effects of T on lumbar spine were inversely correlated with pretreatment T concentration (284). A further meta-analysis by Tracz et al (285) included 8 RPCTs which enrolled a total of 365 patients. Compared with placebo IM testosterone was associated with an 8% (CI 4%-13%) gain in lumbar BMD and transdermal T had no significant impact. Again T use was associated with a non significant 4% gain in femoral neck BMD. Recently a small additional RPCT confirmed a significant effect on lumbar but not femoral neck BMD (286). Only aromatizable androgens increase BMD (287). Seventy per cent of the bone effects of T seem to result from its transformation into E2.

In conclusion T therapy with aromatizable androgens significantly increases lumbar BMD of older men, but no trials reported the effects of T on fractures, which led Tracz et al (285) to conclude that without bone fracture data, the available trials offer only weak and indirect inferences about the clinical efficacy of T on osteoporosis prevention and treatment in men.

c) Cognitive functions

Fourteen RPCTs have assessed the effect of T therapy on cognitive function of aging men. No meta-analysis of these trials has been published to date. In 6 trials of short duration (12 weeks or less except the 20 weeks trial by Gray et al (165), T therapy was associated with significant improvement of spatial cognition (165,288,289), spatial and verbal memory (289-292), working memory (290) and/or visuospatial skills (293) or constructional abilities (291) either only in the T group, or with respect to the placebo group. Two of these studies included men with mild or moderate Alzheimer’s disease (291,293).

In a study by Cherrier et al (292) association of antazone, an inhibitor of aromatization, cancelled out the effect of T therapy on verbal but not on spatial memory. No significant difference between the T and placebo groups was found in the scores of various cognitive tests administered in 5 other trials of longer duration (either 12 months [294-296], or 5 and 6 months [297,298]. Lastly in one trial a single T ester injection significantly decreased verbal fluency (299) and in a 9 months RPCT of T esters injections, supraphysiological circulating levels of T decreased verbal memory with respect to placebo injections (300).

In conclusion evidence of beneficial effects of T therapy on cognitive functions of elderly men is presently limited. Some short lasting trials support it, but results of studies of longer duration are conflicting. Larger RPCTs of more than 6 months duration are required to confirm their possible clinical significance.

d) Mood:

In a 60 days RPCT in younger men with TD, T therapy led to decreases in anger, irritability, sadness, tiredness and nervousness, and improvements in energy level, friendliness and sense of well-being (301). T therapy has also demonstrated short-term efficacy and tolerability in augmenting antidepressants to alleviate treatment-refractory depression in adult males, but was not effective in treating major depressive disorder in men with TD (256). In older men, 18 RPCTs of T therapy included depression or other mood items in their assessments (no meta-analysis). In most trials these items were only secondary endpoints. No significant improvement was observed in 13 trials (165,288,290,294-297,302-307). Conversely significant improvements of various items were reported in 4 studies: Depression Melancholia Scale (308), Geriatric Depression Scale in a small study of frail, debilitated older men (282), nervousness and insomnia in obese diabetic men (46), and most important greater reduction in Hamilton Depression scale (primary outcome
measure) and higher remission rate (52.9% vs 18.8% in the placebo group) in a 3 months RPCT of only 33 men > 50 years old with subthreshold (or minor) depression and TD (309). In a 6 weeks RPCT of 23 men (median age 50.9 years), remission rate of 53.8% versus 10% on placebo was noted in late onset dysthyemic disorder (263).

**In conclusion** results from multiple RPCTs are conflicting. Most do not support T therapy as a broadly effective antidepressant, but it may be effective in carefully selected populations, or as an adjuvant to antidepressant therapies.

e) **Metabolic and cardiovascular functions:**

Preliminary evidence that T therapy may improve insulin resistance and T2D control in older men has been reviewed in section III. Likewise review of the RCTs reporting a short-term beneficial effect of T therapy in men with CHD may be found in section IV.

f) **Quality of Life**

At least 6 RPCTs have assessed the effects of T therapy on energy and/or fatigue of older men. The beneficial effect of T therapy on these symptoms was significant in 4 of them (46,308,310,311) with respect to the placebo effect or to baseline, and not significant in the 2 others (284,295). Other assessments of well being and quality of life were included, generally as secondary end-points, in at least 13 RPCTs with significant benefits of T therapy in 3 trials (287,310,311), benefits of T therapy limited to only one of the multiple assessed items in 3 trials (121,284,298) and no significant benefit in the 7 other trials (231,296,306,309,312,314).

**In conclusion**, although experienced by many clinicians, the benefits of T therapy on energy, well-being and overall quality of life have not yet been clearly substantiated by RPCTs. However few trials elected these parameters as primary endpoints of the study.

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**VII. DIAGNOSIS OF TESTOSTERONE DEFICIENCY**

1. **CLINICAL SYMPTOMS AND SCREENING**

a) **Symptoms of testosterone deficiency**

The signs and symptoms which commonly lead to screening for androgen deficiency include loss of libido, erectile dysfunction, depression, lethargy, sleep disturbance, irritability, depressed mood, inability to concentrate, visceral obesity, osteoporosis, loss of muscle strength, regression of secondary sex characteristics, decreased interest in activities, gynecomastia and anemia (Table VI).

Nevertheless, all these signs and symptoms are non specific. As developed earlier, TD is also prevalent in men with insulin resistance; type 2 diabetes, MetS, vascular disease and AIDS (71,325).

Age related hormonal changes in the aging male such as TD usually have an insidious onset with slow progression and do not manifest in all men. There is also great interindividual variability in both clinical manifestations and the intensity of each sign and symptom (326).

The clinical working definition of TD syndrome combines both signs/symptoms of low T levels and biochemical parameters which are low or borderline (2,211,327).

b) Are screeners and inventories valid?

Several questionnaires have been proposed to screen for TD in the ageing men. These include the Androgen Deficiency in Aging Males (ADAM) Questionnaire (328), the Aging Male Symptoms (AMS) Scale (329) and the MMAS questionnaire (330). The validation of the ADAM questionnaires represents an attempt in defining a symptoms complex associated with low bioavailable T levels that is similar to the symptoms complex associated with menopause in women. However, many studies revealed no statistically significant correlation between serum T level and the ADAM questionnaire except for men over age 70 (316,331-333). Similarly the AMS Scales showed inconsistent correlation with T level as some authors found good correlation with T or with the ADAM score (334-336) while for others no association of AMS scores (both total and subscales) were noted with all parameters of T measurement in both Western and Eastern population (211,331,333,337). Beutel et al (333) also demonstrated that the ADAM score but not the AMS score are moderately associated with age and they conclude that, based on their high correlations with depression, both seem to measure symptoms associated with depression rather than with symptoms of TD.

**In conclusion**, as illustrated by Table IX, these questionnaires have a good sensitivity for TD, defined in this table by BT (338). But in practice, they are not useful in the diagnosis of TD because they have very low specificity. Neither of these questionnaires replaces a proper history and clinical examination, and better instruments need to be developed (2). Nevertheless, such tools may be useful for monitoring purposes during T therapy (331,349-341) and may predict the opinion of the investigator upon T therapy results (340,341).

Conversely, in men with sexual dysfunction, the Androtest, a structured interview inventory, as opposed to self-reported questionnaires, appears to be a useful screening test in clinical practice as it shows high sensitivity (76%) and specificity (66%) in detecting biochemically low T (< 10.4 nmol/l) (342). However, as the original validated version is in Italian, adaptation in other languages will need further validation.
2. BIOCHEMICAL DIAGNOSIS (4)

Once a patient presents with symptoms causing clinical suspicion of TD, standardized patterns of diagnostics and therapy should be followed. Underlying causes of TD have been described in section II.2.a. Briefly they are disorders located at the testicular source of testosterone, the Leydig cells (primary TD or hypergonadotropic hypogonadism) or at the central regulation unit, consisting of the hypothalamus and the pituitary gland (secondary TD or hypogonadotropic hypogonadism), the latter secreting luteinizing hormone (LH), which stimulates Leydig cells.

**Symptoms of TD also occur in cases of target organ resistance**, mostly due to inherited alterations of the androgen receptor; in this case, elevated concentrations of both testosterone and LH are found, and the androgen-sensitivity index is elevated, pointing to androgen resistance (see below, pharmacogenetic implications).

For diagnostic purposes in suspected male hypogonadism, assessment of total testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (be aware of high-dose hook-effects in prolactin assays: use dilution in case of suspected macroprolactinomas) and estradiol is helpful, as well as calculation of free testosterone from total testosterone and sex hormone binding globulin (SHBG), the latter secreting luteinizing hormone (LH), which stimulates Leydig cells.

**Testosterone circulates in the blood of men and women in several forms.** It is bound tightly to sex-hormone binding globulin (SHBG), loosely to albumin, and unbound to proteins (free). In most, but not all, clinical conditions, a measurement of total T is adequate for the evaluation of a patient. It is widely believed that the SHBG-bound T is not readily available to most tissues, whereas albumin-bound and free T are bioavailable. Because SHBG concentrations can be influenced by many factors (e.g., decreased by obesity, testosterone treatment), there are clinical situations in which measured concentrations of total T may not reflect the bioavailable concentrations or the clinical status of the patient. In these circumstances a supplemental test assessing bioavailable or free T will be helpful in clinical decision-making (343). It is important to note that the reference method for measurement of free T, equilibrium dialysis, requires a sensitive, specific, precise, and accurate assay for total T. The current methods of measurement of total T lack the required sensitivity for samples with very low concentrations, as occur in severely testosterone deficient men; this sensitivity limitation can be corrected by newer methods based on mass spectrometry (344). Vermeulen and coworkers (343) could demonstrate that the FT value calculated by TT / SHBG (according to a second degree equation following the mass action law) as determined by immunoassay (cFT) appears to be a rapid, simple and reliable indicator of BT and FT, comparable to FT values obtained by equilibrium dialysis. An easy to use free calculator of calculated FT and BT can be found on www.issam.ch. So, determination of values of T and SHBG might provide a reasonable index of the androgen status. BT is also a rather reliable index, but it should be mentioned that direct FT assays using a T analogue do not yield a reliable estimate of FT (2,343).

Table IX: Sensitivity and specificity (%) of Screening Inventories (Questionnaire and Structured Interview) for Hypogonadism in Older Men

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
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</thead>
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<td>59</td>
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<td>AMS***</td>
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<td>39</td>
</tr>
<tr>
<td>2) Structured interview</td>
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<td></td>
</tr>
<tr>
<td>ANDROTEST§</td>
<td>68</td>
<td>65</td>
</tr>
</tbody>
</table>

* Massachusetts Male Aging Study
# Morley et al 2006 (338)
§ Corona et al 2006 (342)

** Smith et al 200 (300)
*** Heinemann et al 2006 (341)
Determination of androgen receptor genotype and concentrations of serum dihydrotestosterone should be performed in special cases of suspected androgen resistance.

If the clinical picture, the physical exam including genitalia, and patient's history lead to the suspected diagnosis of Kallmann syndrome or Idiopathic Hypogonadotropic Hypogonadism, basal serum levels of the gonadotropins, testosterone and estradiol will yield valuable information, but stimulation tests are mandatory in such cases of suspected secondary TD. Gonadotropin Releasing Hormone (GnRH) (0.1mg) should be given intravenously and, following, LH and FSH concentrations should be assessed after 30 and 45 minutes to demonstrate, whether the hypothalamus or the pituitary gland are affected. The responsiveness of gonadotropins to a GnRH stimulus is sometimes poor or absent which should not immediately be interpreted as disorder at the pituitary level. The gonadotropic cells in the anterior pituitary often require a certain period of "priming" by means of subcutaneous application of GnRH in a pulsatile manner: for a period of 7 days, 5µg GnRH are released every 90 to 120 min using a portable minipump. If the gonadotropin response (rise of LH and FSH levels > 3 IU / l) to a GnRH bolus is normalized then the hypothalamic origin of the hypogonadism is indicated. When there is permanent resistance to GnRH, a pituitary disorder or mutation of the GnRH receptor have to be suspected.

Testing the Leydig Cell response to hCG is helpful in determination of the testicular potential as well as solving the question whether testes are present in cases of primary TD. To this end, human Chorionic Gonadotrophin (hCG) (5000 IU) is given subcutaneously and testosterone concentrations are measured after 2 to 3 days.

3. LOOKING FOR SIGNIFICANT AETIOLOGIES? (2)

The aetiologies of TD are listed in section II.1. Some of them, mainly pituitary tumors, involve serious risks for health, independently of the consequences of low T. This possibility must be systematically remembered in case of secondary TD (normal or low serum LH), and even more of hyperprolactinemia. Measurements of serum LH and prolactin are therefore to be done in case of TD. In such cases pituitary tumors will be searched for with Magnetic Resonance Imaging (MRI). The possibility that hemochromatosis is revealed by TD should also be remembered and if necessary clarified by determining serum iron and ferritin.

4. PRACTICAL ASPECTS (2)

The laboratory reference values of T and FT show a wider range than those for most other hormones, which makes often difficult to establish whether borderline values of T are normal or abnormal. In a patient whose plasma levels of T fall from the upper to the lower range of normal T levels (a drop of as much as 50%), T levels may well be within the reference range but inappropriately low for that particular individual or his particular age. In addition, if the mostly used immunoassays (by chemiluminescence detection) provide fairly accurate measurements between 10 and 35 nmol/L, their accuracy is considerably less below 10 nmol/L. Lastly reference values vary significantly from laboratory to laboratory and from measurement method to method. It is advisable that every laboratory establishes its own 'normal range' of T in men.

There is no generally accepted lower limit of normal. Following Vermeulen's opinion most authors consider the normal range of T levels in young males also valid for elderly men. A pragmatic approach of which T level is low, which T level is very probably sufficient for an optimum androgenic effect, or is in the borderline area where T levels may be sufficient for certain men but insufficient for others due to the inter-individual variability of the sensitivity to T is described in recommendation 8. The corresponding T levels are in agreement with the levels proposed by another recent consensus (11).

Table X: Factors which increase and decrease SHBG in men (and hence respectively decrease and increase the bioavailable fractions of testosterone)

<table>
<thead>
<tr>
<th>Increase SHBG and decrease BT and FT</th>
<th>Decrease SHBG and increase BT and FT</th>
</tr>
</thead>
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<tr>
<td>- Male aging</td>
<td>- obesity</td>
</tr>
<tr>
<td>- hyperthyroidism</td>
<td>- hypothyroidism</td>
</tr>
<tr>
<td>- estrogens</td>
<td>- androgens</td>
</tr>
<tr>
<td>- cirrhosis</td>
<td>- insulin resistance, hyperinsulinism</td>
</tr>
<tr>
<td>- anti-epileptic drugs</td>
<td>- hyperprolactinemia</td>
</tr>
<tr>
<td>- tamoxifen</td>
<td>- acromegaly</td>
</tr>
<tr>
<td></td>
<td>- hypercortisolism</td>
</tr>
</tbody>
</table>

Table X: Factors which increase and decrease SHBG in men (and hence respectively decrease and increase the bioavailable fractions of testosterone)
Lastly, because the consequences of lower-than-normal value of T may have great impact, such as T therapy for years, if serum T values are so low that T replacement is considered, the measurement has to be repeated a couple of weeks later, together with an assessment of SHBG, LH and prolactin. It has to be remembered that many physical or psychological stresses of daily living may depress temporarily T secretion.

Recommendations 1-3, 5-8, and 29 (prolactin) contain the guidelines referring to the main clinical and biochemical aspects of TD diagnosis. Figure 5 presents an algorithm for the diagnosis of TD summarizing these guidelines.

VIII. TREATMENT OF TESTOSTERONE DEFICIENCY/ANDROGEN THERAPY

1. INDICATIONS, EXPECTED BENEFITS

- There are two primary indications for testosterone therapy in the adult man. One is for the treatment of men with substantially depressed serum T concentrations due to significant disruption of the hypothalamic-pituitary-gonadal axis, such as following hypophysectomy, or in men with absent or atrophic testes (345). Lifetime treatment with T is indicated in these men. A second, more common indication is for the treatment of men exhibiting signs or symptoms of age-related TD (11).

The most frequently used blood test used to confirm the diagnosis of TD is total T (TT), even though it is recognized TT is an imprecise measure of bioavailable T. Values below 10-12 nmol/L (300-350 ng/dl) for TT have been proposed as consistent with TD (11,345). Free T may be a more useful test, but its use is confounded by the availability of different assays with quite different reference values. Values below 180-225 pmol/l (50-65 pg/ml) for cFT have been proposed as consistent with TD when determined by equilibrium dialysis (11,345). A value less than 50 pmol/L (15 pg/ml) for analog free T as determined by RIA has been reported to correlate with clinical symptoms and biochemical outcomes (346,347).

- A 3-6 month trial of empiric therapy may be considered in men with suggestive symptoms but without definitely diagnostic blood test results, since there is no absolute T concentration that reliably distinguishes who will or will not respond to treatment, due to substantial inter-individual variation in T physiology (13). One study of hypogonadal men undergoing T therapy revealed similar subjective response rates whether total T was <200 ng/dl, 200-300 ng/dl, or greater than 300 ng/dl ("normal"), as long as all men had free T < 15 pg/ml as measured by RIA with T analogue (347).

- Emerging indications for T therapy include ED that is poorly responsive to PDE5 inhibitors (193); decreased bone mineral density (348); and depression resistant to standard anti-depressant medications (349). Although there is inadequate evidence to date to support a formal recommendation for these indications, a growing literature suggests that treatment may be reasonably considered in individual cases based on clinical circumstances. In addition, it seems likely that the indications for T therapy will broaden in the near future based on recent evidence documenting important beneficial relationships between normal serum T and general health outcomes such as diabetes, cardiovascular disease (29), and longevity (100), though some studies are conflicting as concerns CVD and longevity (see sections II.2.d.).

2. RISKS, CONTRA-INDICATIONS

a) Potential risks for the prostate:

Growth of the prostate tissue is testosterone-dependent, which has led to think that T may play a role in prostate pathology and especially prostate cancer (PCa). This speculation was considerably fuelled by the beneficial effects of androgen deprivation in men with recurrent or metastatic PCa, since the initial paper by Huggins et al in 1941 (350). In fact careful review of literature shows that there is no compelling evidence for an association of T levels with prostate diseases.

Most observational studies failed to find correlations between circulating T levels and prostate pathology. No clear correlation with PSA, prostate volume or Benign Prostatic Hyperplasia (BPH) (351,352). Hypogonadism may be associated with reduced total prostate volume (353). But after the 4th decade, age is a more important determinant of prostate size than T, since prostate volume increases regardless of androgen deficiency or replacement (354), and is not associated with T levels (355). Likewise only a small number of the 21 longitudinal studies which examined the possibility that high serum androgen levels are related to increased cancer risk found such an association (356). The pooled analysis of 18 of these studies, involving > 3800 men with cancer and > 6438 men without cancer, found no relationship between the serum levels of 6 different androgens and cancer risk (357). Conversely, case-control studies found correlations of prostate cancer prevalence or severity with low serum T. In hypogonadal men the rate of prostate biopsies positive for cancer was twice higher in those with a T level in the lower tertile compared with those in the highest tertile (358). In other studies low T was associated with high Gleason scores, more advanced stages at presentation, higher recurrence rate following radical prostatectomy, and worse survival (359,360).

Augmentation of serum T levels for replace-
Figure 5: Algorithm for the diagnosis and management of testosterone deficiency (modified after Buvat et al 2006 [2])
ment therapy in men with low or low to normal T does not seem more associated with prostate pathology. Table XI shows a compilation of the results of prostate assessments from 21 RPCTs of T therapy which included such men. The 1173 patients included in the T groups had been treated for a total of 9919 months, while the 750 patients included in the placebo groups had been observed for a total of 7613 months. Mean serum PSA significantly increased in the T groups of 6/21 trials and in 1 of the 21 placebo groups. Mean prostate volume measured with ultrasonography in 6 studies significantly increased on T in 2 studies of 6 and 36 months duration, and increased also on placebo in an additional 36 months study. Mean International Prostate Symptoms Score (IPSS) measured in 6 trials (287,298,30 4,307,361,364), and Urine Flow Rate measured in 2 studies (281,361) did not significantly change during the study in any group. Lastly the rates of prostate cancers were very close in the T group (n = 8, 9.56/1000 patient/years) and the placebo group (n = 7.9, 19/1000 patient/years). There was no clear effect of the trials’ duration on prostate changes. One of these RPCTs, by Marks et al (364), is of special interest. The authors conducted a serial prostate biopsy study in men receiving T therapy for 6 months resulting in an increase of the mean serum TT level from 2.82 ng/ml at baseline to 6.3 ng/ml at 6 month. At 6 months follow-up prostate biopsy, there were no changes in tissue levels of T and DHT, prostate histology, tissue biomarkers or gene expression. Cancer was found in 4 of 19 men in the placebo group and 2 of 21 men in the T treatment group.

Calof et al published in 2005 a meta-analysis of RPCTs of T therapy in men > 45 years old which focused on safety (115). Only 9 of the 19 RPCTs were common to the above compilation. Table XII shows the pooled Odd Ratios for prostate adverse events calculated from this meta-analysis. Although the rate for all prostate events was significantly higher in the T group, there was no significant difference for any individual adverse event, including the rate of PCa (respectively 9.2 and 8.3 per 1000 patient/years in the T and placebo groups).

While the studies included in the Calof et al meta-analysis and in the above compilation were all randomized and placebo-controlled, the significance of their pooling may be limited by their short duration: 3 only lasted more than 12 months (24 to 36 months). Recently a retrospective study left its mark on mind by reporting 20 cases of PCa diagnosed in men receiving T therapy for hypogonadism, including 11 cases detected during the 2 first years of therapy but also 9 detected at later stages, 2½ to 8 years after the start (368). However the methodology was very poor, the authors were unable to find how many total patients had really been followed, and nearly half of these 20 men did not have a digital rectal examination prior to T therapy initiation that was done by primary care physicians. This study above all emphasizes the necessity of systematic and careful screening for prostate cancer before any T therapy. In 11 uncontrolled but prospective studies of T therapy, of 6 months to 10 years duration, a systematic prostate monitoring found only 6 prostate cancers in 965 men followed for 1321 years (0.62%, 4.54/1000 patient-years) (in Shabsigh et al 369).

Since androgen deprivation causes prostate cancer regression, it seems paradoxical that T therapy does not appear to cause more rapid prostate cancer growth in non-castrated men (359). Two primary explanations may explain this paradox. First, as shown by Marks et al (364) 2006), T therapy may fail to increase intra-prostatic T or DHT. A second explanation is based on the Saturation Model proposed by Morgentaler and Traish (360). Studies in humans, animals, and prostate cancer cell lines show a limit to the ability of androgens to stimulate prostate growth, benign or malignant. Whereas there is exquisite sensitivity of prostate cancer to changes in serum T at very low concentrations, at higher concentrations the growth rate appears indifferent to such changes. According to Morgentaler and Traish (360), this would be consistent with maximal binding of androgen to the AR at 2-3 nM/l (0.57-0.86 ng/ml).

Although a history of prostate cancer has been considered an absolute contraindication to T therapy, this point is now under active debate for men who are deemed cured. Review of recent literature finds a total of 110 hypogonadal men to whom T therapy was offered after being submitted to radical prostatectomy 2.5 months to 8 years before (table XIII). The duration of T therapy ranged from 3.3 months to 9 years. No clinical recurrence was observed and only 1 patient had PSA recurrence (after 12 months of transdermal TT, 17 months post-radical prostatectomy). Likewise 31 patients were submitted to T therapy for 6 months to 8.5 years after brachytherapy done 6 to 51 months previously for PCa, and 11 men were submitted to T therapy for 6 to 27 months after radiotherapy for PCa (table XIV). Neither clinical, nor PSA recurrence were observed in these patients. Another series of 13 men who elected an Active Surveillance for their PCa chose to undergo T therapy due to symptomatic hypogonadism (378). Follow-up prostate biopsies were performed in six men, revealing no cancer in two, and possible aggravation in only one patient (change in Gleason score from 6 to 7). Lastly, after 1 year of T therapy, Rhoden and Morgentaler (166) observed no significant differences in PSA and in the risk of developing prostate cancer in men with and without Prostatic Intraepithelial Neoplasia found in previous prostate biopsies, the former being considered to be in a higher risk in developing PCa. These data do not support a high risk of PCa progression or recurrence when T therapy is prescribed in hypogonadal men with a history of "low risk" prostate cancer.
<table>
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<tr>
<th>Author, reference</th>
<th>Age (years, mean/range)</th>
<th>Trial duration</th>
<th>Testosterone formulation</th>
<th>Treatment subgroups</th>
<th>Number randomized / completed, all &amp; subgroups</th>
<th>Mean test. level at baseline (nmol/l)</th>
<th>Mean PSA level at baseline (ng/ml)</th>
<th>Mean PSA level at end point (ng/ml)</th>
<th>Prostate volume baseline (mean/ml)</th>
<th>Prostate volume end point (mean/ml)</th>
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<td>TE + finasteride</td>
<td>placebo</td>
<td>24/17</td>
<td>10.1 ± 2.1</td>
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<td>Snyder 1999 (284)</td>
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<td>36 months</td>
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<td>1.6</td>
<td>1.69</td>
<td>ns change</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DHEA 75mg/d</td>
<td>placebo</td>
<td>30/27</td>
<td>13.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ns change</td>
<td>0</td>
</tr>
<tr>
<td>Allan 2007 (361)</td>
<td>63.3 ± 1.1 y.o.</td>
<td>12 months</td>
<td>T. patch 5mg/d</td>
<td>Testosterone</td>
<td>62/42</td>
<td>13.6 ± 0.5</td>
<td>2.1 ± 0.4</td>
<td>2.1 ± 0.5</td>
<td>ns change</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo</td>
<td></td>
<td>31/17</td>
<td>14.05±0.5</td>
<td>1.9 ± 0.4</td>
<td>2.2 ± 0.5</td>
<td>ns change</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Crawford 2003 (287)</td>
<td>60.3 ± 1.9 y.o.</td>
<td>12 months</td>
<td>IM TE 200 mg/2w</td>
<td>Testosterone</td>
<td>51/37</td>
<td>13.8 ± 0.4</td>
<td>1.2 ± 0.2</td>
<td>1 transient ns</td>
<td>ns change</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nandrolone</td>
<td>placebo</td>
<td>18/14</td>
<td>13.2 ± 0.3</td>
<td>1.6 ± 0.5</td>
<td>ns change</td>
<td>ns change</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17/10</td>
<td>15.7 ± 0.5</td>
<td>0.9 ± 0.1</td>
<td>ns change</td>
<td>ns change</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Kenny 2001 (362)</td>
<td>76 ± 4 y.o.</td>
<td>12 months</td>
<td>T Patch 5 mg/d</td>
<td>Testosterone</td>
<td>67/43</td>
<td>BT 3.2±1.2</td>
<td>2.0 ± 1.4</td>
<td>2.6 ± 4.8*</td>
<td>ns change</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo</td>
<td></td>
<td>31/25</td>
<td>14.05±0.5</td>
<td>1.9 ± 0.4</td>
<td>2.2 ± 1.5 ns</td>
<td>ns change</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Legros 2009 (304)</td>
<td>58.6 y.o.</td>
<td>12 months</td>
<td>Oral TU 80 to 240 mg/d</td>
<td>Testosterone</td>
<td>322/243</td>
<td>FT &lt; 0.21</td>
<td>&lt; 4</td>
<td>ns difference + 4 ± 13 % + 17 %</td>
<td>ns change</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo</td>
<td></td>
<td>32/22</td>
<td>BT &lt; 2</td>
<td>1 ± 0.2</td>
<td>no case &gt; 4</td>
<td>ns change</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Sih 1997 (294)</td>
<td>62 ± 2 y.o.</td>
<td>12 months</td>
<td>IM TE 200 mg / 2w</td>
<td>Testosterone</td>
<td>32/22</td>
<td>BT &lt; 2</td>
<td>1 ± 0.2</td>
<td>1.9 ± 0.3</td>
<td>ns change</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo</td>
<td></td>
<td>17/10</td>
<td>1.5 ± 0.3</td>
<td></td>
<td>2.0 ± 0.4</td>
<td>ns change</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Tan 2003 (293)</td>
<td>68 – 80 y.o.</td>
<td>12 months</td>
<td>IM TE 200 mg / 2w</td>
<td>Testosterone</td>
<td>10/9</td>
<td>TT mean 3.6</td>
<td>0.98</td>
<td>1.37 ns</td>
<td>ns change</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo</td>
<td></td>
<td>5/4</td>
<td>?</td>
<td></td>
<td></td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Witt 2003 (363)</td>
<td>60 – 86 y.o.</td>
<td>12 months</td>
<td>oral TU 160 mg/d</td>
<td>Testosterone</td>
<td>76/72</td>
<td>TT</td>
<td>17.0 ± 4.4</td>
<td>ns by 0.1 ± 0.8</td>
<td>ns change</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo</td>
<td></td>
<td>50/72</td>
<td>15.6 ± 4.5</td>
<td>?</td>
<td>ns by 0.4 ± 1.2</td>
<td>ns change</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Cavallini 2004 (308)</td>
<td>66 y.o.</td>
<td>6 months</td>
<td>oral TU 160 mg/d</td>
<td>oral TU</td>
<td>40/72</td>
<td>9.9 ± 1.8</td>
<td>2.0 ± 0.7</td>
<td>20 ± 2.6</td>
<td>ns change</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>carnitine</td>
<td>placebo</td>
<td>45/72</td>
<td>10.5 ± 2.1</td>
<td>1.8 ± 0.8</td>
<td>20 ± 2.6</td>
<td>ns change</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>
Table XI: Impact of testosterone therapy on the prostate in 21 randomized, placebo controlled, trials of men with no history of prostate cancer. (Continued).

<table>
<thead>
<tr>
<th>Author, reference Age (years, mean/range)</th>
<th>Testosterone formulation / Treatment subgroups</th>
<th>Number randomized / completed, all &amp; subgroups</th>
<th>Mean test. level at baseline (nmol/l)</th>
<th>Mean PSA level at baseline (ng/ml)</th>
<th>Mean PSA level at end point (ng/ml)</th>
<th>Prostate volume baseline (mean/ml)</th>
<th>Prostate volume end point (mean/ml)</th>
<th>Prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emmelot-Vonck 2008 (298) 67.2 y.o. 6 months</td>
<td>oral TU 160 mg/d testosterone placebo</td>
<td>237/207 120/104 117/103</td>
<td>TT 11.0 ± 1.9 10.4 ± 1.9</td>
<td>1.6 ± 1.1 1.7 ± 1.3</td>
<td>28.3 ± 12.6 28.0 ± 9.9</td>
<td>30.7 ± 13.1 29.2 ± 10.4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ferrando 2002 (281) &gt; 60 y.o. 6 months</td>
<td>IM TE dose adjusted at serum T level testosterone placebo</td>
<td>12 7/7 5/5</td>
<td>TT # 13</td>
<td>1.4 ± 0.4 1.2 ± 0.4</td>
<td>2.3 ± 0.9 ns/pl 1.3 ± 0.4</td>
<td>44 ± 15 41 ± 8</td>
<td>47 ± 13 35.7 ± 7.7</td>
<td>0</td>
</tr>
<tr>
<td>Giannoulis 2006 (231) 65-80 y.o. 6 months</td>
<td>T patch 5 mg/d test + GH GH alone placebo</td>
<td>80/73 20/? 20/? 20/? 20/?</td>
<td>TT &lt; 4.5</td>
<td>no sign.</td>
<td>no sign. §</td>
<td>no sign. §</td>
<td>no sign. §</td>
<td>0</td>
</tr>
<tr>
<td>Marks 2006 (364) 49 – 78 y.o. 6 months</td>
<td>IM TE 150 mg/2w testosterone placebo</td>
<td>44/40 22/21 21/19</td>
<td>9.7 9.7</td>
<td>1.55 0.97</td>
<td>2.29 * 1.10 *</td>
<td>43.8 36.8</td>
<td>42 29.4</td>
<td>biopsy†</td>
</tr>
<tr>
<td>Steidle 2003 (307) 58 ± 10.6 y.o. 3 months</td>
<td>T gel or patch T gel 50 mg/d T gel 100 mg/d T patch 5 mg/d placebo</td>
<td>406/351 99/89 106/95 102/76 99/91</td>
<td>8.1 ± 2.0 8.1 ± 2.2 8.3 ± 2.4 7.9 ± 2.8</td>
<td>1.17 ± 0.9 1.29 ± 0.6 1.45 ± 1.2 1.13 ± 1.0</td>
<td>no significant change §</td>
<td>no significant change §</td>
<td>no significant change §</td>
<td>0</td>
</tr>
<tr>
<td>Tenover 1992 (311) 57-76 y.o. 3 months</td>
<td>IM TE 100 mg/w testosterone placebo</td>
<td>132/ ? 61/? 71/?</td>
<td>11.6 ± 0.4 11.6 ± 0.4</td>
<td>2.1 ± 0.4 2.1 ± 0.4</td>
<td>+ 2.7 ± 0.5* ns change</td>
<td>33 ± 4 33 ± 4</td>
<td>36 ± 5 36 ± 4</td>
<td>0</td>
</tr>
<tr>
<td>Grinspoon 2000 (126) ? 12 weeks</td>
<td>IM TE 200 mg/2w testosterone placebo</td>
<td>50/43 24/21 26/22</td>
<td>22.5 ± 5.7 23.0 ± 7.3</td>
<td>0.7 ± 0.4 0.7 ± 0.4</td>
<td>+ 0.2 ± 0.3 + 0.1 ± 0.4</td>
<td>ns change ns change</td>
<td>ns change ns change</td>
<td>0</td>
</tr>
<tr>
<td>Casaburi 2004 (366) 55 – 80 y.o. 10 weeks</td>
<td>IM TE 100 mg/w TE alone TE + training placebo</td>
<td>53/47 14/11 13/12 25/24</td>
<td>14.1 ± 4.8 10.4 ± 3.0 9.8 ± 4.3</td>
<td>0.7 ± 0.4 0.7 ± 0.4</td>
<td>ns change ns change ns change</td>
<td>ns change ns change ns change</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Okun 2006 (367) 68.3 ± 10 y.o. 8 weeks</td>
<td>IM TE 200 mg/2w testosterone placebo</td>
<td>30/? 15/? 15/?</td>
<td>13.0 ± 3.6 9.6 ± 4.8</td>
<td>&lt;4</td>
<td>1 ± 1 to 4.6 1 ± 1 to 5.5</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* : p < 0.05, § : rates of PSA increases above 4n/ml : 50 mg gel : 1.8 %, 100 mg gel : 2.4 %, patches : 6.6 %, placebo : 3.2 %, † : prostate biopsy in every case before randomization and at end point, IM : intramuscular, ns : non significant, TE : Testosterone Ester, TU : Testosterone Undecanoate
Table XII: Pooled Odd Ratios for adverse prostate events of testosterone therapy (adapted from Calof et al 2005, (115))

<table>
<thead>
<tr>
<th>Event</th>
<th>Testosterone rate/1000 patient/years</th>
<th>Placebo rate/1000 patient/years</th>
<th>Pooled Odd ratio</th>
<th>95 % Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in IPSS score</td>
<td>5.5</td>
<td>2.8</td>
<td>1.8</td>
<td>0.46,2.52</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>2.2</td>
<td>0</td>
<td>0.99</td>
<td>0.40,2.44</td>
</tr>
<tr>
<td>PSA &gt; 4 ng/ml or 1.5 ng/ml increase during study</td>
<td>57.1</td>
<td>41.6</td>
<td>1.19</td>
<td>0.67,2.09</td>
</tr>
<tr>
<td>Prostate biopsy</td>
<td>38.7</td>
<td>2.8</td>
<td>1.87</td>
<td>0.84,4.15</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>9.2</td>
<td>8.3</td>
<td>1.09</td>
<td>0.48,2.49</td>
</tr>
<tr>
<td>All prostate events</td>
<td>112.4</td>
<td>55.7</td>
<td>1.78*</td>
<td>1.07,2.95</td>
</tr>
</tbody>
</table>

*Odd Ratio significantly different from placebo – IPSS: International Prostate Symptom Score.

Table XIII: Follow-up of testosterone therapy following radical prostatectomy for prostate cancer

<table>
<thead>
<tr>
<th>Author/Year Ref.</th>
<th>N pts</th>
<th>Age (y) Mean/Range</th>
<th>PSA at diagnosis (ng/dl)</th>
<th>Gleason ≤ 6/ ≥ 7</th>
<th>Testost. baseline (ng/dl)</th>
<th>Time to initiation TRT</th>
<th>Type</th>
<th>Duration Mean/Range</th>
<th>Testost. before TRT (ng/dl)</th>
<th>Time Mean/Range</th>
<th>PSA before TRT (ng/dl)</th>
<th>Last PSA during TRT</th>
<th>Clinical Recurr.</th>
<th>PSA Recurr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaufman 2004</td>
<td>7</td>
<td>62</td>
<td>4.4-6.6</td>
<td>6 / 1</td>
<td>19-269</td>
<td>&lt;1 (*) to 9 y</td>
<td>patch 3 depot 2 gel 2</td>
<td>0.5-9 y</td>
<td>214-740</td>
<td>2-13 y</td>
<td>&lt; 0.1</td>
<td>&lt; 0.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Agarwal 2005</td>
<td>10</td>
<td>64.3</td>
<td>5.8-12.6 Mean 7</td>
<td>2 / 8</td>
<td>Mean 197</td>
<td>NM</td>
<td>gel 7 patch 1 IM 2</td>
<td>19 m</td>
<td>Mean 591</td>
<td>19 m (9-19)</td>
<td>&lt; 0.1</td>
<td>&lt; 0.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mulhall 2008</td>
<td>22</td>
<td>61 +/- 9</td>
<td>5.9+/-.3.5 Mean 11 m</td>
<td>13 / 9</td>
<td>228 +/- 94</td>
<td>2.5-118 m mean 11 m</td>
<td>Gel 21 IM 1</td>
<td>14-30 m</td>
<td>427 +/- 269</td>
<td>24 +/- 16 m</td>
<td>undetectable</td>
<td>Undetectable</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Khera 2009</td>
<td>57</td>
<td>64-53-83</td>
<td>5.58 (mean)</td>
<td>NM</td>
<td>Mean 255</td>
<td>36 m</td>
<td>NM</td>
<td>Mean 13</td>
<td>Mean 459</td>
<td>13 m</td>
<td>0.007 (mean)</td>
<td>0.008 (mean)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Khera (5) 2008</td>
<td>6</td>
<td>60</td>
<td>NI</td>
<td>NM</td>
<td>Mean 233</td>
<td>5.3 m</td>
<td>NM</td>
<td>Mean 3.3</td>
<td>Mean 459</td>
<td>Undetectable</td>
<td>&quot;No signific. increase&quot;</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Carrion 2008</td>
<td>14</td>
<td>69</td>
<td>6.05 (mean)</td>
<td>6 / 0</td>
<td>291 Mean</td>
<td>74 m</td>
<td>Gel or IM T</td>
<td>NI</td>
<td>Mean 630</td>
<td>12 m mean</td>
<td>0.1</td>
<td>0.1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NM - Not Mentioned - (*) Indicated as “the same year” without precisions
Table XIV: Follow-up of testosterone therapy after brachytherapy (Brachy) or radiotherapy (radio) for prostate cancer

<table>
<thead>
<tr>
<th>Author/ Year Ref.</th>
<th>Characteristics at Baseline</th>
<th>Androgen Therapy</th>
<th>Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N pts</td>
<td>Age (y) Mean/ Range</td>
<td>PSA at diagnosis (ng/dl)</td>
</tr>
<tr>
<td>Sarosdy 2006 (376) Brachy</td>
<td>31</td>
<td>51-79 Mean 65</td>
<td>0.4-7.4 Mean 5.3</td>
</tr>
<tr>
<td>Carrion 2008 (375) Radio</td>
<td>6</td>
<td>66 (mean)</td>
<td>3.5 (mean)</td>
</tr>
<tr>
<td>Morales 2008 (377) Radio</td>
<td>5</td>
<td>65 52-75</td>
<td>3.8-38 mean : 12.8</td>
</tr>
</tbody>
</table>

(*) then switched to other types according to preference
the number of reported cases is still small, and the duration of follow-up often short, while PCa recurrence may occur late. **Caution regarding T therapy in such men, as well as a minimum interval since treatment of the cancer, remain essential until RCTs of T therapy have confirmed the safety of TT in such cases.**

**In conclusion,** historically androgen administration has been absolutely contraindicated in men suspected of harboring carcinoma of the prostate. **This is today an area of ongoing research and reevaluation.** There is no compelling evidence that T treatment causes prostate cancer or BPH, or prostate cancer progression from a subclinical to a clinical state in the non castrated man. However there is unequivocal evidence that T suppression can reduce growth and symptoms in men with locally advanced and metastatic prostate cancers. Currently adequately powered and optimally designed long-term prostate disease data are not available to determine if there is an additional risk from T therapy. Hypogonadal men > 45 years old should be counselled on the potential risks and benefits of T therapy before treatment, and carefully monitored for prostate safety during treatment.

**b) Potential cardiovascular risks:**

The belief that T is a risk factor for cardiovascular disease (CVD) is based on the observation that men have both a higher incidence of cardiovascular events and higher T levels than women. However, few, if any, data support a causal relation between higher T levels and CVD. As reported above (sections II.2.c., T and metabolism, and II.2.d., T and cardiovascular health, among 17 prospective longitudinal and over 30 cross-sectional studies only 2 longitudinal studies found a weak association of high T levels with incident or existing CVD in men. Conversely T is low in men with CVD in about half of the cross-sectional studies and low T predicted CVD progression or CV events in 4 of the 17 longitudinal studies. In addition T therapy at physiological dose improves several CV risk factors including visceral obesity, and possibly glycemic balance and insulin resistance, and has negligible effects on lipids and lipoproteins, except the possibility of a slight but significant decrease of both total, LDL and HDL cholesterol on IM injections of T esters, and a favourable decrease in lipoprotein a. Interventional studies suggest mainly beneficial effects of T administration on CV health, including symptomatic and ECG improvements in 4 short RPCTs of T supplementation in men with CHD, and improvement of cardiac condition in 2 RPCTs of T therapy in men with heart failure.

In conclusion **current available evidence suggests that T therapy in men is not associated with an important increase in CV adverse events.** Two meta-analyses of RPCTs of T therapy (45,115) found no significant difference between the T and placebo groups for all incident CV events, nor for each type of event (table IV), except an increase in hematocrit over 50% which was significantly more prevalent in the T group (115), and which might augment the risk of thrombosis (2). However, many of the preceding RPCTs included small numbers of men, often healthy, during short durations, and larger trials, measuring CV endpoints, and enrolling men with CVD for longer durations, are needed to be sure of the CV consequences of T therapy in the medium and long terms. The main practical consequence of these data are that hematocrit or hemoglobin level should be monitored in men receiving T therapy so that appropriate measures may be instituted if polycythemia develops. Conversely monitoring lipids is not required for safety reasons if their level was normal at baseline.

c) **Obstructive Sleep Apnea Syndrome:**

Cautionary statements about T therapy in Obstructive Sleep Apnea Syndrome (OSA) appear frequently in the T therapy literature and guidelines, despite lack of convincing evidence that T therapy causes and/or aggravates this syndrome. Also, there is a lack of consistency in the findings connecting T therapy to OSA. Despite the warnings in the package inserts, it is evident that the link between T therapy and OSA is weak, biased by methodological issues in many of the studies, and most studies involved small numbers of men (379).

d) **Infertility:**

All delivery methods for T therapy share as common shortcoming some suppression of the hypothalamic-pituitary-gonadal axis if this axis was previously at least partly functional. This suppression results from a negative feedback mechanism causing decreased intratesticular secretion of T and spermatogenesis. This negative impact on fertility is transient and disappears some months after discontinuation of T therapy. Agents that stimulate the endogenous production of T such as Human Chorionic Gonadotropin or in the mild cases anti-estrogens like clomiphene (380) would theoretically avoid this effect. In young men with hypogonadotropic hypogonadism, long-term T therapy does not compromise forthcoming responsiveness to LH and FSH when they will require fertility (381), and may even in some cases be followed by recovery of pulsatile secretion of gonadotropins with T secretion and spermatogenesis (382). However, a recent report indicates that prior androgen therapy is independently associated with a decrease in the likelihood of achieving conception (383).

e) **Risks linked to aromatisation of testosterone**

Known breast cancer is a classical contra-indication to T therapy. Some flare-ups of missed breast cancers with positive estradiol receptors have been
reported in men shortly after starting T therapy (384). Other cases of this cancer which is very rare in men have also been observed after long-term T therapy (385). Likewise rare cases of increase in a prolactinoma size have been reported in men whose hyperprolactinemia had not been adequately suppressed by dopamine-agonists at the time of starting TT, or even had been so (386). The most frequent consequence of aromatisation of the administered T is gynecomastia.

f) **Contraindications and restrictions for** use of testosterone therapy are summarized in recommendations 18 to 20.

3. **INITIATION, FOLLOW-UP**

Once it has been decided to initiate T treatment, it is usually recommended to start with a short acting formulation, mainly to check tolerance and early side effects, especially polycythemia, and then, possibly, follow with long-acting T, this remaining the choice of the patient and the practitioner.

At initiation of T treatment, individual assessment of comorbidities (as possible causes of symptoms) and potential risks versus benefits of T is particularly important (11).

After initiation of T treatment, patients should be monitored for prostate disease at 3–6 months during the first year, and at least annually thereafter (11).

Should the patient’s prostate cancer risk be sufficiently high (suspicious finding on DRE, increased PSA, or as calculated using a combination of risk factors noted above), transrectal ultrasound-guided biopsies of the prostate are indicated, as in any other patients at risk.

Severe lower urinary tract symptoms (LUTS) evident by a high (>21) IPSS Score due to BPH represents a relative contraindication (although there are no compelling data to suggest that T treatment exacerbates LUTS or promotes acute urinary retention). After successful treatment of lower urinary tract obstruction, this contraindication is no longer applicable.

Hematocrit or Hemoglobin should be measured before starting T treatment and at least every year.

4. **AVAILABLE PREPARATIONS**

There are many T compounds in the market to be used in T therapy. They differ in their formulations, the route of administration, the dose and interval to be used (pharmacokinetics) and also in their safety profiles. The most common available preparations are listed in the **Table XV**.

a) **Oral Formulations**

The oral route is the easiest one to replace T, but the ingested hormone is almost completely inactivated by its first pass through the liver: it is therefore difficult to achieve sustained blood levels with oral formulations and most of them are weakly active (eg. Mesterolone) (1). The 17 alpha alkylated derivatives of T (specially methylT and fluoxymesterone) are more active but due to the potential hepatotoxicity (eg. hepatocellular adenoma, cholestasis, jaundice and hemorrhagic liver cysts), these formulations should no more be

<table>
<thead>
<tr>
<th>Route</th>
<th>Formulation</th>
<th>Dose/Frequency of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Testosterone undecanoate</td>
<td>40-80 mg / 2 to 3 times a day</td>
</tr>
<tr>
<td></td>
<td>Testosterone undecanoate caps</td>
<td>40–80 mg / twice a day</td>
</tr>
<tr>
<td></td>
<td>Mesterolone</td>
<td>75-150 mg / once a day</td>
</tr>
<tr>
<td>Buccal</td>
<td>T Buccal system</td>
<td>30 mg / twice a day</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Testosterone Gel</td>
<td>5-10 mg / once a day</td>
</tr>
<tr>
<td></td>
<td>Scrotal patch</td>
<td>6 mg / once a day</td>
</tr>
<tr>
<td></td>
<td>Non scrotal patch with enhancers</td>
<td>5 mg / once a day</td>
</tr>
<tr>
<td></td>
<td>Non scrotal patch without enhancers</td>
<td>5 mg / once a day</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Crystalline T pellet</td>
<td>600 mg / every 16-26 weeks</td>
</tr>
<tr>
<td>Intramuscular: T esters</td>
<td>T propionate</td>
<td>10-25 mg / twice a week</td>
</tr>
<tr>
<td></td>
<td>T cypionate</td>
<td>50-250 mg / every 2-4 weeks</td>
</tr>
<tr>
<td></td>
<td>T enanthate</td>
<td>50-250 mg / every 2-4 weeks</td>
</tr>
<tr>
<td></td>
<td>T fenilpropionate + T isocaproate + T propionate + T decanoate</td>
<td>50-250 mg / every 2-4 weeks</td>
</tr>
<tr>
<td></td>
<td>T undecanoate</td>
<td>1000 mg / every 10-14 weeks</td>
</tr>
</tbody>
</table>
clinically used (1,388). The only active and safe oral formulation is the T Undecanoate (TU), in oleic acid or in a mixture of castor oil and propylene glycol laureate (T undecanoate caps), encapsulated in soft gelatin. However its absorption is variable and it must be administered with dietary fat, to promote an adequate absorption. Eighty percent of men showed normal plasma T levels with the dose of 120-240 mg/day (389). Oral TU has the advantages of flexible dosage, self-administration and immediate decrease in T serum levels after interruption of treatment.

b) Buccal Formulation

Transbuccal administration provides the absorption of T through the oral mucosa avoiding intestinal pass and liver inactivation. It is presented as a biopellet to be pressed on the gum above the incisor tooth: a buccal film is achieved and should be put between the lower gum and the cheek (390). Men treated with buccal formulation (Striant®) 30 mg twice a day and compared to a group of patients given 5 mg of T gel formulation daily showed no differences in mean T serum levels (391) and its effect in sexual functioning were comparable when giving injectable T enanthate (392).

c) Transdermal Formulations

Transdermal preparations are available either as skin patches or as hydroalcoholic gel and are designed to deliver 5 to 10 mg of T per day (2). They should be used daily and normally provide uniform T serum levels during the treatment. Their efficacy and safety are well demonstrated (390). The patches can be scrotal and non scrotal, and these can be without or with enhancers in order to increase the skin absorption (393). Dose adjustment should be considered since the skin absorption can vary between men. Skin irritation is a common side effect with the patches but uncommon with the gel. Some men – and this is different between cultures - also complain of lack of spontaneity and even shame in using both scrotal and non-scrotal patches. There were some reports of men being dissatisfied in shaving the scrotal skin and difficulties to place and keep in place the patches all time. Patient's compliance with T gel seems much better than with T patches (390). After 5 minutes the gel dries and swimming or having a shower 4 to 6 hours after does not affect T serum levels. Since gel achieves a steady-state level within few days, timing of application is not an issue. Transdermal formulations also have the advantages of flexible dosage, self-administration and immediate decrease in T serum levels after interruption of treatment.

d) Subcutaneous Formulations

Subdermal pellet implants of T are used since 1940 (162). There are many reports showing their benefits but also their complications (eg. infection, extrusion). They need a specialist to be implanted and have a prolonged period of action (around 6 months).

e) Intramuscular Formulations

The intramuscular injection of T administered in oily depot is a route very often used. These formulations can be divided in short and long acting.

- The more frequently used short acting formulations – they have very similar pharmacokinetics - are T Enanthate (TE) and T Cypionate (TC), and must be injected 200 to 250 mg in general in intervals of 2 to 4 weeks. The T propionate has a much shorter half-life and 50 mg should be injected every 2 to 3 days (390). Other formulations containing an association of T esters can be found in some countries (Table XV). The short acting T formulations induce serum peak levels of T 2 to 3 days after injection, with in general a transient supraphysiological level, followed by an exponential decline to subphysiological levels in 10 to 14 days – the serum levels are in general subnormal before the next injection (1). These highs and lows of T may be unpleasant for some men and produce fluctuations in patients' mood, sexual desire and activity, and energy level. (2). They have the advantage of being the most cost-effective formulations and the disadvantage of painful injections and the need of more frequent medical visits.

- The long acting formulation available (T Undecanoate) shows more favorable kinetics than the short acting ones: a first injection of 1,000 mg of TU is followed by a second injection 6 weeks after (loading dose) and then an injection every 12 weeks. It does not reach supra - or subphysiological levels, keeping serum levels physiological within the normal range for 12 weeks of treatment period (Figure 6). Thus, the side effects due to the serum fluctuation levels of T are not observed with this formulation.

There are several studies showing the high efficacy and safety of intramuscular TU (394-396). It must be injected slowly - at least one minute - deeply into the gluteal muscle. TU is generally well tolerated and very few patients relate irritation or pain at the site of injection (390). It has the advantage of requiring only one injection every 3 months.

f) Alternatives to testosterone

1. Oral Clomiphene and other Antiestrogens:

Estrogens exert a negative feedback on gonadotrophin secretion (see Figure 4). Anti-estrogens class 1, due to their antagonistic effects on Estrogen Receptor (ER) in the hypothalamus and pituitary, have the potential to increase serum T levels in men with hypogonadotropic (secondary) hypogonadism by restoring physiological endogenous testosterone secretion, while maintaining testicular volume and, potentially, spermatogenesis. In addition, some anti-estrogens, as tamoxifen, do not act as antagonist in all the tissues, but maintain some estrogenic activity (selective estrogen receptor modulator, SERM) in some tissues as the epididymis (397) and maybe...
the bone. In fact following administration of other SERMs, as raloxifene and toremifene, an increased bone mineral density in GnRH agonist-treated men has been demonstrated in men treated with GnRH agonist and therefore hypogonadal (398). Shabsigh et al (399) reported positive results in terms of T rise with clomiphene citrate (25 mg daily) in a study on 36 men with T deficiency (less than 3 ng/ml), thus confirming previous experiences of Guay et al (380,400) in subjects with ED. However, an improvement of sexual symptoms was described by Guay et al.(380) in ED subjects only after prolonged therapy (four months). A recent study indicates that clomiphene is able to restore normal T and LH levels and to improve sperm motility and erectile function in most (70%) of male patients with prolactinomas and persistent hypogonadism under usual dopaminergic therapy (401). Because an increased estrogen-mediated negative feedback on hypothalamus-pituitary gland has been hypothesized as a possible cause of the obesity-induced T deficiency (see Figure 4), it is conceivable that anti-estrogens may help in restoring T levels in such a common condition. However, only few data are available for clomiphene in the so-called late-onset hypogonadism (402). Also tamoxifen, in a retrospective study in subjects with infertility, was able to increase T and gonadotrophins (403). In conclusion, there are preliminary evidences of some beneficial effect of antiestrogens in restoring testicular function in specific subgroup of ED subjects (secondary hypogonadism/TD). However, long-term double blind, placebo-controlled studies are needed to verify their activity in male subjects with sexual dysfunction and, more important, their safety.

2. HUMAN CHORIONIC GONADOTROPIN (hCG):

Human chorionic gonadotropin (hCG) is purified from the urine of pregnant women and shows the same biological activity as LH, but with a longer half-life. One injection of 5000 units stimulates T secretion for 3 to 5 days on condition that the Leydig cells are responsive. It is mainly used in the condition of hypogonadotrophic (secondary) hypogonadism when fertility is required, in combination with FSH or human menopausal gonadotropins. It is usually administered intramuscularly three times a week at a dose of 1000-2000 units, or twice a week at a dose of 5000 units. T levels should be monitored after 1-2 months of therapy, the day before the next injection. If hCG alone is not sufficient in restoring sperm production, FSH could be added. Responsiveness to hCG is influenced by several factors including testis volume, and the time of onset of hypogonadism (prepubertal versus postpubertal). Side effects of hCG per se are limited, but due to the expected rise in T plasma levels, monitoring would be the same as for T substitution. Once pregnancy has been achieved, patients usually go back on T therapy, due to the higher patient compliance (404).

3. FUTURE ANDROGEN THERAPIES: SELECTIVE ANDROGEN RECEPTOR MODULATORS (SARMs) (REVIEW IN BHASIN ET JASUJA 2009, 405)

Selective androgen receptor modulators (SARMs) are a new class of AR ligands that might change the future of androgen therapy dramatically. The discovery and development of SARMs provides the opportunity to design molecules that exert androgenic activities variable from one tissue to
another to elicit the specific desired activity. An ideal SARM for the treatment of primary or secondary TD would be orally active, with a pharmacokinetic profile consistent with once a day administration, capable or incapable of stimulating the prostate, seminal vesicles, and other sex accessory tissues at doses equipotent to those needed to provide increases in muscle mass and strength along with fat-free mass, support bone growth, and maintain/restore erectile function, libido, virilization, and male habitus. Unlike testosterone, these SARMs are not substrates for 5α-reductase activity. Other activities that are considered undesirable should be diminished or eliminated, such as potential liver toxicity, blood pressure effects and fluid retention, induction of gynecomastia, infertility and overstimulation of erythropoiesis. With improved pharmacokinetic characteristics and tissue-selective pharmacological activities, SARMs can be expected to extend the clinical applications of androgens to osteoporosis, muscle wasting, male contraception and diseases of the prostate. Mechanistic studies with currently available SARMs are able to define the contributions of differential tissue distribution, tissue-specific expression of 5α-reductase, ligand-specific regulation of gene expression and AR interactions with tissue-specific coactivators to their observed tissue selectivity.

Research into SARMs has made dramatic progress over the past decade, and several lead compounds with various chemical structures and in vivo tissue selectivity have been identified and developed, with some proceeding to clinical trials. Most of the discovery and development efforts continue to be devoted to nonsteroidal AR agonists as anabolic SARMs. Meanwhile, there is growing interest in the search for non-steroidal AR antagonists and peptide antagonist as tissue-selective anti-androgens. The mechanism of tissue selectivity of SARMs remains unclear, although tissue-specific expression of 5α-reductase appears to have a role for many of the SARMs that are identified currently. It is not clear if other mechanisms related to SARM action contribute to the observed tissue selectivity in vivo. Future mechanism-based drug design will rely on further investigations of the mechanisms of action of known SARMs, including co-regulator recruitment during the genomic actions of ARs, signaling pathways involved in the non-genomic effects of ARs, and potential tissue-specific distribution.

Clinically, SARMs with improved pharmacokinetic characteristics and tissue selectivity might expand the therapeutic applications of AR ligands to include androgen replacement therapy, muscle wasting, osteoporosis, male contraception, BPH and prostate cancer.

Of the mechanisms that have been proposed to achieve tissue selectivity of AR ligands, the most definitive evidence exists for the role of 5α-reductase. The tissue-specific expression of 5α-reductase makes it a unique contributor to tissue selectivity. Specific inhibition of the type 2 enzyme by finasteride blocks the conversion of T to DHT in the prostate, and T exhibits partial agonist activity in the regrowth of this tissue in castrated rats. Therefore, for SARMs replacing testosterone, which should have relatively low intrinsic activity and/or potency and do not interact with 5α-reductase, tissue selectivity might be caused simply by their partial agonist activity in the prostate. Most SARMs with verified tissue selectivity appear to be partial agonists in the prostate, which indicates that their tissue selectivity is related, at least partially, to the tissue-specific expression of 5α-reductase. If tissue selectivity can be achieved by lack of interaction with 5α-reductase, it might also be achieved by tissue-specific metabolism of the ligands by 5α-reductase. Several approaches might make use of the potential tissue-specific conversion to develop SARMs, including inactive parent compounds that are activated by type 2 5α-reductase in the prostate to form anti-androgens, or AR agonists that are inactivated by type 2 5α-reductase in the prostate, and, finally, AR agonists that are converted to anti-androgens only by type 2 5α-reductase in the prostate. The feasibility of these approaches might be limited by the chemical structures of 5α-reductase substrates. However, the common interaction of T as substrate and ligand of 5α-reductase and AR, respectively, indicate that this might be exploited as another unique therapeutic application of SARMs. The focus will thus be on non-steroidal AR-agonists. Current investigations focus on substances like quinolinone analogs, aryl propionamide analogs, hydantoins analogs, and tetrahydro-quinoline analogs.

4. Practical aspects:

Guidelines referring to the main indications of T therapy in Sexual Medicine, as well as to the main available preparations may be found in recommendations 10 to 17. The algorithm of figure 7 sketches the broad outline of TD treatment.

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**B. ESTRADIOL, ESTRADIOL/TESTOSTERONE RATIO, ESTRADIOL RECEP'TIVITY (406)**

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**I. PHYSIOLOGICAL REMINDER:**

The testosterone/estradiol ratio represents aromatase activity since low testosterone levels may result from lower production or higher metabolism to estradiol by the enzyme aromatase. Also conditions of insulin resistance or hyperglycaemia most likely result in reduced androgen synthesis by mitigating Leydig cell
Man with Testosterone Deficiency Syndrome

Signs and/or symptoms AND repeatedly low testosterone level

Assess possible contraindications or cautions to be taken in use of testosterone therapy

- hematocrit, prostate, others (including breast, severe obstructive sleep apnea syndrome, severe heart failure)

If obese or overweight, advise losing weight

Exercise, low calorie diet, +

medical/surgical intervention

Interested in fatherhood

Not interested in fatherhood

Therapy that stimulates endogenous T secretion

(if LH is not elevated)

- human Chorionic Gonadotropins [+ FSH]

- Anti-estrogens

Testosterone therapy

Follow-up at 3 and 6 months

Signs & symptoms, weight, serum T, Ht, PSA

Improved

Continue (bi)annual follow-up including after age 40 annual DRE

Not improved after 6 months

Consider discontinuation

Search for other causes/treatments

Figure 7: Algorithm for the treatment of the Testosterone Deficiency Syndrome
response to gonadotrophins; but, in addition, also the central regulatory unit seems to be attenuated by the aromatization product of testosterone: estradiol (aromatase is mainly located in fat tissue and, thus, obesity might trigger hypogonadism also by inhibition of gonadotrophin release via the activated hypothalamic estrogen receptors).

Aromatase belongs to the cytochrome P450 family and forms an electron-transfer complex with its partner, NADPH-cytochrome P450 reductase. Because of the membrane-bound character and heme-binding instability, no crystal structure of aromatase has been reported so far. Hence, aromatase polymorphism may play a pivotal role in facilitating the effects also of testosterone as a variable degrader and modulator of this steroid.

II. CARDIOVASCULAR EFFECTS OF ESTROGENS:

Protective roles of estrogens against cardiovascular disease has been appreciated for many years until the equivocal results of cardiovascular outcomes in clinical trials on hormone replacement therapy were reported. Although new ongoing trials aim to resolve these discrepancies, it is obvious that cardiovascular effects of estrogens are complex and diverse also in men.

To understand further effects of estrogens, the detailed knowledge on the specific role of both classical estrogen receptor (ER) subtypes and G protein-coupled receptor are of importance. The pattern of ER-alpha and ER-beta expression in various tissues, the genomic and non-genomic estrogens versus subtype selective ER-alpha and ER-beta stimulation on isolated tissues and in different knockout animal models are of pivotal importance. As ER-alpha and ER-beta are expressed differentially, the pattern depends on tissue, sex and diseased condition. However, a clear role for each ERs have to be finalised with focus on mechanisms and by exploring the potential of ERs-selective agonists for clinical utility.

III. ESTROGENS AND THE PROSTATE:

Special attention should be paid to prostate tissue: both androgens and estrogens play a marked role in the prostate and are critical for normal prostate growth and development. The role of androgens in the prostate and in prostate disease is well known, however, the role for estrogens in the prostate and in prostate disease is complex and is still only just beginning to be appreciated.

Our understanding of the role and action of estrogens in the prostate has advanced significantly recently due to important discoveries, including the discovery of a second estrogen receptor subtype (ER-beta), the detection of aromatase in the prostate, and the identification of rapid nongenomic estrogen signaling. We now know that estrogens are essential for normal tissue homeostasis within the prostate and that too little or too much leads to perturbation of the glands growth and the emergence of disease. We are also beginning to recognize the importance and differential roles of the estrogen receptors ER-alpha and ER-beta. Specifically, the activation of ER-alpha leads to aberrant proliferation, inflammation, and the development of premalignant lesions, while, in contrast, the activation of ER-beta is critical in prostatic stromal-epithelial cell signaling and mediating antiproliferative effects that balance the proliferative action of androgens on the epithelium.

These data have established the importance and complexity of estrogen action. We now know that estrogens have the capacity to exert both beneficial and adverse effects in the prostate via ER-beta and ER-alpha, respectively. Based on this, the selective targeting of estrogen action may form the basis of new therapies for prostate disease.

C. OTHER HORMONES

I. PROLACTIN

1. PHYSIOLOGICAL ROLE

Prolactin (PRL) is a 23 kDa-polypeptide secreted by pituitary lactotroph cells. Circulating forms of prolactin include, beside the usually predominant monomer form (23 kDa), high molecular forms such as macroprolactin (>100 kDa), a biologically inactive complex of PRL and IgG. PRL secretion is mainly inhibited by dopamine (DA), via D2 receptors, and stimulated by serotonin and thyrotropin-releasing hormone (TRH), the three-aminoacid peptide, which stimulates also thyrotropin (TSH) secretion (review in Sobrinho, 407).

In mammals, the main physiological role of PRL is, during gestation, to prepare the breast for milk production, and, during puerperium, to stimulate lactation. During breast-feeding, PRL secretion is maintained elevated by suckling, via a peripheral nervous loop. It is likely that PRL is also involved in regulation of a variety of brain functions, overall directed to organize and coordinate behavioural and neuroendocrine adaptations during pregnancy and lactation. In addition, PRL inhibits ovulation, by blocking the pulsatile secretion of GnRH, therefore providing to breast-feeding women a natural method of contraception (2, 408). According to these important actions of PRL, knocking out PRL gene in mouse resulted in female infertility.
In contrast to the importance of PRL in female reproduction, the physiological role of this hormone in males is still obscure. Gene deletion of PRL or of its receptor does not alter male reproductive fitness, although this receptor is expressed in the brain, testis, male accessory glands and even in the penis. Several studies have shown that PRL increases following male orgasm (review in Kruger et al [409]), hypothesizing a negative feedback control of this PRL surge on sexual motivation, contributing, therefore, to the post-orgasmic refractory period. However, it is noteworthy that the post-orgasmic rise in PRL is relatively modest and similar in men and women, who are less prone to post-orgasmic refractoriness and satiety. In addition PRL increases during other emotional, stressful, or disturbing conditions (including venipuncture) or following stimulation of the nipple or areola (2,410).

It has been demonstrated that a low PRL response to a serotonergic challenge could be considered a mirror of a blunted central serotoninergic function (411). Recent data indicate that also circulating prolactin, in the normal physiologic range, could mirror the central serotoninergic tone. In fact, among males consulting for sexual dysfunction, hypoprolactinemia (i.e. prolactin levels in the lowest quartile) is associated with particular psychobiological features, often considered as reflecting a low serotoninergic signalling. These include a higher prevalence of premature ejaculation and anxiety symptoms along with MetS and arteriogenic ED (412).

2. HYPERPROLACTINEMIA: PATHOPHYSIOLOGICAL ASPECTS

Although the physiological role of PRL in males is still poorly understood, the association between hyperprolactinemia (HPRL) and derangements in both the reproductive and sexual behaviors is better defined. The prevalence of mild HPRL (PRL >420 mU/L or 20 ng/ml) in male subjects with sexual dysfunction is quite variable, ranging from more than 13% to less than 2% (2,408). In these subjects, severe HPRL (SHPRL, PRL > 735 mU/L or 35 ng/ml) is a relatively rare event (less than 1%; 2,408). Milder forms of HPRL (MHPRL) do not play a significant role in the pathogenesis of male SD. Conversely, SHPRL has a negative impact on sexual function, impairing sexual desire - as well as erectile function - and T production (2,408). It has been demonstrated that in subjects with SD, a severely reduced libido is associated with a 10-fold increase in the prevalence of SHPRL (408). A PRL-induced hypogonadism, which is frequent but not constant, and results from a PRL-dependent decrease of LH secretion, could explain, at least partially, this association (2,408). PRL may also play a direct role in the control of male sexual desire. Among hypogonadal subjects with HPRL, prolactin-lowering drugs are able to restore both T levels and libido (408), while TT alone is not as effective (2,410).

The relationship between HPRL and erectile function is under debate. Some authors have suggested a possible pathogenetic link between severe ED and SHPRL (2,408). In a consecutive series of 51 men with SHPRL and prolactinoma compared to 51 age-matched normal controls, 96.7% of the former vs 13.7% of the latter (p<0.0001) had a reduction of the nocturnal erections although only 50% of the patients complained about sexual disturbances (413). The number of nocturnal erections correlated with the PRL levels. Following treatment with cabergoline, NPT normalized in 60% of patients who had normalized PRL levels and in 8% of patients who did not. However, in a series of 2146 men with SD, Corona et al. did not confirm a significant association between SHPRL and severe ED after adjustment for confounders (408).

Among patients with MHPRL, repeat blood sampling revealed normal PRL values in almost one half of cases, most probably due to venipuncture stress. On the other hand, the same study (408) confirmed that in patients with SHPRL, false positive cases could derive also from the presence of a macroprolactin (9.4%). SHPRL underlined an organic problem in the hypothalamic-pituitary region in 2/3 and a drug-induced condition in almost 1/3 of cases, being, therefore, a condition to be carefully addressed. Several medications can induce HPRL via a number of neuroendocrine mechanisms, including an impairment of dopaminergic transmission or an increase in serotoninergic or opioidergic transmission. Estrogens directly stimulate PRL synthesis (review in Molitch [414]). The use of selective serotonin reuptake inhibitors has been associated with a mild HPRL and a decreased sexual desire (415). SSRI-associated hypoactive sexual desire was still present after adjusting for PRL levels, therefore suggesting a PRL-independent effect of this class of anti-depressant on libido (415). Table XVI summarizes the main causes of HPRL.

3. CLINICAL ASPECTS

a) Sexual dysfunctions of hyperprolactinemic men:

A compilation of over 300 hyperprolactinemic men found sexual dysfunctions in 88%, including ED in almost every case (410). The most typical pattern associated ED with hypoactive sexual desire (HSD). As reported above, nocturnal erections are reduced in most men with SHPRL (408,413). Measuring systematically PRL in over 2100 men with mixed SDs, Corona et al (408) found no association between ED and HPRL, but 92% of the studied population complained about ED which may have reduced
1. PHYSIOLOGIC
   - Stress (including venopuncture)
   - Sleep
   - Orgasm
   - Exercise
   - Breast nipple or areola stimulation

2. PSEUDO-HYPERPROLACTINEMIA
   - Macroprolactin

3. PATHOLOGIC
   a) Hypothalamic-Pituitary Stalk Damage
      I) HYPOTHALAMIC TUMORS
         - Germinomas and other germ tumors
         - Gliomas
         - Astrocytomas
         - Craniopharyngiomas
         - Meningioma
         - Metastases
      II) INFLTRATIVE AND INFECTIVE DISORDERS
         - Langerhans' histiocytosis
         - Sarcoidosis and tuberculosis, syphilis
         - Encephalitis
      III) HEAD TRAUMA

   b) Pituitary diseases
      I) PITUITARY TUMORS
         - Prolactinoma
         - Acromegaly
         - Plurihormonal adenoma
         - Macroadenoma with stalk compression
      II) INFLTRATIVE
         - Primary hypophysitis
         - Sarcoidosis and tuberculosis, syphilis
         - Fungal, parasitic, viral
      III) HEAD TRAUMA
      IV) EMPTY SELLA
      V) X-IRRADIATION

   c) Systemic disorders
      I) CHRONIC RENAL FAILURE
      II) HYPOTHYROIDISM
      III) EPILEPTIC SEIZURES
      IV) HERPES ZOSTER

   d) Drug induced
      I) ANTIPSYCHOTICS AND OTHER DOPAMINE RECEPTOR BLOCKERS (INCLUDING ANTIEMETIC)
         - Phenothiazines (chlorpromazine, mesoridazine, thioridazine, fluphenazine, perphenazine, trifluoperazine)
         - Butyrophenones (haloperidol, pimozide, fluspirilene, penfluridol, risperidone)
         - Benzamides (sulpiride, amisulpride, levosulpiride, cisapride, metoclopramide)
         - Thioxanthenes (chlorprothixene, thiothixene)
      II) DOPAMINE SYNTHESIS INHIBITORS: α-METHYLDOPA
      III) CATECHOLAMINE DEPLETORS: RESERPINE
      IV) ANTIDEPRESSANTS
         - Selective serotoninergic reuptake inhibitor (SSRI; citalopram, paroxetine, sertraline, fluoxetine, fluvoxamine, escitalopram)
         - Serotoninergic-noradrenergic reuptake inhibitor (SNRI)/ atypical antidepressants (venlafaxine, trazodone, mirtazapine, bupropion)
         - Tricyclic (chlorimipramine, amitriptyline)
      V) OPIATES
      VI) H₂ ANTAGONIST
         - Cimetidine
         - Ranitidine
      VII) CALCIUM CHANNEL BLOCKERS:
         - Verapamil
      VIII) HORMONES
         - Estrogens
         - Antiandrogens
      IX) ANTICONVULSIVANTS:
         - Phenytoin
the chance of such an association. In their series SHPRL but not MHPRL was significantly associated with HSD. However HSD was absent in one third of men with SHPRL. Gynecomastia was not associated with HPRL. Retarded ejaculation and anorgasmia have also been observed, mostly associated with ED (410), but sometimes isolated (416). In the above series of mixed SDs, retarded ejaculation was associated with HPRL, but no more after adjustment for the use of hyperprolactinemic drugs (417). Some cases of retrograde ejaculation cured by dopamine-agonist therapy have also been reported (418).

b) Prevalence of hyperprolactinemia in men with erectile dysfunction:

Routine determinations of serum PRL found HPRL in 1 to 5% of ED patients. Compiling the 10 largest series of literature led to a prevalence of SHPRL at 0.62% and of pituitary adenomas at 0.38% among 8700 ED patients (2). In addition 1.5% of these patients had MHPRL. Though low, these figures are somewhat higher than the prevalence in the general population (SHPRL in 0.27%, and pituitary tumors in 0.03% among over 13000 Asian men) (419,420).

Prevalence of hyperprolactinemia in men with other sexual dysfunctions: It is also very low. No SHPRL was found in consecutive series of men consulting for HSD without associated ED (n=53), non drug-induced anorgasmia/retarded ejaculation (n=74), and premature ejaculation (n=124) (410).

4. DIAGNOSIS

a) Routine or selective prolactin measurement?

Although SD may be for a long time the only symptom of male HPRL, a curable cause which may be linked to a life-threatening pituitary adenoma, the very low prevalence of SHPRL can hardly justify routine PRL measurement, especially in ED patients. Restricting it to those men with low T would have led to miss 6 of 12 SHPRLs and 3 of 7 pituitary tumors found in 1800 ED patients (156). Likewise sexual desire may be normal in many ED patients with HPRL (410,421). Combining both criteria would be more efficient. Reassessing the results of 1370 consecutive ED patients, Buvat (410) found that by restricting the measurements to those men with HSD or serum T < 4 ng/ml (low + low normal values), they would have saved over 50% of the measurements while missing only one of 10 SHPRLs, and none of 6 pituitary tumors. PRL should also be measured in case of isolated HSD, and retarded or absent orgasm.

b) Measuring serum prolactin:

Blood must be sampled fasting, preferably following a 20 min rest to reduce the stress linked to venipuncture. In case of result > 20 ng/ml (400 mUI/l), the test should be repeated after discontinuation of any drug likely to increase PRL (table XVI), if possible 20 min after insertion of a catheter. This would eliminate almost 50% of MHPRLs found at first assay (408). If not already checked, serum T and TSH should be measured in the same time.

c) Screening for macroprolactins:

In case of non drug-induced SHPRL associated with a normal T and/or a normal sexual function, it is recommended to screen for these biologically inactive variants of PRL with high molecular weight, which constitute "false HPRLs". This may be done by means of PRL chromatography or, in a cheaper way, precipitation with polyethylene glycol. Macroprolactinemas account for 10 to 22% of all HPRLs (2) and are found in about 1% of the general population (419). Exceptional macroprolactinemas associated with biologic activity or with a pituitary adenoma have been reported (2,408,422).

d) Looking for significant etiologies:

Drug-induced HPRL accounts for 17% (423) to 26% (408) of HPRLs in men with SD (table XVI). Secondary HPRL may also result from hypothyroidism (significant association with high serum TSH [408], renal insufficiency and cirrhosis, and to any process disturbing the hypothalamic-pituitary dopaminergic transmission (including different types of hypothalamic and pituitary tumors). Primary HPRL may be idiopathic, but in most men it is associated with a PRL-secreting pituitary adenoma (prolactinoma). Macroprolactinomas (> 10 mm diameter), as other types of hypothalamic or pituitary tumors, are likely to result in tumorous complications: visual disturbances, or even blindness, due to compression of the optic chiasma, and hypopituitarism, which may become life-threatening if decompensated (figure 8).

Any non drug-induced HPRL must therefore benefit from a scan or better a MRI of the hypothalamic-pituitary area, especially in case of SHPRL. In a compilation of 8700 ED patients by Buvat et al (2), 67% (31/46) of those with SHPRL harboured a pituitary tumor. Macroprolactinomas are the most prevalent in these men (413). Some microprolactinomas (diameter < 10 mm) have also been reported in men with SD and MHPRL (408,421).

e) Additional investigations to be done in case of macroprolactinoma:

Campimetry and assessment of the main pituitary...
functions to detect a possible hypopituitarism are recommended and will be better achieved by an endocrinologist. De Rosa et al (413) found 10 hyperthyroidisms and 3 hypoadrenalisms among 41 men with macroprolactinomas.

5. TREATMENT OF SEXUAL DYSFUNCTIONS OF HYPERPROLACTINEMIC MEN

Dopamine-agonist agents (mainly bromocriptine and more conveniently cabergolide which often requires a single administration per week) should be the first choice treatment in case of SHPRL. In most cases these prolactin-lowering agents normalize every aspect of sexual function, in addition to the serum PRL and T levels. They may also shrink the associated prolactinomas, or at least prevent their growth (408,410,424). Conversely, the success rate of these agents does not exceed the placebo effect in the MHPRL-associated SDs (2).

Transphenoidal removal may also be proposed in case of prolactinoma. It may definitely cure both the tumor and the HPRL (425), and protect against any further tumorous complication. However dopamine-agonist therapy is more often chosen as first line treatment at least in case of microprolactinoma, since tumorous extension or complications seldom occur with this therapy (2,424). In case of macroprolactinoma, hypogonadism may persist despite the return to a normal PRL level. Such patients require the combination of T therapy with dopamine-agonist therapy. T therapy alone might stimulate the growth of the pituitary tumor through the aromatization of T into estradiol (2).

II. GROWTH HORMONE

1. PHYSIOLOGICAL ROLE:

Growth hormone (GH) is a 191-amino acid polypeptide synthesized and secreted, under control of growth-hormone releasing hormone (GHRH, positive) and somatostatin (SRIF, negative) of somatotroph cells in the anterior pituitary (426). Its secretion is also positively regulated by the 28-amino acid peptide ghrelin, synthesized primarily in peripheral tissues, as stomach. The primary role of GH is to promote linear bone growth, through the promotion of insulin-like growth factor 1 (IGF-1) synthesis in the liver and other peripheral tissues. GH also has general metabolic effects that result in a positive protein balance. It increases lipolysis, which causes the release of free fatty acid from adipose tissue. Carbohydrate metabolism is also affected, through the stimulation of neoglucogenesis. The availability of this alternative fuel allows for the utilization of the spared proteins for growth. The GH receptor is a monomeric 620-amino acid protein of the class I cytokine-hematopoietin receptor superfamily, homologous with the receptors of PRL, interleukins 2-7, erythropoietin, and colony-stimulating factor. Each GH molecule binds to two receptors, forming a dimer that is directly translocated to the nucleus or primes a JAK2-dependent cascade of intracellular phosphorylation, where signal-transducing activators of transcriptional proteins (STATs) play a major role. This hormone is used clinically to treat children’s growth disorders and adult growth hormone deficiency. A number of factors are known to affect GH secretion, such as age, gender, diet, exercise, stress, and other hormones, as well as sex steroids. In particular, androgen stimulates, while estrogen inhibits, GH release.

2. GONADAL AND SEXUAL FUNCTIONS IN MEN WITH EXCESSIVE OR DEFICIENT GH SECRETION:

- GH excess (acromegaly): The most common disease of GH excess is a pituitary tumour composed of somatotroph cells of the anterior pituitary, casing a syndrome known as acromegaly. Acromegaly is a relatively rare condition, with an estimated prevalence of 20-60 cases per million. Measurement of the serum concentration of GH or of its induced protein IGF-1 has become a pivotal criterion in both the diagnosis of the disease and the establishment of cure after appropriate (surgical and/or medical) treatment. The pituitary adenoma may become large enough to cause headaches, impair vision by pressure on the optic nerves, or cause deficiency of other pituitary hormones by displacement. Secondary hypogonadism is a relatively common feature of acromegaly (427-429). Prolonged GH excess thickens the bones of the jaw, fingers and toes. Accompanying problems can include muscle weakness, insulin resistance and pressure on nerves, casing carpal tunnel syndrome. Cardiomyopathy and an increased mortality rate due to cardiovascular events are common. Although impotence and decreased libido is often reported as a symptom of acromegaly in textbooks (426), it is still unclear if it is due to the excess of GH or to the compression by the GH-producing tumour of the neighbouring gonadotrophin producing cells. An excess of PRL, caused by mixed hyperproduction of GH and PRL or by compression of the pituitary stalk, is a common feature of acromegaly, which can partially contribute to the sexual dysfunction. Moreover, due to the similarity of GH and PRL receptors, GH excess induces PRL-like effects and can induce galactorrhea. Patients with acromegaly have also prostate enlargement (429), which can be partially normalized upon disease control by surgery or medical therapy (427,428). It has been demonstrated that in acromegalic subjects, adequate surgical and or medical therapy can also partially revert hypogonadism, although an irreversible hypogonadism has been described in those with larger adenomas (427-429). In none of these studies (427-429) was acromegaly-related sexual dysfunction was in-
vestigated. In subjects with acquired GH deficiency in adulthood, GH supplementation increases prostate size, an effect that was further potentiated by androgen supplementation in those who were also hypogonadal (430). These findings suggest a direct relationship between GH/IGF-1 axis and prostate size, at least in the youngest subjects.

- GD deficiency: Because in the aging male a progressive reduction of GH release and IGF-1 synthesis has been described (review in Sherlock et Toogood [431]), the effect of GH, with and without T supplementation, has been tested in controlled trials. Only a small, short-term (one month) controlled trial in older individuals that were not GH or T-deficient assessed sexual function. Neither GH nor T affected the number of sexual intercourses or mood (432).

3. POSSIBLE EFFECTS OF GH ON THE PENILE MECHANISMS OF ERECTION?

It has been suggested that GH can induce peripheral vasodilation by increasing endothelial nitric oxide (NO) synthesis or activity through an IGF-1 induced effect (433) or through a post-translational phosphorylation of eNOS (434). In addition it has been demonstrated that GH supplementation enhances NOS-containing nerve fiber regeneration in both the intracavernosal and dorsal nerves after experimental unilateral cavernous nerve neurotomy in the rat (435). In isolated human penile strips GH can induce a dose-dependent relaxation, along with an increase in cGMP (436). However, all these effects were obtained at a relatively high concentration of GH. A modest, but significant, increase in cavernosal concentrations of GH has been described during the physiological process of erection in men (436,437). Such an increase is, however, at least 3 orders of magnitude lower than those required to induce a 30% relaxation on “in vitro” human strips (436). In a study of ambulatory men no correlation was found between peripheral GH levels and all the dimensions of the AMS questionnaire, including sexual function (438). In a small series of patients with organic, but not psychogenic ED, peripheral GH levels were found lower than in age-matched controls (439). In the same study cavernous GH level, in both organic and psychogenic ED, was not different from the peripheral one (439).

4. CONCLUSIONS:

Prevalence of ED and decreased libido is increased in acromegalic patients (426). However it is still a matter of debate whether GH has a direct role in inducing these disorders or if the cause of reported male sexual problems is the accompanying TD or PRL increase. Hence, due to the low prevalence of acromegaly in the general population, GH or IGF-1 determinations are not recommended as first line examination in male subjects with sexual dysfunction. Further studies on GH and erection are strongly encouraged.

III. MELANOCORTINS: ALPHA MSH AND OTHER PRO-OPIO-MELANOCORTIN DERIVATIVES

Melanocortins (MC) are a family of peptides, including adrenocorticotropic hormone (ACTH) and α-, β- and γ-melanocyte-stimulating hormones (MSH), derived from the cleavage of a large precursor peptide: pro-opiomelanocortin (POMC). Both α-MSH and β-MSH interacts with specific MC receptors (MCRs), MCR3 and MCR4, within the hypothalamus and the limbic system, and, in the experimental animal, mediate a typical behaviour syndrome including grooming, stretchings and yawnings, spontaneous penile erection and ejaculation and increased sexual receptivity. Two synthetic analogs of α-MSH have been developed for human use. The first called melanotan (afamelanotide, formerly CUV1647) is on track for registration for its photoprotective properties and the second is called bremelanotide (formerly PT-141), and developed by Palatin Technologies (440). Bremelanotide is a cyclic heptapeptide under development for its erectogenic properties. Preliminary studies indicate that, following intranasal or subcutaneous administration, bremelanotide resulted in healthy men and in men with ED in a statistically significant erectile response (see in Miner and Seftel (440) and Hellstrom (441) for reviews). In a recent randomized, double-blind, placebo controlled study in ED men, a favorable response with bremelanotide has been reported in 33.5% of subjects, as compared to 8.5% in the placebo group (442). Patient’s satisfaction with intercourse was also greater in the treated group. However, in all the studies drug-related adverse effect were present, as nausea, yawning and flushing, which, somehow, limited the attractiveness towards this treatment. There are also concerns regarding a possible increase in blood pressure.

IV. OXYTOCIN

Debackere and colleagues (443) in the 60’s originally postulated that oxytocin (OT) could be released in the male circulatory system during sexual activity. In fact, using a cross-circulation technique, they found that a manual stimulation, per rectum, of seminal vesicles, prompted a milk-ejection response in the female partner. Further studies demonstrated that a surge of OT happens during male sexual activity, peaking during or after orgasm. This evidence in humans matches data from many other species. In addition, because pharmacological administration of OT increases the number of ejaculated spermatozoa in different animal species, including human, a physiological role for oxytocin during ejaculation has been hypothesized. OT receptors are abundantly expressed in the human male genital tract. However conclusive data on effects of OT on human ejaculation are still lacking (444,445).
Brain OT plays an important role in the regulation of male sexual behaviour, facilitating erection and orgasm in different experimental animals through an action on paraventricular nuclei of the hypothalamus (446). Intranasal administration of OT makes human men more trusting and reduces anxiety and psychosocial stress (446). However compelling evidence showing that OT facilitates pair bonding in humans as it does in animals is still lacking. In addition, in a double blind, placebo controlled study, a specific effect of intranasal OT on appetitive, consummatory and refractory sexual behaviour was not found (447), even though an anecdotal report indicates that intranasal OT can facilitate orgasm in an otherwise anorgasmic male (448).

V. DEHYDROEPIANDROSTERONE (DHEA) (review in 2,449)

1. BIOSYNTHESIS OF ADRENAL ANDROGENS

DHEA is synthesized in the zona reticularis of the adrenal gland, and is sulfated via sulfotransferase into DHEA-Sulfate (DHEA-S), which is thought to be the storage form of DHEA. The majority opinion is that there is free interconversion between DHEA and DHEA-S. The production follows an age-dependent pattern: decreasing with age. While serum DHEA-S concentration does not vary throughout the day, DHEA secretion follows a diurnal pattern similar to that of cortisol.

2. MECHANISMS OF ACTION OF DHEA:

DHEA is considered as a prohormone, which is converted peripherally to other sex steroids (especially T and E₂), and the steroid produced depends on the particular 17-hydroxylase enzymes predominating in that particular tissue.

Recently, a putative receptor specific for DHEA has been identified on endothelial cell plasma membranes that structurally related steroids failed to compete for binding, which has been shown to acutely increase NO release from intact vascular endothelial cells. These effects may be both genomic and nongenomic, and are independent of other steroid hormone receptors. These findings have possible implications for DHEA as an antiatherogenic compound, as DHEA independently inhibited human vascular smooth muscle cell proliferation in vitro, and in vivo (450), possibly by regulating cell cycle relevant proteins through a cytoplasmic steroid-hormone-independent pathway (451), especially Gi/o protein-mediated and ERK ½ dependent, (452). Iwasaki et al (in 2) demonstrated that both DHEA and DHEA-S had possible anti-inflammatory and immunomodulatory effects by inhibiting proinflammatory cytokine-induced transcription, an effect that neither estradiol or testosterone could duplicate.

3. PATHOPHYSIOLOGY OF DHEA DEFICIENCY

Primary adrenal insufficiency manifests symptoms of androgen deficiency through a lack of DHEA as well as a variety of non-endocrine medical conditions. The age-related decline in DHEA levels may correlate with many age-related phenomena such as diabetes, insulin resistance, hypertension, atherosclerosis, coronary artery disease, decreased bone mineral density, cancer and dementia. Depression and other mood disorders, eating disorders and chronic stress states have also been reported. In the MMAS, DHEAS was the only hormone which showed a strong (negative) correlation to the prevalence of ED among 17 investigated hormones including T and estradiol. Exogenous corticosteroids can decrease adrenal DHEA synthesis as adrenolytic drugs, like mitotane, and inhibitors of corticosteroid synthesis, like ketoconazole, can reduce adrenal production of DHEA.

4. MEASUREMENT OF DHEA

Measuring DHEA blood levels is generally not recommended because of its circadian secretion during the day and its short terminal half-life of approximately 4.5 hours. The measurement of DHEA-S is preferred because of more stable levels in the blood due to its longer half-life of approximately 24 hours. The measurement of DHEA-S can be performed at any time during the day.

5. DHEA REPLACEMENT IN ADRENAL INSUFFICIENCY

Adrenal insufficiency has been traditionally treated with glucocorticoids alone or with mineralocorticoids, but treating the concurrent androgen deficiency with DHEA has not yet reached standard of care, despite the obvious decrease in quality of life including decreased vitality, increased fatigue, reduced physical function, and sexual dysfunction. RCTs of DHEA replacement in adrenal insufficiency have given conflicting results: DHEA improved overall well-being, mood, and sexual functioning in the majority of the studies, which mainly included women. Insulin sensitivity and lipid profiles have benefited. However, other studies did not confirm these effects.

6. DHEA THERAPY IN HEALTHY AGING SUBJECTS

DHEA improved overall sense of well-being compared with placebo in an earlier study of a mixed cohort of men and women which used a questionable methodology. But other studies failed to show benefit in aging men. Regarding improvement in sexual function, the effects of DHEA administration have been conflicting, demonstrating benefits in older women, but none in aging men (2,453). A randomized, placebo-controlled trial in 40 ED patients claimed improvement on 50 mg DHEA administered for 6 months, but
objective data were missing in this paper. A recent review of the effects of endogenous and exogenous DHEA on cardiovascular disease risks reiterates the inconsistencies regarding the metabolic effects of DHEA supplementation, and suggests that positive effects have not been consistently shown.

7. OTHER PROPOSED USES FOR DHEA THERAPY

Beneficial effects on mood have been observed while using DHEA as treatment for depression and dysthymia, but only minor and transient improvements in cognitive performance were observed in Alzheimer’s Disease. In terms of bone health, the beneficial effects of DHEA supplementation are felt to be minor though proven in elder women in a 12 months RPCT (453). DHEA supplementation has been shown to reduce the frequency of flares and decrease steroid dose requirements in systemic lupus erythematosus. The potential for immunoregulatory effects of DHEA has been reinforced by the presence of specific binding found in murine T cells. Specific binding of DHEA on muscle cells suggests the possibility of DHEA therapy in muscular disorders.

8. CONCLUSIONS

DHEAS is the most abundant circulating sex steroid which is converted to other steroid sex hormones, and also may have a direct action on its own cell membrane receptor. DHEA deficiency has been correlated with symptoms of androgen deficiency and its supplementation has been shown to be beneficial to patients with primary and secondary adrenal insufficiency. However, studies looking at the effects of DHEA supplementation on other conditions have been inconsistent to date. The new data on DHEA has shed some important information, but we have a long way to go before we feel that we understand the complete physiology of DHEA and its therapeutic implications (454).

VI. THYROID HORMONES

1. PHYSIOLOGICAL ROLE:

The thyroid gland produces, under TSH control, two major active hormones, thyroxine (T4) and tri-iodothyronine (T3), which circulate in human blood tightly bound to carrier proteins, including thyroxine binding globulin (TBG). Free fractions of thyroid hormones are the biologically active hormones (FT4 and FT3), which regulate protein, fat and carbohydrate metabolism. Hence, there are no organs or tissues even partially unaffected by thyroid diseases. For instance, both hypothyroidism and hyperthyroidism result in clear alterations in the cardiovascular and mental state. However, the association between thyroid diseases and SD in men has not been systematically studied until recently.

2. HYPERTHYROIDISM AND SEXUAL FUNCTION:

In a consecutive series of 755 men presenting with SD, a two-fold greater prevalence of hyperthyroidism was evident among the men with premature ejaculation (PE) (455). According to this finding, Carani et al (456) in a small multicentre, prospective study, demonstrated that most (50%) hyperthyroid patients have PE, a prevalence that was substantially reduced (15%) by treating the underlying disease, with a consequent doubling of ejaculatory latency. A recent study in a Turkish population essentially confirms an association between the hyperthyroid state and premature ejaculation, which was substantially ameliorated by therapy of the thyroid disease (457). However Waldinger et al (458) did not find any relationship between PE and thyroid dysfunction in a cohort of 620 men with life-long PE, what logically suggests that the association with hyperthyroidism is restricted to the acquired type of PE.

3. HYPOTHYROIDISM AND SEXUAL FUNCTION:

In Carani’s study (456) it was also shown that medical treatment of the opposite state, hypothyroidism, resulted in a two-fold decrease in ejaculatory latency and a reduction in delayed ejaculation. Hence, the view that thyroid hormones regulate the ejaculatory reflex is gaining credence. Carani’s study also suggests that low sexual desire and ED may be related to hypothyroidism and can be normalized by thyroid hormones therapy (456). The underlying pathogenetic mechanisms are not completely clarified. Although it is possible that a hypothyroidism-induced PRL rise could mediate these negative effects on male sexuality, a direct role of thyroid hormones on reproductive tissues has also been postulated. A role for hyperthyroidism-induced anxiety was also envisaged (455,457). A recent study (459), in a limited number of ED patients, indicated that ED is extremely common in males with thyroid dysfunction. Treatment of the latter restored erectile function. Hence, more studies are needed to clarify the role of thyroid hormones on male sexual response.

VII. EPIDEMIOLOGY AND MANAGEMENT OF SEXUAL DYSFUNCTIONS IN THE DIABETIC MAN

Numerous researchers have attempted to understand and to quantify “normal” sexual behaviors. A systematic approach to male sexual (dys)function, specifically on sexual desire disorder, arousal difficulties and orgasms disorders must involve diabetes mellitus as a pivotal pathological entity.
1. EPIDEMIOLOGY OF SEXUAL DYSFUNCTIONS IN RELATION TO DIABETES MELLITUS

The prevalence of erectile dysfunction (ED) in men with diabetes mellitus (both type 1 and 2) is widespread and was largely investigated in a very elaborate and representative cross-sectional study of 9,868 Italian men. The age range was 20 to 69 years. The overall prevalence of ED was 35.8%, and increased with age, it was 4.6% in men in their 20’s and 45.5% in men older than 60 years. Of paramount importance is that independent factors of influence within the background setting of disturbed glucose control were duration and control of diabetes, obesity, complications of diabetes and cigarette smoking (460).

2. DIABETES-RELATED SEXUAL DYSFUNCTIONS IN MEN

Sexual dysfunction is any problem that regularly interferes with a person’s sexual performance. Men with diabetes are more likely than nondiabetics to experience sexual dysfunction. Sexual problems that may affect diabetic men include erectile dysfunction, ejaculation problems, and low levels of testosterone. Sexual dysfunction in people with diabetes often involves damage to blood vessels (diabetic angiopathy) or nerves (diabetic neuropathy). This damage often results from poorly controlled glucose. Other common factors that contribute to sexual dysfunction include obesity, fatigue, depression, medications, urinary tract infections, yeast infections and overactive bladder. Signs and symptoms vary according to the type of dysfunction the patient is presenting with. Diagnosis begins with a medical history and physical examination. Diagnosis should include also urine tests, nerve tests depending on the patient’s gender and type of dysfunction involved.

Diabetes is known to cause multiple medical (461), psychological (462), and sexual (463) dysfunctions. Impaired sexual function in men is a well-documented complication of diabetes. Several studies have shown that men with diabetes are at increased risk for erectile dysfunction, that it occurs at an earlier age (464–467), and that it is related to longer duration of diabetes, poor metabolic control, and the presence and number of diabetic complications. The debate about the etiology of sexual dysfunction of patients with diabetes is, however, still ongoing. Because patients with diabetes are at risk for vascular and neurological complications and psychological problems, they are at risk for both organogenic and psychogenic sexual dysfunction (463). Therefore, attempts to clarify the etiology of sexual dysfunction have proposed neurological, vascular, endocrine, and psychological factors; medication use; or a combination of both (465–467). It has been hypothesized that the etiology of sexual dysfunction in men with diabetes is linked with somatic factors (463).

Changes in sexual functioning are common as people age. Having diabetes, however, can result in earlier onset and increased severity of sexual problems. Diabetic men are more likely than nondiabetics to experience sexual dysfunction. Depending on the cause of sexual dysfunction, its onset may be sudden and temporary, or gradual and permanent. Many people with diabetes also suffer from high blood pressure, obesity, dyslipidemia, general fatigue, infections, hormonal conditions, bladder problems or depression, all of which can also contribute to sexual problems. Patients experiencing sexual difficulties must be encouraged to discuss these issues openly with their partner, and then seek appropriate treatment.

3. TYPES OF SEXUAL DYSFUNCTIONS IN DIABETES MELLITUS

a) Erectile dysfunction (ED) Men with diabetes are three times more likely to experience ED than those without diabetes (460). In addition, men with diabetes and ED may experience the problem 10 to 15 years earlier in life than nondiabetics. It is not uncommon for a man seeking treatment for erectile dysfunction to learn that he has diabetes. ED such serves also as a portal men’s health.

b) Male hypogonadism: Beginning in middle age, this condition is common in men, but more common in diabetic men. Recent research suggests that hypogonadism may also be associated with insulin resistance, the progression of type 2 diabetes and possibly heart disease (468-470).

c) Retrograde ejaculation: This is typically caused by failure of the urethral sphincters due to damage of the autonomic nerve system. Men experiencing this problem may notice that a small amount of semen is discharged during ejaculation, which may cause fertility problems (469,470).

d) Premature ejaculation: Factors that may contribute to this common condition include diabetes, cardiovascular disease, nerve damage, urethritis, or even hypogonadism (469,470).

e) Retarded or absent ejaculation: This difficulty occurs even in the absence of ED and libido issues. Risk factors for delayed ejaculation include diabetes, high blood pressure, nerve disease, prostate problems, and use of medications, like beta blockers and SSRI antidepressants (469,470).

4. MANAGEMENT OF SEXUAL DYSFUNCTIONS IN DIABETIC MEN

Risk factor modification by controlling the blood glucose levels is the essential and first step. Decreasing glucose concentrations will correct certain metabolic abnormalities, but the use of insulin sensitizers will further increase blood flow by decreasing insulin resistance. A second step is the treatment of the re-
lated factors, such as hypertension, obesity and any diabetic complication (470). The treatment of diabetic ED should begin with a review of potential risk factors and it must involve the partner and the relationship. In 9,496 adults with diabetes the incidence of modifiable risk factors was higher in the population with diabetes versus controls: hypertension (56% vs 22%), hyperlipidemia (41% vs 20%), obesity (78% vs 57%) (471).

Hypertension is significantly associated with abnormal glucose metabolism and the overall risk of cardiovascular events (11). Especially the use of angiotensin converting enzyme inhibitors or AT-1 blockers has been shown to increase blood flow in diabetic men (470).

Treatment of hypogonadism accompanying insulin resistance may correct many of the symptoms of androgen deficiency, and also improve erectile dysfunction, depending, of course, on how many other medical co-factors are present, especially how far vascular damage has advanced (470,471).

Phosphodiesterase inhibitors are a symptomatically working very efficient tool to help patients with ED, also including men with diabetes. Diabetic men often have clinical or subclinical neuropathy and their production of nN0 will be decreased. This is why the results of these agents are not as positive in men with diabetes mellitus as with other risk factors for ED. According to a Cochrane Review, sufficient evidence exists that PDE-5 inhibitors form a care that improves erectile dysfunction in diabetic men, but neither vardenafil, tadalafil nor sildenafil have been steadily proven to be most beneficial in diabetes mellitus induced ED (472).

Other therapies of ED and sexual dysfunctions in men with diabetes may be administered according to the indications, guidelines and patient-related individual experience as well as preference. These may include intraurethral alprostadil, penile self injection therapy, vacuum constriction devices and penile prosthesis. Testosterone therapy may be indicated as a monotherapy or in combination with other ED therapies (470).

D. RECOMMENDATIONS

I. DIAGNOSIS OF TESTOSTERONE DEFICIENCY

1. DEFINITION OF TESTOSTERONE DEFICIENCY (TD). (GRADE B)

- Testosterone Deficiency is a clinical AND biochemical syndrome, frequently associated with age and comorbidities, and characterized by a deficiency in testosterone and relevant symptoms.

- It may affect the function of multiple organ systems and result in significant detriment in the quality of life, including alterations in sexual function.

2. CLINICAL DIAGNOSIS. (GRADE A TO C)

- The clinical manifestations of Testosterone Deficiency are variable.
  - Sexual dysfunction, in particular Hypoactive Sexual Desire (GrA), Erectile Dysfunction (GrB), Delayed Ejaculation (GrC), are prominent and often the presenting symptoms.
  - Visceral obesity is often associated, and muscle mass and very likely bone mineral density are diminished (GrA).
  - Diminished strength, alterations in spatial cognition and mood may be associated (GrC).
  - The physical examination is, frequently, unhelpful. But small testicular size, alterations in testicular consistency and hair distribution, gynecomastia, and small prostate size can be detected.
  - Not all the manifestations need to be evident simultaneously and their intensity shows marked inter-individual variability.

3. TESTOSTERONE DEFICIENCY AND METABOLIC DISEASES: SCREENING. (GRADE B)

- Patients with clinical conditions associated with insulin resistance (obesity, type 2 diabetes, metabolic syndrome) should be screened for TD since it is often co-morbid.

- In these clinical conditions, it is important to measure Sex Hormone Binding Globulin – SHBG - to estimate calculated Free Testosterone – cFT, which is very well correlated to the value of FT measured by the reference assay, equilibrium dialysis.

4. TD AND METABOLIC DISEASES: POSSIBLE BENEFITS OF TREATMENT. (GRADE A)

- Visceral obesity should be appropriately managed because it is significantly associated with subsequent vascular events.

- Visceral obesity seems to be both the cause and the consequence of testosterone deficiency.

- In subjects with TD Testosterone Therapy improves body composition by moderately decreasing fat mass and increasing lean body mass. Preliminary data indicate a positive effect.
of T therapy on glycaemic control. However, such secondary benefits require further confirmation by large scale studies.

5. TESTOSTERONE AND CARDIOVASCULAR DISEASES. (GRADE C)
- Cardiovascular disease is often associated with low testosterone. All men with testosterone deficiency, as well as all men over 40 years of age or those younger with a strong family history should have their cardiovascular risk factors assessed and addressed.
- Routine testosterone measurement is not advised in men with cardiovascular disease without symptoms of TD like hypoactive sexual desire, ED, visceral obesity or diabetes, until randomised controlled trials of T therapy have confirmed its utility.

6. QUESTIONNAIRES. (GRADE B)
- A number of questionnaires have been proposed to help towards screening for or diagnosing TD.
- Many are sensitive but not specific.
- In subjects with sexual dysfunctions, structured interviews as Androtest demonstrate enough sensitivity and specificity to raise the suspicion of testosterone deficiency.
- However the diagnosis of TD should not be based exclusively on questionnaires or structured interviews.

7. BIOCHEMICAL DIAGNOSIS. (GRADE C)
- In patients with Erectile Dysfunction, and/or Hypoactive Sexual Desire, and/or Retarded Ejaculation, these investigations are recommended:
  - serum sample for Total Testosterone (TT) determination.
  - In case of a low level we recommend:
    - to repeat the TT determination
    - together with SHBG (to calculate free T [FT]),
    - and serum LH, and prolactin measurements.

8. THRESHOLD LEVELS FOR THE BIOCHEMICAL DIAGNOSIS OF TD. (GRADE C)
- There are no generally accepted lower limits of normal total testosterone. There is, however, general agreement that:
  - TT > 12 nmol/l (3.5 ng/ml or 350 ng/dl) does not usually require substitution.
  - Based on the data of young hypogonadal men, men with TT < 8 nmol/l (2.3 ng/ml or 230 ng/dl) usually benefit from testosterone treatment.
  - Between these levels :
    - measuring FT by equilibrium dialysis or calculating it from TT and SHBG levels may be helpful. A lower limit of 225 pmol/l (65 pg/ml) is accepted by many.
    - A Testosterone Therapy test may be envisaged for 3-6 months. Beyond that time, T therapy would be continued only in case of substantial benefit.
  - Clinical judgment should be exercised for men who have symptoms and are above these levels.

9. OTHER HORMONAL ALTERATIONS. (GRADE C)
- It is recognized that significant alterations in other endocrine systems occur in association with aging but the significance of these changes is not well understood, particularly in relation to sexual function.
- Generally, determinations of Estradiol, Cortisol, DHEA or DHEA-S, Melatonin, GH and Insulin-like Growth Factor-1 are not indicated unless the corresponding endocrine disorders are suspected based on the clinical signs and symptoms.

II. TESTOSTERONE THERAPY

10. INDICATION FOR TESTOSTERONE THERAPY. (GRADE C)
- A clear indication
  - a clinical picture
  - together with biochemical evidence of hypoandrogenism should exist prior to initiation of androgen therapy.

11. AGE AND TESTOSTERONE THERAPY. (GRADE C)
- In the absence of definite contraindications, age is not a limiting factor to initiate Testosterone Therapy in men with TD.

12. INDICATION OF TESTOSTERONE THERAPY IN MEN WITH SEXUAL DYSFUNCTION. (GRADE A TO C)
- Men with TD and:
  - Hypoactive Sexual Desire (GrA),
  - Erectile Dysfunction (GrB),
Retarded Ejaculation (GrC) are candidates for Testosterone Therapy.

Absence of an appropriate response after adequate testosterone treatment for 3-6 months (GrC) calls for further investigations to rule out associated co-morbidities (GrA).

13. COMBINATION THERAPY WITH TESTOSTERONE AND PHOSPHODIESTERASE TYPE V INHIBITORS. (GRADE B)

- Evidence is emerging suggesting a therapeutic synergism with the combined use of Testosterone and PDE5-Is in men with Erectile Dysfunction and low testosterone. These observations are preliminary and need additional studies.

- However, combination therapy can be considered in TD men who have not improved with T alone.

- In addition it is recommended to measure testosterone in case of PDE5-I failure if not previously done.

14. TESTOSTERONE COMMERCIAL FORMULATIONS. (GRADE A AND C)

- Current commercially available preparations of T (with the exception of the 17α-alkylated ones) are safe and effective (GrA).

- The treating physician should have sufficient knowledge and adequate understanding of the advantages and drawbacks of each preparation.

- The patient should be given the opportunity to actively participate in the choice of testosterone formulation (GrC).

15. SERUM TESTOSTERONE LEVELS TO BE ACHIEVED WITH TESTOSTERONE THERAPY. (GRADE C)

- The purpose of testosterone treatment is to bring and maintain serum testosterone levels within the physiological range. Supraphysiological levels are to be avoided.

- No evidence exists for the need to maintain a circadian rhythm of serum testosterone levels.

16. OTHER FORMS OF ANDROGEN THERAPY. (GRADE B)

- The use of other androgens such as:
  - Dehydroepiandrosterone (DHEA)
  - Dihydrotestosterone

  has not been proven to be effective specifically in male sexual dysfunctions.

- Anti-estrogens may raise endogenous testosterone on condition of intact hypothalamic-pituitary gonadotrophic centers. No data are presently available regarding their long-term safety in men.

17. ANDROGEN ABUSE OR MISUSE. (GRADE C)

- Testosterone Therapy should be used only when specific indications exist, and to achieve serum levels of testosterone in the physiological range.

- Its (ab)use for performance enhancement may expose to serious complications, and is to be strictly condemned.

III. CONTRA-INDICATIONS AND CAUTIONS FOR USE

18. PROSTATE SAFETY. (GRADE C)

- Historically androgen administration has been absolutely contraindicated in men suspected of, or with a history of prostate cancer.

- This is an area of ongoing research and reevaluation. There is no compelling evidence that T treatment causes prostate cancer or prostate cancer progression in the non castrated man (L1).

- Testosterone Therapy is contra-indicated in men with clinical evidence of prostate cancer until more evidence on safety is available.

- Men with TD >45 years old should be informed before treatment on the benefits of T therapy, the limits of knowledge concerning prostate safety, and the fact present data are reassuring.

19. TESTOSTERONE THERAPY AFTER TREATMENT FOR PROSTATE CANCER. (GRADE C)

Testosterone Therapy after treatment for prostate cancer

- Men successfully treated for prostate cancer and suffering from confirmed, symptomatic TD are candidates for TRT, after a prudent interval (depending on the type of cancer treatment), if there is no evidence of residual cancer.

- The risks and benefits must be clearly understood by the patient and the follow-up must be particularly careful.

- Safety data are limited, but early reports are reassuring. However, the clinician must exercise caution together with adequate knowledge of the advantages and drawbacks of androgen therapy in this situation.

20. BREAST CANCER. (GRADE A)

- Testosterone Therapy is contra-indicated in men with breast cancer.
21. CAUTIONS IN THE USE OF TESTOSTERONE THERAPY. (GRADE B AND C)

- Men with:
  - Significant erythrosis (hematocrit > 52%) (GrC)
  - Severe symptoms of Bladder Outlet Obstruction (GrC)
  - Should not be started on Testosterone Therapy without prior improvement of the co-morbid condition.

- Follow-up of such men should be especially careful, as that of men with:
  - Severe Obstructive Sleep Apnea Syndrome though no scientific evidence exists in favor (or against) a causal relationship between testosterone and this syndrome (GrC).
  - Severe congestive heart failure, due to the risk of fluid retention in case of overdosing (GrB).

22. TESTOSTERONE THERAPY AND FERTILITY. (GRADE C)

- Candidates for Testosterone Therapy should be informed that this therapy may temporarily suppress spermatogenesis. In case of desired fertility, alternative therapies such as gonadotrophins or anti-estrogen may be useful.

- In men with hypogonadotrophic TD, long-term testosterone supplementation does not preclude forthcoming responsiveness to gonadotrophins, but may prolong the time required to obtain pregnancy.

23. MONITORING: LIVER. (GRADE A)

- Currently available preparations are largely free of hepatic toxicity. Liver function studies are not required prior to onset of therapy.

- Despite the lack of evidence, most manufacturers (for regulatory purposes) include warnings about hepatic risks in their product insert.

24. MONITORING: LIPIDS AND GLYCAEMIA. (GRADE A)

- Monitoring lipids and glycemia is not required for safety, but may be so for monitoring efficacy of other aspects of treatment.

25. MONITORING: PROSTATE. (GRADE A AND C)

- In men > 40 years old, PSA is mandatory:
  - as baseline parameter of prostate health prior to Testosterone Therapy, then 3, 6, 12 months later and then every year if no significant change.
  - Digital Rectal Examination is also required at baseline and, at least, every year (GrC).

- Transrectal Ultra-Sound guided prostate biopsies are indicated only for changes or abnormalities in the DRE or PSA (absolute value or velocity from the second year) (GrA).

26. TESTOSTERONE THERAPY AND CARDIOVASCULAR HEALTH. (GRADE B)

- Testosterone Therapy is not associated with markedly increased cardiovascular risk until 36 months of use, and replacement can be advocated on conventional established clinical grounds. However the possibility of T therapy induced polycythemia should be considered.

- Preliminary evidence suggests the possibility of beneficial effects of Testosterone Therapy on cardiovascular function. The body of evidence supports the need for long term placebo controlled randomised trials of testosterone replacement in hypogonadal men with regard to morbidity and mortality.

27. MONITORING: HEMATOCRIT. (GRADE C)

- Polycythemia (hematocrit > 52%) may develop during Testosterone Therapy (L1). Periodic hematological assessment is indicated:
  - Before treatment
  - 3, 6, 12 months after the start
  - Then annually if no significant change

- Dose adjustments, change of preparation, phlebotomy, or discontinuation of treatment may be necessary.

28. MONITORING: MOOD. (GRADE B)

- Testosterone Therapy results in variable improvements in mood and well being.

- The development of negative behavioral patterns (aggressiveness, hypersexuality) during treatment has been associated with T Therapy. There is no evidence of such effects in the recent literature.
V. OTHER HORMONES LIKELY TO PLAY A ROLE IN MALE SEXUAL DYSFUNCTIONS

29. PROLACTIN. (GRADE C)
   - Hyperprolactinemia is an uncommon cause of Erectile Dysfunction.
   - However, determination of serum prolactin is recommended in cases associated with Hypoactive Sexual Desire, and when biochemical TD has been documented, because it can be associated with serious and treatable diseases.

30. THYROID HORMONES. (GRADE B AND C)
   - Associations between hyperthyroidism and premature ejaculation (GrB), and between hypothyroidism and retarded/delayed ejaculation, and hypoactive sexual desire (GrC) have been reported.
   - An increased prevalence of both hyper- and hypothyroidism has been reported in men with Erectile Dysfunction (GrC).
   - Thyroid hormones disorders should be suspected in ejaculatory disorders. Thyroid hormone measurement is not indicated in other sexual dysfunctions, unless based on the presence of corresponding clinical signs and symptoms of thyroid diseases (GrC).
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Committee 15

Priapism Recommendations

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CONCLUSIONS

PRIAPISM RECOMMENDATIONS

RECOMMENDATIONS FOR FUTURE RESEARCH IN PRIAPISM
Priapism describes a persistent erection arising from dysfunction of the mechanisms regulating penile tumescence, rigidity and flaccidity. A correct diagnosis of priapism is a matter of urgency requiring identification of the underlying hemodynamics. Committee 15 to the International Consultation on Sexual Medicine (ICSM 2009) was charged with developing an evidence-based guideline on priapism. Committee 15 sought to define the types of priapism, and address pathophysiology, epidemiology and effective management of priapism.

Previous scientific organizations including the American Urological Association Guidelines Committee 2003 (www.auanet.org) and the International Society for Sexual Medicine Standards Committee 2006 (www.issm.info) have noted that the literature was comprised mainly of small case series and individual case reports, and included inconsistent definitions and methods with little long-term outcome data. Some recent case series have included detailed methodology: duration of priapism, etiology of priapism and erectile function outcomes. Recommendations in this report are based on best practices as defined by prior AUA guidelines and ISSM standards, contemporary case series, and bench research. Using the International Consultation of Urologic Diseases modification of Oxford Centre for Evidence Based Medicine Guidelines, the level of evidence for recommendations cited in this review are Level 3 / 4, grade C (www.cebm.net).

The basic science supporting current concepts in the pathophysiology of priapism, and clinical research supporting the most effective treatment strategies are summarized in this review. Suggestions for future research are made. These recommendations were presented in a public forum and have been amended following debate and comments from the International Consultation on Sexual Medicine – Paris, July 10-13, 2009.

I. DEFINING PRIAPISM

Priapism is a full or partial erection which continues more than 4 hours beyond sexual stimulation and orgasm or is unrelated to sexual stimulation.

1. ISCHEMIC PRIAPISM (VENO-OCCCLUSIVE, LOW-FLOW)

Ischemic priapism is a persistent erection marked by rigidity of the corpora cavernosa, and little or no cavernous arterial inflow. In ischemic priapism there are time dependent changes in the corporal metabolic environment with progressive hypoxia, hypercarbia, and acidosis. The patient typically complains of penile pain and the examination reveals a rigid erection. The condition is analogous to a muscle compartment syndrome, with well documented histologic changes occurring to the corporal smooth muscle by 12 hours. Interventions beyond 48 - 72 hours of onset may help relieve erection and pain, but have little benefit in preserving potency. Histologically by 12 hours corporal specimens show interstial edema, progressing to destruction of sinusoidal endothelium, exposure of the basement membrane, and thrombocyte adherence at 24 hours. At 48 hours thrombi can be found in the sinusoidal spaces and smooth muscle necrosis with fibroblast like cell transformation is evident.[1]

Ischemic priapism is an emergency. When left untreated resolution may take days and erectile dysfunction invariably results.

2. STUTTERING PRIAPISM (INTERMITTENT)

Stuttering priapism characterizes a pattern of recurrence. The term has historically described recurrent unwanted and painful erections in men with sickle cell disease.[2] Patients typically awaken with an erection that persists for several hours. Unfortunately males with sickle cell disease (SCD) may experience stuttering priapism from childhood; in these patients the pattern of stuttering may increase in
frequency and duration leading up to a full episode of unrelenting ischemic priapism. Unfortunately any patient who has experienced an episode of ischemic priapism is also at risk for stuttering priapism.

3. NON-ISCHEMIC PRIAPISM (ARTERIAL, HIGH-FLOW)

Non-ischemic priapism is a persistent erection caused by un-regulated cavernous arterial inflow. Typically the corpora are tumescent but not rigid and the penis is not painful. A history of blunt trauma to the penis or an iatrogenic needle injury is common. Whatever the mechanism of injury, the result is a disruption of the cavernous arterial anatomy creating an arterio-venous fistula. The cavernous environment does not become ischemic and cavernous blood gases do not show hypoxia, hypercarbia or acidosis. This type of priapism once properly diagnosed, may not require emergent intervention. Beyond the acute trauma patients do not complain of pain. Normal erectile function has been reported after recovery from the initial event, despite persistence of non-sexual partial erection.

II. HISTORY OF PRIAPISM

The term priapism has its historical origin in reference to the Greek god Priapus, who was worshiped as a god of fertility and protector of horticulture. Priapus is memorialised in sculptures for his giant phallus. The first recorded account of priapism in English medical literature is recorded in the Lancet and attributed to Tripe in 1845.[3] In 1914 Frank Hinman Senior published a landmark article describing the natural history of priapism.[4] In 1960 his son Frank Hinman Jr. proposed that venous stasis, increased blood viscosity and ischemia were responsible for priapism and emphasized that failure to correct these abnormalities in the penile environment was essentially responsible for treatment failures.[5]

Advances in our understanding of the physiology of erection and the pathophysiology of erectile dysfunction further substantiated the early hypothesis that prolonged veno-occlusion within the corporal bodies is analogous to a compartment syndrome. In 1983 Hauri demonstrated the radiologic differences between veno-occlusive and arterial priapism.[6]

Frank Hinman Sr. in 1914 first described ‘acute transitory attacks of priapism’ as opposed to persistence or rapid recurrence of a single episode. The actual term of stuttering priapism is attributed to Emond et al 1980 in observations of patients with sickle cell disease in a Jamaican clinic.[7] Stuttering priapism episodes were seen to increase in frequency and length leading up to major, unrelenting events of ischemic priapism. Attempts to manage these same sickle cell patients with stuttering ischemic priapism resulted in the early recommendations for hormonal suppression of nocturnal erections and stuttering priapism with estrogen.[2]

Nonischemic priapism is a rare condition, occurring far less commonly than ischemic priapism. It is invariably associated with antecedent perineal or penile trauma. It was first described in the English literature in a 1960 report by Burt et al.[8]

III. EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF PRIAPISM

1. ETIOLOGY OF ISCHEMIC PRIAPISM (VENO-OCCulsive, LOW-FLOW)

Ischemic priapism accounts for more than 95% of all priapism episodes. The erection of ischemic priapism may begin with sexual stimulation, with or without the administration of pharmacologic agents. Once an erection persists beyond 4 hours, and is not relieved by cessation of sexual stimulation or orgasm, the physiologic phenomena of ischemic priapism have begun. Erections lasting up to four hours are by consensus defined as ‘prolonged’; all manufacturers of erection facilitating pharmacotherapies (oral, injectable and intraurethral) recommend that the patient seek out emergent medical consultation for prolonged erection.

In 1986 Pohl et al reported on 230 cases. The etiology of priapism was identified as idiopathic in the majority, 21% of cases were associated with alcohol or drug use/abuse, 12% with perineal trauma and 11% with sickle cell disease.[9] This and other reports on the etiology of priapism are greatly influenced by the prevalence of sickle cell disease. The life-time probability of a man with sickle cell disease developing ischemic priapism ranges from 29-42%.[7] Although the etiology of veno-occlusive priapism is predominated by sickle cell disease, there is a wide variety of associations in the literature from urinary retention to insect bites.[10]

a) Sickle Cell Disease

Blood dyscrasias are a risk factor for ischemic priapism. The mechanism of SCD priapism has been presumed to be stagnation of blood within the sinusoids of the corpora cavernosa during physiologic erection and sickled erythrocytes obstructing venous outflow from the corporal bodies.[11] In Nelson and Winter’s series of cases they noted that sickle cell disease (SCD) was the primary etiology of ischemic priapism in 23% of adult cases and 63% of pediatric cases.[12] Sickle cell hemoglobinopathy accounts for at least a third of all cases of priapism and indeed prevalence of ischemic priapism will vary significantly with the population of males in a community with SCD. From Emond et al’s 1980 observational study comes the most commonly quoted prevalence: among 104 men attending an outpatient sickle cell clinic in Kingston, Jamaica the prevalence of priapism among men with homozygous sickle cell (SS) disease was 42%.[7]
Table 1: Etiologies of Priapism.

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-adrenergic receptor antagonists</td>
<td>Prazosin, terazosin, doxazosin, tamsulosin</td>
</tr>
<tr>
<td>Anti-anxiety agents</td>
<td>Hydroxyzine</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Heparin, warfarin</td>
</tr>
<tr>
<td>Anti-depressants and anti-psychotics</td>
<td>Trazodone, bupropion, fluoxetine, sertraline, lithium, clozapine, resperidone, olanzapine, chlorpromazine, thioridazine, phenothaizines</td>
</tr>
<tr>
<td>Anti-hypertensives</td>
<td>Hydralazine, guanethidine, propanol</td>
</tr>
<tr>
<td>Drugs (recreational)</td>
<td>Alcohol, cocaine (intra-nasal and topical), crack cocaine, marijuana</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Straddle injury, coital injury, pelvic trauma, kick to penis/perineum, arteriovenous or arteriocavernous bypass surgery, urinary retention</td>
</tr>
<tr>
<td>Hematologic dyscrasias</td>
<td>Sickle cell disease, thalassemia, leukaemia, multiple myeloma, haemoglobin Olmsted variant, fat emboli associated with hyperalimentation, hemo-dialysis, glucose 6-phosphate dehydrogenase deficiency</td>
</tr>
<tr>
<td>Hormones</td>
<td>Gonadotropin-releasing hormone (in hypogonadal men), testosterone</td>
</tr>
<tr>
<td>Infectious (toxin mediated)</td>
<td>Scorpion sting, spider bite, rabies, malaria</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Amyloidosis, Fabry’s disease, gout</td>
</tr>
<tr>
<td>Neoplastic (metastatic or regional infiltration)</td>
<td>Prostate, urethra, testis, bladder, rectal, lung, kidney</td>
</tr>
<tr>
<td>Neurogenic</td>
<td>Syphilis, spinal cord injury, cauda equina compression, autonomic neuropathy, lumbar disc herniation, spinal stenosis, cerebral vascular accident, brain tumor, spinal anesthesia, cauda equina syndrome</td>
</tr>
<tr>
<td>Vasoactive erectile agents</td>
<td>Papaverine, phentolamine, prostaglandin E1, oral phosphodiesterase type 5 inhibitors, combination therapy</td>
</tr>
</tbody>
</table>

Tarry and Duckett (1987) found a 6.4% incidence of priapism in an outpatient clinic for children with sickle cell diseases.[13] Adeyoju et al (2002) in an international multicenter observational study of sickle cell disease, cited mean age of onset at 11 years with one quarter ischemic priapism cases presenting during prepubertal years, and rare first time presentation by third decade of life.[14] Based on the World Health Organization global prevalence map of sickle cell disease Aliyu (2008) estimates that 20-25 million individuals worldwide have homozygous SCD; 12-15 million in sub-Saharan Africa, 5-10 million in India and 3 million in other world regions; 70,000 patients with SCD live in the United States.[15]

Contemporary science has identified the molecular pathophysiology behind many of the complications of sickle cell. The sickle cell genetic mutation is the result of a single amino acid substitution in the beta-globin subunit of haemoglobin. The clinical features are seen in homozygous SCD patients: chronic hemolysis, vascular occlusion, tissue ischemia and end-organ damage. HbS polymerizes when deoxygenated, injuring the sickle erythrocyte, activating a cascade of hemolysis and vaso-occlusion. Membrane damage results in dense sickling of red cells, causing adhesive interactions among sickle cells, endothelial cells and leukocytes. Hemolysis releases hemoglobin into the plasma. Free Hbg reacts with nitric oxide (NO) to produce methemoglobin and nitrate. This is a scavenging reaction; the vasodilator NO is oxidized to inert nitrate. Sickled erythrocytes release arginase I into blood plasma, which converts L-arginine into ornithine, effectively removing substrate for NO synthesis. Oxidant radicals further reduce NO bioavailability. The combined effects of NO scavenging and arginine catabolism result in a state of NO resistance and insufficiency termed: hemolysis-associated endothelial dysfunction.[15-18]

Hemolysis and reduced nitric oxide availability are currently thought to be responsible for SCD pulmonary hypertension, leg ulcers, priapism and stroke. Increased blood viscosity is thought responsible for painful crises, osteonecrosis and acute chest syndrome. SCD patients with priapism have a fivefold greater risk of developing pulmonary hypertension. SCD priapism is also associated with reduced haemoglobin levels and increased haemolytic markers: reticulocyte count, bilirubin, LDH and aspartate aminotransferase.[19] Cerebral vascular accidents are more frequent, close to episodes of full blown priapism; the ASPEN syndrome (priapism, exchange transfusion and neurological events) describes cerebral vascular accidents in SCD patients who have received exchange transfusions.[20] Sickle cell trait is considered a benign condition; a few complications have been associated with extreme physical
b) Iatrogenic Priapism: Complication of Treating ED

Injection of intracavernous vasoactive medications for ED is the cause of priapism that many Urologists will encounter; prolonged erection is more commonly reported than priapism. In a review of worldwide reports on intracavernous injection (ICI) programs Junemann et al (1990) noted that diagnostic injection resulted in 5.3% of men getting ischemic priapism and 0.4% of men reported priapism after injecting at home. In papaverine based ICI programs reports of prolonged erections and priapism are poorly differentiated, and range from 0 – 35%. In worldwide clinical trials of the Alprostadil Study Group, prolonged erection (defined as 4-6 hours) was 5% and priapism (> 6 hours) was described in 1% of subjects. In papaverine / phentolamine / alprostadil ICI programs prolonged erections have been reported in 5% - 35 of patients.

c. Oral Phosphodiesterase type 5 Inhibitors

Generally all PDE5 inhibitors have similar side effects related directly to their mode of action, tissue content of substrate, and pharmacologic selectivity for type 5 inhibition versus other phosphodiesterase enzymes: headache, flushing, dyspepsia, rhinitis, light sensitivity and myalgia. Morales et al (1998) analyzed data from 4274 men who received double-blind treatment with sildenafil or placebo for up to six months, and 2199 who received long-term open-label sildenafil for up to one year. No cases of priapism (erection lasting longer than 4 hours) were reported. In a study of 130 patients with sickle cell disease Adeyoju et al (2002) reported that 46 (35%) had a history of stuttering priapism.

3. ETIOLOGY AND PATHOPHYSIOLOGY

3.1. Non-ischemic Priapism

Priapism caused by unregulated cavernous arterial inflow. The epidemiology data on non-ischemic priapism is almost exclusively derived from small case series or individual case reports. Non-ischemic priapism is much rarer than ischemic priapism and the etiology is largely at-
tributed to trauma. Injuries most commonly reported are to the crura or corporal bodies; the forces may be blunt or penetrating resulting in laceration of the cavernous artery or one of its branches within the corpora. The mechanisms include: straddle injury, coital trauma, kicks to the penis or perineum, pelvic fractures, birth canal trauma to the newborn male, needle lacerations, complications of penile diagnostics, and vascular erosions complicating metastatic infiltration of the corpora.[40-44] Although blunt trauma is the most commonly reported etiology, high-flow priapism has been described following surgical interventions: cold-knife urethrotomy, Nesbitt corporalplasty, deep dorsal vein arterialization.[45,46] Any mechanism which lacerates a cavernous artery or arteriole can produce unregulated pooling of blood in sinusoidal space with consequent erection.

Contemporary reports suggest that high flow priapism may have a unique sub-variety. Several authors have noted that following either aggressive medical management of ischemic priapism with aspiration and intracavernous alpha adrenergic injections or surgical shunting that priapism may rapidly recur with conversion from ischemia to high flow. High-flow priapism has been reported following medical and surgical management of ischemic priapism.[47-49] Color Doppler ultrasound in these cases reveals formation of an arteriolar-sinusoidal fistula as in typical high flow priapism or on rare occasion a high flow hemodynamic state of the cavernous arteries with no evident fistula formation. The committee proposes that this subtype of high flow priapism be suspected in cases where rapid recurrence, persistence of priapism with partial penile rigidity or stuttering priapism not associated with pain is evident. This non-fistula type of arterial priapism is the result of dysregulation of cavernous inflows. Non-fistula arterial priapism is a rare complication of medical or surgical management of ischemic priapism.[50-52]

Non-ischemic priapism is typically delayed in onset compared to the trauma; especially if the injury was the result of blunt forces.[53] Sustained partial erection may develop within 24 hours. It is believed that the hemodynamics of a nocturnal erection disrupt the clot and the damaged artery/arteriole ruptures; the unregulated arterial inflow creates a sinusoidal fistula. As healing progresses with clearing of clot and necrotic smooth muscle tissue, the fistula forms a pseudocapsule. Formation of a pseudocapsule at the site of fistula may take several months.

4. PRIAPISM IN CHILDREN

Priapism in children and adolescents is most commonly related to SCD. The literature suggests that the prevalence of priapism in pediatric sickle cell clinics is 2-6%. [40] The majority of SCD priapism is ischemic. In the newborn period fetal hemoglobin predominates, not hemoglobin S.[44] SCD phenotypes related to ischemic or occlusive crises are unlikely to be evident while fetal hemoglobin persists. Newborn priapism is an extremely rare phenomenon with only limited case reports and rare application of contemporary diagnostic modalities. Erection is frequently elicited in males during the newborn period. In newborn males simple tactile stimulation such as diaper changing, bathing, urethral catheterization may result in erection; the erection quickly subsides following cessation of stimulation. Fewer than 20 cases of newborn priapism have been reported in the literature; rarely has etiology been defined: polycythemia, blood transfusion and birth canal trauma.[54-57] The majority of cases have been conservatively managed with spontaneous resolution reported from hours to days. Minimally invasive diagnostics (color Doppler ultrasound, see Evaluation below) should be performed.[58-59] In pediatric patients who develop priapism following trauma an effort should be made to localize the arteriolar-sinusoidal fistula, Hatzichristou et al 2002 have reported that direct manual compression will soften the erection. They note that this non-invasive therapy likely works in children and not adult males, because the perineum has considerably less subcutaneous fat and crural bodies may be more easily compressed.[60]

IV. THE MOLECULAR BASIS OF ISCHEMIC AND STUTTERING PRIAPISM:

Advances in our understanding of the molecular basis of priapism have drawn significantly from both in vitro and in vivo experimental studies using animal models. There is emerging data on the true inciting mechanisms involved in ischemic priapism. Ischemic priapism consists of an imbalance of vasoconstrictive and vasorelaxatory mechanisms predisposing the penis to hypoxia and acidosis. In vitro studies have demonstrated that when corporal smooth muscle strips and cultured corporal smooth muscle cells are exposed to hypoxic conditions significant apoptosis results, and alpha-adrenergic stimulation fails to induce corporal smooth muscle contraction.[61-64] Extended periods of severe anoxia significantly impair corporal smooth muscle contractility and causes smooth muscle cell death and ultimate fibrosis of the corpora cavernosa. In experimental animal models of ischemic priapism, lipid peroxidation, an indicator of injury induced by reactive oxygen species (ROS), and increased hemoxygenase expression occurs in the penis during and after ischemic priapism.[65,66]

Additional pathophysiologic mechanisms involved in the progression of ischemia-induced fibrosis are the upregulation of hypoxia-induced growth factors. An example of one such pleiotropic cytokine is transforming growth factor beta (TGF-β). TGF-β is a cytokine which is vital to tissue repair. However,
excess amounts may induce tissue damage and scarring and upregulation of TGF-β occurs during hypoxia and in response to oxidative stress.[66,67] It is hypothesized that TGF-β may be involved in the progression of the corporal tissue to overt fibrosis.[68,69]

There are several genetically engineered animal models displaying priapic behavior and these too have provided important insights. Transgenic mouse models of sickle cell disease manifest priapism, supporting their use in studies to elucidate the pathogenic mechanisms of sickle cell disease-associated priapism in humans.[70,71] There have been two major discoveries in elucidation of the molecular mechanism of ischemic priapism. Mi et al have shown that transgenic sickle cell mice corpora cavernosa have enhanced smooth muscle relaxation to electrical field stimulation (Mi 2008).[72] Transgenic sickle cell mice and mice lacking endothelial nitric oxide synthase (eNOS) gene expression display supraphysiologic erections and spontaneously phasic priapic activity in vivo.[73,74] Observations of the abnormal erectile responses in these mice were fundamental in spurring ahead recent investigations establishing aberrant nitric oxide (NO) and adenosine regulation in the penis as a mechanism of ischemic priapism especially as it relates to sickle cell disease.

Endothelial cells actively regulate basal vascular tone and vascular reactivity, by responding to mechanical forces and neurohumoral mediators with the release of a variety of relaxing and contracting factors. In the penis, the vascular endothelium is a source of vasorelaxing factors such as NO and adenosine as well as vasoconstrictor factors such as RhoA/Rho-kinase. Recent evidence suggests that in states of priapism there may be aberrant NO and adenosine signaling thus identifying a potential role for NO/cGMP as well as adenosine and RhoA/Rho-kinase signaling in the pathophysiology of ischemic priapism.[72,75,76] eNOS-/- mutant mice have an exaggerated erectile response to cavernous nerve stimulation and have phenotypic changes in erectile function consistent with priapism.[76,77] Mice lacking the eNOS gene manifest a priapism phenotype through mechanisms involving defective phosphodiesterase type 5 (PDE5) regulatory function in the penis, resulting from altered endothelial nitric oxide/cGMP signaling in the organ.[77,78] Supporting this hypothesis, PDE5 expression is significantly reduced in corpora cavernosa smooth muscle cells (CCSMC) grown under anoxic and hypoxic cell culture conditions.[78] Chronic endothelial-NO deficiency in eNOS-/- mutant mice also influences other signaling molecules in the penis, in particular the RhoA/Rho-kinase system which is known to exert significant contractile effects in the penis.[73] In priapism contexts, the cyclic nucleotide cGMP is produced in low steady state amounts under the influence of priapism-related destruction of the vascular endothelium and thus reduced endothelial nitric oxide activity; this situation thereby downregulates the set point of PDE type-5 function, secondary to altered cGMP-dependent feedback control mechanisms.[76,77,79] Under these conditions, when NO is neuronally produced in response to an erectogenic stimulus or during sleep-related erectile activity, cGMP production surges in a manner that leads to excessive erectile tissue relaxation because of basally insufficient functional PDE type-5 to degrade the cyclic nucleotide. Additionally, reduced Rho-kinase activity in concert with PDE5 dysregulation may contribute to the susceptibility of corporal tissue to excessive relaxation via two distinct molecular mechanisms (enhanced vasorelaxation by uninhibited cGMP and less contractile effects of Rho-kinase). Transgenic sickle cell mice also have significant reductions in penile NO/cGMP signaling leading to deficient PDE5 expression/activity as well as reduced RhoA/Rho-kinase expression from which they manifest enhanced erectile responses and recurrent priapism.[76] Another potential cause of enhanced corporal smooth muscle relaxation in sickle cell disease-associated priapism is elevated penile adenosine levels thus causing the corpora cavernosa to be in chronically vasodilated state.[72] Taken together, these data suggest that ischemic priapism and most importantly stuttering priapism is a direct result of NO imbalance resulting in aberrant molecular signaling, PDE5 dysregulation, adenosine overproduction, and reductions in Rho-kinase activity, translating into enhanced corporal smooth muscle relaxation and inhibition of vasoconstriction in the penis.

V. EVALUATION AND DIAGNOSIS OF PRIAPISM

1. HISTORY

In order to initiate appropriate management, the physician must determine whether the underlying priapism hemodynamics are ischemic or nonischemic. Emergency management of ischemic priapism is recommended. Ischemia should be suspected if the patient has progressive penile pain, associated with the duration of erection; has used known drug associated with priapism; has sickle cell disease or another blood dyscrasia; has a known neurologic condition especially those affecting the spinal cord. Stuttering priapism history is one of recurrent episodes of prolonged erections, usually non-resolving morning erections or sexually stimulated erections. Nonischemic priapism should be suspected when: there is no pain, there is a history of coital trauma, or blunt trauma to the penis. The onset of post-traumatic high flow priapism in adults and children may be delayed by hours to days following the initial injury.
2. PHYSICAL EXAMINATION

Inspection and palpation of the penis is recommended. In ischemic priapism the cavernous bodies are rigid and the penis is tender to palpation. In high flow priapism the cavernous bodies are tumescent not rigid. Depending on the time since trauma there may be ecchymosis of the penis or perineum. Although malignancies are rare etiologies of priapism, examination of the abdomen, testicles, perineum, rectum and prostate will help identify a cancer primary. If physical examination reveals the penis is nontender, tumesced or partially erect - nonischemic priapism is suspected. In children and adults with high flow priapism depending on the location of trauma and time since the traumatic event there may be residual bruising and some tenderness to palpation.

3. LABORATORY TESTING

Evaluation should include a CBC, WBC with blood cell differential, platelet count and coagulation profile to assess anemia, to rule out infection, to detect hematologic abnormalities and to insure that the patient can safely tolerate surgical interventions should initial medical management fail. A sickle cell prep and haemoglobin electrophoresis should be requested. Other hematologic abnormalities may cause priapism and should be sought if etiology is unknown: leukaemia, platelet abnormalities, thalassemia. An elevated reticulocyte count is non-specific and may be elevated in both priapism due SCD and thalassemia. Urine and plasma toxicology should be done if recreational narcotic or prescription psychoactive drugs are suspected from psycho-social history. A corporal blood gas by aspiration is recommended in the emergency evaluation of priapism. The corporal blood aspirate is essential to differentiate ischemic from nonischemic priapism.

4. PENILE IMAGING

Color duplex Doppler ultrasonography (CDU) of the penis and perineum is recommended in the evaluation of priapism, if this technology is available. CDU is an adjunct to the corporal aspirate in differentiating ischemic from nonischemic priapism (Figure 1). Patients with ischemic priapism will have no blood flow in the cavernous arteries; the return of the cavernous artery waveform will accompany successful detu-
mescence. Patients with nonischemic priapism have normal to high blood flow velocities detectable in the cavernous arteries. CDU may also localize the site of trauma in high flow priapism.[23] Examination of the entire penile shaft and perineum is recommended; this can be done with the patient supine, but frog legged (Figure 2). Penile arteriography should be reserved for the management of high flow priapism, when embolization is undertaken; arteriography is too invasive as a diagnostic procedure to differentiate ischemic from nonischemic priapism.[81] Penile blood gas assessments become confusing following interventions. Color Doppler ultrasound should always be considered in the evaluation of a full or partial erection following treatments for ischemic priapism. The differential diagnosis includes: resolved ischemia with penile edema, persistent ischemia, conversion to high flow priapism. Lue 2002 has reported on the use of intracavernous pressure monitoring during interventions for priapism, to predict resolution or recurrence.[11] Intracavernous pressure monitoring technology is generally available in operating rooms and not in the clinic.

There have recently been reports on the use of magnetic resonance imaging in priapism. Kirkam et al 2008 noted that there are three possible roles for MRI to help in the assessment of priapism; the first would be in the imaging of a well established arterio-l-sinusoidal fistula.[82] The authors acknowledge a limitation of MRI is resolution; MRI can not demonstrate small vessels as clearly as high-frequency Doppler sonography or angiography. The second would be in ischemic priapism to demonstrate the presence and extent of tissue thrombus and corporal smooth muscle infarction. Ralph (2009) used MRI in the prospective management of 50 patients with refractory ischemic priapism failing medical / surgical management (24-720 hours).[83] Patients underwent MRI to characterize the extent of smooth muscle necrosis prior to placement of penile prosthesis. The third role for MRI would be in the imaging of corporal metastasis causing priapism.

VI. MEDICAL TREATMENTS

1. ISCHEMIC PRIAPISM

Historically, first aide was applied by the patient or recommended by a health practitioner unfamiliar with the hemodynamics of priapism; these interventions included: ejaculation, ice packs, cold baths, cold water enemas. Each of these remedies was thought to end erection by inducing vasoconstriction. Some historical reports advised voiding and exercise. Oral sympathomimetic drugs such as terbutaline, pseudoephedrine and etileferine have been reported superior to placebo in reversing prolonged erection (< 4 hours) initiated by intracavernous injection therapies with efficacies of 28 – 36%.[84]

The recommended treatment of ischemic priapism is the decompression of the corpora cavernosa by corporal aspiration. Aspiration will immediately soften the erection and relieve pain. Aspiration alone may relieve priapism in 36% of cases. The AUA Guidelines Panel (2003) advised that there was not sufficient data to conclude that aspiration followed by saline intracorporal irrigation was any more effective than aspiration alone.[80] However, Ateyah (2005) reported that a combination of blood aspiration and cold saline irrigation effectively terminated priapism in 66% of cases compared to aspiration alone 24%.[85] In view of the limited data on the efficacy of cold saline in relieving ischemic priapism, the committee’s recommendation is that penile blood aspiration be performed in the initial treatment of ischemic priapism.

Aspiration followed by the intracavernous injection of sympathomimetic drugs is the standard of care in the medical treatment of ischemic priapism.[80] Sympathomimetic pharmacotherapeutics (phenylephrine, etilephrine, ephedrine, epinephrine, norepinephrine, metaraminol) cause cavernous smooth muscle contraction. In the laboratory normal smooth muscle preparations from humans shows concentration dependent contractions upon exposure to phenylephrine, if the corporal environment is well oxygenated and has a normal pH.[61,86] Broderick and Harkaway (1994) described time dependent changes in the corporal environment beginning within 6 hours of prolonged erection.[62] Animal models of ischemic priapism have demonstrated impairment in smooth muscle contraction with progressive acidosis, hypoxia and glucopenia.[61,64,86,87] Corpus cavernosum specimens form patients presenting with pro-
Figure 2
longed priapism show no contractions to high dose phenylephrine in vitro. AUA Guidelines 2003 noted significantly higher resolution of priapism following sympathomimetic injection with or without irrigation (43 to 81%) compared to aspiration with or without irrigation (24 to 36%).[80] Phenylephrine is a selective alpha-1 adrenergic receptor agonist without beta mediated ionotropic and chronotropic cardiac effects; it is the agent of choice by consensus recommendation.[80,88] There are no comparative trials of sympathomimetics in the management of priapism. Case reports vary in efficacy from 43 – 81%, with time dependent efficacies for each agent reported. Phenylephrine is usually diluted in normal saline with a concentration of 100-500 mcg/ml and given in 1 ml dosages every 3 - 5 minutes. Dosing should be intermittent over the course of an hour.[80] There are no comparative dosing regimens available, nor are there dose tolerating studies to report. It is this committee’s recommendation that phenylephrine be concentrated as 200 mcg/mL in saline and be administered intermittently as 0.5 mL to 1.0 mL doses every 5-10 minutes to a maximum dosage of 1 mg (up to 10 separate injections of 0.5 mL [100 mcg] or 5 separate injections of 1 mL [200 mcg] ). Extremes of age and existing cardiovascular diseases should be taken into consideration during intracavernous sympathomimetic dosing. Serial or continuous monitoring of blood pressure and pulse should be performed during and immediately following intracavernous injection of sympathomimetic drugs. Potential side-effects of intracavernous sympathomimetics include headache, dizziness, hypertension, reflex bradycardia, tachycardia, and irregular cardiac rhythms. Davila (2007) reported subarachnoid hemorrhage in a case of sickle cell disease ischemic priapism.[89] The patient was a 24 year old African American male who reported sudden and severe headache immediately following phenylephrine intracorporal dosing of 500 mcg/mL repeated every three minutes for 4 mL.

Sickle cell disease and hematological malignancies are rare but important causes of ischemic priapism. Classically, treatment of hematologically-induced ischemic priapism involved analgesics, hydration, oxygen, bicarbonate and blood transfusion. However, systemic therapy alone is not effective management of SCD priapism.[90] A recent report suggested that blood transfusion may have no effective role in the treatment of sickle cell-induced priapism.[20] Reports from hematology centers suggest high success rates using penile aspiration/irrigation and intracavernous sympathomimetics for this type of priapism.[91]

2. STUTTERING PRIAPISM

Various factors need to be considered when treating stuttering priapism. Although an episode may last < 4 hours, increasing frequency or duration of stuttering episodes may herald a major ischemic priapism. Multiple frequent visits to the ER to resolve the priapism are disruptive to the patient's life and embarrassing. If attacks follow sexual activity, patients may become sexually avoidant.[14,39] Safety and efficacy of various treatments are poorly characterized in the literature. The side effects of recommended medications should be understood by the patient. Patients on chronic medical therapy to decrease the frequency of stuttering episodes may significantly benefit from performing a single sympathomimetic intracorporal injection at home as part of a personal treatment algorithm.[92,93] Multiple treatment options have been described: oral and injectable alpha adrenergic agonists, terbutaline, digoxin, anti-sickling agent hydroxycabamide, oestrogens, GnRH analogues, antiandrogens, baclofen, gabapentin and recently phophodiesterase type-5 inhibitors.[39] Etilefrine is an alpha agonist available as oral or injectable in some countries. Maximum oral dosing is 100 mg in 24 hours.[94] Okpala (2002) followed 18 men (17 SCD patients and one with sickle trait) all with history of stuttering priapism. Patients were given etilefrine in escalating dosages from 25 mg at bedtime to a maximum of 100mg each day. Stuttering episodes were reduced in frequency and duration in 72%. In children a very small series of six SCD children were followed with dosing twice daily with 0.25 mg/kg of etilefrine.[95] The experience of multiple investigators using oral alpha adrenergic dosing in the management of SCD stuttering ischemic priapism suggests that oral alpha adrenergics at limited daily dosing should be considered in the management of stuttering priapism; drug therapy is typically initiated at bedtime.

a) Hormonal Therapies

The primary action of systemic hormonal therapy in stuttering priapism is the suppression of the androgenic effects on penile erection. Attempts to treat stuttering priapism with hormones have exploited known regulators of male sexual function by targeting the pituitary gland (GnRh agonists), suppressing pituitary function through feedback inhibition (diethylstilbestrol), blocking androgen receptors (antiandrogens) and reducing testicular and adrenal synthesis (ketonazole). In the only randomized placebo-controlled trial, a synthetic oestrogen, diethylstilbestrol, (DES) caused termination of the stuttering episodes in all patients subjected to treatment.[96] However, in more than 50% of patients (5 out of 9) recurrence occurred after treatment cessation. Similar results are described by others in case reports.[95,97] Long-term estrogen therapy is not recommended due to the potential cardiovascular side-effects. GnRH analogues, goserelin acetate and leuprolide acetate, have been described in case reports.[97, 88] Chronic dosing with GnRH analogues in combination with as needed penile injection of alpha adrenergics have been reported in the management of ischemic stuttering priapism.[99]
Discontinuation of GnRH analogues typically leads to stuttering resumption. Anti-androgens carry their actions by direct suppression of the penile androgen receptors. These agents including, lutamide, bicalutamide and clomadinone, have been able to cause considerable relief of stuttering priapism in a number of case reports.[100-102]

**b) Baclofen**

Studies in both rats and humans suggest that baclofen inhibits penile erection and ejaculation, through GABA receptor activity. In rats stimulation of GABAB beta-receptors in the lumbosacral spinal cord inhibits erection in rats.[103-105] Denys et al 1998 reported on nine men with multiple sclerosis or spinal cord injuries who were treated for 44 months with intrathecal baclofen for muscle spasticity; 8 of 9 reported decreased erectile function which reversed upon cessation of baclofen.[106] Rourke et al 2002 first reported on the use of orally nightly baclofen 40 mg in the management of recurrent priapism in patients with neurological lesions.[107] D’Aleo et al 2009 are the first to report on the use of an intrathecal pump dosing baclofen 180 mcg daily for the management of skeletal muscle spasm and recurrent priapism in a patient with spinal cord injury; the patient was refractory to treatment with oral dosing of 75 mg/day, but responded to a test dosage of 25 mcg intrathecally.[108] The neurologic literature generally fails to categorize these erectile events as ischemic or non-ischemic. Triggering events may be tactile nonsexual stimulation causing repeated—reflexogenic erections. Better characterization of these unwanted reflexogenic erections is needed to characterize hemodynamics, inciting events, duration and impact on erectile function. In non-neurogenic patients baclofen daily dosing is associated with drowsiness, nausea, complaints of fatigue, and ED. Recurrent reflexogenic erections are clearly an unwanted condition associated with muscle spasticity in men with spinal cord lesions and neurologic disease, but it remains to be demonstrated that the duration and hemodynamics of such erectile events are similar to ischemic stuttering priapism in SCD.

c) **Phosphodiesterase Type 5 Inhibitors in the Management of Ischemic Priapism: A Counter-Intuitive Treatment Strategy**

Bialecki and Bridges (2002) first reported on sildenail having a paradoxical effect in controlling stuttering priapism in three patients with SCD.[109] Although this proposal would immediately seem illogical based on the knowledge that PDE5 inhibitors exert erectogenic effects, there is a scientific basis for using these agents to treat priapism. In a small case series, Burnett and colleagues have shown that daily sildenail or tadalail therapy reduces ischemic priapism episodes in men with stuttering priapism.[110] Accordingly, when used in long-term dosing regimen unassociated with erection stimulatory conditions, PDE5 inhibitor therapy alleviates recurrent priapism episodes in men with sickle cell disease-associated priapism and idiopathic priapism without affecting normal erectile capacity.[71,111] The working theory is that surges of cGMP go unchecked because of downregulated levels of PDE type 5; this results in stimuli like nocturnal erection resulting in unchecked corporal smooth muscle relaxation. In initial series, the short-acting PDE5 inhibitor sildenail citrate was given in a dose of 25 mg oral daily dosage, with escalation to 50 mg daily. Subsequently these investigators have reported on tadalail at 5 to 10 mg oral dosing taken three times weekly. Multi-center, randomized, double-blind, placebo controlled clinical trials are under. PDE5 Inhibitors should be started under conditions of complete penile flaccidity, not during a stuttering episode. Efficacy is seen after a week or more of dosing.

### VII. SURGICAL MANAGEMENT OF ISCHEMIC PRIAPISM

Surgical management of ischemic priapism is indicated after repeated penile aspirations and injections of sympathomimetic injections have failed or if such an attempt has resulted in significant cardiovascular side effects. The previous International Consultation 2004 recommended corporal aspiration and alpha-adrenergic agonists for at least one hour prior to surgery.[88] Early surgical intervention is ideal in patients with malignant or poorly controlled hypertension or for men who are using monoamine oxidase inhibitor medications that have contraindications to alpha agonist administration. A comprehensive discussion which includes baseline erectile function, duration of priapism, risks and benefits of the surgery, and erectile dysfunction should be held with the patient/guardian and an informed consent form signed by the patient/guardian.

1. **SHUNTING**

The ISSM Standards Committee (expert opinion) have stated that shunting is to be considered for priapism events lasting ≤ 72 hours. Consideration should be given to foregoing shunting in priapism events lasting longer, in particular where cavernous thrombosis is evident and no blood can be aspirated from the corporal bodies.[88,112] It is generally accepted that the longer an episode of ischemic priapism lasts the greater the likelihood of compromised erectile function will be in the future. Previous reviews have concluded that priapism lasting longer than 24 hours was associated with a 90% erectile dysfunction rate.[113] Evidence based recommendations based on erectile function outcomes are few. One recent study does document erectile function outcomes by contemporary standards (International Index of Erectile Function). Bennett and Mulhall
(2008) carefully documented 39 cases of sickle cell disease priapism presenting to their emergency room over eight years; men were routinely interviewed for erectile function status within four weeks of priapism/interventions.[114] Of the 39 African American men followed, 73% acknowledged prior episodes of stuttering; 85% had previously been diagnosed with SCD; only 5% had been counseled or were aware that priapism was a complication of SCD. A standard protocol of aspiration and phenylephrine was performed; shunting for failure of medical management was performed in 28%. In those patients where priapism was reversed, spontaneous erections (with or without use of sildenafil) were reported in 100% of men with priapism reversed < 12 hours; 78% reversed by 12 – 24 hours; 44% reversed by 24 – 36 hours. No patient reported spontaneous erections after priapism duration of > 36 hours.

The objective of shunt surgery is oxygenation of the corpus cavernosal smooth muscle (CCSM). The technical goal of shunting in ischemic priapism is to re-establish outflow from the cavernous bodies by creating a communication to the glans, or corpus spongiosum or directly to a vein (Figures 3,4,5). Shunt procedures are subdivided into 4 groups:[115]

- Percutaneous distal shunts (Winter[116], Ebbehoj[117], Lue[118])
- Open distal shunt (Al-Ghorab[119,120], Burnett[121])
- Open proximal shunt (Quackles[122], Sacher[123])
- Saphenous vein (Grayhack[124]), Superficial or Deep Dorsal Vein (Barry[125])

One of the factors involved in the success of shunts is shunt patency. Patency of a shunt can be verified in the operating room and recovery room in a number of ways.[126,127] While open shunt procedures are likely to result in higher shunt patency rates, there is no data comparing percutaneous and open distal shunts; the surgeon must be guided by familiarity with various techniques. In cases where a distal shunt fails, a proximal shunt is indicated. This decision to proceed more aggressively (open distal shunting, proximal shunt or a vein shunt) may be made in the operating room after the completion of the initial percutaneous shunt, if oxygenated blood is not present within the corporal bodies, intracavernous pressures do not fall, the penis does fails to detumesce and refill with compression, or color Doppler ultrasound shows no cavernous artery inflow. Shunt outcome should be immediately assessed by:

- Visualization of bright red blood in corporal aspirate
- A corporal blood gas
- Color Doppler ultrasound
- Measurement of intracavernosal pressure
- Penile compression maneuver (squeeze and release)

The most commonly performed proximal shunt is the unilateral shunt, described by Quackles in 1964 (Figure 6). Proximal corpus cavernosum to spongiosum (CC – CS) shunt procedures require a trans-scrotal or perineal approach.[122] There is no data comparing bilateral (Sacher[123]) and unilateral CC - CS shunts. Typically, bilateral shunts are staggered; right side and left side are separated by a distance of at least 1cm in an effort to minimize the risk of urethral stricture at the point of CC - CS communication. In cases where proximal shunt fails, some have advocated performing a saphenous vein bypass or deep dorsal vein procedure (Figure 7). A wedge of tunica albuginea is removed and the vein is anastamosed end to side of CC. There are no comparative trials of vein shunting for ischemic priapism. Authors site a significant risk of saphenofemoral vein thrombus and pulmonary embolism with vein shunting.[128]

2. IMMEDIATE IMPLANTATION OF PENILE PROSTHESIS

Some authorities have suggested performing immediate penile prosthesis implantation for ischemic priapism. The time point at which this becomes a reasonable option is unclear. However, any discussion pertaining to early prosthesis insertion should be documented and include a comprehensive review of the theoretic advantages and actual risks (infection, mechanical malfunction, urethral injury, device erosion). The natural history of untreated ischemic priapism or priapism refractory to interventions is severe fibrosis, penile length loss and erectile dysfunction. The advantages of early penile implantation are preservation of penile length, and technically easier implant insertion. Ralph (2009) reported on 50 patients with ischemic priapism. All patients failed conservative management with the instillation of alpha-adrenergic agents [200 mcg phenylephrine repeated to a maximum dosage of 1500 mcg].

Unsuccessful shunts were performed in 13/50 cases.[83] Mean duration of priapism was 209 hours (range 24 – 720 hours). All patients had evidence of cavernous smooth muscle necrosis on MRI and all 50 underwent insertion of penile prosthesis in the acute setting of refractory ischemic priapism. Revision rates were significant, 12/50 patients. The infection rate of 6% was also notably high, and likely related to multiple factors including ischemic tissues and preceding penile interventions.
VIII. INTERVENTIONAL ANGIOGRAPHY IN THE MANAGEMENT OF ARTERIAL (NON-ISCHEMIC, HIGH-FLOW) PRIAPISM

It is very important to stress that non-ischemic priapism is not an emergency and spontaneous resolution may result, without any significant adverse effects on erectile function. There are no comparative outcome studies of intervention versus conservative management in high-flow priapism; there are sufficient case descriptions especially in children to recommend initial watchful waiting. Thus, observation is primarily recommended for this type of priapism. Conservative measures include: ice applied to the perineum and site-specific compression. In view of the current literature, the committee concludes that cavernous aspiration/irrigation and intracavernous sympathomimetics have no role in the treatment of non-ischemic priapism.

Patients demanding immediate relief can be offered selective arterial embolization. The pathognomonic arteriographic finding is an arterial-lacunar fistula; a characteristic intracavernosal cone-shaped blush of contrast is seen at the site of the cavernous artery or arteriole laceration (Figure 2). Permanent (e.g., coils, acrylic glue) and temporary (e.g., autologous clot) embolization techniques have been described. The success rate of treatment of high-flow priapism with selective embolization is quite high, 89% regardless of the embolization material used. Similar results have been reported by others. However, it should be noted that a single treatment of embolization carries a recurrence rate of 30-40%. The most notable side-effect of arterial embolization is erectile dysfunction. Although it was previously reported that non-permanent embolization material cause less erectile dysfunction that permanent ones (5 vs 39%), more recent reports employing a standardized assessment tool (IIEF) in long-term evaluation of post-embolization erectile function describe similar rates of dysfunction, ranging between 15 and 20%. Other reported adverse effects include penile gangrene, gluteal ischemia, purulent cavernositis and abscess of perineum.

Several reports describe combined ultrasound compression with selective arterial embolization to increase success rate in the treatment of non-ischemic. Puppo (1985) compared perineal duplex ultrasound and concomitantly preformed selective internal pudendal arteriography showing excellent sensitivity in detecting the arterial-lacunar fistula on ultrasound that is seen angiographically (12 of 12 cases). If the follow-up clinical examination is equivocal for recurrence of high-flow priapism, a perineal duplex Doppler ultrasound can determine the need for repeat arteriography and embolization.

IX. SURGICAL MANAGEMENT OF ARTERIAL (NON-ISCHEMIC, HIGH-FLOW) PRIAPISM

Arterial priapism is not a urologic emergency. Non-ischemic priapism is painless, there have been reports of partial erection persisting for years. Any intervention must follow a comprehensive discussion with the patient regarding risks and benefits of any of the procedures advocated by the clinician. In cases of long-standing arterial priapism where a

Table 5: Surgical Management of Ischemic Priapism.

- Document accurately baseline erectile function, duration of priapism, history of stuttering and prior interventions.
- Ensure an adequate trial of corporal aspiration and alpha-agonist administration.
- Obtain informed consent.
- Commence with a distal percutaneous shunt.
- Define the patency of the shunt prior to sending patient to recovery room.
- Conduct serial postoperative examination to demonstrate shunt patency.
- Perform an open distal shunt technique or proceed to proximal shunting, if erection persists.
- After shunting follow up with patient on erectile function outcomes and therapies.
- Consider penile prosthesis at the time of presentation:
  - If patient has failed aspiration and sympathomimetic intracavernous injection
  - If patient has failed distal and proximal shunting
  - If ischemia has been present for > 36 hours
- Consider an MRI prior to surgery or corporal biopsy at time of implant to document corporal smooth muscle necrosis.
pseudocapsule around the fistula has developed, surgical ligation has been reported to be successful. Formation of a pseudocapsule may take weeks to months following trauma. Corporal exploration prior to the formation of a pseudocapsule may result in ligation of cavernous artery rather than selective ligation of the fistula. Currently this intervention is reserved for patients: who do not wish to pursue expectant management; or who are poor candidates for angio-embolization or refuse the procedure; or where technology is not available; or when angioembolization has failed.[112,137,138] The surgical approach is transcorporal. Intra-operative Doppler ultrasound guidance is recommended.

CONCLUSIONS
Prompt diagnosis and appropriate management of priapism are necessary to spare patients ineffective interventions and maximize erectile function outcomes. Future research is needed to understand corporal smooth muscle pathology associated with genetic and acquired conditions that result in ischemic priapism. Documenting erectile function outcomes based on duration of ischemic priapism, time to interventions, and types of interventions is needed to establish evidence-based guidance. Better documentation of onset of high-flow priapism in relation to time of injury, and response to conservative management versus angiographic or surgical interventions is needed to establish evidence-based guidance.

Table 6: Surgical Management of HIGH-FLOW Priapism.

- Arterial priapism is not emergency and may be managed conservatively.
- Diagnosis is best made by penile/perineal duplex Doppler ultrasound.
- Angioembolization represents first-line intervention.
- Where angioembolization fails or is contraindicated surgical ligation is reasonable.
- Document pre-operative erectile function/dysfunction
- Obtain informed consent prior to surgical intervention.
Ischemic priapism associated with sickle cell disease requires intracavernous treatment. A hematologist may provide concurrent systemic therapies but the best resolution rates are achieved with therapies directed at the penis.

Oral therapy is not recommended for the treatment of acute ischemic priapism.

Shunt surgery should be considered for all cases of veno-occlusive priapism failing aspiration and intracavernous injection of sympathomimetics. Patients should be counseled that erectile function outcomes decline significantly when priapism has lasted greater than 24 - 36 hours and that complete ED is anticipated if priapism persists for greater than 36 hours.

A distal cavernoglanular shunt should be the first choice of shunting procedures because it is technically easier to perform than proximal shunting.

Percutaneous distal shunting is less invasive than open distal shunting and may be considered first. There are a number of distal shunting procedures and the surgeon should be familiar with these procedures and their complications. Open distal shunting should be considered if percutaneous shunting fails. There are no comparative trials of safety, efficacy or erectile function outcomes for percutaneous versus open distal shunting techniques.

If distal shunting fails, then proximal shunting is recommended. Proximal shunting establishes a communication between the corpora cavernosa and spongiosa at the base of the penis. The surgeon must be aware of the unique anatomic relationship between the corpus spongiosum and urethra. Shunting may also be accomplished with vein grafting to the corpora cavernosa. Venous shunts have increased the risk of thromboembolism.

Following pharmacologic or surgical reversal of ischemic priapism, penile tumescence rather than complete flaccidity may be evident. A phenomenon of conversion to high-flow has been described. In cases where the examination may be equivocal, Color Doppler ultrasonography or cavernous blood gas are recommended (if this technology is available) to demonstrate restoration of cavernous flows.

In men presenting with ischemic priapism of duration > 36 hours or failing interventions, severe erectile dysfunction is inevitable. Consideration may be given to implantation of a penile prosthesis for unresolved ischemic priapism. Complications related to immediate implantation of penile prosthesis for unresolved ischemic priapism are significantly high, but delayed placement of penile prosthesis is technically challenging due to corporal fibrosis, and outcomes may be compromised due to penile shortening. The patient must be fully informed of the risks of immediate implantation. The surgeon must be familiar with the additional technical concerns posed by weaknesses in the tunica albuginea from prior shunting procedures.

STUTTERING ISCHEMIC PRIAPISM

The goals of managing a patient with stuttering ischemic priapism are: prevention of future episodes, preservation of erectile function, and balancing the risks versus benefits of various treatment options.

A trial of daily oral sympathomimetic therapy (alpha adrenergic) may be used in the management of patients (adults and children) with stuttering ischemic priapism associated with hemoglobinopathies. Dosing efficacy should be monitored for frequency and duration of stuttering episodes, blood pressure and normal erectile capacity.

A trial of daily oral PDE5 inhibitor therapy may be used in the management of patients (adults and children) with stuttering ischemic priapism associated with hemoglobinopathies. Dosing should be initiated under conditions of complete penile flaccidity. Dosing efficacy should be monitored for frequency and severity of stuttering episodes, and PDE5 inhibitor side effects and normal erectile capacity.

A trial of gonadotropin-releasing hormone (GnRH) agonists or antiandrogens may be used in the management of adult patients with stuttering priapism. Hormonal agents should not be used in patients who have not achieved full sexual maturation and adult stature. Chronic GnRH or antiandrogen dosing in adult males may affect libido, may affect fertility, cause gynecomastia, cause hot flushes, promote osteoporosis, and worsen sexual function.

Intracavernous injection of phenylephrine (by the adult patient or parent) should be considered as an adjunct to daily systemic therapies in patients with stuttering ischemic priapism. When administered at home for prolonged morning erections, an injection of a intracavernous sympathomimetic may overt a full blown episode of ischemic priapism.

NON-ISCHEMIC PRIAPISM (HIGH-FLOW, ARTERIAL)

Aspiration with or without injection of sympathomimetic agents is not recommended as treatment for high-flow priapism.

Color Doppler ultrasonography (if this technology is available) of the penis and perineum is recommended in the evaluation of priapism, when the history or examination suggests penile trauma.

The initial management of nonischemic priapism may be observation. Immediate invasive interventions (embolization or surgery) can be performed at the request of the patient, but should be preceded...
by a thorough discussion of chances for spontaneous resolution, risks of treatment-related erectile dysfunction and lack of significant consequences expected from delaying interventions.

Penile arteriography is invasive and should not be used as diagnostic procedure to differentiate ischemic from non-ischemic priapism. Penile arteriography should be reserved for the management of high-flow priapism, when embolization is elected.

Selective arterial embolization is recommended for the management of non-ischemic priapism in patients who request treatment. The embolization with either temporary or permanent materials may cause ED. Overall success rates with embolization are high, although a single treatment carries a recurrence rate of 30-40%. There are no comparative outcome studies of selective pudendal catheterization and embolization techniques.

There are no comparative trials of embolization versus surgery in the management of high-flow priapism; the decision to pursue one technique or the other must be based on availability of technology and skills of the physicians. Surgery requires either ligation of a cavernous artery or intra-operative identification of the fistula and excision of the arteriolar-sinusoidal pseudocapsule. Ligation of a cavernous artery may result in ED. Excision of a pseudocapsule and selective ligation of the fistula is more likely to preserve erectile function.

Color Doppler ultrasound guidance is recommended for the intra-operative management of high-flow priapism.

RECOMMENDATIONS FOR FUTURE RESEARCH IN PRIAPISM

BASIC SCIENCE

Future research should include animal models to study the pathophysiology of ischemic priapism. These models should examine the clinical observation that interventions for ischemic priapism may result in a phenomenon of conversion to high flow. Specific questions need to be addressed: Is cavernous arterial dysregulation a normal post-ischemic response? When do post-ischemic high flows resolve? Future research should characterize the molecular dysregulations in stuttering ischemic priapism.

CLINICAL RESEARCH

Sickle cell patients should receive education on priapism and its management. Recent studies suggest that only 5% of sickle cell disease patients recalled learning that priapism was a complication of SCD.

Case-based reports of priapism should document: pre-priapism erectile function by patient and partner; duration of priapism with respect to initiation of each intervention; history of stuttering priapism; recovery of erectile function.

Future reports should make use of standardized erectile function questionnaires.

Consideration should be given to multi-center, randomized, double-blind, placebo controlled clinical trials for the prevention of stuttering priapism in high risk patients (sickle cell disease).

Comparator trials are needed in: daily dosing of oral alpha-adrenergic agents versus phosphodiesterase type 5 inhibitors for stuttering priapism; distal shunting techniques; delayed management versus immediate interventions for high flow priapism.

In patients with refractory ischemic priapism studies should examine outcomes and complication rates for immediate versus delayed prosthetic implants (patient/partner satisfaction, rates of infection, tunica perforation, erosion, and revision).

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Committee 16

La Peyronie’s Disease, Penile Trauma, Gender Reassignment, and reconstructive surgery

Chairmen:
L.A. LEVINE,
D. RALPH

Members:
N. GONZALEZ-CADAVID
V. MIRONE
S. PEROVIC
M. SOHN
M. USTA
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La Peyronie’s Disease, Penile Trauma, Gender Reassignment, and reconstructive surgery

L.A. LEVINE, D. RALPH
N. GONZALEZ-CADAVID, V. MIRONE,
S. PEROVIC, M. SOHN, M. USTA

A. PEYRONIE’S DISEASE

INTRODUCTION

Peyronie’s disease is both a physically and psychologically devastating problem for the affected male. Currently it is considered a wound healing disorder that presents with a fibrous inelastic scar of the tunica albuginea which is currently believed to occur in the genetically susceptible individual following some form of trauma to the penis. In the flaccid state, a palpable scar develops which in the erect state causes a variety of deformities, including curvature, shortening, narrowing, and hinge effect. In the early phase there is oftentimes an inflammatory component which causes pain. This inflammatory pain tends to resolve with time, but because of the deformity, intercourse may be compromised or impossible. Peyronie’s disease is also frequently associated with erectile dysfunction, and a variety of other comorbid disorders, including diabetes, hypertension, dyslipidemia, and low testosterone. Peyronie’s disease was named after François Gigot de la Peyronie, who first described this disorder and offered treatment recommendations in 1743. In spite of over 265 years passing since de la Peyronie’s description, we still do not fully understand the etiopathophysiology nor is there a recognized, reliable, and effective nonsurgical treatment for this disorder. As a result, Peyronie’s disease remains a treatment dilemma for the practicing physician.

I. EVALUATION OF PATIENTS WITH PEYRONIE’S DISEASE

1. INTRODUCTION

One of the most important aspects in the management of patients with Peyronie’s disease is the initial assessment and counseling. It is imperative that the patient receives information about the etiology, natural history of the disease, treatment options and understands the prognosis so that real expectations can be met with subsequent greater patient satisfaction. The quality of life of both the patient and partner may be significantly affected, with an increased risk of depression, low self-esteem and relationship difficulties being common [1].

The incidence of 3.2% in the Cologne questionnaire study of 8000 men highlights the increase in the number of patients presenting with Peyronie’s disease [2]. In this study the prevalence increased from 1.5% for 30-39 year-old men to 6.5% for men over 70. Several studies have suggested that younger men may present with more advanced disease. In one study, men less than 40 years of age were more likely to present with multiple plaques, more complex curvatures and were more likely to be diabetic [3]. Overall, approximately 30% of patients will have diabetes which has been found to be associated with advanced curvatures and vasculogenic erectile dysfunction [4,5]. Two thirds of patients with Peyronie’s Disease are likely to have risk factors for arterial disease and therefore worsening long term erectile function [5].

Peyronie’s disease is a progressive disorder with nearly half of men having disease progression if left untreated. In a recent study by Mulhall et al. 246 men diagnosed with Peyronie’s disease and followed for one year without treatment demonstrated that 12% improved, 40% remained stable, and 48% worsened [6].

In most cases, Peyronie’s disease may be divided into an acute inflammatory phase and a chronic phase. During the former, there may be penile pain and curvature progression although the pain typically resolves spontaneously within 6 -18 months from onset in most patients [6].
2. PATIENT EVALUATION

The diagnosis of Peyronie's Disease is usually apparent from the patient history and penile examination. The main points to gather from the history are whether the disease is still active, the nature of the curvature and the presence of erectile dysfunction (Table 1). This data collection can be facilitated by utilizing a disease-specific questionnaire (Table 2) [7].

Patients with a short disease duration (< 12 months), penile pain or a recent change in penile deformity are still likely to have active inflammatory disease and therefore are not surgical candidates and would be more likely to benefit from medical therapy.

Penile pain may be persistent in the inflammatory stage of the disease but is usually only present during erection. The pain is not usually severe in nature but may interfere with sexual function although spontaneous improvement usually occurs as the inflammation settles within 6 months and almost all men will experience pain resolution by 18 months (94% of 246 men treated conservatively) [6,9].

Table 1
Salient features to assess in Peyronie’s Disease.

- Duration of disease
- Penile Pain
- Stability – acute vs. chronic
- Presence of Plaque or induration
- Penile deformity – angle, direction, indentation, waisting, hinge-effect
- Penile length
- Erectile function
- Normal, ED (psychogenic, structural, vascular)
- ED risk factors

Table 2. Peyronie’s Disease patient questionnaire.

<table>
<thead>
<tr>
<th>PEYRONIE’S DISEASE PATIENT QUESTIONNAIRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLEASE CIRCLE THE MOST ACCURATE ANSWER OR FILL IN THE BLANKS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. History</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. When did you first notice the presence of Peyronie’s Disease?</td>
</tr>
<tr>
<td>2. What was your first symptom?</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Did your penis deform over ( \text{duration} )?</td>
</tr>
<tr>
<td>Stable</td>
</tr>
<tr>
<td>3. Have you had pain in your penis during intercourse before developing Peyronie’s Disease?</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>4. Did you have any change in your penis shape?</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>5. Have you had any other uncomfortable symptoms?</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>6. Are you currently undergoing treatment for Peyronie’s Disease?</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>7. Do you have a family history of Peyronie’s Disease?</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>8. Has your penis curvature worsened over time?</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>9. How long?</td>
</tr>
<tr>
<td>10. Would you describe your penis curvature as</td>
</tr>
<tr>
<td>Up</td>
</tr>
<tr>
<td>11. Have you noticed any shrinking or loss of length of your penis?</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>12. If so, how much?</td>
</tr>
<tr>
<td>13. Have you noticed any color changes?</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>14. If so, how?</td>
</tr>
<tr>
<td>15. Have you noticed any pain or tenderness?</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>16. If so, where?</td>
</tr>
<tr>
<td>17. Have you noticed any changes in erection?</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>18. If so, how?</td>
</tr>
</tbody>
</table>

**Table 1**

**Table 2**

**Table 2.** Peyronie's Disease patient questionnaire.
Table 2. Peyronie’s Disease patient questionnaire. (continued)

<table>
<thead>
<tr>
<th>The following questions ask you to grade the quality of your erections. Please circle the number that best describes the quality of your erections.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prior to developing Peyronie’s Disease, would you grade your erection as:</td>
</tr>
<tr>
<td>GRADE</td>
</tr>
<tr>
<td>2. Do you have any difficulty maintaining your erection after penetration?</td>
</tr>
<tr>
<td>( ) No ( ) Yes</td>
</tr>
<tr>
<td>3. Do you currently have an erection in the morning before you urinate?</td>
</tr>
<tr>
<td>( ) No ( ) Yes (Norelco)</td>
</tr>
<tr>
<td>4. Do you currently experience pain at night and notice an erection?</td>
</tr>
<tr>
<td>( ) No ( ) Yes (Norelco)</td>
</tr>
<tr>
<td>5. At the present time, are you capable of having sexual intercourse?</td>
</tr>
<tr>
<td>( ) Yes ( ) No (Norelco)</td>
</tr>
<tr>
<td>6. What is your sexual partner preference? ( ) Men ( ) Women ( ) Both</td>
</tr>
<tr>
<td>7. Currently, do you experience pain in your penis during sexual activity?</td>
</tr>
<tr>
<td>( ) No ( ) Yes</td>
</tr>
<tr>
<td>8. Have you experienced pain in your penis at any time when you’ve had Peyronie’s Disease?</td>
</tr>
<tr>
<td>( ) No ( ) Yes (At least but new gyno) (From short list)</td>
</tr>
<tr>
<td>9. Does your partner experience pain during sexual intercourse due to the penis curvature?</td>
</tr>
<tr>
<td>( ) Yes ( ) No (Norelco)</td>
</tr>
<tr>
<td>10. Do you have difficulty with penetration due to (check the one that applies):</td>
</tr>
<tr>
<td>( ) Loss of sensation</td>
</tr>
<tr>
<td>( ) Lack of firmness</td>
</tr>
<tr>
<td>11. Do you feel the presence of Peyronie’s Disease has affected your emotional status?</td>
</tr>
<tr>
<td>( ) No ( ) Yes</td>
</tr>
<tr>
<td>12. Has the presence of Peyronie’s Disease affected your relationship with your sexual partner?</td>
</tr>
<tr>
<td>( ) No ( ) Yes</td>
</tr>
<tr>
<td>13. Do you consider your sexual desirability (normal) (low) (high)</td>
</tr>
<tr>
<td>14. Have you noticed any changes in the curvature of your penis since developing Peyronie’s Disease?</td>
</tr>
<tr>
<td>( ) No ( ) Decreased sensitivity ( ) Normal ( ) Paired sensation</td>
</tr>
<tr>
<td>15. Are you able to ejaculate?</td>
</tr>
<tr>
<td>( ) No ( ) Yes (dry ejaculation) (wet at times)</td>
</tr>
<tr>
<td>16. Are you frustrated by your expectations?</td>
</tr>
<tr>
<td>( ) Yes</td>
</tr>
<tr>
<td>18. Do you currently smoke cigarettes?</td>
</tr>
<tr>
<td>( ) Yes (cigarettes) ( ) Pipes</td>
</tr>
<tr>
<td>19. Have you smoked cigarettes in the past?</td>
</tr>
<tr>
<td>( ) No ( ) Yes (100+ per day) (any form of tobacco)</td>
</tr>
<tr>
<td>20. Do you currently consume alcoholic beverages?</td>
</tr>
<tr>
<td>( ) No ( ) Yes (wine) (beer) (other)</td>
</tr>
<tr>
<td>21. How much? ( ) ( ) drinks per day ( ) ( ) drinks per week ( ) ( ) drinks per month</td>
</tr>
<tr>
<td>22. Have you had a past consumer alcoholic beverages?</td>
</tr>
<tr>
<td>( ) No ( ) Yes (wine) (beer) (other)</td>
</tr>
<tr>
<td>23. How much? ( ) ( ) drinks per day ( ) ( ) drinks per week ( ) ( ) drinks per month</td>
</tr>
<tr>
<td>When did you stop? ( ) ( ) ( ) ( ) ( ) ( )</td>
</tr>
<tr>
<td>24. Are you presently taking medication prescribed by any doctor?</td>
</tr>
<tr>
<td>( ) No ( ) Yes (please list)</td>
</tr>
<tr>
<td>25. Do you have a history of any of the following (check if uncertain new with menopause):</td>
</tr>
<tr>
<td>( ) Heart attack ( ) Stroke ( ) Diabetes ( ) High blood pressure ( ) Hospitalized ( ) Fortunately breast cancer</td>
</tr>
<tr>
<td>( ) Severe creeping injury ( ) ( ) ( ) ( )</td>
</tr>
<tr>
<td>( ) Any other vascular disease ( ) Yes, what ( ) ( ) ( ) ( )</td>
</tr>
</tbody>
</table>

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All the patients have either a well defined plaque or an area of induration that is palpable on physical examination, even though patients may be unaware of it [8]. The plaque is located on the dorsal surface of the penis in two thirds of patients with a corresponding dorsal penile deformity [9]. Lateral and ventral sited plaques are not as common but result in more coital difficulties as there is a greater deviation from the natural coital angle. Multiple plaques located on opposite sides of the penis or plaques appearing in the septum may cause penile shortening with or without a penile deformity [10]. The consistency of the plaque, be it soft, tender, calcified or ossified should be noted as this may act as a guide to management. Calcification may occur at initial presentation or develop over time. It appears that calcification is not a manifestation of a more mature plaque as previously thought. Rather it may represent a different genetic subtype of PD [11].

An assessment of the curvature on erection is best made by an intracavernosal injection of a vasoactive agent. This is more accurate than a home photograph or a vacuum assisted erection test as the latter often underestimates the degree of curvature, either because the erection is not full or the full extent of the curvature is masked by the subcutaneous tissue engorgement [12]. This also allows complex curvatures to be assessed and will aid in the decision for the type of treatment best suited to the individual.

The severe emotional distress that occurs is, in part, due to the deformity, but mainly due to the penile shortening that occurs in almost all patients. It is imperative therefore that the stretched penile length is measured preoperatively so that the patients realize that the length loss postoperatively is mainly due to the disease itself and not to the surgical correction [13, 14]. Clinical depression is remarkably common. In a series of 92 men who completed the CES –D validated questionnaire, 48% were clinically depressed and severely so in 22% of these patients [15].

Erectile dysfunction associated with Peyronie’s Disease has been reported in up to 58% of men [2,5]. It is not uncommon for unsuspected Peyronie’s Disease to be diagnosed at the time of investigation of their erectile dysfunction [16,17]. It is clear, therefore, that erectile dysfunction in Peyronie’s Disease is common and may precede the onset of the deformity. It is usually due to one of 4 factors [1,8]:

a) Psychological (Performance anxiety)

The physical abnormality of the penis can cause anxiety or depression which may be severe enough to interfere with the ability to obtain or maintain an erection.

b) Deformity preventing coitus

The penile deformity may be so severe that penetration is made difficult or even impossible. This is more likely to occur if the deformity is in a ventral or lateral direction, or when a dorsal curvature exceeds 60 degrees. The pain that is sometimes experienced in Peyronie’s Disease may also interfere with the erectile capacity.

c) Flail penis

There are a small group of patients with extensive Peyronie’s Disease who also have circumferential plaques with cavernosal fibrosis. Tumescence is reduced or absent from this segment, and if extensive may result in an unstable penis or hinge effect.

d) Impaired erection

It is often difficult to decipher the cause of the impaired erectile capacity. It may be due to concomitant vascular disease that occurs in 54% of patients with Peyronie’s Disease [5] or to site specific venoocclusive dysfunction through an emissary vein that passes through the Peyronie’s plaque into the dorsal vein of the penis and cannot be compressed between the tunical layers [18]. Patients may present with only a flaccid distal portion of the penis or a soft glans penis, the proximal segment being normal. There is controversy as to the mechanism of this, be it arterial, venous or fibrotic in nature but certainly a significant symptom of advanced organic disease [8]. A detailed history of any arterial risk factors for erectile dysfunction should be noted and an assessment of erectile function best made by the validated International Index of Erectile Function-5 (IIEF-5) questionnaire [19]. A PD specific questionnaire is in development and should aid in the assessment of the man with PD and may prove useful in evaluating quality of life-related changes following treatment.

3. INVESTIGATIONS IN PEYRONIE’S DISEASE

Ultrasound is used to identify the site and consistency of the plaque and is a useful tool in the clinical trial setting to assess penile vascular blood-flow parameters. It can also determine the extent of plaque calcification as those men with extensive calcification have historically been noted to not respond well to non-surgical therapies. Extensive calcification appears to be a primary indication for surgical correction as these plaques do not respond to medical therapy. It is a minimally-invasive technique that is more accurate than x-ray, CT scan, or MRI [20]. A vascular assessment should be performed in all patients with erectile dysfunction as well as those undergoing surgery and is best done using duplex ultrasound [21]. The results of this investigation can often show vascular disease in patients who report normal potency which may influence the subsequent management [22].
Many patients have little in the way of symptoms, and reassurance, particularly that the palpable lump is not cancer and that the pain will resolve, may be all that is necessary.

II. Peyronie’s Disease: Epidemiology-Pathology-Mechanisms

1. Epidemiology: Prevalence and Co-morbidities

The misconceptions regarding the prevalence of Peyronie’s disease (PD) in men and the associated co-morbidities have recently been documented in the USA by a mail survey of primary-care physicians and urologists in Illinois and Wisconsin [23]. Although the sample size was relatively small and the response rates were around 44%, the 250 replies showed that 63% and 48% of the primary care physicians and 41% and 37% of the urologists thought respectively that the prevalence is less than 1% and that PD is not frequently associated with erectile dysfunction.

This confusion among clinicians probably stems from the inadequacy of the initial epidemiological studies, but even in the last decade the same concerns regarding the PD intervention trials stated in a recent PubMed search [24] apply to the more current studies on the true prevalence of PD. Both this article and some previous reviews of the last 4 years [25-29] coincide in asserting a 3-9% prevalence, much higher than what was assumed, with an average onset at 50-60 years of age.

However, as it often occurs in sexual dysfunction related topics, the number of reviews exceeds the paucity of original studies. Table 3 shows that in the last decade only five studies evaluating the prevalence of PD could be identified in five countries. Altogether they detected or enrolled 313 cases, and the total screened population was 8,697 subjects. This would give an average prevalence of 3.6%, which agrees with two large studies in Brazil [30] and Germany [2], with 3.7% and 3.2%, respectively. However, the only study in the USA [31] reported a 8.9% prevalence, even higher than a previous study in Italy with 7.1% [32], and remarkably different from the most recent report, from India, with 2% prevalence [33].

The mean age in these studies was older than 55 years, and penile curvature was present in over 80% of patients whereas painful erection was reported by over half of them in Germany and India, features that are common to all the studies. The question remains why despite a similar presentation, the reported prevalence for PD may differ so considerably, from 2% to 9%, and it may be speculated that this may reflect, at least in part, the impact on different social views on self-reporting versus the methodology employed for clinical detection, or even the diversity of sexual practices.

Epidemiological studies that focus on the primary clinical features and co-morbidities found in PD patients but do not investigate prevalence in the general population are more abundant. Eleven such reports were identified from six countries, and all were based on clinical examination (Table 4). As in the prevalence studies, diagnosis was based on plaque detection, although in a couple of cases they considered either plaque or penile curvature. Overall the studies on Table 4 covered 2,180 patients, with the two largest ones in terms of total population of PD and non-PD patients in Egypt [34,38] and three other studies were conducted in the USA [3,36-37]. Patients were in general 55 years of age or older, and only 10-15% were younger than 40 years of age. [34,38,42] also shown in Table 3 [2,31].

As in one of the prevalence studies already discussed [33] three other reports [3,37,41], identified a history of penile trauma, but surprisingly in view of the prevalent hypothesis of this event being a main factor in the development of PD, only 5 to 13% of patients older than 40 years of age report or remember a traumatic event associated with the onset of PD. The number was higher in younger patients, but disclosed by only 18% of those [3]. Four studies on Table 4 revealed a significant association with erectile dysfunction (ED) in comparison with the non-PD population [35,38,39,41], consistent with two other studies in Table 3 [2,31]. However, the primary suspected culprit for the ED, namely corporal veno-occlusive dysfunction (CVOD), could be found as associated with PD only in the 30-39 years of age patients when using Doppler in a carefully designed study [36]. This opens up the intriguing question of what type of ED is actually more prevalent in the older PD patients than in the non-PD counterparts.

The association with Dupuytren’s disease was only investigated since 1999 in two studies, where it was shown to be highly significant in the older population [3], and affecting 39% of PD patients versus only 1.2% in the controls [42]. Strikingly, PD was significantly associated with a family history of Dupuytren’s but not of PD [42]. However, Dupuytren’s was not seen in patients younger than 40 years of age [3]. An earlier study noted that 20% of PD patients presented with Dupuytren’s [40].

Epidemiological studies were also conducted on diabetes as a co-morbidity and although six studies on Table 3 and 4 [3,5,31,34,37,43], found PD to be significantly associated with diabetes, however three other studies [32,41,42] failed to show this association. One of these reports [3] indicated that diabetes occurred in 50% of PD patients younger than 40 years of age and in 18% of patients over this
age, which is obviously much higher than even the high PD prevalence (8.9%) detected in the general population screened by this group in another study [31]. A 20.3% prevalence of PD in diabetic patients was confirmed by another group [43]. When diabetic patients with PD were compared with PD patients with no risk factors (4) they had a significantly higher severity of PD as shown by penile curvature. Some of these reports provided data supporting a significant association of PD with obesity [34,38,43], hypertension [3,5,36,41], hyperlipidemia [3,5,33,34,37,38], smoking [32,34,37,38,42,43], and pelvic surgical interventions [42]. Interestingly, the more comprehensive study in terms of the multiplicity of the investigated co-morbidities [42], identified by multivariate logistic analysis, TURP and Dupuytren’s contracture as by far having the highest odds ratios (205-207), as compared to the others ranging from 3 to 14.


<table>
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All ages and % rounded up, except for prevalence. PD: Peyronie’s disease; ED: erectile dysfunction; PCS: prostate cancer screening; Hypercholest: hypercholesterolemia; S: significant; NS: non-significant; OR: odds ratio; *: self-reported.
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ETIOLOGY AND HISTOPATHOLOGY

The etiology of PD has been discussed in a number of recent reviews [24-29,44-46] but there is little critical assessment of the interpretations and significance of a very small number of related experimental or observational papers. A widely accepted hypothesis on the etiology of the PD plaque is that it originates from trauma or microtrauma to the erect penis during different types of sexual activities with or without partners [47]. It is based on essentially three types of evidence. On one side, the seminal demonstration of fibrin staining or immunodetection in tissue sections of the PD plaque [47-51], corroborated in human penile sections and an animal model of PD [52], which suggest that fibrin is the remnant of fibrinogen extravasation into the tunica albuginea during a traumatic episode, leading to an abnormal healing process and therefore to a “scar” that would evolve into a palpable plaque. The second is the demonstration that injection of fibrin into the tunica albuginea of the rat elicits a PD-like plaque resembling in certain aspects the histology and evolution of the human PD [52,53]. The third is essentially clinical, i.e., the already discussed epidemiological association of PD with a history of sexually elicited trauma to the erect penis or other forms of invasive interventions, mainly surgical, in the pelvis that may affect the homeostasis of penile tissues.

Table 4. Peyronie’s disease co-morbidities: 1999-2009. (continued)

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All ages and % rounded up, except for prevalences. PD: Peyronie’s disease; ED: erectile dysfunction; diab: diabetes; curv: curvature; Hypercholest: hypercholesterolemia; S: significant; NS: non-significant; OR: odds ratio; *: self-reported.

2. ETIOLOGY AND HISTOPATHOLOGY

The etiology of PD has been discussed in a number of recent reviews [24-29,44-46] but there is little critical assessment of the interpretations and significance of a very small number of related experimental or observational papers. A widely accepted hypothesis on the etiology of the PD plaque is that it originates from trauma or microtrauma to the erect penis during different types of sexual activities with or without partners [47]. It is based on essentially three types of evidence. On one side, the seminal demonstration of fibrin staining or immunodetection in tissue sections of the PD plaque [47-51], corroborated in human penile sections and an animal model of PD [52], which suggest that fibrin is the remnant of fibrinogen extravasation into the tunica albuginea during a traumatic episode, leading to an abnormal healing process and therefore to a “scar” that would evolve into a palpable plaque. The second is the demonstration that injection of fibrin into the tunica albuginea of the rat elicits a PD-like plaque resembling in certain aspects the histology and evolution of the human PD [52,53]. The third is essentially clinical, i.e., the already discussed epidemiological association of PD with a history of sexually elicited trauma to the erect penis or other forms of invasive interventions, mainly surgical, in the pelvis that may affect the homeostasis of penile tissues.
However, three findings weaken this hypothesis. One is the fact that despite the epidemiological association the majority of patients do not have recollection of a traumatic episode during sexual activity [31]. Conversely, the second is the demonstration that a very strenuous torsion of the erect penis practiced by some ethnic groups [54], was not associated with a higher incidence of PD. Obviously, it may be argued that a microtrauma not perceived, or easily forgotten by the patient, may be sufficient to elicit the initial scar, and that only certain types of trauma would damage the complicated interaction between the tunica albuginea and the surrounding well vascularized tissues so as to allow the infiltration of the tunica by blood. Ethnic differences may also play a role in the resistance to develop PD. The third concern is that so far there is no demonstration in animal models that penile trauma causes a PD-like lesion, since surgical injury only induces a transient fibrotic process that behaves as an acute reaction that later regresses [55].

Whatever the interpretation of the etiological role of penile trauma, the association of PD with Dupuytren’s disease and a family history for this condition suggests that a genetic or immune-related process may determine predisposition to this localized fibrosis by modulating the reaction after trauma or microtrauma. This hypothesis has been entertained but so far there is no evidence, simply because no systematic research effort has been conducted in this respect, other than sporadic studies. One of the latest (from 1997) [56] stated: “Our results support the hypothesis that there is some involvement of the immune system in the pathogenesis of Peyronie’s disease, although the available data still appear to be insufficient to formulate a definite pathogenetic hypothesis.” This holds true today, as shown in other subsequent studies [57,58]. The same applies to genetic predisposition, often mentioned in reviews but where no studies that we are aware of have been conducted during the last decade, other than two looking into polymorphisms in the TGFβ1 and alpha-1-antitrypsin gene that were not conclusive [59,60]. As a rule of thumb applicable to other research fields, if a finding has not been followed up by the same group or others in a period of 5 years, its significance is not strong. Similarly, no bacteriological association could be identified [61].

As in other aspects of Peyronie’s disease, no firm conclusion can be achieved on its etiology, other than an assuming that penile trauma or microtrauma is a triggering factor in many cases, and that unknown autoimmune or genetic predisposition may favor the development of the plaque by counteracting processes that would naturally regress it. It may be speculated that patients who present both with PD and Dupuytren’s disease would be the most adequate for a comparison of potential biomarkers or gene associations against patients of either condition alone, and against the non-PD population. In this respect, the current availability of proteomic tools may allow for a better characterization of potential biomarkers than in previous studies [62].

As to the pathology of the PD plaque, this is much better known because there are three lines of evidence on PD plaque histology in comparison to normal tunica albuginea. One is the early literature on the histochemistry, and more recently using immunohistochemistry and other assays, of the human PD plaque [48,50,63-71], showing that the main pathological process is tissue fibrosis, namely the excessive deposition of collagen and extracellular matrix with disorganization of collagen fibers and loss and disorganization of elastic fibers, combined in most cases with fibrin accumulation and different degrees of inflammation. Perhaps the most characteristic feature is the appearance of myofibroblasts, cells sharing the fibroblast/smooth muscle phenotypes that are not normally present in the tunica albuginea [71-74]. Progression is characterized by an increase in fibrosis, and in some calcification and ossification [11,75] where osteoblasts may be identified, that leads to a substantial hardening of the plaque, as seen in at least 15% of patients [20]. Spontaneous regression is a rare event [5,42].

The other evidence stems from the four animal models of Peyronie’s disease where a PD-like plaque develops either by pharmacological intervention, or spontaneously in the tunica albuginea of the rat or mouse: a) the most widely used TGFβ1-induced model [63,72,76-83], where this pro-fibrotic factor or a derived peptide is injected only once into the rat tunica and a plaque resembling the human one is found around 45 days later; TGFβ1 is produced in the human PD plaque and is the main profibrotic factor in multiple tissues [84]; a variation of this rat model, based on successive injections of an adenoviral construct expressing a constitutively active TGFβ1 protein which induces a measurable penile curvature and calcification [85]; c) the fibrin-induced rat model, where a single fibrin injection mimics the extravasation of fibrinogen, initiating an acute inflammation followed by a faster development of the PD-like plaque (about 30 days) [50,52,53]; and d) the tight skin (Tsk) mouse model, where a spontaneous PD-like plaque develops with fibrosis, penile bending, and areas of chondroid metaplasia with heterotypic ossification [86].

The third line of evidence is focused on the identification of the myofibroblast as the key cell in the development of the human and rat plaques, based on the culture of these cells and further in vitro characterization, in comparison to their counterparts obtained from the normal tunica albuginea [44,45,72-74,81-83,87-95]. Myofibroblasts are a common feature in most tissue fibrosis and in abnormal wound healing [96], and their persistence by the inhibition of
programmed cell death leads to scar formation, and this is likely the case in the PD plaque [51]. Several publications from two research groups have shown that myofibroblasts are responsible for the excessive collagen deposition in the plaque and possibly may cause penile bending by their well known contractility, but in addition that they are potentially tumorigenic or acquire this trait upon culture [11,93].

Moreover, these cultures contain pluripotent stem cells expressing specific markers, and are able to form myofibroblasts, smooth muscle cells, and osteoblasts, but not adipocytes, and in a paracrine fashion modulate in dual cell culture the differentiation of a multipotent cell line into osteoblasts and myofibroblasts [11,97]. The presence of stem cells in the normal tunica albuginea may explain the fibrotic and osteogenic progression of the PD plaque upon the release of cytokines following microtrauma to the penis which would stimulate this cell lineage commitment.

3. CELLULAR AND MOLECULAR MECHANISMS

Thanks to the analysis of the human PD plaque and of their cell cultures by a variety of cellular and molecular biology approaches, including DNA microarrays, in comparison to the similar information obtained in animal models, a preliminary picture of the molecular mechanisms operating in the initiation, development, progression, and pharmacological inhibition of plaque formation, or its occasional spontaneous regression, has emerged. It is remarkably similar in many aspects to fibrotic processes in other organs, and specifically in the penile corpora cavernosa in erectile dysfunction [98]. The main features of a rather plausible interpretation, that needs confirmation in certain aspects, are as follows:

Fibrinogen or other blood proteins extravasated into the tunica albuginea accumulate in the PD plaque by a putative inhibition of the fibrinolytic and proteolytic systems [48,50] by so far unknown mechanisms, although plasminogen activation inhibitor (PAI-1) is likely to be a factor [50]. Clotting leads to fibrin formation, and this protein and possibly immunoglobulins trigger the release in the lesion site of TGFβ1, PAI-1, and reactive oxygen species (ROS) [50,52,63,72,99], the main pro-fibrotic factors in the kidney, vascular system, and other organs.

There is a concurrent release of other cytokines, including monocyte chemotactic protein 1 (MCP-1), associated to a substantial acute inflammation that usually persists in a chronic phase [90,100,101], and that is probably responsible for the spontaneous induction of inducible nitric oxide synthase (iNOS) [102].

The combination of these factors, plus other members of the TGFβ1 family, such as myostatin and their common signaling via the Smad pathway [83,95], and other unknown agents, causes excessive collagen deposition, elastin degradation, myofibroblast differentiation from fibroblasts or stem cells in the tunica, oxidative stress, and eventually calcification.

Recent research has focused on why the established scar does not undergo normal remodeling and resolution. It appears from one study that there is an abnormal accumulation of TIMPs and other inhibitors of metalloproteinases and collagenases, as well as a relative paucity of collagenases, thus interfering with the normal breakdown of the accumulated collagen [103], and possibly interfering with therapeutic collagenase administration to the plaque [104].

The PD tissue is in constant cellular and molecular turnover and spontaneous mechanisms of defense develop that try to counteract fibrosis and oxidative stress, among them iNOS induction that produces a steady output of nitric oxide that inhibits collagen synthesis and quenches ROS producing peroxynitrite, and of cGMP that also reduces collagenase administration to the plaque [104].

The therapeutic mimicking of iNOS induction, by either biological modulation via gene therapy with iNOS cDNA [35] or long-term continuous pharmacological treatment with the NOS substrate L-arginine or PDE5 inhibitors [81,82], is able to prevent or even partially regress the development of the PD-like plaque in rat models by inhibiting fibrosis and oxidative stress, not by vasodilation effects. Conversely, blocking iNOS activity with L-NIL intensifies fibrosis in these models [63]. This is remarkably similar to the therapeutic prevention and regression of fibrosis by continuous, long-term administration of PDE5 inhibitors in the corpora cavernosa that leads to the amelioration of erectile dysfunction in rat models [98,108,109].

III. NON SURGICAL MANAGEMENT OF PEYRONIE’S DISEASE

1. INTRODUCTION

Non-surgical therapy has been proposed since the time of de la Peyronie. Due to the lack of a clear understanding of the etiopathophysiology, a cure has not been found. Therefore a variety of treatment options have been used. The most current therapies are reviewed. The value of many published reports has been questioned as most were not
well controlled, oftentimes had a small number of subjects in various phases of stability and with limited reports on objective measures of deformity change. Studies focus on reduction of pain which appears to resolve with time untreated, and reduction of plaque size, which has never been found to correlate with curvature improvement. In the opinion of the authors reduction of erect penile deformity (i.e.-curve, narrowing, shortening) is the most critical outcome measure.

Muller and Mulhall recently reviewed the published literature on PD drug trials in an effort to make subsequent studies more evidence-based and clinically useful. Their recommendations for the ideal PD intervention trial included a randomized, placebo-controlled design with a PD patient set representative of the general PD population and a comprehensive symptom and sign assessment before and at the end of treatment which includes an assessment of at least deformity, pain, and sexual function [24]. Table 5 reviews the methods of curvature assessment.

2. ORAL THERAPY

a) Potassium para-aminobenzoate

The first clinical trial with potassium para-aminobenzoate for treatment of Peyronie's disease was carried out by Zarafonetis et al. in 1959 [110]. To date, two prospective randomised, placebo-controlled, double-blind trials have been published. Shah et al. in 1983 treated 60 men with 12 g daily of potassium para-aminobenzoate or placebo for 12 months [111]. The authors found positive, but not significant improvement, of symptoms for potassium para-aminobenzoate when compared to placebo. More recently, Weidner et al. conducted a placebo-controlled, randomized, double-blind study on 103 patients with a history of less than <12 months of Peyronie's disease with non-calcified plaques and without any other treatment. Patients were randomized into two treatment arms: 51 received potassium para-aminobenzoate (4 x 3g/day for 12 months) and 52 received the placebo [112]. Their results showed a significant decrease of plaque size with the potassium para-aminobenzoate compared to the placebo (-117 vs -26; p = 0.042). No significant differences with regards to a decrease in pain was observed between the two groups (82.6% vs. 77.3%). Pre-existing curvature did not improve (p=0.066), but remained stable for those taking the active drug. In the placebo group, penile curvature worsened significantly in 32.5% of the cases (p<0.001). The authors concluded that potassium para-aminobenzoate appears to stabilize the disorder by preventing the progression of penile curvature in patients in the early stage of disease. This well-done controlled trial needs to be repeated to confirm these conclusions. It also should be noted that this treatment requires taking up to 24 tablets daily and is associated with gastrointestinal side effects.

b) Vitamin E

Vitamin E is the most common non-surgical therapy prescribed by urologists for treating Peyronie's disease [23, 113]. In 1983, a placebo-controlled, double-blind, crossover study demonstrated that no superior effects were achieved with vitamin E when compared to the placebo [114]. In 2007, Safarinejad et al. conducted a well designed double-blind, placebo controlled, randomized study in order to assess the efficacy and safety of oral vitamin E and propionyl-L-carnitine, both separately or in combination, for treatment of Peyronie’s disease [115]. A total of 236 men were randomized to receive 300 mg vitamin E orally twice daily, 1 g propionyl-L-carnitine orally twice daily, 300 mg vitamin E and 1 g propionyl-L-carnitine orally twice daily or placebo for 6 months. After treatment, there was no statistically significant differences between the 4 groups with respect to change in penile curvature (p = 0.9). Pain decreased in 60.4%, 63%, 62.3% and 59.2% of the patients and a reduction in plaque size was noted in 11.3%, 12.9%, 13.2% and 11.1% of patients who were treated with vitamin E, propionyl-L-carnitine, vitamin E plus propionyl-L-carnitine and placebo, respectively (p = 0.1).

This study did not show any significant improvement in pain, curvature or plaque size in PD patients when treated with vitamin E, propionyl-L-carnitine, or vitamin E plus propionyl-L-carnitine when compared with those treated with placebo. The authors concluded that Vitamin E is not recommended for treatment of Peyronie’s disease. To date there is no evidence proving the efficacy of vitamin E in the treatment of Peyronie’s disease, however it continues to be widely used. It is well-tolerated and inexpensive.

c) Tamoxifen

In 1992 Ralph et al. conducted a preliminary study on 36 patients with Peyronie’s disease who received tamoxifen 20 mg twice daily for 3 months. Their results showed that 16 out of 20 patients reported an improvement in penile pain, 11 out of 31 patients reported an improvement in penile curvature and 12 out of 35 patients presented a decrease of at least 1 cm in plaque size. Improvement was observed in 6 of the 8 patients with an inflammatory infiltrate of the plaque who had early stage disease (less than <4 months), but not in any of the 4 patients without an infiltrate. The conclusions of the study emphasized that tamoxifen could be effective in patients with early stage disease [116].

A placebo-controlled, randomized study was carried out in order to assess the effectiveness of tamoxifen in Peyronie’s disease, compared with placebo. 25 patients were treated with tamoxifen 20mg twice daily or placebo for 3 months. Investigators used penile radiography, ultrasound, and pharmacologically-
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*PO- oral; IL-intralesional injection; TOP-topical; PC- placebo-controlled*
induced erections to objectively compare baseline status prior to treatment with a follow-up 4 months later. No statistically significant differences were noted between tamoxifen and placebo with respect to decreased penile pain (66.6% vs 75%, respectively), a reduction in penile deformity (46.1% vs 41.7%, respectively), or a decrease in plaque size (30.7% vs 25%, respectively). This study did not show any advantages in treating Peyronie’s disease with tamoxifen compared to placebo [117].

d) Colchicine

In a 1994 pilot study, 24 patients with Peyronie’s disease who were previously untreated received colchicine orally for 3 to 5 months. The results of this study showed a decrease in plaque size in 12 of the 24 patients, a significant relief in 7 of 9 patients with painful erections and an improvement of penile curvature in 7 of 19 cases. [118].

In 2000, Kadioglu and associates treated 60 men suffering from Peyronie’s disease with oral colchicine. Penile curvature improved in 30% of patients, remained unchanged in 48% and worsened in 21%. 95% of the patients reported relief from pain. Based upon these results, the authors concluded that colchicine may be effective in the early phase of the disease [119].

More recently, the first randomized double-blind, placebo-controlled study with colchicine for treatment of Peyronie’s disease was performed. 84 patients with Peyronie’s disease without calcified plaque received 0.5-2.5 mg of colchicine daily or a placebo for 4 months. After treatment, pain resolved in 60% and 63.6% of the patients treated with colchicine and placebo, respectively (p>0.05). A decrease in penile curvature was shown in 17.1% of patients treated with colchicine and in 18.4% of patients treated with placebo (p>0.05). A reduction in plaque size was noted in 10.5% of patients treated with colchicine and 10% of patients treated with placebo (p>0.05) [120]. The results of this study showed that colchicine is no better than placebo in improving pain, curvature angle, or plaque size in patients with Peyronie’s disease.

e) Vitamin E and Colchicine

A double blind, randomized study published in 2003, evaluated the effectiveness and safety of a combination of vitamin E and colchicine in patients with early stage Peyronie’s disease. 45 patients were randomized into two arms: 22 patients received ibuprofen 400 mg/day for 6 months, while 23 received a combination of vitamin E 600 mg/day plus colchicine 1 mg every 12 h. There was no statistically significant relief in pain response between the groups (p = 0.58) however there was an increase in plaque size in the ibuprofen group, while a reduction was evident (p<0.001) in the combination group. There was also a significant improvement in penile curvature in the combination group (p< 0.001) [121].

f) Acetyl esters of Carnitine

In 2001, Biagiotti and Cavallini evaluated the effectiveness of Acetyl-L-carnitine for the treatment of Peyronie’s disease compared to tamoxifen in a randomised, double-blind study. 48 patients with acute or early chronic stage Peyronie’s disease were randomly assigned to equal groups. Group 1 was composed of 8 patients with acute, and 16 patients with early chronic disease who received tamoxifen 20 mg twice daily for 3 months and group 2 was composed of 7 patients with acute and 17 with early chronic disease, who received acetyl-L-carnitine 1 g twice daily for 3 months. Results showed that acetyl-L-carnitine is significantly more effective than tamoxifen in reducing pain and penile curvature in patients with Peyronie’s disease. No significant difference was noted in the reduction of plaque size between the two drugs. The disease progressed in 13 patients in group 1 (54%) but in only two patients in group 2 (8%; p<0.01). Tamoxifen induced significantly more side-effects than acetyl-L-carnitine. The authors of this small but well designed study concluded that acetyl-L-carnitine is significantly more effective and safe than tamoxifen in the treatment of acute and early chronic Peyronie’s disease [122].

The same research group randomized 60 patients with stable Peyronie’s disease into two subgroups who were treated with verapamil intraplaque injection (10 mg weekly for 10 weeks) plus a 3-month oral propionyl-L-carnitine (2 g/day) or verapamil injection plus oral tamoxifen (40 mg/day) for 3 months. They found that the reduction in pain was the same in both subgroups however propionyl-L-carnitine plus verapamil significantly reduced penile curvature, plaque size, and the need for surgery, as well as increased the International Index of Erectile Function score, while tamoxifen plus verapamil had none of these effects. In this study, the combination of propionyl-L-carnitine and verapamil is recommended as the first therapeutic choice for advanced and chronic Peyronie’s disease [123].

The previous cited study of Safarinejad et al. which was published in 2007, did not show significant improvement in pain, curvature or plaque size in patients treated with oral vitamin E, propionyl-L-carnitine, or a combination when compared with a placebo. This study has demonstrated that propionyl-L-carnitine and Vitamin E are not effective alone or in combination for treating Peyronie’s disease [115].

g) Pentoxifylline

In vitro studies suggested a possible role of the NO-cGMP pathway in the pathogenesis of Peyronie’s disease. An increase of NO levels by administration
of nitrergic agents or inhibitors of phosphodiesterase (PDE), may be effective in preventing progression of or reversing the fibrosis [81]. Brant et al. reported a single case of a patient with Peyronie’s disease who was treated with Pentoxifylline, which is a non-specific PDE inhibitor, at 400 mg three times a day, for 6 months. The patient demonstrated an improvement in penile curvature, erectile function and in the ultrasonographic appearance of the plaque. 

Based upon these observations we can conclude that pentoxifylline deserves further investigation as a treatment for Peyronie’s disease [124]. While such results are interesting, they underscore the need to perform large-scale placebo-controlled studies to further explore the role of agents which may increase systemic levels of nitric oxide in clinical cases of Peyronie’s disease.

3. INTRAPLAEQUInJECTIONS

a) Steroids

Six studies using injectable corticosteroids for the treatment of Peyronie’s disease were published from 1954 to 1980 and all six showed positive outcomes from treatment. However none of the studies were randomized or reliably reported objective measures of deformity change [125-130].

In a single blind, randomized, placebo-controlled study, 30 men suffering from Peyronie’s disease were treated with intralesional betamethasone (group A) or placebo (group B) for 24 weeks. After 12-months the pain upon erection disappeared in 66.6% of the patients of group A and 53.3% of the patients of group B. Penile curvature decreased in 20% of the patients in group A and in 26.6% of the patients in group B. A decrease in plaque volume and consistency was observed in 40% of the patients in group A and in 40% of the patients of group B. The authors concluded that the clinical results of the therapy were due to the mechanical effects of the injection and not to the drug action itself [131].

b) Collagenase

Gelbard and associates conducted a prospective, randomised, placebo-controlled study with intralesional injection of collagenase in patients with Peyronie’s disease. 49 patients were randomised to receive a single intraplaque injection of either collagenase or saline solution and were followed for three months. Overall, 36% of the patients who received collagenase reported a positive response compared to only 4% in the control arm. The results of this study indicated a positive response to penile deformity only in patients with a curvature of less than 30° and the maximum degree of improvement was from 15–20°. The authors considered the absolute angular change too small to suggest any clinical benefit [104].

In 2008, Jordan conducted a prospective, single center, non-placebo controlled study in order to assess the efficacy and safety of intralesional clostridial collagenase injection therapy in a group of patients with Peyronie’s disease. 25 patients received three injections of 10,000 units of clostridial collagenase in 0.25 ml administered over 7 to 10 days and repeated at 3 months. Significant decreases from the baseline were achieved in the mean deviation angle at months 3 and 6, in plaque width at months 3, 6 and 9 and in plaque length at months 3 and 6. More than 50% of patients considered themselves “very much improved” or “much improved” after treatment. Based upon this data, intraplaque injection of clostridial collagenase may prove to be a beneficial treatment of Peyronie’s disease [132]. Clostridial collagenase is currently not available for clinical use. A randomized, placebo-controlled, multicenter phase 2B study will be completed by the end of 2009.

c) Verapamil

Intralesional verapamil injection was introduced by Levine and associates in 1994 [133-135]. Three non-controlled, quasi-experimental design (Oxford 2b) studies have been published demonstrating a measured reduction of curvature after twelve 10mg verapamil injections given every two weeks. Subjects had penile curvature measured after pharmacoinjection induced erection in the office before and at the end of treatment. The mean curvature reduction reported in those responders was 27-30°. The author suggested that this treatment may be offered as first line treatment or with a mature plaque. Subjects with acute (<12 months) or chronic disease responded in a similar manner.

Verapamil has also been shown in vitro to interfere with Peyronie’s plaque derived fibroblast cellular proliferation [136].

In 1998, Rehman et al. published a single-blind, placebo-controlled study in which 14 patients received weekly intraplaque injections of either verapamil or saline once a week for 6 months. Plaque volume decreased in 57% of patients in the treatment arm versus 28% in the control arm. In the verapamil group, the mean plaque volume decreased from 1.42 cm³ before treatment to 0.63 cm³ after treatment. Improvement in erectile function was noted in 43% of the patients treated with verapamil compared to 0% in the control group. 28.6% of the men treated with verapamil reported a decrease in penile curvature, with an average decrease from 37.7° to 29.6° following treatment. No improvement in penile curvature was observed in the saline group. This small, randomized, single-blind study suggests that intralesional injection of verapamil is a reasonable treatment for Peyronie’s disease with noncalcified plaque and penile angulation of less than 30 degrees [137].
The duration of the intralesional verapamil injection protocol may prove to be important with respect to deformity changes as it has been suggested that scar tissue remodels very slowly. One single-arm prospective study of six intralural verapamil injections given every two weeks resulted in 18% of subjects with a measured improvement in curvature (mean reduction 12°) while 60% were unchanged [138]. Therefore if a simple comparison is made between the published non-controlled single-arm, prospective trials of intralural verapamil injections, it appears that prolonged treatment with 12 injections over six months has a treatment advantage over just 6 injections over three months. The number of patients with a measured reduction of curvature following six months of treatment is 42-60% versus only 18% for three months of treatment.

In 2007, an Italian group carried out a randomized, prospective clinical trial with the aim of evaluating the efficacy and safety of three different verapamil dilutions for intralural therapy of Peyronie’s disease. 77 patients were randomly assigned to 3 treatment groups and each patient received 12 intralural injections (1 injection every 2 weeks) of 10 mg verapamil in different dilutions: group 1 received verapamil 10 mg/4 mL, group 2 received verapamil 10 mg/10 mL and group 3 received verapamil 10 mg/20 mL. Plaque size decreased in group 1, but this decrease was significantly greater in group 2 and in group 3. No significant difference was noted in penile curvature for all three groups. Pain relief was significantly greater in group 3 than in other groups. Group 3 had end diastolic flow velocity (EDV) during dynamic echocolor Doppler ultrasonography of the penis that were significantly lower than those in groups 1 and 2. This data supports the hypothesis that dilution of 10 mg of verapamil to a volume of 20 mL with injectable saline is able to improve the efficacy of intralural injections without significantly increasing the side effects [139]. Although large scale, placebo-controlled trials have not been conducted, intralural Verapamil injections can be recommended for the treatment of non-calcified acute or chronic plaques to stabilize disease progression or possibly reduce penile deformity.

d) Interferon

Hellstrom and associates conducted a single-blind, multicenter, placebo controlled, parallel study to assess the safety and efficacy of intralural interferon alpha-2B (IFN) for treatment for Peyronie’s disease [140]. 117 patients with chronic Peyronie’s disease (≥ 12 months) and a penile curvature of at least 30° were treated with either IFN or saline intralural injections biweekly for 12 weeks. Curvature improvement was noted in both groups, but more subjects responded in the IFN group (27%) than in the controls (8.9%). The mean improvement of curvature in the treatment arm was 13.5°. 67.7% of the IFN patients reported pain relief after injections compared to 28.1% of the controls. A percent change in plaque size was seen in both patient groups, but was larger in the IFN-treated patients (54.6%) than in the control group (19.8%). No statistically significant difference was noted in the IIEF score between the two groups. Results of this study showed that intralural IFN alpha-2B may be beneficial for men with Peyronie’s disease. These findings offer the largest and best-controlled trial of intralural therapy for Peyronie’s disease, as well as supports its use and demonstrates the lack of clinical benefit following intralural injection of saline. It is significantly more costly than verapamil and has been associated with flu-like side effects.

A recent trial compared the safety and efficacy of intralural interferon-alpha 2b (5.0 x 10^6 IU weekly x 12) alone or combined with oral vitamin E (400 IU BID) versus vitamin E alone. Thirty men entered this prospective randomized trial. Penile deformity was assessed before and 12 weeks after the injection treatment had ended with a full erection following intracavernous injection. At the 6-month follow-up visit there were no statistically significant changes in the objective measures of curvature or plaque size compared to the initial findings within each group or among the three groups. Subjectively there was no significant change in penile pain or quality of sexual intercourse. These authors concluded in this relatively small study that intralural interferon-alpha 2b either alone or in combination with vitamin E has limited benefits with significant side effects [141].

4. OTHER NON INVASIVE THERAPY

a) ESWT

It is very difficult to compare results from trials on extracorporeal shock wave therapy (ESWT) for the treatment of Peyronie’s disease because of the wide variations between the machines and therapeutic schedules used at different centers. However several studies report the efficacy of ESWT in Peyronie’s disease but the more recently published studies with specific documentation of the symptoms before and after treatment do not reveal a beneficial impact on the most important symptoms of penile curvature and plaque size [142-144]. In 2004 Hauck et al. published an exploratory meta-analysis in order to clarify the effect of shock wave therapy in Peyronie’s disease. A rigorous confirmatory meta-analysis was not possible because of the considerable differences in the patient selection of the study groups (medical history, symptom severity). Also, the choice of outcome measures was inconsistent and measurement was not standardized. Moreover, the definition of what constituted success varied from study to study. Results from 17 studies were compared with natural history outcomes and data from the control groups from 2 previous controlled ESWT studies. Results
differed in all outcome parameters in the 17 different series. The decrease in plaque size ranged from 0% to 68% of the cases, while an assessment of curvature reported no significant findings in 74% of the cases and a decrease in penile pain varied from 56% to 100%. Improvement of sexual function was observed in 12% to 80% of the patients. These various findings could be explained by the different groups of patients studied, the evaluation methods utilized, as well as the study designs used. Overall results suggest that ESWT has an effect on reducing penile pain and possibly on improving sexual function. Nevertheless, its effect on plaque size and penile curvature is not impressive and more varied than its beneficial effects shown on penile pain. The authors concluded that ESWT is not an evidence-based therapy for Peyronie's disease [145].

In order to evaluate the long-term effects of ESWT in Peyronie's disease, Srirangam et al. followed 38 patients for a mean period of 44 months (range 42-48). 10 patients out of 38 (26%) required corrective surgery for ineffective ESWT. Of the remaining 28 patients, 18 (47% of the total) showed a statistically significant reduction in penile curvature (mean reduction 33.2° +/- 14.4). No benefit or worsening was noted in 10 of the patients (24%). 16 patients out of 24 with pain (66.6%) reported relief after ESWT. 18 out of the 28 patients (65%) who did not undergo surgery reported erections suitable for intercourse. The treatment was well tolerated [146].

In 2009, Palmieri et al. published the first double blind, randomized, placebo-controlled trial evaluating extracorporeal shock wave therapy for the treatment of Peyronie's Disease [147]. One hundred patients with a history of PD not >12 months duration who had not received previous treatments for PD were enrolled in the study. These men were randomly assigned to receive either ESWT or placebo. Erectile function was assessed with the IIEF-5 questionnaire, pain was evaluated with a visual analog scale (VAS; 0–10), plaque size was measured in cm², and penile curvature was measured in degrees. After the first 12 weeks, a significant improvement of mean VAS score, mean IIEF-5 score and mean QoL score was seen. Nevertheless, mean plaque size and mean curvature were unchanged in the ESWT group, while a slight non-significant increase was observed in the placebo group. After 24 weeks, while mean IIEF-5 score and mean QoL score remained stable in the ESWT group, mean VAS score was significantly lower when compared with baseline in both groups. Moreover, mean plaque size and mean curvature were significantly higher in the placebo group when compared with both baseline and ESWT values. The authors concluded that ESWT appeared effective in reducing penile pain. Although no significant differences were observed in patients receiving ESWT for plaque size and penile curvature, the worsening of such values in the placebo group may suggest at best a potential beneficial effect of ESWT on disease stabilization.

b) Iontophoresis

In 2000, Riedl et al., in a prospective, non-controlled study, treated 100 patients from 28 to 70 years old (mean age 53.6) with Peyronie's disease with iontophoresis using dexamethasone, verapamil and lidocaine for 3 to 10 weekly treatments. Pain resolution was noted in 96% of patients, decrease in plaque size in 53% and improvement of penile curvature in 37%. Impaired sexual function was improved in 19 of 43 patients (44%). The treatment was well-tolerated and was more effective in patients with a short history of disease (less of 12 months). The authors recommended iontophoresis with those drugs as a first-line choice in non-surgical management of Peyronie's Disease [148].

In a randomized, double-blind controlled trial, 92 patients were randomized into two treatment groups: group 1 (47 patients) was treated with iontophoresis with verapamil 5 mg and dexamethasone 8 mg and group 2 (49 patients) was treated using lidocaine, as the control treatment. In group 1, reduction of plaque size was observed in 100% of patients (median plaque volume decreased from 824 to 348 mm³), improvement of penile curvature in 57% of patients (median curvature decreased from 43 to 21 degrees) and pain resolution was seen in 76%. The reduction of pain in the control group that received lidocaine was only temporary. The other symptoms did not improve in the control arm. 51% of patients in group 1 presented an improvement in sexual function while in the control group no significant improvements were observed. Results of this study reveal that electromotive administration of verapamil and dexamethasone for Peyronie’s disease is a safe treatment that induces significant decreases in penile curvature and plaque volume, and a durable decrease in pain [149].

Nevertheless, in 2007, Greenfield and Levine published a randomized, double-blind, placebo-controlled trial on 42 patients with Peyronie's disease [150]. Patients were randomized into two arms: group 1 received 10 mg verapamil in 4 cc saline solution. Patients in group 2 received 4 cc saline only. Treatments were delivered twice weekly for a total of 3 months. Researchers found that there were no significant differences between groups with respect to patient age, disease duration or pretreatment curvature, although a greater percent of patients had improvement in pain and curvature in the group treated with verapamil (p>0.5). The authors concluded that EMDA therapy should be considered only for the patient whose primary complaint is pain or in the patient with mild to moderate curvature (<45°) who declines intralelosional injection therapy or surgical reconstruction [150]. They also concluded that since both groups had a similar reduction in
curvature, that it may be the energy delivered to the tunic rather than the drug which induced the deformity change.

c) Penile Traction Devices

It is well-documented that gradual expansion of tissue by traction, also known as mechano-transduction, results in the formation of new connective tissue by cellular proliferation in several tissue models including bone, muscle and Dupuytren’s scar [151-153]. Levine and associates published a prospective pilot study on 10 patients treated with daily application of a penile extender device for 2–8 h per day for 6 months [154]. Results showed a mean reduction of curvature of 33% (ranging from a 10° to 45° improvement and resulting in a reduction in average curvature from 51° to 34°), an increase in flaccid stretched penile length in all subjects ranging from 0.5–2.0 cm, and an improvement in hinge effect in all those with advanced narrowing or indentation. No patients noted recurrence or worsening of curvature during 6 months of follow-up, and there was no evidence of local skin changes, ulceration, change in penile sensation, or worsening of curvature. Of course, long term and larger scale studies are needed in order to assess the effectiveness of this kind of treatment [154]. Gontero et al. also studied the effects of traction therapy on 15 men with stable Peyronie’s Disease in a prospective non-controlled trial. They did not report significant mean reduction of curvature (4°) but significant length gain was noted after 6 months of daily treatment [155]. Possible explanations for the discrepancy between these two published reports include that in the Gontero study, penile deformity was not routinely measured in the office, and 37% of the patients had a calcified plaque which is known to compromise outcomes for non-surgical therapy. Traction therapy is the newest addition to the non-surgical armamentarium for Peyronie’s disease and shows promise for reduction of curvature as well as recovery of some lost length and girth. As this treatment is non-invasive and appears safe and effective when used properly, the authors recommended use of this therapy. Future studies are ongoing to examine the effects of traction combined with intralesional injections and/or oral agents.

5. CONCLUSION

Non-surgical therapy for Peyronie’s disease has taken many forms. There do appear to be treatment options including intralesional injection and most recently traction therapy which appear at a minimum to stabilize progression of the disease and may improve deformity as well as sexual function. Clearly new, properly designed, randomised placebo-controlled trials with balanced study samples are needed to confirm the benefit of non-surgical therapy. Non-surgical therapy is an option that should be offered to the patient who has unstable disease and is therefore not a surgical candidate and to those men who are not ready to proceed with surgery regardless of the duration or severity of their Peyronie’s Disease.

IV. PEYRONIE’S DISEASE: SURGICAL THERAPY

1. SURGICAL INDICATIONS

The indications for surgical correction of the penile deformity associated with Peyronie’s disease begins with having stable disease. The concept of stable disease has not been clearly defined, but it is generally accepted to be at least six months where there has been no change in the deformity and that pain with erection or during plaque palpation has resolved. The surgical candidate should also describe a compromise or inability to engage in coitus secondary to deformity or inadequate rigidity. In addition, patients who have extensive plaque calcification are typically best treated with surgery, as non-surgical approaches have not been shown to be beneficial in this circumstance. Lastly, the patient who wants the most rapid and reliable result should select a surgical approach [26,156] (Table 6).

Table 6 Surgical indications

<table>
<thead>
<tr>
<th></th>
<th>Stable disease (≥ 6 months with no pain and stable deformity)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Compromised or inability to engage in coitus</td>
</tr>
<tr>
<td></td>
<td>Extensive plaque calcification</td>
</tr>
<tr>
<td></td>
<td>Failed conservative treatment</td>
</tr>
<tr>
<td></td>
<td>Wants the most rapid and reliable result</td>
</tr>
</tbody>
</table>

2. SURGICAL CONSENT

The preoperative consent is critical for preparing men with Peyronie’s disease for surgery (Table 7).

Table 7 Informed consent topics

<table>
<thead>
<tr>
<th></th>
<th>Incomplete/Recurrent curvature</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Loss of erect penile length</td>
</tr>
<tr>
<td></td>
<td>Diminished sexual sensation and delayed orgasm</td>
</tr>
<tr>
<td></td>
<td>Diminished rigidity</td>
</tr>
</tbody>
</table>

Many of these men are depressed, have marked reduction of self-esteem, and often times have unattainable expectations regarding the outcome from surgical reconstruction [15]. Therefore, a
detailed discussion on persistent or recurrent curvature should be initiated with the accepted goal of making the patient “functionally straight”, which is loosely defined as a curvature of less than 20 degrees [157]. Loss of length is most likely to occur with plication procedures, particularly in those with ventral curvature [158]. In addition, there may be diminished rigidity, which has been shown to occur regardless of the surgical approach. Clearly, those who have suboptimal preoperative rigidity have a higher risk of post-operative erectile dysfunction. The incision and grafting technique appears to increase the risk of post-operative ED and, therefore men who have borderline to inadequate erections pre-operatively, should avoid grafting procedures or be prepared to need subsequent penile prosthesis implantation [159]. Lastly, there is a risk of decreased sexual sensation. This has been infrequently reported in the published literature, but it seems for the most part it rarely compromises orgasm and ejaculation.

Surgical algorithms have been published to guide the choice of surgical approach (Table 8).

Table 8. Peyronie’s Disease surgical algorithm.

I. When rigidity adequate preoperatively with or without pharmacotherapy
   A. Tunica Plication when—
      i. Curvature < 60-70 degrees
      ii. No destabilizing hour-glass or hinge
      iii. Predicted loss of length < 20% erect length
   B. Plaque Incision/ Partial Excision and grafting when—
      i. Curvature > 60-70 degrees
      ii. Destabilizing hinge
II. When Rigidity suboptimal
   A. Penile prosthesis implantation

Two main pre-operative factors contribute to this decision, including penile rigidity and severity of deformity [161-163]. When rigidity is adequate, with or without drug assistance, two approaches have been suggested including tunica plication techniques, which are recommended when there is a simple curvature of less than 60-70 degrees, and no hour glass deformity, and when the presumed loss of length caused by the plication will be less than 20% of total erect length. For men who have more complex curvature greater than 60 degrees, and/or a destabilizing hour-glass or hinge effect then plaque incision, or partial plaque excision and grafting is preferred. It is important to stress that this approach is recommended for men who have good quality, preoperative erections.

3. SURGICAL APPROACHES

a) Plication Procedures

This review of surgical approaches begins with the plication procedures, which are designed to shorten the long side of the penis. If the curvature is in a dorsal direction, the plaque causes shortening of the dorsal aspect, and, therefore to correct the curvature with plication, the ventral aspect is shortened. This approach is based upon the Nesbit procedure where an erection is created and a wedge of tunica is excised from the convex, (longer) side, then the edges are reaproximated to create the shortening effect [164]. Currently, there are many variations of the plication procedure, which include procedures where a portion of the tunica is not excised, but instead plicated such as the Essed-Schroeder technique [165]. The Yachia technique utilizes the Heinke-Mikowitz principle where a vertical incision is closed transversely so as to shorten the convex side of the penis [166]. The tunica albuginea plication technique (TAP) corrects the deformity by plicating a series of paired incisions into the tunica without exposing the underlying cavernosal tissue [157]. The 16-dot procedure utilizes an extended Lembert type of suturing technique [167]. In this procedure, a dorsal curve is corrected with sutures placed into the tunic on both sides of the urethra, then progressively tied down so as to create shortening and straightening. There is no tunica incision or tissue excision performed; therefore, the correction of deformity relies upon the non-absorbable sutures. All these procedures appear to adequately straighten the penis with little risk of compromising erectile function. It is critical that during the performance of any straightening procedure the surgeon is able to induce an erection, usually by needle injection of saline by pump or syringe.

Table 9 demonstrates the results with various plication procedures with respect to straightness, post-operative ED, sensation, and follow-up.

The advantages to the plication approach are that they are simple, minimally invasive, and tend to preserve potency in most patients. The disadvantages are that they can result in penile shortening, which has been shown to be exacerbated by correction of curvature greater than 60 degrees, and/or a ventral curvature where dorsal plication is necessary [158]. Lastly, plication procedures may worsen an existing hour-glass or hinge effect, particularly if large plications are used.

b) Incision or Partial Excision and Grafting Techniques

Surgical grafting techniques include plaque incision or partial excision. Historically, total plaque excision was designed to “remove the diseased tunica”
but this causes an unacceptably high rate of post-operative erectile dysfunction. This has been suggested to occur as a result of a compromised veno-occlusive mechanism, due to changes in the relationship between the cavernosal tissue and the overlying tunic or graft [168]. Therefore, minimizing the excision or making simple releasing incisions have been recommended so a smaller graft may be used [169].

The search for the ideal graft continues. As of this time, no ideal graft has been identified, which would take reliably, not contract, be resistant to infection and preserve erectile capacity (Table 10).

Table 10. Graft types.

<table>
<thead>
<tr>
<th>I. Autologous</th>
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<tbody>
<tr>
<td>• Dermis</td>
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<tr>
<td>• Vein</td>
</tr>
<tr>
<td>• Temporalis Fascia</td>
</tr>
<tr>
<td>• Tunica Vaginalis</td>
</tr>
<tr>
<td>• Buccal Mucosa</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Non-Autologous; Allografts</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Processed human cadaveric</td>
</tr>
<tr>
<td>- Pericardium</td>
</tr>
<tr>
<td>- Dermis</td>
</tr>
<tr>
<td>- Fascia Lata</td>
</tr>
<tr>
<td>- Dura mater</td>
</tr>
<tr>
<td>• Processed Animal Grafts; Xenografts</td>
</tr>
<tr>
<td>- Bovine Pericardium</td>
</tr>
<tr>
<td>- Porcine small intestinal submucosa</td>
</tr>
<tr>
<td>- Porcine dermis</td>
</tr>
</tbody>
</table>

Currently, it appears that the nature of the graft is less likely the determining factor with respect to post-operative ED. On the other hand, it is most likely due to patient selection with respect to pre-operative erectile status and operative technique [159]. Larger grafts, men older than 60 years old, and those with ventral grafting also appear to have a higher risk of post-operative erectile dysfunction [162,171]. A variety of autologous grafts have been used including dermis, tunica vaginalis, temporalis fascia, buccal mucosa, and fascia lata [173]. The most frequently used autologous graft currently in use is saphenous vein, which requires a separate incision to harvest, adding a risk of local side effects, and longer operating time with a second incision to heal. Synthetic grafts were used historically, including polyester (Dacron) and polytetrafluoroethylene (PTFE), but these have not
been met with enthusiasm because of the increased risk of infection, an unnatural feel and may have the potential for more local inflammation and fibrosis [174]. The modern era of grafts include off-the-shelf processed human cadaveric tissue or xenografts. These are felt to be advantageous because they can reduce operating time substantially, they appear to have similar mid-term outcome results as compared to autologous grafts, and there is no harvest morbidity. These grafts include human and bovine pericardium, porcine small intestinal submucosa (SIS), and porcine and human dermis. All these grafts undergo an extensive processing to clear the tissue of cells, bacteria, viruses, and presumably prions. As of this time there has been no report of host viral infection secondary to processed allograft or xenograft implantation.

The operative procedure is done essentially the same for all grafting techniques— an artificial erection is created demonstrating the curvature and the penis is typically degloved using a circumcising incision allowing exposure of the entire shaft of the penis. In the area of maximum curvature, Buck’s fascia containing the neuro-vascular bundle is elevated, either from a pair of parallel incisions lateral to the urethral ridge allowing elevation of Buck’s fascia dorsally, or by coming through the bed of the deep dorsal vein. It is felt that the deep dorsal vein approach may not offer adequate lateral exposure, which would be especially important for patients who have severe lateral indentation or hour-glass deformity. The elevation process is best performed with loupe magnification and bi-polar electrocautery so as to reduce the likelihood of injury to the neuro-vascular tissues. Once Buck’s fascia is properly elevated an artificial erection is recreated, demonstrating the area of maximum deformity. Surgeons differ in their approach as to whether a simple modified H-like incision should be made to the area of maximum curvature or whether partial plaque excision is recommended, particularly when there is significant indentation and/or calcification. Regardless, the goal is to remove as little plaque as possible, but to allow proper correction of the deformity by expanding the tunic in both girth and length. Edygio has championed the geometric principle approach to graft sizing [175]. This technique has proven useful in his hands, but a recent report suggested a higher risk of post operative ED [172]. Once the graft is positioned, Buck’s fascia is reapproximated to provide support and a vascularized cover over the graft.

**c) Post-Operative Care and Rehabilitation**

Following surgery, post-operative rehabilitation is recommended to enhance recovery of erectile function. Massage and stretch therapy, is performed by grasping the glans penis and pulling it gently and repeatedly away from the body while also gently massaging the graft area. This is initiated two weeks after surgery and performed twice a day for four weeks. It is advised that the patient’s partner get involved in the rehabilitation process to lessen the anxiety associated with the resumption of sexual activity for both partners. Bedtime phosphodiesterase inhibitors have been recommended to begin seven to ten days after surgery and to be maintained for 6 weeks, in order to enhance nocturnal erections, stretch the tissue, encourage nourishment of the graft [159], and possibly reduce the risk of post-operative ED. Finally, the use of external penile traction therapy has been noted to reduce post-operative penile shortening for patients who have undergone either plication or grafting procedures. Traction is initiated two to three weeks post-operatively when the circumcising incision has adequately healed and is performed on a daily basis for a minimum of two to eight hours for three months [176]. Table 11 outlines the results from published reports on grafting, on average 74-100% of patients were adequately straight, with a post-operative erectile dysfunction ranging from 5-53%. Long-term follow up reports on grafting are limited and found in Table 12. Kalsi, et al, studied 40 patients who underwent vein grafting and followed for at least five years. They reported a post-operative erectile dysfunction rate of 22.5% and a loss of length was noted in 35% [177]. At the 2004 Annual Meeting of the American Urological Association Society, Montorsi, et al reported on 50 patients with a five year follow-up after venous grafting where there was either persistent or recurrent curvature in 12%, length loss in 100%, post-operative ED in 22%, diminished orgasm in 41%, and overall patient satisfaction of only 60% [178]. Taylor and Levine recently reported a mean follow-up of just short of five years on 111 patients undergoing partial plaque excision with processed human pericardial grafting where the patients reported persistent or recurrent curvature of greater than 20 degrees in 8% (none required surgical correction), a measured loss of stretched penile length was found in 47%, but was subjectively reported by 65% of patients. The post-operative ED rate was 24% with 31% noting diminished sensation, but 89% experienced normal orgasm. Overall, patient satisfaction was reported at 76% [157]. Post-operative traction therapy had not been introduced for these studies.

Recent studies have also examined the risk of post-operative erectile dysfunction following penile grafting procedures [170,172]. For the most part, no significant contribution was found due to duration of disease, vascular risk factors (including diabetes, hypertension, elevated lipids and smoking), a dorsal or lateral curvature, graft or tunica defect size, or whether there was pre-operative narrowing or hinge effect. A higher risk of erectile dysfunction was found in those who underwent grafting for ventral curvature and there was a trend towards increased ED risk for men over the age of 60 [159]. In this published...
analysis, the primary component which helped predict an increased risk of post-operative ED was when the patient reported pre-operative diminished rigidity.

b) Penile Prosthesis Implantation with Straightening Maneuvers

Finally, for those men who have poor quality erections and/or do not respond adequately to pharmacological therapy for their erectile dysfunction, penile prosthesis implantation is recommended. Table 13 reviews the recommended surgical algorithm for men with PD and ED [160,162]. Prosthesis alone may result in satisfactory straightening of the penis for those with mild deformity, but when residual curvature is more than 30 degrees, manual modeling is recommended [179]. Manual modeling should be performed with care. Once the prosthesis is placed and the corporotomies are closed, the prosthesis is inflated with a surrogate (i.e. outside the body) reservoir of saline to demonstrate the deformity. The surgeon will then model the penis by bending it in the contralateral direction to the curvature maintaining the pressure on the bent penis for 30 to 60 seconds. The tubing between the pump and the cylinders should be occluded with rubber shod hemostats, so as to protect the pump from high pressure damage. In addition, when performing the modeling process, pressure on the glans penis should be avoided to prevent a urethral erosion by the cylinder tip. An alternative approach is to pre-place plication sutures in the 16-dot method before implanting the prosthesis and then tying them down to correct the curvature. Regardless of the approach, if there is residual curve less than 30 degrees, no further treatment is recommended, as the prosthesis will act as an internal tissue expander and will likely result in correction of deformity in six to nine months. On the other hand, if there is substantial residual curvature, then releasing incisions can be made on the concave side, often times through the same scrotal incision or may require degloving of the penis with elevation of Buck’s fascia. If these incisions create a tunic defect greater than 2 cm in any dimension, patching is recommended to decrease the risk of cicatrix contracture resulting in recurrent curvature or herniation of the cylinders. An off-the-shelf graft is now recommended to fix the tunic defect. Freshly harvested dermal grafts are not recommended as there is risk of transferring bacteria within the dermal tissue increasing the possibility of post-operative infection.

4. CONCLUSION

This review is intended to be a guide to making decisions about surgical correction of Peyronie’s disease. The intent is that it will be useful to the practicing surgeon so that they may provide appropriate advice to their patients regarding the proper surgical procedure. The most critical part of the surgeon’s role in the preoperative phase is to set appropriate expectations for the patient and to review the potential complications of surgery, including incomplete straightening, recurrent curvature, shaft shortening, diminished sensation and erectile dysfunction. Although surgical correction of Peyronie’s disease has historically had a negative reputation, the more recent refinements in technique make it a viable and successful treatment option for the properly selected patient.
Table 11. Peyronie’s Disease published reports—Grafting Procedures

<table>
<thead>
<tr>
<th>Author</th>
<th>Date of Publication</th>
<th>Patient #</th>
<th>Procedure Type</th>
<th>%Straight</th>
<th>%with ED</th>
<th>Diminished Sensation (%)</th>
<th>Mean Follow-up Duration (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knoll et al [185]</td>
<td>2007</td>
<td>162</td>
<td>Plaque Incision with small intestine submucosa grafting-SIS</td>
<td>91</td>
<td>21</td>
<td>No change in biothesiometry</td>
<td>38</td>
</tr>
<tr>
<td>Hatzimouratidis, Hatzichristou et al [186]</td>
<td>2002</td>
<td>17</td>
<td>Tunica Albuginea Free Grafting</td>
<td>100</td>
<td>0</td>
<td>Not reported</td>
<td>39</td>
</tr>
<tr>
<td>Lue et al [187]</td>
<td>1998</td>
<td>112</td>
<td>Plaque incision with venous grafting</td>
<td>96</td>
<td>12</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>Gelbard et al [169]</td>
<td>1996</td>
<td>69</td>
<td>Plaque incision and temporalis fascia grafting</td>
<td>74</td>
<td>14</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Egydio et al [175]</td>
<td>2002</td>
<td>33</td>
<td>Tunica Albuginea Incision and Bovine Pericardial Grafting</td>
<td>87.9</td>
<td>Not reported</td>
<td>Not reported</td>
<td>19</td>
</tr>
<tr>
<td>Levine et al [188]</td>
<td>2003</td>
<td>40</td>
<td>Tunica Albuginea Incision and Human Pericardial Grafting</td>
<td>98</td>
<td>30</td>
<td>Not reported</td>
<td>22</td>
</tr>
<tr>
<td>Breyer et al [189]</td>
<td>2007</td>
<td>19</td>
<td>Porcine Small Intestine Submucosa Graft-SIS</td>
<td>63</td>
<td>53</td>
<td>Not reported</td>
<td>15</td>
</tr>
<tr>
<td>Hsu et al [190]</td>
<td>2007</td>
<td>48</td>
<td>Plaque incision with venous grafting</td>
<td>90</td>
<td>5</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Table 12. Published long-term (5 year) follow-up studies on grafting

<table>
<thead>
<tr>
<th>Author</th>
<th>Date of Publication</th>
<th>Patient #</th>
<th>Procedure Type</th>
<th>%Straight</th>
<th>%with ED</th>
<th>ED - 24%</th>
<th>Decreased organ - 60%</th>
<th>Curve Recurrent persistent - 8%</th>
<th>Length Loss - 100%</th>
<th>Patient satisfaction - 85%</th>
<th>Mean Follow-up Duration (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Kalsi, et al</td>
<td>&gt;5y follow-up</td>
<td>40</td>
<td>saphenous vein graft</td>
<td>22.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>II. Montorsi, et al</td>
<td>&gt;5y follow-up</td>
<td>50</td>
<td>saphenous vein graft</td>
<td>12%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III. Taylor &amp; Levine</td>
<td>Mean 58 mos follow-up</td>
<td>111</td>
<td>Tutoplast® processed human pericardial graft</td>
<td>41%</td>
<td>65%</td>
<td>31%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV. Levine et al</td>
<td>&gt;5y follow-up</td>
<td>50</td>
<td>saphenous vein graft</td>
<td>12%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V. Breyer et al</td>
<td>&gt;5y follow-up</td>
<td>30</td>
<td>saphenous vein graft</td>
<td>35%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI. Hsu et al</td>
<td>&gt;5y follow-up</td>
<td>10</td>
<td>saphenous vein graft</td>
<td>35%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VII. Taylor et al</td>
<td>&gt;5y follow-up</td>
<td>40</td>
<td>saphenous vein graft</td>
<td>22.5%</td>
<td></td>
<td></td>
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Table 13. Surgical algorithm with penile prosthesis

- Placement of inflatable prosthesis
- Manual modeling if residual curve > 30°
- Plaque releasing incision if residual curve > 30°
- Patient satisfaction - 76%
- ED - 24%
- Curve recurrent persistent - 8%
**RECOMMENDATIONS**

1. **Peyronie’s Disease (PD) -Overview  Grade A**
   PD is a physically and psychologically devastating problem manifest by fibrous inelastic scar of the tunica albuginea, which results in palpable scar causing penile deformity (e.g. bending, narrowing, hinging, shortening), as well as painful erections, all of which may lead to difficulty with intromission. It remains a therapeutic dilemma. There are relatively few high-level evidence-based therapeutic studies.

2. **Prevalence of Peyronie’s Disease  Grade B**
   Multiple demographic studies have been performed world-wide indicating a prevalence rate of 3-9% in adult men. Therefore PD is not a rare disorder.

3. **Natural History  Grade C**
   The natural history of PD has been evaluated in only a few level 2&3 studies indicating that spontaneous deformity resolution is not common and remains less than 13%.

4. **PD-Pathogenesis  Grade C**
   PD is a wound healing disorder occurring in a presumed genetically susceptible individual whose tunica albuginea responds inappropriately to an inciting event (i.e. trauma) with a proliferative, fibrotic reaction resulting in an exuberant, inelastic scar. A closer understanding of the etiopathophysiology is not yet established.

5. **Common Comorbidities  Grade D**
   Multiple comorbidities have been identified, including ED, hypertension, diabetes mellitus, hyperlipidemia, low testosterone and Dupuytren’s disease. It remains unclear whether any of these contribute to the development of PD.

6. **Clinical Diagnosis-Overview  Grade D**
   There is no international standard for evaluation or reporting on treatment outcomes for PD. A detailed history should be obtained focusing on onset, duration, pain and deformity.

7. **Clinical Diagnosis-Objective Assessment  Grade D**
   Suggested objective measures include: measuring stretched penile length, and describing plaque location (dorsal, ventral, septal, proximal, distal, etc.)

8. **Clinical Diagnosis-Plaque Size  Grade D**
   Plaque measurement is inaccurate by any modality, as well as operator dependent and therefore is not a reliable assessment of treatment response.

9. **Clinical Diagnosis-Duplex Ultrasound  Grade D**
   Dynamic duplex ultrasound provides assessment of plaque calcification, vascular flow parameters and objective measures of deformity. It is a useful but not necessary test.

10. **Candidates For Non-Surgical Therapy  Grade C**
    Men with early phase disease (i.e. <12 months induration) manifest by unstable or progressive deformity and painful erections as well as those not psychologically ready or interested in surgery may be considered candidates for non-surgical therapy.

11. **Oral Therapy  Grade B**
    There is evidence that there is no benefit with respect to deformity reduction with any oral therapy, including Vitamin E, Potassium Aminobenzoate, Colchicine, Tamoxifen, and Carnitine.

12. **Treatment-Injection Therapy**
    Intralesional injection may be used with the following admonitions:
    - **Steroids**-no objective measures of therapeutic benefit.  Grade D
    - **Verapamil**-appears to make scientific sense but no large scale placebo-controlled trials.  Grade C
    - **Interferon**-One (Level 1) placebo-controlled trial showed an outcome benefit with interferon over saline.  Grade B
    - **Collagenase**-Several small non-controlled trials showed limited benefit. It is currently being studied in a phase 2b trial.  Grade D

13. **Treatment-Topical Verapamil  Grade D**
    As there are no independent controlled trials and no evidence of adequate levels within the tunica albuginea, no recommendation is possible for topical Verapamil.

14. **Treatment-Topical Energy- Iontophoresis  Grade C**
    Several controlled trials had evidence of reduced deformity following iontophoresis treatment using verapamil and dexamethasone.

15. **Treatment-Shock Wave Therapy  Grade B**
    There is evidence that ESWT does not improve PD-related deformity.

16. **Treatment-Traction Therapy  Grade C**
    Early evidence from two small non-controlled prospective trials have reported a reduction of deformity and increased penile length with traction therapy.
17. Non-Surgical Treatment Overview Grade C  
Non-surgical treatment has limited evidence of benefit, but multiple reports of deformity stabilization or reduction makes it reasonable to offer EMDA, and/or intralesional injection of verapamil or interferon, and/or traction therapy.

18. Surgical Treatment Grade C  
Surgery remains the gold standard for correcting erect penile deformity in the man with stable disease.

19. Indications for Surgical Reconstruction Grade C  
Surgical reconstruction is indicated in the man who has stable disease for ≥ 6 months, painless deformity, compromised or inability to engage in coitus secondary to deformity and/or inadequate rigidity, when there is extensive plaque calcification, and for the man who desires the most rapid and reliable result.

20. Surgery-Pre-Operative Consent Grade D  
The pre-operative consent is critical to set proper outcome expectations for the patient. It is imperative to have a discussion on the risks of persistent or recurrent curvature, loss of erect length, diminished rigidity and decreased sexual sensation.

21. Surgical Algorithm Grade C  
Several surgical algorithms have been published with general agreement that for men with adequate pre-operative rigidity, some form of tunica plication procedure is best for those with curvature less than 60° and with no hour-glass deformity resulting in a hinge-effect. For those with more severe deformity (>60° and/or hourglass) and good pre-operative rigidity, incision or partial excision and grafting is recommended.

22. Surgery-Plication Procedures Grade C  
There is no evidence that one surgical approach provides better outcomes over another, but curvature correction can be expected with low risk of new ED or sensory change.

23. Surgery-Grafting Procedures Grade C  
There is no evidence that surgical outcomes are consistently better with one graft type, and overall there is an increased risk of post-operative ED. Autologous grafts require more time and a second incision. Allograft and Xenograft procedures appear shorter in duration with no reported transmission of disease. Synthetic grafts increase the risk of infection and are not recommended.

24. Surgery-Penile Prosthesis Grade C  
Penile prosthesis implantation with additional maneuvers to correct the deformity is recommended when there is pre-operative ED not responsive to oral medication (PDE-5 Inhibitors).

25. Surgery-Penile Prosthesis Grade D  
Following prosthesis implantation the following maneuvers are recommended including manual modeling followed by plaque incision if the residual erect curvature exceeds 30°. If a tunica defect in excess of 2 cm is noted after incision, then grafting the defect is recommended to reduce the risk of post-operative recurrent curvature or cylinder herniation. Autologous dermal grafts should not be placed over a prosthesis due to the increased risk of infection.

26. PD Surgery-Overview Grade D  
Following published surgical algorithms is imperative, as well as obtaining a pre-operative consent to set proper outcome expectations for the patient. A plication procedure is indicated for less severe deformity (≤60°) and when there is borderline ED, while grafting is reserved for severe deformity (>60-70° +/- hinge with normal erectile function) and requires an experienced surgical team. Lastly, prosthesis placement is indicated with additional maneuvers for those men with refractory ED and PD.

REFERENCES


81. Valente EG, Vernet D, Ferrini MG, Qian A, Rajfer J, Gonzalez-Cadavid NF. L-arginine and phosphodiesterase (PDE) inhibitors counteract fibrosis in the Peyronie’s fibrotic plaque and related fibroblast cultures. Nitric Oxide 2003; 9: 229-44.


86. Lucettelli M, Lunghi B, Finesschi S. A new mouse model of Peyronie’s disease: an increased expression of hypoxia-induciblefactor-1 target genes during the development of


B. PENILE TRAUMA

I. PENILE FRACTURE

Penile fracture is defined as the traumatic rupture of the tunica albuginea. It usually occurs during sexual intercourse when the erect penis is thrust against the partner’s symphysis pubis or perineum [1,2,3,4]. Other causes, particularly in Middle Eastern countries, include masturbation, compression of a nocturnal erection and from “Taghaandan”, a process of kneading and snapping the erect penis to achieve detumescence [4].

The site of the fracture usually occurs laterally or ventrally, in the mid to lower shaft, where the outer and inner fibres of the tunica are less prominent. These areas thin to 0.25mm on expansion and with the high intracorporal pressure during forced straining are liable to rupture [3,5].

1. PRESENTATION

The classical presentation includes a cracking sound at the moment of injury, a sharp pain, detumescence, swelling and ecchymosis [1,2,3,4]. The typical appearance has been named as ‘eggplant deformity’ or ‘aubergine sign’ by some authors [3,4,6]. A palpable defect in the tunica albuginea can occasionally be felt but usually the swelling conceals this sign. It is important to remember that a concomitant urethral injury, partial or complete, may occur in 2% - 20% of patients [1,6,7].

2. INVESTIGATION

Imaging is useful to confirm the diagnosis of a tunical or urethral injury and to possibly exclude alternative diagnoses such as a ruptured dorsal vein or suspensory ligament injury which could be managed conservatively [8]. If the site of the tear is visualised then this also would help in choosing the type of surgical access to be used. Imaging should be used if the equipment and expertise is available and time permitting but these are only supplementary to the clinical assessment which should take priority.

Cavernosography has been shown to be reliable in the diagnosis of penile fracture with 100% accuracy in one series of 21 patients that went on to a surgical repair [9]. Non invasive techniques such as grey scale and colour Doppler ultrasound can be useful but is operator dependant [10]. MRI scanning is likely to be more accurate but may not be available in all units [3].

A urethral injury should be suspected in all cases particularly if there has been urethral bleeding or that a ventral tear has been diagnosed. Retrograde urethrography may be used pre-operatively to diagnose this but may become unnecessary if a surgical exploration is to be performed. In this situation the urethra can be directly inspected at the fracture site with or without an on-table urethrogram with methylene blue or betadine [6].

3. TREATMENT

Conservative management of a penile fracture with catheterisation, compression dressings, analgesia, antibiotics and erection-inhibiting agents should be avoided. Complications including painful erection, penile deformity, arterial-venous fistulae, hematomas, abscess formation and erectile dysfunction due to venous leakage [3,12,13,14] may occur in over 30% of patients.

Once diagnosed, surgical exploration is widely accepted as the ‘gold standard’ therapeutic option in men presenting with penile fracture even in the event of a delayed presentation (48 hours after injury) [3,4,7].

Even after surgical repair long term erectile dysfunction may be present in 17% of patients and they should be warned of this [4]. Surgical intervention commences with either a degloving incision, often combined with a circumcision, or a local incision over the fracture site if known. The haematoma is then evacuated and the tunical tear repaired. The urethra is inspected and repaired by mucosal apposition without debridement or spatulation. Any subsequent stricture formation can be dealt with at a later [1,3,4,15,16].

A study comparing the long term outcomes of surgical and conservative treatment in men with penile fracture showed a 92% and 59% patient reported satisfaction rate respectively, thus suggesting immediate surgery seems superior to non operative therapy [14].

II. PENILE PENETrATING TRAuMA

Penetrating trauma to the penis should be explored immediately with an anatomic repair performed. The management of bullet injuries depends on velocity. Low velocity injuries of the urethra should be primarily reconstructed while ‘high’ velocity injuries should be managed by diversion and delayed reconstruction of urethral strictures, or correct penile curvature which commonly occur secondary to damage to the surrounding tissues [17].

III. DEGLOVING INJURIES OF THE PENIS

Degloving injuries are encountered in cases in which the penis or scrotal skin is trapped and stripped from the deeper structures. In such cases bleeding is usually not a problem due to the lack of large
vessels in this space. The injured area, if clean, should be dressed in sterile saline-soaked bandages and immediately reconstructed using partial or full thickness skin grafts [9].

IV. AMPUTATION OF THE PENIS

The treatment of penile amputation includes surgical replantation of the amputated part, tailoring of the remaining penile stump, or total phallic reconstruction at a later date.

Reimplantation with microsurgical reanastomosis is the most widely accepted approach which gives the most physiologic and aesthetic results [18]. In the absence of a microvascular surgeon, and where the patient's condition permits, transfer to an appropriate unit should be performed. The amputated distal portion of the penis should be cleaned, wrapped in a sterile saline bandage, placed in a sterile plastic bag and kept on ice. Surgically, the penis is stabilized by stenting the urethra and completing a two-layer spatulated urethral reanastomosis using 6-0 polydioxanone suture on the mucosa and 4-0 on the corpus spongiosum. The cavernosal arteries are bilaterally anastomosed with 11-0 nylon sutures if possible followed by the approximation of the tunica albuginea. Finally, the dorsal arteries (11-0 nylon), dorsal vein (10-0 nylon) and dorsal nerve sheaths (10-0 nylon) are reapproximated [17, 18].

Total phallic reconstruction is considered for patients in whom replantation is impossible. This is best performed using the free forearm flap, first reported by Chang and Hwang, to give a sensate phallus with a neourethra [19]. A penile prosthesis implantation is performed after the recovery of sensation of the neophallus to allow rigidity for sexual intercourse.

Figure 1. Ultrasound and MRI image of penile fracture.
RECOMMENDATIONS

1. Recommendation for Penile Fracture
   Grade C
   Imaging (Cavernosography, US or MRI) can be used for localisation of the injury, while retrograde urethrogram (pre/peri op) can be performed if there is a suspicion of a urethral injury. The ultimate decision for surgery is based on clinical findings and once diagnosed, there is no indication for conservative management.

2. Recommendation for Penile Skin Loss Injuries
   Grade
   There is evidence to support surgical replacement of shaft skin with either split, mesh or full thickness skin.

3. Recommendation for Penile Amputation
   Grade D
   Critical warm and cold ischaemia time is unknown. Surgical re-attachment is therefore a clinical decision and is best performed by an experienced microsurgeon. Psychological evaluation should be offered to patients who self mutilate. If re-implantation fails or is impossible, patients should be referred for phalloplasty at an appropriate time interval.

REFERENCES

C. GENDER REASSIGNMENT AND PENILE RECONSTRUCTION

• GENDER REASSIGNMENT

I. GENITAL GENDER REASSIGNMENT IN TRANSSEXUAL PATIENTS

1. INTRODUCTION

Transsexualism (TS) or Gender Identity Disorder (GID) is defined as a strong and persistent cross-gender identification with the patients’ discomfort with his/her sex and the sense of inappropriateness in the gender role of that sex (Diagnostic and Statistical Manual of Mental Disorders, fourth revision, text revision [DSM-IV-TR]) [1].

Gender reassignment surgery together with hormonal therapy is generally accepted as a somatic method to resolve this discomfort by altering a person’s external sexual characteristics to resemble those of the opposite sex [2].

The prevalence of GID among the general population and the ratio between male to female has a country variation reflecting different cultural and social conditions and the ability to keep registers. Most countries have a male:female ratio of 3:1 although a ration of 1:1 has been noted in Serbia [3, 4, 5, Table 1].

The World Professional Association for Transgender Health (WPATH), formerly known as the Harry Benjamin International Gender Dysphoria Association (HBIGDA) continuously updates Standards of Care (SOC) for diagnosis and treatment of transsexual patients as well as the criteria for surgical procedures [6]. At present a minimum age of 18 years is demanded for gender reassignment surgery although hormonal treatment may start earlier than this [7].

2. DIAGNOSIS

The diagnosis of GID is determined by mental health professionals, who firstly have to exclude any underlying medical condition such as schizophrenia or a personality disorder and to exclude alternative diagnoses such as transvestism and fetishism. A thorough medical examination is also mandatory to exclude an intersex condition [5].

Patients must spend a period of time living in their chosen gender before being considered for surgery. This Real Life Test is usually for one year although hormone therapy may be commenced earlier to help the adjustment [6, 8].

The following sections deal with genital surgery in this group of patients. Other reassignment procedures of breast surgery and hysterectomy are well defined and established, even if their performance in transsexual patients may require specific skills and knowledge.

II. GENITAL REASSIGNMENT SURGERY IN MALE-TO-FEMALE TRANSSEXUAL PATIENTS

1. SURGICAL AIM

The surgical aim is to create a perineogenital complex as feminine in appearance and function as possible. The perineogenital area should be free of poorly healed areas, scars and neuromas. The neovagina should ideally be lined with moist, elastic and hairless epithelium. Its depth should be at least 10 cm and its diameter should be 30 mm [9].

Bilateral orchiectomy, amputation of the corpora cavernosa, creation of the neovaginal cavity, lining of this cavity with hairless skin, reconstruction of a urethral meatus in such a way, that the direction of the urinary stream is downward in a sitting position and finally the construction of labia and clitoris have been defined as the five major steps for surgery in all recent techniques [2, 5, 10, 11, 12, 13, 14, 15].

<table>
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</table>

MF-TS= male-to-female transsexuals; FM-TS= female-to-male transsexuals
2. OPERATIVE TECHNIQUES
Usually penoscrotal skin flaps are used for lining of the neovagina and for vulval reconstruction [2, 5, 10, 11, 12, 13, 14, 15, Figure 1]. The inverted penile skin is used as a tube and augmented by a triangle of perineoscrotal flap for construction of the posterior introitus. Modifications with the inclusion of a pedicled and opened urethral segment allows for diameter enlargement and better lubrication [14]. For patients with a short penis and/or radical circumcision the length of the inverted penile flap may be augmented by split skin or full scrotal skin after thinning and epilation [10, 16]. Intraoperative sacrospinous ligament fixation for neovaginal prolapse prevention has been proposed recently and the creation of a sensitive and well-vascularized neoclitoris has become a standard step of the procedure [17, 18]. This may be facilitated by a reduction glansplasty with preservation of the neurovascular bundle for sexual sensation which is essential [5, 6, 10, 13]. Complete resection of the corpora cavernosa and partial resection of the corpus spongiosum help to refine the vestibulum and introitus area to avoid obstruction during intercourse due to arousal induced swelling of erectile tissue [5, 10, 12, 16]. Reconstruction of the prepuce of the clitoris, of the labia minora and of a female appearing mons pubis should be performed using a variety of techniques [5,10,13,15, Figures 2,3,4]. Labia majora generally can be formed during the primary procedure from the remaining scrotal skin [ 5, 10]. Postoperatively patients have to remain in bed for 5-6 days with an intravaginal dilator in place. Regular dilation of the neovagina has to be maintained life-long at varying intervals [10].

3. POSTOPERATIVE RESULTS
From previous reports it becomes obvious that complications, readmissions and reinterventions significantly dropped after switching to newer operative techniques as described above [19]. From a comparative study by Eldh et al it can be concluded that overall 80 % of the patients were content with the surgical result and 32 of 40 patients reported satisfaction with their neovaginal volume after introducing penoscrotal flaps for skin lining [19]. This data was confirmed in another study of 66 patients, where a 75% satisfaction rate with vaginal volume was noted [16]. If the neurovascular bundle was preserved, an 80-87% clitoral orgasm rate can be achieved [5, 19, 20].

The largest follow up study of 232 patients operated on by a single surgeon showed a satisfaction rate of 94% although most patients had additional genital surgery [21]. Complications included vaginal stenosis (8%), misdirected urinary stream (33%), urethral stenosis (4%), genital pain (9%), clitoral necrosis(3%) and anorgasmia (18%). Other lower urinary tract symptoms of a degree of incontinence may occur in 19% of patients [22]. An overview of expected complications is shown in Table 2.

The new sexual experience can be expected to be improved and pleasurable in > 80% of patients with long term genital sensitivity being retained [23, 24]. These results have been confirmed in other studies with satisfaction rates of 80% [25]. Vaginal depth was considered adequate by 61%, urinary problems reported by 27 % and 48% were able to achieve orgasm.

The most recent report on the physical, mental and sexual health in 50 patients showed that transsexual operated women functioned well on a physical, emotional, psychological and social level. With respect to their sexuality, they suffered from specific difficulties, concerning arousal, lubrication and pain. These findings confirmed a previous report by the same authors that stated an overall satisfaction rate of 86% [15,26]. All results are summarized in Table 3.

III. GENITAL REASSIGNMENT SURGERY IN FEMALE- MALE TRANSSEXUAL PATIENTS

1. SURGICAL AIM
The ideal aims of phallic construction should ideally address the following requirements [27]:

1) It should involve a limited number of surgical stages
2) The formation of a competent neourethra to allow micturition in a standing position
3) It should create a phallus that has both tactile and erogenous sensibility
4) It should allow for enough bulk to tolerate the insertion of a penile prosthesis
5) It should be aesthetically acceptable to the patient
6) There should be minimal scarring and disfigurement and no functional loss in the donor area

The actual variety of free and pedicled flaps used for phalloplasty suggests that there does not yet exist one single ideal technique, which could fulfill all demands in neopenis formation, even if the radial free forearm flap seems to emerge as most widely used alternative [2,5]. There is however agreement that a complete functional neopenis formation can still not be reached in one operative session.
Patients often have different desires with regards to the type of genital surgery and the amount of morbidity from scarring that is acceptable to them. Therefore all phalloplasty techniques should be offered to the patient even if it means referral to an alternative unit. Hysterectomy, oophorectomy and vaginectomy may be performed prior to phallus formation or during one of the stages of phalloplasty depending on the surgical preference. Vaginectomy is usually done at the same time as the proximal urethral reconstruction [5].

The options available include metoidioplasty, the use of local flaps or free microvascular flaps.

Metoidioplasty is the creation of a micropenis by lengthening of the clitoris from the release of the ventral clitoral chordae, urethral advancement to the tip of the clitoris using vaginal and labial flaps and finally scrotal formation by approximation of the labia majora [28, 29, Figure 5]. Phallus length is dependent on the initial androgen clitoral enlargement and never long enough to house a penile prosthesis for sexual intercourse. Despite the high complications of urinary fistulae and strictures with revision rates up to 88%, to stand to void is often all that is desired by some patients and so this method should still be offered [5].

Flaps more suited to total phallic construction has led to the development of the use of infraumbilical skin and groin flaps [30-33]. The phallus is often wedged shaped with minimal sensation and often without a urethra. A neourethra can be fashioned from a

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
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Table 3. Satisfaction results of vaginoplasty in transsexual patients

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</table>

2. OPERATIVE TECHNIQUES

Patients often have different desires with regards to the type of genital surgery and the amount of morbidity from scarring that is acceptable to them. Therefore all phalloplasty techniques should be offered to the patient even if it means referral to an alternative unit. Hysterectomy, oophorectomy and vaginectomy may be performed prior to phallus formation or during one of the stages of phalloplasty depending on the surgical preference. Vaginectomy is usually done at the same time as the proximal urethral reconstruction [5]. The options available include metoidioplasty, the use of local flaps or free microvascular flaps.

Metoidioplasty is the creation of a micropenis by lengthening of the clitoris from the release of the ventral clitoral chordae, urethral advancement to the tip of the clitoris using vaginal and labial flaps and finally scrotal formation by approximation of the labia majora [28, 29, Figure 5]. Phallus length is dependent on the initial androgen clitoral enlargement and never long enough to house a penile prosthesis for sexual intercourse. Despite the high complications of urinary fistulae and strictures with revision rates up to 88%, to stand to void is often all that is desired by some patients and so this method should still be offered [5]. Flaps more suited to total phallic construction has led to the development of the use of infraumbilical skin and groin flaps [30-33]. The phallus is often wedged shaped with minimal sensation and often without a urethra. A neourethra can be fashioned from a
pedicled tube of labial skin in a one or two stage procedure, to allow patients to void in a standing position, although urethral complications can be as high as 70% [34]. Despite this, in a series of 85 female to male patients, a 68% patient satisfaction rate was reported with 16 patients also able to have penetrative sexual intercourse without the insertion of penile prosthesis [34, Figure 6].

Musculocutaneous thigh flaps based on the gracilis muscle have been reserved for a salvage procedure as generally the cosmetic and functional results are poor due to muscular contracture [35].

The gold standard technique for total phallic construction is with the use of free flaps first described by Chang [36]. The reconstructive procedure involved the creation of ‘a tube within a tube’ using forearm skin with the urethra fashioned from the non hair bearing area and the whole flap base on the radial artery. The arm is subsequently grafted with split or full thickness skin with a resultant morbid scarring. With the advent of microsurgical techniques, microvascular anastomoses are fashioned as well as nerve coaptation of the antebrachial nerves to the dorsal nerve of the clitoris and to the ilioinguinal nerves to form a sensate and cosmically acceptable phallus. [Figure 7]. Following the success of this series many teams have adopted this technique and applied some modifications in flap design in order to improve the cosmesis of the neophallus and to minimize the overall complication rate that may occur in up to 45% of cases. In particular the shape of the forearm flap has been modified in order to improve the blood supply to the flap and to reduce the risk of meatal stenosis [37– 40]. In a further attempt to minimize donor site morbidity, free osteocutaneous iliac flaps have been introduced with a neourethra fashioned by prelaminated tunneling of a skin graft; [41].

After urethral continuity has been confirmed and the phallus has become sensate, a penile prosthesis is then inserted to give rigidity for sexual intercourse [5]. Inflatable prostheses are generally used to minimize the risk of erosion and are often inserted in stages together with testicular prostheses. Anchorage of the prosthesis is aided by placing the rear part in a Dacron or PTFE sock that is sutured to the pubis [41, Figure 8].

3. POSTOPERATIVE RESULTS

The results of the radial forearm flap phalloplasty give excellent satisfaction rates of 80 – 85% although complication rates are high as shown in Table 4.

Due to the complex nature of the operation, possible complications are numerous and should be explained in detail to the patients. Traditionally local flaps without the need for microsurgical vascular anastomoses are less prone to complications than free flaps. From recent publications of experienced high-volume centers, it becomes obvious that the more complex the primary procedure, the more possible complications that occur, independent from the surgeon [5,34,39,40]. Partial or total skin necrosis of the phallus is not uncommon and a third of patients will have a urethral complication (Table 4).

### Table 4. Complication rates in forearm flap phalloplasty.

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<tr>
<th>Author</th>
<th>n</th>
<th>Phallus loss%</th>
<th>Urethral fistula/stricture %</th>
<th>Prosthesis loss %</th>
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<tr>
<td>Monstrey</td>
<td>81</td>
<td>4</td>
<td>42</td>
<td>20</td>
</tr>
<tr>
<td>Lerche</td>
<td>56</td>
<td>5</td>
<td>37</td>
<td>29</td>
</tr>
<tr>
<td>Garaffa</td>
<td>129</td>
<td>3</td>
<td>35</td>
<td>25</td>
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Even if revisions for urethral problems are successful, nearly half of the patients report urinary symptoms of a reduced urinary stream, dripping or recurrent urinary infections [22].

Penile implant complications are common due to the excessive use of prosthetic material [Table 4]. In the largest series of 129 implants, a revision rate of 41% was reported at 30 months follow-up, with an erosion/infection rate of 20% [44].

Nevertheless, the vast majority of patients do not regret having undergone such complex procedures. More than 80% may reach orgasm or sexual satisfaction by stimulation or sexual intercourse, if clitoral nerves can be successfully adapted to correspondent sensory nerves of the forearm flap [5, 24, 39]. In contrast to male to female surgery, patients must be informed, that a functionally and aesthetically appealing genital reassignment can only be reached by a staged procedure, eventually followed by one or more revisions due to complications [5, 45].

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Figure 1. Components necessary for vaginoplasty.

Figure 8. Components for penile prosthesis.

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Figure 2. Result of first stage after 6 month of male to female genital reassignment surgery.

Figure 3. Result of additional corrective surgery for mons-pubis-plasty and clitoris reduction genital reassignment surgery.

Figure 4. Final result 3 months after corrective surgery.

Figure 5. Metoidioplasty final result.

Figure 6. Phalloplasty using local flaps from pubic skin.

Figure 7. Forearm flap phalloplasty (‘tube within a tube’) still attached to the arm.

Figure 8. Phalloplasty with penile implant inflated.
• PENILE RECONSTRUCTION

I. PENILE AUGMENTATION

1. INTRODUCTION

Insufficient penile size is a source of anxiety for men who often seek augmentation using one of a variety of techniques, some used centuries ago [46]. The injection of exogenous substances into the penis or stretching with external weights has been popular in different cultures with the focus on “bigger is better” [47].

The “small penis syndrome (SPS)” may be defined as an anxiety about insufficient penile size despite the clinical examination being normal [48]. It may be part of a body dysmorphic disorder (BDD), a psychiatric condition which frequently leads to depressive episodes and social isolation, or part of a psychosis [49].

However, the attractiveness of the male genitalia has a much lower priority ranking for women than men. In one survey, 90% thought that girth was more important than length [48,50,51] and others have shown that 85 % of women are satisfied with their partners penile size compared to 55 % of men being satisfied with their length [52].

In the early 1970’s, surgical methods to lengthen the penis were by pediatric urologists [53]. The surgical principle of dividing the suspensory ligament and visual elongation of the penis by an infrapubic VY-plasty or similar regional advancement-flaps was adapted to adult men by Roos, who published a large series of 260 cases in 1994 [54].

It can be estimated that from 1990 to 1997 more than 10,000 men have undergone this or a similar procedure in the USA , the vast majority of which have a normal sized penis [55].

Due to a growing number of complications and litigation after failed penile augmentation procedures, main stream sexual medicines societies regard these procedures as “experimental surgery” without proven safety or efficacy data [56].

Due to the recently published comprehensive reviews and the growing number of innovative operative techniques in this field, the need for an evidence based systematic evaluation is essential [46, 57, 58].

2. PENILE SIZE

The measurement of penile dimensions is a basic requirement for evaluating the success-rates of penile enlargement surgery. Different study populations and measurement methods may explain the variance of the average penile size in various studies. The stretched penile length is a good guide to the potential erect length, but stretched penile girth does not reliably reflect erect girth [56, 59]. Overall, the average penile length in the flaccid state is 9-9.5 cm and depends on several situational variables. Average erect length ranges from 12.8 – 14.5 cm with an average girth of 10 -10.5 cm. Two standard deviations away from the mean equates to a micropenis being defined as that which measures < 7.5cm erect. The various studies describing normal penile dimensions are shown in Table 5 [56].

3. CONDITIONS CAUSING PENILE SHORTENING

Penile shortening may be associated with certain medical and surgical conditions, including penile cancer, penile trauma, Peyronie’s Disease, excessive skin loss, buried penis, epispadias and hypospadias and intersex disorders [56, 57, 60-62].

The general consensus is that patients suffering from these conditions are candidates for penile lengthening or other reconstructive procedures [53, 57, 58, 61].

These operations may be challenging and may demand a variety of reconstructive procedures including phalloplasties and penile prosthesis-implantation [57,61, Figure 9]. A broad spectrum of techniques has been published, mostly in small case-series or case reports [60, 62-67]. The level of evidence to support these procedures is low, however, due to the severity of these conditions, surgical relief by an experienced reconstructive surgeon using individualized surgical approaches can be recommended.

4. PENILE AUGMENTATION PROCEDURES

a) Penile lengthening procedures

The mainstay of penile lengthening procedures are a combination of release of the suspensory ligament of the penis, resection of supra- and/or infrapubic fat and penopubic skin advancement. Detachment of the suspensory ligament from the symphysis pubis allows forward movement of corpora and enables the flaccid penis to extend closer to its erect length. Reattachment and resulting penile reshortening may be prevented by filling the defect with either fat or other types of bio-compatible material (autologous vascularized fat or silicone spacers) [57]. In most studies the infrapubic incision is closed as an inverted VY-plasty [68]. Postoperative traction on the penis is recommended by most authors for several months to maintain the length gain, using penile weights, vacuum constriction devices or mechanical penile stretching systems [53, 57, 58, 68].

It should be pointed out, that the above mentioned techniques only allow an “optical” penile lengthening.
One technique of “true” penile lengthening consists of complete penile disassembly with interposition of a rip cartilage between the mobilized glans and corpora [69]. The authors performed the operation in 19 patients and reported an increase in erect and flaccid penile length of between 2 and 4 cm with a follow-up of 3 years.

The literature reports an extremely wide spectrum of success and patient satisfaction rates with penile augmentation procedures [53,57,58]. For example, Panfilow reported a mean lengthening in the flaccid state of 2.4 cm after 12 months with a satisfaction rate of 97% in 88 patients [70]. However, Li et al reported a mean increase in stretched penile length of 1.3 cm with an overall satisfaction rate of only 35% in a series of 42 patients with 16 months follow-up [68]. Long term satisfaction data are scarcely found in the literature and complications of penile lengthening procedures may be significant. Penile reshortening seems to be the major complication as well as loss of sensation, angling of the penis downward due to lack of support and hypertrophic hairbearing scarring of the penile shaft. [53,57, 71,72].

The use of penile stretching systems without previous operative penile lengthening may be an alternative in future studies. A pilot-phase II prospective study published by Gontero et al showed a mean penile flaccid length increase of 2.3 cm and erect length increase of 1.7 after 6 months of daily use of the device [73]. A previous pilot study by Levine et al. in patients with Peyronie’s disease had shown similar effects with length gain of up to 2.5 cm and curvature correction [74].

b) Penile girth enhancement techniques

Penile girth enhancement techniques are also controversial. Metallic mercury or Vaseline injections as well as allograft surgical implantation have been described with deleterious effects and complications [75-77]. Hylaroronic acid gel injections have been described for glans augmentation in a single study [78]. The injection of autologous fat was initially thought to be a promising technique but is now considered unpredictable due to irregularity and nodule formation from fat reabsorption [57]. The use of dermal fat grafts consisting of all layers of skin and the underlying subcutaneous tissue after removal of the epidermis seemed to offer more reliable results, but was accompanied by significant complications of persistent postoperative penile oedema and induration, venous congestion and possible skin injury [57, 71,72, 87]. Penile curvature due to fibrosis and penile shortening can also occur if inadequate graft take or infection occurs. Nevertheless a recent peer-reviewed paper reported a good subjective and objective outcome of the procedure in well selected patients [79].

Perovic reported the use of biodegradable scaffolds seeded with autologous fibroblasts for penile girth enhancement in 84 patients, followed-up for a median of 24 months [80]. A mean increase in flaccid girth of 3.15 cm and in erect girth of 2.47 cm was reported with 81% of patients satisfied with the result. Postoperative complications of skin necrosis or infection occurred in 10 of the 84 patients. With the recent advances in tissue-engineering, possible further applications for phallic reconstruction have been tested in animal models and might be expected to be translated into clinical use soon [81].

The technique of bilateral longitudinal incisions of the tunica albuginea with saphenous grafting to enhance girth was reported in 39 patients [83]. Penile diameter increases of 1.2 – 2.1 cm was observed without complications and complete satisfaction at 9 months follow-up. Similar results have been reported using synthetic grafts [84].

The injection of liquid silicone into the penile shaft is a highly controversial issue. Whereas FDA-approved trials of liquid injectable silicone (LIS) for soft tissue augmentation are currently being conducted in the USA, the use of any liquid silicone substance outside of a protocol should be discouraged [46]. Only the microdroplet-technique in which very small
volumes of LIS (up to 0.75 ml) is injected for soft tissue augmentation. In order to reach satisfactory results in penile girth enhancement 30 to 60 ml of LIS injection are needed with the possibility of disastrous complications [82, Figure 10].

CONCLUSIONS

From the literature it is not possible to draw evidence-based conclusions on a possible future role of penile enlargement procedures [46, 57, 58]. Most men consulting for penile augmentation have a normal sized penis and thus a surgical solution is being used to address a psychological condition [48, 55]. A well conducted recent study showed that the vast majority of patients with a normal sized penis chose not to undergo penile augmentation surgery after participating in a structured management and counseling protocol developed for this purpose [85]. Psychological assessment using validated questionnaires should always precede any surgical procedure in this group of patients [48, 86].

The current surgical techniques of penile lengthening and girth enhancement do not have proven efficacy when evaluated by objective and subjective outcome, and the complications can be significant [57]. Until reliable data is available, penile augmentation should be offered only to patients with congenital or acquired anomalies when reconstruction of the penis is required for sexual function [57]. The possible use of non surgical alternatives such as stretching devices should be assessed in future studies using validated instruments for subjective and objective evaluation.

RECOMMENDATIONS

1. Definition of Gender Identity Disorder/Transsexualism Grade A

The desire for at least 2 years, to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone therapy.

2. Male to Female Genital Surgery Grade B

Bilateral orchiectomy, amputation of the corpora cavernosa, creation of a neovaginal cavity that is lined by hairless skin, the formation of a sensate neoclitoris and an esthesic vulval appearance are the aims of genital surgery. The outcome may be achieved in one or two stages with satisfaction rates of 80% expected.

3. Female to Male Genital Surgery Grade B

Breast reduction, oophorectomy, hysterectomy and vaginectomy should be offered to all patients. There are many phalloplasty techniques involving local or free flaps and microsurgery. Patients should be warned that multiple stages are often needed with high urethral and prosthetic complication rates. However, a universal satisfaction rate of 80% should be expected. Metoidioplasty can be offered to those who wish to stand to void but do not want sexual intercourse.

4. Recommendations For Penile Augmentation

– Indications Grade D

A stretched penile length of < 7cm should be considered as a micropenis with many surgical techniques being recommended. The indications for augmentation in men with a normal sized penis cannot be drawn from the literature.

– Surgical Techniques Grade D

Figure 9. Before and after forearm flap phalloplasty for extrophy penis.

Figure 10. A 26 year old patient two years after liquid silicone injection into the penile shaft: massive granuloma formation.

Figure 10.
● There are many lengthening techniques described with variable success rates
● The complications may be significant
● Stretching devices may be an alternative treatment option
● All operative methods of girth enhancement have no proven efficacy outcome data
● Liquid silicone injection should be discouraged
● Psychological assessment should proceed any surgical approach

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Committee 17

Disorders of Organism and Ejacuation in Men

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Disorders of Organism and Ejaculation in Men

Chris G McMahon, David Rowland
Carmita Abdo, Juza Chen, Emmanuele Jannini
Marcel D Waldinger

I. INTRODUCTION

Ejaculatory dysfunction is one of the most common male sexual disorders. The spectrum of ejaculatory dysfunction extends from premature ejaculation, through delayed ejaculation to a complete inability to ejaculate (known as anejaculation), and includes retrograde ejaculation.

The sexual response cycle can usefully be conceptualized as having four interactive stages: desire, arousal, orgasm, and resolution. Within the sexual response cycle, orgasm/ejaculation in men is both a biological (reproductive) and psychological (reward) endpoint. Arousability and arousal—distinct but interrelated constructs—are precursors to this endpoint. Arousability and/or sexual libido are psychological constructs used to explain variability in the intensity and/or desire for a sexual response. Arousability might best be conceptualized as the organism’s readiness to respond. This state of readiness depends on both internal (hormonally “primed” diencephalic brain structures) and external (appropriate partner and situation) stimulus conditions. Sexual arousal or excitement—the organism’s actual response to the stimulus conditions—represents both a subjective/cerebral state of sympathetic activation and peripheral physiological responses (e.g., erection) that prepare the man for sexual activity. During sexual activity, increasing levels of sexual arousal reach a threshold that triggers the ejaculatory response, which then typically terminates the sexual episode for the male. The subjective (brain) perception of urethral distension and bladder neck closure of the emission phase of ejaculation is associated with the sensation experienced as “ejaculatory inevitability.” The perception of the striated muscle contractions and resulting semen expelled during ejaculation, mediated through sensory neurons in the pelvic region, gives rise to the experience of orgasm, a distinct cortical event, experienced phenomenologically both cognitively and emotionally.

Sexual dysfunction may involve disruption of any of the above phases [1]. This four-stage model is consistent with the overall paradigm shift within urology, where both organic and psychogenic factors are recognized and integrated into our understanding of sexual function and dysfunction. Conceptualizing four stages provides a better heuristic platform for understanding ejaculatory dysfunctions as secondary to disruptions of any stage in the ejaculatory process, leading to appropriate and specific treatments [2].

Specific to ejaculation and orgasm, the latency to ejaculation, that is, the time (and more importantly, the amount of stimulation) extending from the onset of penile stimulation to the moment of ejaculation, represents a continuum of time that shows variation across men and, within men, across situations. Although the great majority of men appear to reach ejaculation and orgasm following several minutes of penile vaginal stimulation and are, along with their partners, quite satisfied with the latency of their ejaculatory response, others report dissatisfaction. For example, some men ejaculate very rapidly after, or sometimes even prior to, penetration and do so with minimal stimulation. Others may ejaculate only with great difficulty or not at all, even following prolonged stimulation. These conditions, as noted above, represent subsets—at opposite ends of the spectrum—that fall into the categories of male ejaculatory disorders.
II. THE ANATOMY AND PHYSIOLOGY OF THE EJACULATORY RESPONSE

The anatomy and physiology of ejaculation is still not clearly understood. The ejaculatory reflex comprises sensory receptors and areas, afferent pathways, cerebral sensory areas, cerebral motor centres, spinal motor centres and efferent pathways. Neurochemically, this reflex involves a complex interplay between central serotonergic and dopaminergic neurons, with secondary involvement of cholinergic, adrenergic, oxytocinergic and gamma aminobutyric acid (GABA)ergic neurons.

The ejaculatory process integrates actions that occur in the central (CNS) and peripheral nervous systems (PNS). Structures in the CNS that are involved in ejaculation include the medial preoptic area (MPOA), nucleus paragigantocellularis (nPGi), posteromedial bed nucleus of the stria terminalis, posterodorsal medial amygdale, and the medial parvicellular subparafascicular nucleus of the thalamus. While the MPOA is involved in stimulation of ejaculatory response, the nPGi has an inhibitory influence: specifically, descending serotonergic pathways from the nPGi to the lumbosacral motor nuclei inhibit ejaculation. The MPOA can inhibit the nPGi which in turn results in ejaculation [3]. Several brain areas are activated after ejaculation by ascending fibers from the spinal cord and may have a possible role in satiety and the post-ejaculatory refractory time [4].

Based upon functional, central and peripheral mediation, the ejaculatory process is typically subdivided into three phases: emission, ejection (or penile expulsion), and orgasm. (Table 1) Emission consists of contractions of seminal vesicles (SV) and the prostate, with expulsion of sperm and seminal fluid into the posterior urethra, and is mediated by sympathetic nerves (T10 to L2). Ejection is mediated by somatic nerves (S2 to S4), and involves pulsatile contractions of the bulbocavernousus and pelvic floor muscles together with relaxation of the external urinary sphincter. Ejection also involves a sympathetic spinal cord reflex upon which there is limited voluntary control. The bladder neck closes to prevent retrograde flow; the bulbocavernous, bulbospongiosus and other pelvic floor muscles contract rhythmically, and the external urinary sphincter relaxes. Intermittent contraction of the urethral sphincter prevents retrograde flow into the proximal urethra [5].

Orgasm is the result of cerebral processing of pudendal nerve sensory stimuli resulting from increased pressure in the posterior urethra, sensory stimuli arising from the verumontanum and contraction of the urethral bulb and accessory sexual organs.

1. THE EJACULATE

The ejaculate can be divided into several fractions by serial biochemical analysis [6]. It comprises secretions from the seminal vesicles, and prostate and bulb-urethral (Cowper’s) glands, as well as spermatozoa. It is produced when the combined secretions of the prostate and the contents of the ampullary parts of the vasa deferentia are washed out by fluid from the seminal vesicles and expelled from the urethra [7]. The spermatozoa are stored in the tails of the epididymides and the vas deferens ampullae. Approximately 50-80% of the entire ejaculatory volume is contributed by the seminal vesicles, 15-30% by the prostate gland, and a small portion from the bulbo urethral (Cowper’s) glands which are rich in enzymes and plasminogen activator [8]. Spermatozoa normally constitute less than 0.1% of the ejaculatory volume. The first fraction of the ejaculate contains the maximum number of spermatozoa, and subsequent fractions contain sequentially less. Acid phosphatase, citric acid and zinc that emanate from the prostate are also in highest concentration in the initial fractions of the ejaculate.

Table 1: The three stages of normal antegrade ejaculation

| Emission | Sympathetic spinal cord reflex (T10–L2)  
Genital and/or cerebral erotic stimuli with considerable voluntary control  
Peristaltic contraction of epididymis and vas deferens  
Contraction of seminal vesicles and prostate  
Expulsion of spermatozoa/seminal/prostatic fluid into posterior urethra  
Ejaculatory inevitability sensation resulting from distension of posterior urethra |
|---|---|
| Ejection | Parasympathetic spinal cord reflex (S2–S4)  
Limited voluntary control  
Rhythmic contractions of bulbocavernous/pelvic floor muscles  
Bladder neck closure  
Relaxation of external urinary sphincter |
| Orgasm | Build-up and release of pressure in posterior urethra  
Smooth muscle contraction of accessory sexual organs and urethral bulb  
Sensation due to cerebral processing of pudendal nerve sensory stimuli |
Subsequent fractions contain fructose from the seminal vesicles, which increases in concentration towards the end of the ejaculatory process. The pH of the ejaculate increases in successive fractions as the acid component provided by the prostate is serially mixed with the more alkaline contribution of the fructose rich fluid from the seminal vesicles.

2. NEUROLOGICAL CONTROL OF EJACULATION AND ORGASM

The ejaculatory reflex, including its sensory and motor pathways, and spinal and cerebral areas, is shown in Figure 1 and 2 (Figure 1,2) [9, 10].

a) Sensory receptors and areas

The mucosa of the glans penis contains specialized sensory receptors, the Krause Finger corpuscles. These receptors discharge along afferent nerves to the spinal cord and brain when repetitive and cumulative stimulation applied to the glans penis exceeds the excitation threshold. Sensory information from the penile shaft, perineum, testes and variable extra genital erotogenic organs (e.g. nipples, anal sphincter) modulates—usually enhancing—afferent information from the Krause Finger corpuscles.

b) Afferent pathways

Sensory information from the glans penis travels along afferent pathways to the spinal cord. Sensory fibers of the pudendal nerve that are contained within the dorsal nerve of the penis extend to the S4 level, and autonomic fibers within the hypogastric plexus transmit information to the sympathetic ganglia located along the spinal cord.

c) Cerebral control of ejaculation and orgasm

Seminal emission and ejaculation are controlled centrally by the paraventricular nucleus of the anterior hypothalamus (PVN) and the MPOA (Figure 1) [11].

The MPOA is located rostral to the anterior hypothalamus and appears to have a pivotal role in augmenting copulatory behavior. Electrical stimulation of the MPOA can elicit seminal emission or ejaculation in monkeys and rats [12]. Electrical stimulation of the MPOA also elicits the urethrogenital reflex in rats, which may mimic orgasm in humans [10, 13]. This response occurs in the absence of genital stimulation and is usually elicited in anesthetized, spinal-transected rats by distending the urethra with saline and then suddenly releasing the pressure. This release results in rhythmic firing of the hypogastric, pelvic, and motor pudendal nerves and rhythmic contractions of the perineal muscles, similar to those seen during orgasm in humans.

Microinjection of moderate doses of a mixed D1/D2 dopamine agonist (apomorphine), or of a pure D1 agonist (thienopyridene), into the MPOA promotes erections and copulation of male rats, apparently by increasing parasympathetic tone [14, 15]. Higher doses of a mixed D1/D2 agonist, or of a selective D2 agonist, favor seminal emission and ejaculation [13]. Reduced libido during the ejaculatory refractory period may result from decreased dopamine release in the nucleus accumbens, a major terminal of the mesolimbic dopamine tract [16]. Dopamine is released in the MPOA of male rats in the presence of an estrous female and increases during copulation [17]. The levels of extracellular dopamine in the MPOA may regulate the phases of copulation, with high levels triggering ejaculation.

Figure 1: Emission and ejaculation are centrally integrated and highly co-ordinated processes. The brain structures involved in the control of ejaculation include the thalamus, structures in the hypothalamus such as the medial preoptic area (MPOA) and the paraventricular thalamic nucleus (PVN), structures in the midbrain such as the periaqueductal grey nucleus (PAG) and structures in the pons such as the paragigantocellular nucleus (nPGi). These structures integrate sensory ejaculation-related inputs from the genital areas with higher excitatory and inhibitory controls.
In a series of sophisticated rat experiments involving selective pharmacologic and/or radiofrequency lesions, Liu et al demonstrated that the parvocellular neurons of the hypothalamic PVN mediate erectile function in rats, whereas the magnocellular PVN neurons mediate ejaculation [18]. Oxytocinergic PVN neurons possibly modulate the male sexual response, as evidenced by increased cerebrospinal fluid concentrations of oxytocin after ejaculation, augmented male sexual behavior following intraventricular administration of oxytocin, and decreased seminal emission in rats with lesions of the parvocellular PVN neurons. The MPOA is also important to the cholinergic influence on sexual behavior. Injections of the cholinergic agonists oxotremorine and carbachol stimulate sexual behavior in male rats as demonstrated by a reduced number of intromissions preceding ejaculation, whereas injection of scopolamine reduces the number of animals intromitting and ejaculating [19]. The paragigantocellular (nPGi) reticular nucleus in the ventral medulla is a supraspinal locus of descending inhibitory influence on spinal nuclei mediating ejaculatory reflexes in the male rat [20], and approximately 78% of the descending neurons from nPGi are serotonergic [21]. Lesions of the nPGi facilitate both the elicitation of the urethrogenital reflex and reflexive penile erections [22]. Selective serotonin neurotoxin lesions of the nPGi or transection of the spinal cord release the urethrogenital reflex from tonic inhibition, allowing the reflex to be elicited by urethral distension. However, stimulation of the MPOA can elicit the reflex, even if the nPGi and spinal cord are intact, suggesting that the MPOA may inhibit the nPGi as well as stimulate an excitatory site.

d) Spinal motor centers

It has been known for many years that men with complete transaction of the thoracic spinal cord are often able to ejaculate with appropriate peripheral stimulation. Therefore, the fact that ejaculation can occur in the absence of neuronal input from the brain indicates an independently functional reflex arc of the spinal cord, which mediates the ejaculatory reflex and is located distal to the thoracic spine. A spinal center, located at the Th12 L1-L2 spinal level, is controlled by the sympathetic nervous system and is responsible for emission (Figure 2,3). A second center, located at the S2-S4 level, is controlled by the somatic nervous system and is responsible for expulsion. The position of the lumbar spine between the brain and peripheral nerves allows this area to be the center for the integration of afferent and efferent neuronal information. Since the lumbar and sacral portions of the spinal cord are known to be critical in the regulation of other pelvic organ processes, it is possible that this area also regulates ejaculation [23]. The existence of a lumbar spinal ejaculation pattern generator (EPG) was proposed in 1991 [24]. Further investigation by retrograde axonal tracing studies confirmed that neuronal fibers from the lumbar spinal cord innervate the bulbospongious muscle and the prostate [25], and that the relevant neuronal cell bodies are located in the L3-L4 segment of the spine [26]. It has also been demonstrated that these specific lumbar neurons are activated with ejaculation but not with other components of sexual response in rats [27]. This finding was supported by the earlier study’s results demonstrating that injury to the lumbar spine at this segment level in rats specifically interrupts ejaculation [28].

The lumbar spinothalamic neurons (LSt) have axonal connections to the thalamus [29]. They have efferent projections to pudendal somatic motor neurons as well as to sympathetic and parasympathetic preganglionic neurons [28], and are adjacent to neurons modulating afferent sensory input from the penis via the pudendal nerve. Recently published results may indicate the precise localization of a lumbar spinal center critical to both the initiation and maintenance of ejaculation [25, 30]. Specifically, stimulation of the LSt neurons leads to ejaculation of semen in anesthetized rats and to ejaculation of motile spermatozoa in rats. Also found were marked increases in vas deferens (VD) and spermatic vesicle (SV) pressure, constantly followed by increased electrical activity of the bulbospongious muscle in all animals treated with stimulation of the LSt neurons. These effects were maintained despite T10 spinal transaction, injury to the hypogastric and pelvic nerves, and transaction of the dorsal penile nerves. In contrast, direct injection of a GABA agonist into the LSt neurons prior to electrical stimulation prevented the increase in VD and SV pressure and electrical activity of the bulbospongious muscle. Application of the same GABA agonist immediately after LSt stimulation blunted bulbospongious electrical activity. Such results provide strong evidence that LSt neurons with cell bodies located in the L4 spinal segment represent an essential anatomical component in the regulation of ejaculation [23].

e) Efferent pathways

The efferent pathways mediate the ejaculatory motor responses of emission and ejection (expulsion).

1) EMISSION

Emission is controlled by the sympathetic nervous system. The cell bodies of the sympathetic neurons are located in the lateral columns of the gray matter in the thoracolumbar segments of the spinal cord. Efferent sympathetic nerves emerge from the ventral roots of the spinal column at Th12-L2 to reach the sympathetic chains bilaterally (Figure 2). The nerves proceed via the thoracic sympathetic chain to the caudal (inferior) enteric plexus, the major/minor splanchnic nerves, the celiac/cranial mesenteric plexuses, and the intermesenteric nerves. Descending nerves from these ganglia
Figure 2. Central control of ejaculation is mediated via spinal ejaculation centres including lumbar spinothalamic (LSt) cells which integrate peripheral signals from the genital areas with excitatory and inhibitory control from supraspinal centres such as the nucleus paragigantocellularis (nPGi). The spinal ejaculation generators send co-ordinated outputs to the anatomic structures that allow ejaculation to occur.

Figure 3. The spinal ejaculation generator (LSt cells) controls the prostate and the bulbospongiosus (BS) muscle. The spinal ejaculation generator projects to the parasympathetic (L5–S1) and sympathetic (T13–L2) preganglionic neurons, and DM motoneurons (L5–L6). The parasympathetic centres project to the prostate via the major pelvic ganglion (MPG) and the pelvic nerve (PN). The sympathetic centres project to the prostate through the intermesenteric ganglion (IMG) and the hypogastric nerve (HN). The motoneurons of the BS muscle project to the muscle through the motor branch of the pudendal nerve. (BS: bulbospongiosus; DM: dorsomedial nucleus; HN: hypogastric nerve; IMG: intermesenteric ganglion; L: lumbar segment of spinal cord; LSt: lumbar spinothalamic; MPG: major pelvic ganglion; PN: pelvic nerve; T: thoracic segment of spinal cord; VH: ventral horn)
encircle the aorta on each side before joining in
the midline to form the hypogastric plexus just
below the bifurcation of the aorta. The nerves
proceed via the lumbar sympathetic chain and the
lumbar splanchnic nerves to the caudal mesenteric
plexus. The intermesenteric nerves and all lumbar
splanchnic nerves merge into the inferior mesenteric
and superior hypogastric plexuses. The caudal
mesenteric plexus mainly innervates the colon via
the colonic nerve from which paired hypogastric
nerves arise. The junction of the hypogastric nerve
and the pelvic nerve constitutes the pelvic plexus in
the pelvis, which is an integration of sympathetic and
parasympathetic nervous systems. The branches
from this plexus innervate the epididymis, vas
deferens, seminal vesicle, prostate, bladder neck
and urethra (Figure 2) [31].

Norepinephrine is released from the axon terminal
of the postganglionic neurons of the seminal tract
in response to sympathetic signals passing through
the hypogastric nerves. Norepinephrine activates
smooth muscle alpha, adrenergic receptors,
causing a rise in intracellular calcium, actin myosin
interaction, vas deferens smooth muscle contraction,
a marked elevation of intraluminal pressure in the
caudal epididymis/proximal vas, and propulsion of
spermatozoa out to the ampulla. This ampullary wall
distension and nerve signals trigger contraction of
the ampulla to emit the content into the posterior
urethra. Many substances, including acetylcholine
and neuropeptide Y, might modulate neurotransmitter
release and/or the resting tone of the smooth muscle
of the vas deferens. Both nerve signal and distention
of the wall of the ampulla might trigger contraction
of the ampulla to emit the content into the posterior
urethra. Retrograde axonal tracing methods have
demonstrated that the majority of post-ganglionic
neurons distributed in the vas deferens originate from
the pelvic plexus [32]. The pelvic plexus receives
neural input from both the hypogastric and pelvic
nerves. Electrical stimulation of the hypogastric
the pelvic plexus elicits contraction of the vas deferens, while
stimulation of the pelvic nerve causes no detectable
motor responses [33]. Histochemical studies of the
vas deferens have also shown that the adrenergic
fibers mainly innervate the smooth muscle layers,
whereas cholineric fibers chiefly innervate the
subepithelial layer [34].

Almost all the lumbar splanchnic nerves originate
from L2 and/or L3 lumbar sympathetic ganglia (cor-
responding to L1-2 spinal levels) [34]. Preservation
of the L2 and/or L3 lumbar splanchnic nerve in retro-
peritoneal lymph node dissection of testicular cancer
allows preservation of ejaculatory function [35]. Par-
tial interruption of the pathway from the spinal cord
to the seminal tract would be expected to cause ins-
sufficient closure of the bladder neck and retrograde
ejaculation. Complete interruption of the pathway is
likely to cause failure of emission.

The anatomical architecture of the peripheral sym-
pathetic nervous system suggests probable cross-
innervation and has been confirmed in the dog and
rat [36]. Some signals in the lumbar splanchnic nerve
cross to the other side of the body at the level of the
caudal mesenteric plexus and/or the pelvic plexus.
Preganglionic axons in the hypogastric nerve prob-
ably provide a bilateral innervation to postganglionic
neurons in the pelvic plexuses, which also exhibit
crossing to the bilateral vasa deferentia [36].

The pudendal nerve arises from the S2-4 segments
of the sacral spinal cord and does not enter the pel-
vic plexus, but exits the pelvis through the greater
sciatic foramen, re-enters it through the lesser sci-
atic foramen, and innervates the perineal striated
muscles (Figure 2). Rhythmic contractions of these
perineal striated musculatures, including the bulboc-
cavernosus and ischiocavernosus muscles, propel
the seminal fluid. Sacral spinal cord injury patients
usually show dribbling ejaculation due to the lack of
contribution of the musculature.

2) EJECTION/EXPULSION

Ejection is controlled by the parasympathetic nervous
system. Efferent somatic fibers emerge from the an-
terior horn of the S2-S4 spinal segments (Onuf's nu-
cleus) and travel in the motor branch of the pudendal
to innervate the striated muscles of the pelvic
floor, including the bulbospongiosus and bulbocaver-
nosus muscles. Rhythmic contractions of the bulboc-
cavernosus, ischiocavernosus, and other pelvic floor
striated muscles propel seminal fluid into the ure-
thra. These muscles are innervated by the pudendal
nerve and show excitement during ejaculation. Shaik
measured the electromyographic (EMG) response of
the bulbocavernosus, ischiocavernosus muscles and
the external urethral sphincter during ejaculation
induced by glans penis vibration and demonstrated
that the ejaculatory mechanism consists of two dis-

tinct reflexes [37]. One is the glans vasal reflex which
is responsible for the emission phase, and the other
is the urethromuscular reflex which is responsible for
the ejection phases of ejaculation. In another study
in dogs, Shaik reported increased electrical activ-
ity of the pelvic floor muscles and the external anal
sphincter (EAS) and the urethral sphincter (EUS)
during electroejaculation [38]. He suggested that
the increased puborectalis muscle activity might
express the prostatic secretions into the posterior
urethra, that the levator ani contraction elevates the
prostate and partially straightens the prostatic mem-
branous urethral kink that might occur during erec-
tion, and that the EAS and EUS contractions are
believed to abort the urge to defecate or urinate and
prevent leak of feces, flatus, or urine during coitus.
The rhythmic EUS contraction at ejaculation might act
as a “suction ejection pump,” drawing the geni-
tal fluid into the posterior urethra while relaxed and
jecting it into the bulbous urethra upon contraction.
3. NEUROCHEMICAL CONTROL OF EJACULATION

Many neurotransmitters are involved in the control of ejaculation, including dopamine, norepinephrine, serotonin, acetylcholine, oxytocin, GABA and nitric oxide (NO) [4]. Of the many studies conducted to investigate the role of the brain in the development and mediation of sexuality, dopamine and serotonin have emerged as essential neurochemical factors.

a) Dopaminergic control

It has long been known that treatment with dopaminergic drugs has a significant effect on the sexual behavior of rodents. Kimura et al attributed the dopaminergic system, particularly that in the anterior hypothalamus, with a sexual facilitatory role [39]. Five types of dopaminergic receptors have been identified. On a pharmacological basis, these subtypes have been divided into two families, D1 and D2. A possible sexual response regulatory role of dopamine is suggested by the observation that dopamine is released in the MPOA of male rats in the presence of an estrous female, and progressively increases during copulation, eventually triggering ejaculation [16].

b) Serotonergic control

Whereas dopamine promotes seminal emission/ejaculation via D2 receptors, serotonin is inhibitory.

The development of antibodies against 5-HT and autoradiographic techniques have enabled identification of detailed 5-HT receptor locations [40]. Currently, at least 16 different receptors have been characterized, e.g., 5 HT1a, 5 HT1b, 5 HT2a, 5 HT2b, etc. [41]. Although the function and localization of many of these receptors are becoming increasingly clear, much remains unknown.

Serotonergic neurons are widely distributed in the brain and spinal cord and are predominantly found in the brainstem, raphe nuclei, and the reticular formation.

Serotonergic neurons use a variety of different mechanisms to self-regulate their own activity. Synaptic cleft 5 HT and 5-HT neurotransmission are regulated by somatodendritic 5 HT1A autoreceptors, presynaptic 5 HT1B 1D autoreceptors, and a 5 HT transporters re-uptake system (Figure 4). Large numbers of 5 HT transporters (5-HTT) are located predominantly on axonal terminals but are also found on the serotonergic cell bodies and their dendrites and glial cells. As 5-HT is released into the synaptic cleft from presynaptic axonal vesicles, 5 HT transporters re-uptake and remove 5 HT from the synaptic cleft, preventing overstimulation of the postsynaptic receptors. After blockage of 5 HT transporters by selective serotonin reuptake inhibitor class drugs (SSRIs), synaptic cleft

Figure 4. Synaptic cleft 5-HT and 5-HT neurotransmission are regulated by somatodendritic 5-HT1a autoreceptors, presynaptic 5-HT1B 1D autoreceptors and a 5-HT transporters re-uptake system.
5-HT increases but is counteracted by activation of 5-HT1A autoreceptors which inhibit further 5-HT release. Activation of 5-HT1A receptors is attenuated or blocked by activation of 5-HT2C receptors. It has been shown that 5-HT2C and 5-HT1A receptors play important roles in the speed and ease of ejaculation. Stimulation of the 5-HT2C receptor with 5-HT2C agonists results in delay of ejaculation in male rats, whereas stimulation of post-synaptic 5-HT1A receptors results in shortening of ejaculation latency [42]. Waldinger et al suggested the hypothesis that men with premature ejaculation (PE) may have hyposensitivity of 5-HT2C and/or hypersensitivity of the 5-HT1A receptor [3, 43].

4. SIDE EFFECTS OF SPECIFIC DRUGS ON EJACULATION

a) Evidence based primarily on animal studies

Dopamine. The centrally acting neurotransmitter dopamine is known for its involvement in control of male rat sexual behavior. Taking the parameters of mount and intromission frequencies and latency to ejaculation as measures of copulatory activity, most reports indicate that dopamine has a stimulatory effect on ejaculation that is exerted via D2 receptors. Enhancement of the ejaculatory behavior and the decrease in intromission frequency stimulated some authors to call this altered behaviour a rat model for “early ejaculation”. Some dopamine (DA) receptor agonists, such as apomorphine, N-n-propyl-norapomorphine, lisuride and 3-(3-hydroxyphenyl)-N-n-propyl-piperidine (3-PPP) may cause ejaculation in male rats with receptive females sooner and after fewer penile intromissions than controls. The doses of DA agonists needed to produce “early ejaculation” in male rats are within the low dose range needed to stimulate DA autoreceptors. In this manner, it is suggested that this phenomenon in rats results from inhibition of DA neurotransmission [44].

Morphine. Several studies have shown that systemic and central administration of morphine inhibits male rat sexual behavior. It is suggested that the inhibitory effects of morphine may be mediated by the kappa receptor [45]. However, in one study, a small proportion of male rats reacted differently on a low dose of systemic morphine: there was a decrease of ejaculation latency, and in the number of intromissions prior to ejaculation [45]. In another recent study, morphine had marginal effects on sexual motivation in general, but reduced ambulatory activity in male rats. In this study, neither dopamine nor opioids seemed to be important for sexual incentive motivation [46]. These conflicting results indicate that enkephalines may have only a modulating role on sexual behavior in the rat.

Ecstasy. The amphetamine analog MDMA, better known as the recreational drug ecstasy, is known and feared for its neurotoxic properties. It reduces brain concentrations of serotonin by inhibition of the metabolism and by long lasting degeneration of 5-HT nerve terminals, as well as by decreasing the number of 5-HT uptake sites. In an experiment with male rats, Dornan and collaborators found that a chronic administration of MDMA caused fewer rats to display mounting behavior, and an increase in ejaculation latency in the responders [47]. These results are conflicting with the above described studies with serotonin receptor agonists and antagonists, because a decrease in central 5-HT would cause an increase in male rats’ sexual behaviors. Probably, since MDMA has such dramatic effects in the brain, other factors may have played an important role in this experiment.

GABA. The neurotransmitter gamma aminobutric acid (GABA) occurs in the brain tissue. Two distinct types of GABA receptors are recognized: GABAa and GABAb. There is some evidence that the GABAb receptor agonists (like baclofen) inhibit sexual behavior in male rats, independently from the effects on motor systems. But in other study, baclofen was ineffective in reduce sexual behavior in male rats while muscimol (a GABAa receptor agonist) when given into the paraventricular nucleus of the hypothalamus reduce dose-dependently male rats sexual behavior [48].

Yohimbine. The alpha2 adrenoceptor blocking agent yohimbine has been known for its aphrodisiac properties in rats and humans. In male rat studies, it increased mounting behavior without the need for physiological levels of serum testosterone. When looking at the effects on ejaculation, a decrease in ejaculation latency, intercopulatory interval, and post ejaculatory interval is found. Others alpha2- adrenoceptor antagonists, such Rauwolscine and Idazoxan also have stimulatory effects on ejaculatory function in animal models [49].

b) Specific drug effects in human studies

Monoamine oxidase inhibitors. The monoamine oxidase inhibitors (MAOIs) are mainly used in the treatment of neurotic or atypical depression. These drugs increase the levels of epinephrine, norepinephrine, dopamine, and serotonin. The MAOIs have been known for their sexual side effects, with an incidence up to 20-40%. Delayed or inhibited ejaculation is reported for isocarbazid, phenelzine and tranylcypromine.

Cyproheptadine. Cyproheptadine is an antihistaminic, formerly used in Cushing’s disease and anorexia nervosa. It also increases serotonin levels in the brain. Several reports indicate that cyproheptadine is able to convert drug induced orgasmic failure in both men and women.

Benzodiazepines. A number of benzodiazepines effective in treating generalized anxiety and panic attacks are also known to inhibit ejaculation in some
men, presumably by enhancing gamma-aminobutyric acid (GABA). These drugs include diazepam, lorazepam, flunitrazepam, flurazepam, nitrazepam, chlordiazepoxide, and alprazolam. However the effect on ejaculation is not so intensive as that other psychotropics such SSRIs. Less than 10% of men experience an inhibition of ejaculation with these anxiolytic drugs [50].

Stimulants. Amphetamine is a stimulating drug with affinity for different receptors in the central nervous system. It stimulates release of dopamine, inhibits monoamine oxidase and blocks the reuptake of both catecholamines and serotonin. In male rats, methamphetamine inhibits intromittent and ejaculating behavior [51]. It is reported to delay ejaculation in subjects without ejaculatory dysfunction. Cocaine is an addictive “recreational” drug and stimulates the central nervous system through blocking of monoamine transporters. Different reports confirm that delayed ejaculation appears to be the most common sexual side effect.

Dopamine antagonists. Dopamine antagonists block central dopamine receptors and are clinically used as antipsychotics or neuroleptics. Ejaculation may be prevented by centrally acting dopamine receptor blockers such as pimozide, sulpiride and haloperidol [44, 52]. Thioridazine and chlorpromazine delay ejaculation but also block adrenergic receptors [53]. Atypical neuroleptics such as risperidone and clozapine, that block dopamine and serotonin receptors have been reported to delay ejaculation.

Alpha 1-blocking agents. Potent alpha-adrenergic blocker agents such as phenoxybenzamine hydrochloride, alphuzosine and terazosine suppress ejaculation by inhibition of the sympathetic nervous activation of the ejaculatory reflex [54-57].

Nitric Oxide Donors. NO-donors such as sodium nitroprusside, S-nitroso-glutathione, S-nitroso-N-acetylcysteine, S-nitroso-N acetylcysteine-ethylester and linsidomine have been demonstrated to reduce adrenergic tension in isolated human seminal vesicle strip preparations. A potential role for these agents in the treatment of early ejaculation exists [58].

Antidepressants. Selective Serotonin Reuptake Inhibitors class antidepressants (SSRI) increase synaptic cleft 5-HT levels delay ejaculation probably by action on 5-HT2 and 5-HT3 receptors. The antidepressants nefazodone (5-HT2 antagonist) and mirtazapine (5-HT2 and 5-HT3 antagonist) antagonize these receptors and produce no clinically significant ejaculatory delay [59]. Tricyclic class antidepressants inhibit ejaculation in a dose dependent manner due to their anticholinergic and alpha-adrenergic antagonistic properties [60].

The influences of different drugs on ejaculation are delineated in Table 2.

5. SUMMARY

In summary, despite the significant progress in understanding the anatomy and physiology of ejaculation, our knowledge of the anatomy and physiology of ejaculatory disorders, including premature, inhibited (or delayed), and painful ejaculation, remains incomplete. Many critical central, peripheral and other mechanisms yet require clarification, and further animal and human basic and clinical investigations are warranted.

III. PREMATURE EJACULATION: DEFINITION, EPIDEMIOLOGY, & PATHOPHYSIOLOGY

1. DEFINITION AND CLASSIFICATION

a) Traditional definitions

Both DSM-IV-R and ICD-10 provide definitions of premature ejaculation. Specifically, DSM-IV-R [61] defines premature ejaculation as “the persistent or recurrent ejaculation with minimal stimulus before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity. The disturbance causes marked distress or interpersonal difficulty. The early ejaculation is not due exclusively to the direct effects of a substance (e.g., withdrawal from opioids).”

ICD-10 [62] indicates “the general criteria for sexual dysfunction must be met. There is an inability to delay ejaculation sufficiently to enjoy lovemaking, manifest as either of the following. Occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 seconds of the beginning of intercourse); ejaculation occurs in the absence of sufficient erection to make intercourse possible. The problem is not the result of prolonged absence from sexual activity.”

These two sources provide similar though not identical conceptual frameworks for classifying an individual as having premature ejaculation. Included in both is reference to three general criteria: short ejaculatory latency, concomitant distress or a lack of sexual satisfaction, and a lack of self-efficacy regarding the condition. This last component is noted as “ejaculation before the person wishes” in DSM IV-R, and the “inability to delay ejaculation sufficiently to enjoy lovemaking...” in ICD-10.

b) Operationalizing the criteria

Each of the three criteria above has been operationalized, although not always with consistency [63]. The first criterion – short ejaculatory latency – is
Table 2. Effects of drugs on ejaculation

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
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<th>MECHANISM OF ACTION</th>
<th>EFFECT ON EJACULATION/ORGASM</th>
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<td>Opioids</td>
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<td>MECHANISM OF ACTION</td>
<td>EFFECT ON EJACULATION/ORGASM</td>
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typically operationalized by intravaginal ejaculatory latency time (IELT), defined by the number of seconds/minutes between vaginal intromission and ejaculation. ICD-10 indicates that latencies of 15 sec or less are consistent with a PE diagnosis but provided no evidence for this cut-off point. In both a stopwatch study and a self-reported IELT study in an unselected cohort of men with lifelong PE, 90% of men ejaculated within 60 seconds, and about 10% within 1 to 2 minutes after vaginal penetration [64, 65]. In two studies in unselected cohorts of men in the general male population of five countries (Netherlands, UK, Spain, Turkey and the USA), the IELT, measured with a stopwatch and a blinded timer device, showed skewed distributions, with median values of 5.4 min (range: 0.55 to 44.1 min) and 6.0 min respectively (range: 0.1 to 52.1 min) [66, 67]. Using values beneath 0.5 and 2.5 percentiles as statistical standards of abnormality, both studies showed that IELT values under 60 seconds were indeed abnormal in the cohort of the general male population.

In recent years, there has been a debate whether latencies should be exactly timed (e.g., using chronometers of some sort) or whether estimations by the man and/or his partner are sufficiently accurate to quantify this short ejaculation criterion. Currently, it seems that the use of a stopwatch is the most objective and accurate instrument to measure the ejaculation time. Interestingly, the use of a blinded timer device in male volunteers of the general population provided a similar IELT distribution as in men of the same countries who used a stopwatch [67]. However, this study also showed that in these men self-perceived IELT highly differed from stopwatch measured IELT [67]. This result contrasts with the outcome of two studies in men with lifelong PE that showed that the majority of men were quite accurate in estimating their ejaculatory latencies [64, 65]. Therefore, it may be concluded that the stopwatch method is in general an accurate way to measure the IELT, may offer greater precision and less bias, and might best be used in epidemiological studies of the IELT in the general male population. On the other hand, both stopwatch and self-perceived IELT measurement are adequate tools to measure IELT in cohorts of men with lifelong PE. However, self-perceived IELT assessment may lead to less accurate values in men with IELTs greater than 1 minute.

Mere temporal latency—that is, penile time spent intravaginally—does not capture a relevant defining characteristic of PE, namely “ejaculation with minimal stimulation” (DSM-IV-TR). As a result, the “number of penile thrusts” to ejaculation probably represents a more valid assessment of the amount of penile stimulation. However, IELT is generally considered the more reliable measure and is, within the larger population of men, correlated with the number of penile thrusts [68]. The second criterion—self-efficacy, or the patient’s ability to control the dysfunctional condition—distinguishes men who ejaculate rapidly because they are incapable of prolonging their latency from those who do so for any number of other reasons, including ones related to the situation or the partner. In recent research, self-ratings of “control over ejaculation” have been used successfully as a self-efficacy measure that differentiates PE men from sexually functional men [69-71]. Men with PE rate their ejaculatory control around 2 to 4 (1 = not at all; 7 = complete control), whereas functional men typically rate their control at 4 or higher. Since actual control over the ejaculatory reflex is itself something of a matter of debate, measures of self-efficacy more relevant to assessing successful treatment of PE may include such items as the “ability to delay ejaculation” or to “the ability to overcome early ejaculation”.

The third criterion—concern or distress about the condition—is usually satisfied by the fact that the man (often with his partner) approaches the clinic seeking help for the sexual problem. In situations where participants are recruited into an experimental or clinical investigation, several questions might be included in a screening questionnaire that directly addresses the issue of concern or distress. Most commonly these items query the man (and when possible his partner) about his general level of sexual satisfaction, with further elaboration about anxiety or concern surrounding the sexual problem and about the quality of the sexual relationship. Standardized measures of general anxiety (e.g., BSI [72]), sexual functioning (e.g., GRISS [73]) or dyadic distress (Dyadic Adjustment Scale [74]) might also be included to further assist in operationalizing this criterion.

c) ISSM definition of lifelong premature ejaculation

Based on the aforementioned considerations, the International Society for Sexual Medicine (ISSM) organized an international panel to convene in Amsterdam in 2007 to develop a consensus definition for premature ejaculation. The ISSM panel concluded that there were insufficient data for an evidence-based definition of acquired premature ejaculation. However, it succeeded in formulating an evidence-based definition of lifelong premature ejaculation [75]. According to this new definition, lifelong premature ejaculation is characterized by: an ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration; an inability to delay ejaculation on all or nearly all vaginal penetrations; and with negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy.

d) Classifications of premature ejaculation

In 1943, Schapiro proposed a distinction of premature ejaculation into Types A and B [76]. Men
with Type B have always suffered from a very rapid ejaculation (or short latency), whereas in Type A, the rapid ejaculation develops later in life and is often associated with erectile dysfunction. In 1989, these types were respectively referred to as lifelong (primary) and acquired (secondary) premature ejaculation.) [77]. Over the years, other attempts have been made to identify various classifications of PE, including several that have been incorporated into PE definitions (e.g., global vs. situational, the effect of a substance, etc.). In 2006, Waldinger [78, 79] proposed a classification of premature ejaculation according to a “syndromal” approach and suggested adding two new categories, “Natural Variable Premature Ejaculation” and “Premature-like Ejaculatory Dysfunction.”

(Table 3) In the category of Natural Variable Premature Ejaculation, men suffer only occasionally from rapid ejaculations or short latencies. This pattern might be regarded as part of the normal variability of ejaculatory performance in men rather than a symptom of an underlying psychopathy. In the category of Premature-like Ejaculatory Dysfunction, men subjectively experience and/or voice complaints of premature ejaculation, while having typical or even long ejaculatory latencies of 4-20 minutes. Thus, including the longstanding “lifelong” and “acquired” classifications, four premature ejaculation syndromes are defined [80].

1) **Lifelong Premature Ejaculation**

With lifelong PE, ejaculation occurs too early at nearly every intercourse, with (nearly) every woman, and from about the first sexual encounters onwards. Based on self-selected samples, the majority of these men (80-90%) ejaculate intravaginally within 30-60 seconds, and most of the remainder (10%) between 1-2 minutes. (Figure 5) The ejaculation remains rapid during life in the majority (70%) of these men or may be aggravated during the course of aging (30%). Some men ejaculate during foreplay, before penetration (ejaculatio ante portas), or as soon as their penis touches the vagina (ejaculatio intra portas). No accepted cure for lifelong PE is known, but various drugs (including SSRIs) and psychotherapy treatments may be effective in postponing the ejaculatory response [80].

2) **Acquired Premature Ejaculation**

Complaints of men with acquired PE differ in relation to the underlying somatic or psychological problem. In these men, premature ejaculation occurs at some point in a man’s life after experiencing normal ejaculatory latencies; the onset may be either sudden or gradual. The appearance of the PE may be due to (i) urological dysfunctions, for example, erectile dysfunction or prostatitis [81], although there is yet debate as to the role of prostatitis in acquired PE, (ii) thyroid dysfunction [82], and (iii) psychological or relationship problems [83, 84]. The acquired form of premature ejaculation may be cured by medical and/or psychological treatment of the underlying cause [80].

3) **Natural Variable Premature Ejaculation**

Men exhibiting this pattern only coincidentally and situationally experience short ejaculatory latencies. This type of response should not be regarded as a symptom or manifestation of underlying psychopathy but of normal variation in sexual performance. The syndrome is characterized by the following symptoms. (i) short ejaculatory latencies are inconsistent and occur irregularly, (ii) the ability to delay ejaculation, that is, to withhold ejaculation at the moment of imminent ejaculation, may be diminished or lacking, and (iii) the experience of diminished control of ejaculation is associated with either a short or normal ejaculation time, that is, an ejaculation of less or more than 1.5 minutes. Treatment of these men should consist of reassurance and education that this pattern of ejaculatory response is normal and does not need drug treatment or psychotherapy [80].

4) **Premature-like Ejaculatory Dysfunction**

Men under this classification experience or complain of premature ejaculation while the ejaculation time is in the normal range, i.e. around 2-6 minutes, and in some instances the ejaculatory latency may even
be of very long duration, i.e., between 5-25 minutes [80]. This response should not be regarded as a symptom of medical or (neuro)biological underlying pathology although psychological and/or relationship problems may underlie the complaint. The syndrome is characterized by the following symptoms: (i) subjective perception of consistent or inconsistent short ejaculatory latency during intercourse, (ii) preoccupation with an imagined early ejaculation or lack of control of ejaculation, and (iii) the intravaginal ejaculatory latency time (IELT) in the normal or even long range (i.e., an ejaculation that occurs between 3 and 25 minutes), and (iv) the ability to delay ejaculation may be diminished or lacking.

As the duration of the ejaculation latency in these men is normal, the experience of the response is not related to a medical or neuro-biological disturbance [80]. Rather, there is either a misperception of the actual ejaculation time, for various reasons, or the ejaculation latency is too short for the female partner to attain an orgasm. Complaints of these men may be alleviated by the various sorts of psychotherapy and treatment should not a priori assume the use of pharmaceuticals. However, evidence-based controlled trials are required to investigate the optimal treatment for couples affected by this pattern of responding.

2. THE PREVALENCE OF PREMATURE EJACULATION

Although various epidemiological studies have shown that about 20-30% of men have complaints of premature ejaculation [85], reliable information on the prevalence of lifelong PE and acquired PE in the general male population is lacking. As the prevalence of IELTs of less than 1 minute in unselected male cohorts in mainly Western countries is about 1-3%, the prevalence of lifelong PE may be rather low. With regard to the prevalence of acquired PE, data are essentially lacking, in part related to the lack of an evidence-based definition for this condition. Taking into account recent epidemiological data that about 25% of men are discontent with their ejaculation response time, the duration of which is rather equal to the normal ejaculation time in men [67], and accepting the recently proposed PE subtype of Premature-like Ejaculatory Dysfunction, it may be that discontent with ejaculatory response time may have greater prevalence than actual premature ejaculation, particularly when the latter is defined by a 1 min IELT.

3. ETIOLOGY OF PREMATURE EJACULATION

Historically, attempts to explain the etiology of premature ejaculation have included a diverse range of biogenic and psychological theories (Table 4). Most such proposed etiologies have not been strongly grounded in empirical evidence. Psychological theories include the effect of early experience and sexual conditioning, anxiety, sexual technique, the frequency of sexual activity, and psychodynamic/developmental explanations. Biogenic explanations include evolutionary theories, penile sensitivity, central neurotransmitter levels and receptor sensitivity, degree of arousability, the speed of the ejaculatory reflex, and the level of sex hormones. The lack of an operationalized definition for PE and the presence...
of methodological problems related to the use of inadequate definitions used are common problems in many of these studies. Finally, the determinants of PE are undoubtedly complex and multivariate, with the etiology of lifelong premature ejaculation likely different from that of acquired premature ejaculation.

a) Lifelong premature ejaculation

The determinants of lifelong premature ejaculation are currently unknown. However, genetic and epigenetic factors may play a role in its development, and several hypotheses are currently under investigation.

1) Genetic predisposition

A familial predisposition to premature ejaculation was first reported by Schapiro in 1943 [76] and since then, others have hypothesized that IELT varies according to a continuum in the general male population and that this variation is genetically determined [86]. In support of this, a small study reported that 10 of 14 first-degree male relatives of men with lifelong PE also suffered from PE with an IELT of less than 1 minute [87], generating odds ratio of a familial occurrence of PE that far exceeded the incidence within the general community. Thus, Schapiro's initial contention that PE may have a genetic component may have validity.

Waldinger et al hypothesised that lifelong early ejaculation in humans may be explained by either hyposensitivity of the 5-HT2C and/or hypersensitivity of the 5-HT1A receptor [86]. Specifically, they suggested that men with low 5-HT neurotransmission and probable 5-HT2C receptor hyposensitivity may have an ejaculatory threshold genetically "set" at a lower point and therefore ejaculate quickly and with minimal stimulation and often prior to reaching their erectile threshold. In contrast, men with a genetically determined higher set point could sustain more prolonged and intense sexual stimulation and could exert more control over ejaculation. Finally, men with a very high set point may experience delayed or absent ejaculation despite prolonged sexual stimulation and achieving a full erection [88]. Treatment with an SSRI class drug may activate the 5-HT2C receptor, adjust the ejaculatory threshold set point, and thus delay ejaculation. The extent of ejaculatory delay may vary widely in different men according to the dosage, the frequency of administration of the SSRI, and the genetically determined ejaculatory threshold set point. Cessation of treatment results in re-establishment of the previous set point within 5-7 days in men with life long PE. Identification of the specific 5-HT receptor subtypes involved in early ejaculation would be possible by administering subtype selective 5-HT2C or 5-HT1A receptor ligands, but unfortunately such agents are not yet available for human use.

Both animal models and human data have been invoked to support the idea that ejaculatory latency is naturally distributed and constitutionally influenced. In various sexual behavior tests in male Wistar rats, a continuum of the ejaculation latency has been demonstrated [89]. Moreover, in an unselected cohort of men in five countries (Netherlands, UK, Spain, Turkey and the USA), the IELT distributed in a skewed pattern with a median IELT of 5.4 minutes (range: 0.55 to 44.1 min) [66], confirming IELT variation across men. (Figure 6) A preliminary indication for a genetic basis for ejaculatory latency was recently demonstrated by Janssen and colleagues [90] who reported that gene polymorphism of the 5-HT transporter (5-HTT) is associated with the rapidity of ejaculation in men with lifelong PE. Men with lifelong PE and with LL-genotype have 100% shorter latencies than men with SS-genotype of the 5-HTTLPR. This study suggested that the short IELTs in men with lifelong PE may be associated with more gene polymorphism of 5-HT metabolism and gene polymorphism of other neurotransmitters. A survey with questionnaires in

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<td>Chronic Pelvic Pain Syndrome (CPPS)</td>
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Finnish twins has also demonstrated that genetic factors may play a role in premature ejaculation [91]. However, a methodological limitation of this study was a lack of objective IELT measurement in these men and the absence of a distinction between lifelong and other forms of PE.

2) SEROTONERGIC SYSTEMS IN EJACULATION: AN ATTEMPT TO UNDERSTAND THE NEUROCHEMISTRY OF PE

Male rat studies (Table 5) have demonstrated that serotonin (5-hydroxytryptamine: 5-HT) and 5-HT receptors are involved in the ejaculatory process. As far as is currently known, 5-HT2C, 5-HT1A and 5-HT1B receptors determine the speed of ejaculation. For example, studies with d-lysergic acid diethylamide and quipazine, which are nonselective 5-HT2C agonists, suggest that stimulating 5-HT2C receptors delays ejaculation [92]. However, 2,5-dimethoxy-4-iodophenyl-2-aminopropane, which equally stimulates 5-HT2A and 5-HT2C receptors, also increases ejaculation latency [93] whereas the selective 5-HT2A receptor agonist 2,5-dimethoxy-4-methylamphetamine does not have this effect [92]. On the other hand, activation of postsynaptic 5-HT1A receptors by the selective 5-HT1A receptor agonist 8-hydroxy-2-(di-n-propylaminotetralin) in male rats results in shorter ejaculation latency [92]. Administration of selective serotonin reuptake inhibitors (SSRIs) results in higher levels of 5-HT in the synapse due to active blockade of 5-HT transporters in the presynaptic membrane [86]. Initially, the 5-HT level is only mildly increased, but due to desensitization of the 5-HT1A and 5-HT1B/1D autoreceptors, 5-HT levels in the synapse increase highly. The higher levels of 5-HT consequently activate the post-synaptic 5-HT2C and 5-HT1A receptors [86, 94]. Acute administration of clomipramine and SSRIs does not lead to a significant change in sexual behavior of male rats [95]. However, chronic administration with fluoxetine [96] and paroxetine [97] significantly delays ejaculation latency in male rats. Chronic administration of fluvoxamine, however, exerts only a mild change in male rat sexual behavior.

Based on 5-HT2C and 5-HT1A receptor interaction data in animals, it has been hypothesized [86, 88, 98] that men with premature ejaculation have a hypopensitivity of the 5-HT2C and/or hypersensitivity of the 5-HT1A receptors. (Table 5) The hypothesis that activation of postsynaptic 5-HT receptors delays ejaculation is supported by numerous studies in humans with different SSRIs. However, in these studies it is not obvious whether similar receptor subtypes, that is, 5-HT2C and 5-HT1A receptors, are also involved in human ejaculation since SSRI treatment activates many different postsynaptic subtype receptors. To address this issue, two human studies with the 5-HT2C blocking antidepressants, nefazodone [99] and mirtazapine [100], were performed. In a double-blind placebo controlled study with the 5-HT2C/5-HT2A receptor antagonist and 5-HT/noradrenaline reuptake inhibitor nefazodone, 400 mg nefazodone daily did not exert any ejaculation delay, in contrast to either 20 mg paroxetine daily or 50 mg sertraline daily, both of which induced significant delays. In a similar study the 5-HT2C/5-HT3 receptor antagonist and noradrenergic and...
specific serotoninergic antidepressant mirtazapine did not induce ejaculation delay compared with the significant delay resulting from 20 mg paroxetine daily. In both studies nefazodone and mirtazapine did not delay ejaculation. Further studies with selective 5-HT2C and 5-HT1A agonist and antagonists may yet elucidate undiscovered pharmacological mechanisms underlying the ejaculatory process.

b) Acquired premature ejaculation (A-PE)

As with many other sexual symptoms, the notion that men with PE are a homogeneous group is erroneous [101]. As mentioned earlier, Shapiro [102] initially classified men with PE into two subgroups: those with lifelong PE (i.e., from the beginning of active sexual life) or those who acquired the condition after a period of normal ejaculatory control. And, indeed, those classified in this latter group may themselves show a variability in symptoms and etiologies [60, 76, 81, 82, 84, 103-115]. For example, acquired PE may be absolute/generalized (irrespective of partners or context) or situational (relative to a partner and/or context), and the condition may vary greatly in its frequency and severity [116].

The definition of acquired PE (A-PE) is an ongoing process. While it has been relatively easy to define lifelong PE on the basis of existing data [75], similar objective parameters have thus far not been produced for A-PE. Although no logical reasons exist for suspecting substantial differences in intravaginal latencies (IELTs) and patient reported outcomes (PROs) in patients with lifelong or acquired PE, the lack of evidence-based IELT and PRO data has thus far frustrated the efforts of scientific societies and consensus conferences to reach a definition of acquired PE, with the only consensus at this juncture being that acquired PE occurs after a period of normal ejaculatory control. The obvious inferring of this is that lifelong PE is more likely to be sustained by congenital causes, while the acquired form must be grounded in psychological events or organic noxae able to affect the complex mechanism of ejaculation.

The pathophysiology of acquired PE may be either neurobiogenic (endocrine, urologic, neurobiologic) or psychogenic, or in some instances, both [117]. In other words, A-PE may be viewed as a psychoneuroendocrine and urological symptom with possible comorbidity with another sexual disturbance: thus A-PE has been correlated with psychological, neurological, hormonal, and urological conditions and diseases, and other sexual symptoms such as ED. Since the psychological etiology is largely treated in other sections of this chapter, the following discussion focuses on organic pathologies. As with the psychological aspects of PE [118], no single neurological, endocrine, or urological pathology listed here has been demonstrated to be a direct cause of A-PE. Rather, all these must be considered, at best, pathological conditions associated with PE, thereby deserving medical attention and treatment in order to maximize the therapeutic efforts toward alleviating the symptoms of PE. In other words, rather than causes or determinants, the candidate etiologies of A-PE listed here should be regarded as organic risk factors (Table 4).

1) Neurological risk factors

Although logical, the association between PE and hypersensitivity is still under debate. The sensitivity of the glans, the organ triggering ejaculatory reflex, undoubtedly has an important role in the ejaculatory mechanism, and possibly in some forms of PE. Penile sensation is unique when compared to other body regions [119]. The human glans penis is covered by stratified squamous epithelium and a dense layer of connective tissue, equivalent to the dermis of normal skin. The majority of nerve terminals are free nerve endings (FNEs) which are present in almost every dermal papilla as well as scattered throughout the deeper dermis. FNEs are characterized by an incomplete Schwann cell investment and contain irregularly scattered neurofilaments and neurotubules, clusters of mitochondria, vesicles of variable size, and various inclusions. The unique corpuscular receptor of the glans penis consists of axon terminals that at an ultrastructural level resemble a tangled skein of FNEs. Simple Pacinian and Ruffini corpuscles have occasionally been identified, predominantly in the corona glandis [120].

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</table>

Table 5: Level of Evidence - The Effects of Drugs on Orgasm and Ejaculation
On these anatomical bases, it has been shown that patients with PE, not necessarily with the acquired form, may have hypersensitivity and hyperexcitability of the glans penis, which may give rise to uncontrolled ejaculation and which therefore may contribute to the risk for organically based PE [121]. Evoked sacral potentials have in fact been used to study the bulbocavernous reflex in men with PE [122]. In perineal and perianal measurements, the amplitudes of the evoked responses were greater in men with PE relative to controls, thereby suggesting a reflex hyperexcitability or an impaired "modulation" of the motor neurons of the pudendal nucleus in men with PE. On the glans penis and penile shaft, sensory threshold values in patients with PE have been found significantly lower than those in normal potent men [123]. Furthermore, using somatosensory evoked potential, patients with PE showed greater cortical representation of sensory stimuli from the genital areas than normal ejaculators [124]. However, Rowland and colleagues found thresholds for premature ejaculators to be commensurate with controls, while men with erectile dysfunction or combined erectile dysfunction and PE showed significantly elevated thresholds [125]. Although premature ejaculators did not show penile hypersensitivity, there was a significant correlation in this group between ejaculation latency and threshold. Overall, these findings argue against a primary role for penile sensitivity in ejaculation latency and suggest that other somatic or cognitive factors may play a more critical role in PE. Furthermore, faster conduction along the pudendal sensory pathway or a greater cortical representation of the sensory stimuli from the genital area or hyperexcitability of the BC reflex has not been consistently confirmed in patients with PE [126]. This lack of effect was further confirmed using a vibrometer with precision and reproducibility higher than analogue-type biothesiometers [127]. Such findings suggest that the electrophysiological approach is probably not sufficient to clarify some causes of either lifelong or acquired PE, although more investigation in this area of research is warranted [128].

2) **Endocrine risk factors**

Hormones play a central role in the machinery of emission-ejaculation [129]; thus pathological hormonal levels have the potential to directly or indirectly affect ejaculatory control [130]. An example occurs with thyroid hormone, although with respect to this hormone, the hormone condition may affect ejaculatory latency just as the condition of PE may affect or modify the hormone level itself. Similar patterns may occur with respect to the relationship between testosterone and prolactin levels and A-PE.

- **The role of sex steroids**

  Low serum testosterone levels have been inconsistently associated with PE [131, 132]. However, some reports have anecdotally suggested that hypogonadism may be a cause of delayed or retarded ejaculation. Testosterone plays a crucial role in male sexual response, acting at both the central and peripheral levels, and it is a clear determinant of motivation to seek sexual contact. Several studies on hypogonadal men have demonstrated that testosterone replacement has an unequivocal role in restoring sexual desire, spontaneous sexual thoughts, and attraction to erotic stimuli. The testosterone-dependency of PDE5 expression and activity has also been demonstrated in other portions of the male genital tract (MGT) such as the vas deferens, a critical effector for semen emission and ejaculation [133].

Recent data suggest that testosterone plays a facilitating role in the control of ejaculatory reflex [134], with different testosterone levels identifying different subsets of ejaculatory disturbance. While higher testosterone levels characterize PE, lower testosterone levels have been associated with delayed ejaculation. Taken together, these data suggest a role for androgens in the mechanism of ejaculation [134], and both central and peripheral systems have been advocated to explain this association. The first explanation is psycho-endocrinal. Testosterone, in addition to its action on sexual response, profoundly influences male behavior. High testosterone in human adults is associated with leadership, toughness, personal power, and aggressive dominance [135]. Rowland considers some cases of delayed ejaculation to represent the uncoupling of subjective arousal and genital response—where genital reaction is preserved in the face of diminished subjective sexual arousal [136]. It could thus be speculated that hypogonadism and a related reduction in sexual confidence and aggressiveness could play a critical role in the control of ejaculation timing, reducing the internal cues for reaching orgasm and ejaculation. The second hypothesis is neurological. Recent data from animal models seem to support the central action of testosterone in the control of the ejaculation reflex. Keleta et al [137] have demonstrated that long-term testosterone treatment in rats significantly decreased 5-HT in the brain. Another intriguing possibility involves the peripheral role of testosterone in regulating MGT motility. In rabbit hypogonadism, PDE5 is less expressed and biologically active in the vas deferens [138], but testosterone administration completely reverses these alterations. Hence, it is possible that hypogonadism-associated delayed ejaculation is due to an increased inhibitory nitric tone on MGT smooth muscle cells. A "mechanical" effect of testosterone action in ejaculation control is also possible. A hypogonadism-induced reduction in semen volume may perturb the dynamics of the seminal bolus propulsion, possibly explaining ejaculation difficulties in some men. In fact, low testosterone directly reduces ejaculate volume which may result in a lack of stimulation of accessory glands...
such as the prostate and seminal vesicles, which are well-known androgen targets. Finally, the explanation that the observed testosterone differences are the consequences of sexual disturbances mirror differences in sexual behaviour, such as copulation frequency [139].

In conclusion, several possible mechanisms may relate androgen levels with the complex machinery of ejaculation. Clinical studies are currently in progress to further establish the role of testosterone on ejaculatory dysfunction.

- The role of prolactin

In a consecutive series of studies investigating 2,531 patients interviewed using the SIEDy structured interview (a 13-item tool for the assessment of ED-related morbidities) [140] and the Middlesex Hospital Questionnaire [141] for the evaluation of psychological symptoms, low prolactin (PRL) levels were found to be associated with PE and anxiety symptoms [142]. However, low PRL seems to be an effect rather than a cause of PE. In fact, many psychological disturbances (such as stress and frustration related to chronic or acquired inability to enjoy sex) are able to provoke a neuroendocrine imbalance, such as that of the central serotoninergic system, mirrored by the relative hypoprolactinemia found in patients with PE.

- The role of thyroid hormones

The impact of thyroid hyper- and hypo-function in male sexual function has been studied only recently. This lack of previous analysis is probably the consequence of: i) the apparently low clinical significance given to male sexual symptoms in comparison with the systemic effects of thyroid hormone excess and defect; ii) the paucity of clinical studies, as thyroid disease is less common in men than women; and iii) the embarrassment of patients and physicians when discussing sexual dysfunction in the "traditional" setting of the endocrine outpatient clinic [143]. Nevertheless, a high prevalence of A-PE has been found in hyperthyroid patients, whereas delayed ejaculation has been the major sexual complaint in hypothyroid men [144, 145]. Both the premature and delayed ejaculatory dysfunctions have been reversed on achievement of euthyroidism in the absence of any other treatment for the sexual symptom. Interestingly, suppressed levels of TSH (as a marker of hyperthyroidism) have been demonstrated in A-PE [145] but, obviously, not in patients with lifelong PE [146]. Such findings suggest direct involvement of thyroid hormones on the physiology of ejaculation.

As the specific relationship between thyroid hormones and ejaculatory mechanisms is currently unknown, three possible sites of action have been suggested: the sympathetic nervous system, the serotoninergic pathway, and the endocrine/paracrine system. Most manifestations of thyrotoxicosis and sympathetic nervous system activation overlap, thereby suggesting a similar action on ejaculation, a reflex largely dependent on sympathetic and parasympathetic tone. However, plasma catecholamines and their urinary metabolites are usually normal in hyperthyroidism [147]. On the other hand, some studies have found that thyroid hormones augment sensitivity to a-adrenergic agonists by increasing a-adrenoceptor density and Gs/Gi protein ratio through an over-activation of adenylate cyclase [148]. This action leads to increased sympathetic activity with normal circulating catecholamine levels. In hyperthyroid patients, the increased adrenergic tone may trigger both premature and delayed ejaculation, either acting directly on smooth muscle contractility/relaxation or indirectly on anxiety and irritability. The opposite may occur in hypothyroid patients [149]. Considering the neuropsychological reactions to thyroid hormone excess (hyperkinesia, nervousness, anxiety, emotional lability), PE may also be a non-specific disease-related complaint, disappearing when a euthyroid state is achieved. However, in light of the widespread distribution of thyroid hormone nuclear receptors within the brain, it can be hypothesized that iodothyronines specifically alter the central serotoninergic pathway [150], leading to diminished ejaculatory control. In animals with experimentally-induced hypothyroid states, increased serotonin turnover in the brainstem is consistently reported [151], and thyroid hormone replacement is associated with increased cortical serotonin concentrations and augmentation of serotonergic neurotransmission by desensitization of the serotonin inhibitory 5-HT1A (auto-inhibition) [151]. Finally, delayed ejaculation is a common and therapeutically useful side effect of serotonergic drugs, indicating that this pathway is fundamental for ejaculatory control.

Another possible way that thyroid hormones may affect the ejaculatory mechanism is through estrogen metabolism. Hyperthyroidism increases levels of sex hormone binding globulin (SHBG), which binds androgens with higher affinity than estrogens, leading to a relative hyperestrinism. It has been demonstrated in hypogonadic rabbits that estrogens, but not androgens, fully restore oxytocin-induced epididymal contractility, up-regulating oxytocin receptor gene and protein expression, and that deprivation of endogenous estrogens induces oxytocin hypo-responsiveness [152, 153]. As oxytocin is closely involved in the ejaculatory mechanism [154] both centrally [155] and peripherally [156], this may account for the close correlation between hyperthyroidism and premature ejaculation. As an ancillary possibility, thyroid hormone receptors have been described in the animal [157] and human testis [158], and may also be present in other male genital tract structures, triggering ejaculation. Finally,
although excluded in the original report [144], some cases of PE in hyperthyroidism are comorbid with impotence, which may in turn exacerbate the loss of ejaculatory control [159].

3) **Urological risk factors**

- The role of the prostate

For unexplained reasons, the relationship of prostate and PE was largely neglected in the past but now has been attracting increasing interest. This neglect is particularly surprising since the main function of the prostate is to store and secrete the clear, slightly basic fluid that constitutes up to one-third of the volume of semen. The prostate also contains smooth muscle that helps expel its secretions during ejaculation.

In the classic model explaining the human ejaculatory process, the emission, with formation of a “pressure chamber” created in the prostatic urethra, is followed by expulsion (rhythmic bulbospongiosus muscle contractions) of seminal fluid [160]. The first phase is mediated by activated adrenergic contractions of the smooth muscle in the capsules of the testes, seminal tract, and genital glands, including the prostate. This pressure build-up is claimed then to “trigger” the intermittent relaxation/contraction of the distal sphincter and activate the contractions of the striated pelvic musculature, especially that of the bulbocavernosus, which forcefully expels the semen along the urethra by powerful, rhythmical spurts. Electric waves discharged from the prostate at rest seem to produce prostatic contractions that appear to be responsible for increases in the prostatic urethral pressure [161]. Shafik [162] noted that, at ejaculation, the intermittent and significant increase in wave variables and urethral pressure coincided with the ejaculatory spurs and apparently denotes intermittent prostatic smooth muscle contractions. These prostatic contractions seem to squeeze the prostatic secretions into the prostatic urethra. However, some important pieces of experimental evidence, against the notion that “distension” of the prostatic urethra by the entering semen is the probable trigger for the ejaculation reflex, have been produced. a) Alpha-adrenergic blocking agents (phenoxybenzamine, phentolamine) prevent the discharge of semen into the urethra but do not inhibit the initiation of ejaculation despite there being no fluid to ejaculate (dry orgasms), nor do they change significantly the subjective experience of orgasm [163]. Moreover, a healthy subject could experience a dry emission/ orgasm with a complete absence of secretions. b) It has been reported that a decrease in echogenicity of the prostatic urethra during the pre-ejaculatory phase signifies the secretion and movement of prostatic fluid to the prostatic urethra, which in turn leads to the inevitability of expulsion [7] and that the prostatic urethra is distended 3-5 sec before the start of seminal expulsion [164]; however, in 8 normal healthy volunteers, the expulsion of the contents of the seminal vesicles into the inframontanal urethra always occurred without prior ballooning of the prostatic urethra [165], suggesting that a “pressure chamber” does not appear to be formed before prostatic contractions take place. c) In copulating male rats, urethral stimulation by the ejaculate does not contribute to the activation of the striated muscle component of the ejaculation reflex [166], further suggesting that candidate sites for the ejaculation “trigger” could be present in the penile glans, spinal cord, and/or the brain.

Although the formation of the “pressure chamber” in the prostatic urethra is currently undetermined, it is well known that the antegrade propulsion of seminal fluid into the distal urethra requires coordinated dynamic changes at the bladder neck, prostatic urethra, and external sphincter [167].

- Effects of prostatic disorders on ejaculatory process

Prostate inflammation/infections have been anecdotal-correlated with PE [168]. Jannini and co-workers first demonstrated, using the Meares and Stamey test [169], a relatively high prevalence of prostatic inflammations and infections in men with PE. Furthermore, this sexual symptom is in turn common in subjects with prostatitis [170]. Following the report of these findings, the European Association of Urology (EAU) Guidelines on Ejaculatory Dysfunction recognized that “PE may be strictly organic (e.g. prostatitis-related),” and thus prescribed rectal examination with evaluation of the prostate in patients with ejaculatory disturbances [171].

Assuming that the relationship is causal, prostatic inflammation may alter sensations arising from the male genital tract such that the man is unable to recognize the emission phase [116], an effect that has been replicated by other researchers. Prostatic inflammation or infections (variously demonstrated or simply admitted by patients in a population survey) have been found in 3,115 patients with PE (variously defined) examined in several countries, with a prevalence ranging from 15 to 64% (Table 6). Inversely, PE has been found in 2,360 patients with prostatitis and/or lower urinary tract symptoms (LUTS) (Table 7). Note that LUTS have been also related with retarded and painful ejaculation [172, 173].

Some researchers argue that the correlation between prostatitis and PE is actually mediated via prostatitis-induced erectile dysfunction [174]. However, the physiological correlation between the machinery of erection and prostate function is quite poor, while—considering the physiological role of the prostate—the physiological correlation between ejaculation and this gland is robust, so this latter possibility cannot be ruled out, at least in patients with such comorbidity. However, other authors have been able to cure A-PE using only a specific antibiotic treatment
against the bacteria responsible of prostatitis [175-177]. Thus, although the relationship between prostate problems and ejaculatory response is not fully elucidated, examination of the prostate, always important in the andrological setting, may be critical during assessment of patients with A-PE [178].

4) OTHER SEXUAL SYMPTOMS AS RISK FACTORS

Sexual dysfunctions such as hypoactive sexual desire disorders or erectile dysfunction may be either the cause of or consequence of A-PE. Furthermore, A-PE may result from female sexual dysfunctions such as vaginismus or dispareunia. Inversely, a partner’s sexual dysfunction may also result from A-PE.

- Premature ejaculation and erectile dysfunction

Even though a patient may present with PE, the clinician should assume neither its presence nor singularity. For example, some patients consider it easier and less humiliating to admit to a rapid ejaculation caused by “enthusiasm” than to other more “stigmatizing” sexual dysfunctions such as ED. For this reason, the possibility that other sexual problems co-exist with the PE should routinely be investigated. Although most men with lifelong PE do not suffer from concomitant erectile dysfunction [3], PE co-exists in about 1/3 of patients complaining of erectile dysfunction [145]. In fact, PE correlates significantly with erectile dysfunction in all of the regions tapped by the Global Study of Sexual Attitudes and Behaviors [85].

In some instances, PE and ED may form a vicious circle, where a man trying to control his ejaculation instinctively reduces his level of excitation (which can lead to erectile dysfunction), or where a man trying to achieve an erection basically attempts to do so by increasing his excitation and arousal (which can lead to PE) (Figure 7). Thus, although reduced time to ejaculation is only rarely an early manifestation of erectile dysfunction, it may occur when the man has an unstable erection due to fluctuation in penile blood flow. In this case, the man may reach ejaculation quickly to compensate for the weak erection.

Furthermore, some men with PE may express their complaint using language that suggests an erectile problem, indicating how they are unable to keep their erection or to “last” (due actually to penile detumescence after ejaculation occurs rapidly). Furthermore, erectile dysfunction may be superimposed on lifelong PE by efforts to minimize sexual excitement. Finally, PE and ED may be further linked in that lack of ejaculatory control may generate reactive impotence, due to anxiety arising from poor sexual performance.

- Premature ejaculation and low sexual desire

Hypoactive sexual desire may lead to PE, due to an unconscious desire to abbreviate unwanted penetration. Similarly, diminished sexual desire can be a consequence of chronic and frustrating PE. Interestingly, low sexual desire may be due to a lack of sexual arousal, such as in erectile dysfunction. Premature ejaculation and low desire, singly or in combination, are, in fact, significantly associated with severe rather than mild erectile dysfunction at presentation [179]. There is limited but increasing evidence to support a potential role for PDE5Is used alone or combined with daily or on-demand SSRIs in the treatment of A-PE in men with comorbid erectile dysfunction [180].

- Partner sexual dysfunction

Finally, female sexual dysfunctions (such as anorgasmia, hypoactive sexual desire, sexual aversion, sexual arousal disorders, and sexual pain disorders, as vaginismus [181]) may also be related to acquired PE. The female dysfunction may be secondary to the male PE with or without erectile dysfunction, and can be considered as a frequent complication of this condition. In other cases, PE may be the result of hidden female arousal difficulties [182]. Such

Table 6: Prevalence of prostate inflammation in patients with premature ejaculation

<table>
<thead>
<tr>
<th>Author/s</th>
<th>n. Patients</th>
<th>Incidence of Prostatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screponi E et al.[170]</td>
<td>46</td>
<td>48.56%</td>
</tr>
<tr>
<td>Xing JP et al.[512]</td>
<td>106</td>
<td>40.46%</td>
</tr>
<tr>
<td>Fasolo BC et al.[513]</td>
<td>2658</td>
<td>15%</td>
</tr>
<tr>
<td>Shamloul R et al.[114]</td>
<td>153</td>
<td>52.64%</td>
</tr>
</tbody>
</table>

Table 7: Note that LUTS have been also related with retarded and painful ejaculation.

<table>
<thead>
<tr>
<th>Author/s</th>
<th>n. Patients</th>
<th>Incidence of Prostatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screponi E et al.[170]</td>
<td>26</td>
<td>61.5%</td>
</tr>
<tr>
<td>Xing JP et al.[512]</td>
<td>120</td>
<td>47.5%</td>
</tr>
<tr>
<td>Lian CZ et al.[513]</td>
<td>1749</td>
<td>33.7%</td>
</tr>
<tr>
<td>Gonen M et al.[114]</td>
<td>66</td>
<td>92%</td>
</tr>
<tr>
<td>Trinchieri A et al.[200]</td>
<td>399</td>
<td>55.5%</td>
</tr>
</tbody>
</table>
partner influences emphasize the need to diagnose and treat the couple, not simply the patient [183].

5) A POSSIBLE FLOW-CHART FOR THE DIAGNOSIS OF A-PE

Current literature suggests that no particular diagnostic efforts can be performed in the normal clinical practice to recognize the etiology of lifelong PE [184]. In contrast, evidence of an acquired PE condition should maximize the effort to identify the etiology of the PE and to alleviate its possible cause.

Together with a careful sexological and medical anamnesis [185], physical examination is the keystone of the diagnosis of A-PE. In the large majority of patients with A-PE, it is in fact unnecessary to use instrumental or laboratory tools. The first diagnostic aim is to perform a differential diagnosis with subclinical [186], mild, or overt erectile dysfunction, which can be causal of, contributing to, or simply comorbid with A-PE. It is in fact mandatory to recognize such relationships so as to avoid therapeutic failure using both psychotherapy and/or drugs.

A simple neurological examination helps to rule out evident neurological diseases and, together with several anamnestic questions, hyperthyroidism. A digital prostate examination, routine in an andrological setting for all men over 40, is useful in identifying possible evidence of inflammation or infection, confirmed with the Meares and Stamey test and eventually echoscan if necessary [187].

Patients with A-PE should be clinically evaluated for currently suspected etiologies including: psychological, neurological, hormonal and urological, and for co-morbidity with another sexual dysfunction [188]. Etiological therapies (psychological, sexological, pharmacological) should be performed first when possible whereas symptomatic treatment (psychological, sexological, pharmacological) should further be considered in patients unresponsive or poorly responsive to etiological therapies.

In conclusion, although the absence or deficiency of ejaculatory control is among the most common sexual problems [189], the acquired subtype of PE is still under-diagnosed and under-treated, despite the fact that it can be successfully treated [190]. However, with increased medical awareness, careful diagnosis and sub-typing, recognition of the pathogenic mechanism in individual patients, and the forthcoming availability of new drugs specifically designed for PE, clinicians will be provided new opportunities to treat the severe suffering of many patients suffering from this condition.

IV. THE TREATMENT OF PREMATUR EJACULATION

1. PSYCHOLOGICAL CONSIDERATIONS AND TREATMENT

a) The psychological burden of premature ejaculation

Premature ejaculation (PE) exerts a significant psychological burden on men, their partners, the male/partner relationship, and their overall relationship [191]. For example, recent empirical studies in which diagnostic criteria were specified verified decreased sexual satisfaction as an identifying factor in men with any sexual dysfunction [63, 192, 193]. Men with PE show other negative effects, including a general negative affect associated with sexual situations, and more intense feelings of embarrassment/guilt, worry/tension and fear of failure [84, 194]. Relative to men without PE they indicate decreased self-confidence, increased distress and interpersonal difficulty, and mental preoccupation with their condition [84, 193]. Because partner satisfaction may play a greater role in PE than ED, it is not surprising that
relationship dysfunction is reported as the second most common negative effect of PE [84, 195]. PE is not only associated with marital discord [196], but the insecurity of men with PE about satisfying the partner also serves as an obstacle to initiating and maintaining new relationships [195, 197].

Further evidence of the significant and negative impact of PE on psychological and relationship functioning in men and their partners has been documented through a study using a large sample size and validated outcome measure reports [191]. Men with PE reported significantly lower frequency of and satisfaction with intercourse, greater personal distress and interpersonal difficulty, and lower self-esteem and confidence in their sexual and overall relationship with their partner. The impact of PE was not felt just by the man, as women were well aware of the lack of control over ejaculation by the male partner. And they too reported lower sexual satisfaction, and higher personal distress and interpersonal difficulty. Although not clinically dysfunctional, partners of men with PE report more problems related to general sexual functioning than women who do not have a partner with PE.

Thus, the negative psychosocial impact or burden of PE provides an essential element in the characterization of PE, yet it remains distinct and independent of ejaculatory control and IELT. In fact, not all men with a short IELT are distressed by the condition [191], and IELT only weakly correlates with other dimensions associated with PE, including lack of ejaculatory control, low sexual satisfaction, and high personal distress and interpersonal difficulty. Accordingly, using dimensions beyond simple ejaculatory latency to characterize premature ejaculation, particularly those related to concern, distress, and other negative consequences, is critically important to the understanding and diagnosis of PE [191].

b) Psychological treatment of premature ejaculation

Psychotherapy and behavioral interventions improve ejaculatory control by helping men/couples to: (1) learn techniques to control and/or delay ejaculation, (2) gain confidence in their sexual performance, (3) lessen performance anxiety, (4) modify rigid sexual repertoires, (5) surmount barriers to intimacy, (6) resolve interpersonal issues that precipitate and maintain the dysfunction, (7) increase communication [198, 199], and (8) come to terms with feelings/thoughts that interfere with sexual function. Regarding this last point, for examples of the kinds of thoughts and cognitions that are likely to disrupt sexual function in men with PE, see Table 8. Present day psychotherapy for premature ejaculation most often represents an integration of psychodynamic, systems, behavioral, and cognitive approaches within a short-term psychotherapy model [200-209]. The guiding principles of treatment are to learn to control ejaculation while understanding the meaning of the symptom and the context in which it occurs. However, only 5 studies have compared psychotherapy techniques for PE, either versus a control condition (remaining on a waiting list) or against other psychological treatments. [205-209], (Table 9) Three studies have compared psychotherapy in combination with pharmacotherapy against psychotherapy or pharmacotherapy alone. [210-212]One study has compared pharmacologic treatment against a behavioural intervention.[213] Overall, there is little evidence to date that psychological interventions are effective in the treatment of lifelong PE.

1) The rationale for psychological/behavioral strategies

Even though a physiological basis for some types of PE has been suspected for years [214, 215], until recently treatment options relied, quite understandably, mainly on behavioral and psychological procedures. First, psychological factors such as anxiety and negative affect have frequently been associated with sexual dysfunctions such as PE [1, 200] and therefore treatment addressing such issues has represented a logically consistent approach. In contrast there had been little or no evidence pointing to a physiological mechanism that might underlie PE. Second, until the past eight years, few tested and well-tolerated biologically based therapeutic procedures were available to clinicians for the treatment of PE. And third, the psychological-behavioral strategies for treating PE have been at least moderately successful in alleviating the dysfunction [216].

Although the new and often more expedient pharmacological therapies are overshadowing these traditional psychological-behavioral methods in the treatment of PE, the psychological-behavioral approach remains an attractive option for several reasons. The treatment is specific to the problem, is neither harmful nor painful, is less dependent on the man’s medical history, produces minimal or no adverse side effects, encourages open communication about sexuality in the couple which is likely to lead to a more satisfying sexual relationship [217, 218], and has a permanence about it. Once the techniques have been learned and incorporated into lovemaking, PE men continue to have access to strategies that help them control their ejaculation. At the same time, there are drawbacks to the psychological-behavioral approach: it is time-consuming, often requires substantial resources of both time and money, lacks immediacy, requires the partner’s cooperation, and has mixed (and less well-documented) efficacy [219, 220].

2) Empirically supported psychological approaches

In addition to countering the current trend toward
pharmaco-therapeutic treatment for PE, clinical practitioners considering the use of behavioral and psychological strategies as part of their treatment protocol face particular difficulties. Strong pressure exists to provide a therapeutic treatment that fails within today's cost containment managed care environment and that meets the criteria of being empirically validated or at least empirically supported. To be considered "empirically supported," a therapeutic approach must be backed by (1) at least two studies showing it more effective than a waiting-list control group, or (2) at least two studies demonstrating effectiveness but which may have flawed sample heterogeneity, or (3) by a series of case studies in which the client sample was clearly specified and the treatment procedure described in a detailed manual.

Because of the tension between therapeutic and research objectives, it has been difficult to conduct carefully controlled, well-conceived studies that simultaneously provide needed treatment to clients whose lives are being adversely affected by their PE. As a result, there have been few treatment vs. matched-control tests of behavioral-psychological therapy on PE men, and relatively few self-as-control, waiting list, or even no-control studies [220]. More importantly, the lack of specific treatment protocols and of research funds to carry out well-designed studies to test those protocols has diminished the attractiveness of these approaches relative to evolving pharmacological strategies [221, 222]. Therefore, at this juncture the majority of psychotherapy treatment outcome studies can be characterized as underpowered, unblinded trials, with none meeting the requirements for high level evidenced-based studies. Existing research has generally used small to moderately sized cohorts of subjects who received different forms of psychological interventions with limited or no follow-up. Generally, active treatment was not compared to placebo, control or wait list groups [83].

3) Details of Successful Psychological-Behavioral Methods of Treatment for PE

Several psychological-behavioral strategies enjoying substantial popularity among sex therapists have at least come close to meeting the criteria of empirically-supported. The first is the "start-stop" method, developed by Semans [223] and later modified to become the "stop-squeeze" method by Masters and Johnson [224] in their sex therapy clinic. Another method, advocated by Kaplan [225], is a variant of start-stop method. These three methods suppress the urge to ejaculate primarily by stopping sexual stimulation, but the one substitutes a squeeze of the glans penis for a pause in stimulation at the point of impending ejaculation.

The stop-squeeze method calls for the man to signal his partner as the ejaculatory urge builds. The couple then stops the sexual stimulation and the partner applies manual pressure to the glans of the penis until the urge is reduced, though not to the point where the erection is lost. Different amounts of time for the squeeze have been advocated, but there is no evidence to support any particular duration. Rather, an individualistic approach that balances urge reduction while maintaining a moderate level of sexual arousal appears most effective [204]. With this strategy, the man must pay careful attention to his sexual sensations and stop activity well before ejaculatory inevitability. The stop-squeeze method is typically employed first with masturbation in a cycle of three pauses before proceeding to orgasm. Once successful, the method then progresses to a cycle of two pauses with intercourse in the female superior position, and finally to a cycle of two pauses with intercourse in the lateral position. This training requires an almost exclusive focus on the male's experience of sexual stimulation and needs. While Masters and Johnson's initial report of only a 2% short-term failure rate and 3% long-term failure for the stop-squeeze method revolutionized a field of PE treatment, subsequent studies have reported much lower success rates, in the neighborhood of 50-60% [226-228]. Long term success rates may be even lower. Undoubtedly, the success rates reported by Masters and Johnson were influenced by their carefully-selected clients, the intense format of their treatment, and the relatively high sexual naiveté of couples common during that era.

A variant start-stop behavioral approach to the treatment of PE men was developed by Kaplan

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Table 8: Eight forms of cognitive distortions that may interfere with sexual function in men with PE, as adapted from Rosen, Leiblum, and Spector. [508]

<table>
<thead>
<tr>
<th>Cognition Type</th>
<th>Cognition Distortion</th>
</tr>
</thead>
<tbody>
<tr>
<td>All or nothing thinking</td>
<td>&quot;I am a complete failure because I come quickly&quot;</td>
</tr>
<tr>
<td>Overgeneralization</td>
<td>&quot;If I had trouble controlling my ejaculation last night, I won't be able to this morning&quot;</td>
</tr>
<tr>
<td>Disqualifying the positive</td>
<td>&quot;My partner says our lovemaking is satisfying because she doesn't want to hurt my feelings&quot;</td>
</tr>
<tr>
<td>Mind reading</td>
<td>&quot;I don't need to ask, I know how she felt about last night&quot;</td>
</tr>
<tr>
<td>Fortune telling</td>
<td>&quot;I am sure things will go badly tonight&quot;</td>
</tr>
<tr>
<td>Emotional reasoning</td>
<td>&quot;Because a man feels something is true, it must be&quot;</td>
</tr>
<tr>
<td>Categorical imperatives</td>
<td>&quot;Shoulds&quot;, &quot;Ought to&quot; and &quot;Musts&quot; dominate the man’s cognitive processes</td>
</tr>
<tr>
<td>Catastrophizing</td>
<td>&quot;If I fail tonight my girlfriend will dump me&quot;</td>
</tr>
</tbody>
</table>

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Table 9: Details of successful psychological-behavioral methods of treatment for PE.

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Table 10: Details of successful psychological-behavioral methods of treatment for PE.
Table 9: Level of Evidence - Psychotherapy for Premature Ejaculation

<table>
<thead>
<tr>
<th>Author/s</th>
<th>Study Type</th>
<th>Level Of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowe JC, Mikulas WL, [205]</td>
<td>Self Administered Written Program</td>
<td>3</td>
</tr>
<tr>
<td>Golden JS, Price S et al, [206]</td>
<td>Sex Therapy</td>
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[225] because it better simulated the final behaviors required to prolong ejaculation latency during intercourse. Weekly outpatient therapy resulted in a high success rate (80-90%) in men with primary, generalized PE (i.e., with all partners and often during masturbation). The combination of the start-stop method with marital therapy for couples who showed "resistance" (discussed below) during the treatment process has also been quite successful in men with secondary PE [1, 200]. Although Kaplan’s high success rates have been challenged, the differential procedures for patients with primary versus secondary appear to be a robust finding [228].

Detailed descriptions of both the stop-squeeze and start-stop behavioral methods have been provided in the literature [204, 221, 227], with different therapists emphasizing their own variations. Some therapists advocate using techniques such as slowing down, breathing deeply, or moving in a circular fashion, techniques that many men without PE develop without conscious awareness [227]. Others advocate adding a stage of ejaculatory control training with oral sex as an intermediate step between masturbation and coitus for couples who are comfortable with this particular activity. [204] Still others emphasize the importance of providing the couple with accurate information about the sexual response cycle and its physiological underpinnings [229, 230]. Almost all agree that intercourse position is a relevant factor: The female superior and lateral positions allow for greater control than the male superior position [227, 231].

**c) Parameters affecting psychological treatment**

The general procedures described above rather than any specific variations have received the strongest empirical support for effective treatment of PE. Furthermore, the purported lack of efficacy of various psychological/behavioral strategies may result less from the specific behavioral techniques associated with stop-squeeze/start methods and more to a lack of attention to the parameters and context surrounding the treatment. In addition, long-term adherence is likely to be as much a mitigating factor for behavioral and psychological efficacy as it is with pharmacotherapeutic efficacy.

Three factors are important to successful outcomes when behavioral and psychological strategies are used. First, the man's attention to and awareness of sexual and visceral sensations must be heightened. Second, the couple must de-emphasize the focus on coitus and develop a broader range of sexual expression. And third, the man, and to a lesser degree his partner, must develop alternative cognitive and behavioral strategies to enhance ejaculatory control. Beyond these specific techniques, the man's motivation for treatment and openness to behavioral interventions and the partner's positive assessment of the relationship are significant predictors of positive therapeutic outcomes. In addition, a number of parameters, including the frequency of treatment, treatment format, and success in dealing with patient resistance and relapse appear to affect treatment efficacy with psychological-behavioral strategies.

**1) Frequency and intensity of treatment**

The two-week inpatient/intensive outpatient format originally described by Masters and Johnson offers advantages of great intensity and rapid change. Nevertheless, time, cost, and insurance factors make this sort of treatment unrealistic for most couples [204]. However, research does suggest that long intervals between sessions (bi-weekly or monthly) are insufficient during the early phase of therapy. The most effective treatment begins with 1-2 weekly sessions in order to provide adequate support for the change process, to allow time for the couple to practice behavioral assignments at home, and to "unlearn" adjunctive behaviors (discussed below) that might exacerbate the dysfunction.

Because the long term benefits of psychological-behavioral treatment for PE often decline over time, treatment that lacks sufficient intensity or duration increases the likelihood of a "relapse," that is, a reappearance of early ejaculation symptomatology [228]. If the couple is not adequately prepared for such relapses, the resulting setback
can lead to sexual avoidance, the development of comorbid dysfunction (e.g., lack of desire or erectile problems), and other adverse secondary effects.

The concept of relapse prevention has begun to be incorporated into sex therapy: Therapists may schedule periodic “booster or maintenance” sessions such that patients are scheduled for follow-up in 6 months. In addition to working out any “glitches” that have interfered with patient’s progress [232], such sessions can help couples deal with relapses common to men with sexual problems. Strategies from the relapse prevention model [233], originally developed for the management of substance abuse, suggest that initial treatment intensity and duration should be designed to reduce the likelihood of relapse. For example, weekly treatment should continue until marked progress is made. Then, larger treatment intervals serve to maintain change and deal with difficulties that arise, with periodic sessions continuing six months after success is attained [227, 229]. A further implication of the relapse prevention model is the need to plan for an appropriate response, should relapse occur. This includes decreasing the negativity associated with the setback by predicting its occurrence and assisting the couple in developing coping strategies to deal with the relapse. If follow-up appointments are yet continuing, the couple’s success in dealing with the relapse should be discussed in the session; if treatment has ended, the couple should be instructed to resume therapy if they are unable to cope with relapses.

2) TREATMENT FORMATS

A number of alternative formats for the treatment of PE have been investigated, including the use of bibliotherapy, group versus individual therapy, couples versus individual therapy, and marital versus sex therapy. Clinical research supports the use of bibliotherapy combined with some type of therapist contact for men having high motivation and relatively straightforward PE without co-morbid disorders [204, 229]. Specifically, psychoeducational interventions, often combining bibliotherapy and therapist intervention, can be useful in helping the couple rework their behavioral repertoire or “sexual script” [234]. For example, men with PE often limit foreplay because they fear becoming too excited too quickly. As a result, intercourse may become mechanical and rigid, yet these strategies seldom help the man delay ejaculation. By modifying rigid and narrow scripts, psychoeducational strategies enable the couple to explore the first steps toward establishing a more satisfying sexual life [226]. However, PE men who have complicating factors such as individual or relationship difficulties (which includes the majority of sex therapy clients) or concomitant erectile problems benefit less from reliance on this short-term, limited format.

Data on group (vs. individual) treatment for PE are mixed. Some investigations have found the two formats equivalent whereas others have not [227]. Use of group therapy is primarily a matter of the couple’s preference and openness to receiving treatment in this structure. Some couples benefit from knowing that their sexual problems are not unique and from hearing how other couples deal with them. A group format also provides an opportunity for men and women to meet with same-sex peers. On the other hand, most men find PE a highly sensitive issue (as is the couple’s overall sexuality) and are not comfortable discussing the topic in the presence of others. At present, the research literature cannot be used to defend either an exclusive use of a group format (which certain insurance plans might prefer) or an exclusive avoidance of group format (which some practitioners might prefer).

Treatment of PE in an individual format, however, is not as successful as working with couples. Individual treatment in the absence of a partner precludes the opportunity to practice behavioral and cognitive strategies in-situ. Still, instances arise when individuals are bothered by their PE and thus seek treatment without a partner. In such instances the stop-squeeze and start-stop techniques may be adapted to masturbation, especially when intensity of arousal is enhanced by adding a lubricant and using erotic literature or fantasy [221]. This self-sexuality training can be complemented with education about the female and male sexual response cycles. Training of ejaculatory control through masturbation typically entails a goal of 15 minutes of sexual stimulation of varying intensity before reaching orgasm.

The relative importance of marital vs. sex therapy is an issue that has received some attention from researchers, but results are not sufficiently clear to yield specific answers. The question may be framed in the following way: Does marital therapy lead to enhanced sexual functioning or does sex therapy lead to enhance marital functioning. Generally, marital therapy prior to sex therapy for couples with significant relationship issues leads to better outcomes in sexual functioning, while marital therapy in non-distressed couples does not typically lead to improved sexual functioning. Conversely, sex therapy in non-distressed couples often does lead to improved marital functioning.

3) DEALING WITH RESISTANCE, INCLUDING PRIOR SELF-STRATEGIES

Some patients who seek counseling for PE exhibit various forms of “resistance” to the traditional behavioral approaches. Sources for this resistance include situations where the dysfunction maintains a sexual equilibrium or hides the female partner’s sexual disorder or concerns; where the individual or couple has unrealistic expectations about sexual performance; where major relationship problems exist; where part-
ner deceit is present; and where PE is the consequence of a major health problem [216]. Given the increasing attention to emerging pharmacological solutions for sexual problems, the refusal to reasonably explore cognitive/behavioral and relationship issues and the insistence on taking the “right pill” are becoming new sources of resistance.

Related to the concept of treatment resistance is the issue of “home remedies.” Prior to treatment, PE men may adopt coping strategies that actually worsen the condition [218], that is, the attempted solutions contribute to rather than ameliorate the problem [235]. For example, most PE men assume that paying less attention to the sexual stimuli through active distraction might help control their ejaculation. Yet this strategy counters the greater attention to sexual sensations needed to gain control over the timing of ejaculation. As a result, this remedy typically leads to an unsatisfying orgasm as well as PE and may result in avoidance of sexual situations altogether. A second home remedy involves harder and faster thrusting by the man during his orgasm in an attempt to satisfy his partner. This strategy decreases the awareness of the sexual sensations of the ejaculatory response needed to gain greater control and reduces the enjoyment of the orgasm due to increased anxiety and focus on sexual performance. A third home remedy is for the man to apologize for the premature ejaculation, an act that exacerbates existing feelings of anxiety and guilt and is likely to lead to avoidance. Many couples report that an exclusive focus on the duration and quality of intercourse directly contradicts a healthy focus on developing a mutually satisfying sexual life. Indeed, a strong focus on coitus is counterproductive, particularly since many men without PE ejaculate within several minutes of intromission and a sizable percentage of women achieve orgasm through direct clitoral stimulation, not through intercourse [218].

Kaplan’s work of combining sex therapy with interpersonal approaches and accurate information about sexual functioning provides a model for working through these sources of resistance and challenging the negative coping strategies that might have developed in response to the dysfunction. At times, the “working through” process itself may result in progress even if the reason for the resistance is unclear. But for most couples, a careful preliminary assessment will help prepare the therapist for impediments to progress that can arise within treatment [1].

4) Treating the Person vs. Treating the Penis

One of the great benefits of incorporating behavioral and/or psychological counseling into a treatment regime is that such approaches are more likely to address the psychoaffective and relationship concerns surrounding the dysfunctional response. The affective component of sexual response has long been theorized to play a role in causing or sustaining sexual dysfunction in men [200, 236, 237], with recent research verifying that compared with sexually functional men, men with PE exhibit higher negative and lower positive affect in response to erotic stimulation [238, 239]. What has been unclear is whether the high negative and low positive affect in PE men is part of the original etiology or cause of the dysfunction, or whether it represents a reaction to failed genital response that then serves to exacerbate the problem.

Research actually supports both possibilities [194]. For example, positive emotions such as pleasant/enjoyable increase in men with PE who respond to the ejaculatory-retarding effects of clomipramine treatment, but negative affects such as guilt/embarrassed and tense/worried do not show comparable decreases. In other words, pharmacotherapy appears effective in reinstating positive emotional responses to sexual stimuli in men with PE, but negative emotions are not diminished, even when ejaculatory latencies are increased by as much as several minutes. Thus, even when pharmacological treatment is effective, further therapeutic strategies that emphasize open communication and relaxation with the partner to ease embarrassment and tension may further assist the client in overcoming negative dispositions associated with the dysfunction.

At a broader level, this study illustrates that the interpersonal dynamics that result from the dysfunction—including such factors as avoidance of intimacy on the part of the man and subsequent anger and distress on the part of the partner—may not always be reversed by a genital solution. In such situations, psychological and interpersonal issues may need to be addressed, at least if increased sexual satisfaction and an improved sexual relationship are viewed as important outcomes. Equally important is the recognition that because pharmacotherapy can alleviate a sexual dysfunction, the cause of their problem is not necessarily rooted in aberrant or dysfunctional biological systems. Quite the contrary, sexual dysfunction caused by any number of different somatic, psychological, or interpersonal factors may respond positively to pharmacotherapeutic intervention. That is, any intervention targeted at the mechanics of ejaculation is likely to be effective in rectifying the genital component of the problem, independent of its cause [240].

Thus, the goals of integrated therapy extend far beyond establishing simple control over ejaculation. That is, the therapy typically addresses a myriad of issues related to affective response, re-establishment of confidence, and couples’ interaction dynamics, all with the goal of increasing overall sexual and relationship satisfaction [241].
d) Evaluating treatment

Because different types of treatment intervene at different stages in the dysfunctional response sequence in PE men, the choice of outcome measures depends partly on the specific treatment that is implemented. A treatment plan for PE, for example, may primarily address the endpoint of sexual satisfaction (e.g., with a somatically based problem in which pharmacological treatment is not an option). Alternatively, it could address ejaculatory latency (e.g., pharmacological treatment) which in turn affects sexual satisfaction, or it might address ejaculatory control (e.g., behavioral-cognitive techniques), which subsequently affects both ejaculatory latency and sexual satisfaction. For example, psychological-behavioral strategies instruct patients in the use of mental imagery, behavioral techniques (e.g., adjusting intercourse position, using pauses, etc.), and relationship interactions to develop greater control over the timing of ejaculation. In achieving such control, IELT would be lengthened and greater satisfaction attained. In this treatment, all three measures—ejaculatory control, IELT, and satisfaction—are relevant endpoints, as the focus of the intervention is on developing better ejaculatory control which, in turn, affects both IELT and satisfaction. Indeed, in using all three measures, the researcher or clinician is better able to verify the specific processes through which sexual satisfaction, the ultimate endpoint, is affected.

In contrast, pharmacotherapeutic treatment is aimed at inhibiting the ejaculatory reflex and may not necessarily enable greater control over the timing of ejaculation other than by delaying it. But, as with any medical treatment in which the patient is a «passive» recipient of a treatment procedure, pharmacotherapy—in delaying the ejaculatory reflex—may give the man with PE a greater sense of control over his sexual problem. As a result, assessment of self-efficacy by using a measure such as «ejaculatory control» is perhaps less germane to pharmacotherapy studies than assessment of the other two characteristics of PE—ejaculation latency and general sexual satisfaction. Indeed, research indicates that while men who respond positively to the ejaculatory-inhibiting effects of clomipramine show substantial increases in both IELT and satisfaction, the effect on self-reported «ejaculatory control» tends to be modest [70, 242]. Nevertheless, assessment of self-efficacy in pharmacotherapy studies may be warranted, as increased self-efficacy is undoubtedly related to overall satisfaction with the treatment procedure. However, self-efficacy in such studies might be better assessed with items asking about «the ability to delay ejaculation» or «the ability to control/avoid the premature ejaculation» than with one that specifically assesses «ability to control ejaculation (or its timing).»

Evidence-based research into both the methodology, content, duration and intensity

as well as the short and long term results of psychological treatment of PE is encouraged

Level 3 evidence to suggest that all men seeking treatment for PE should receive basic psychosexual education

Graded levels of patient and couple counselling, guidance and/or relationship therapy, either alone or ideally in combination with PE pharmacotherapy should be offered as a treatment option for most men with PE

Grade C Recommendation

2. PHARMACOLOGICAL TREATMENT

In 1943 Schapiro [76] described the use of topical anaesthetic ointment to delay ejaculation. The use of anaesthetics to diminish the sensitivity of the glans penis is probably the oldest known form of treating premature ejaculation. In 1973 the first report of successful ejaculation delay by clomipramine was published [243]. However, in the 1970s and 1980s, drug treatment of premature ejaculation was not used extensively. The introduction of the serotonergic tricyclic clomipramine and the SSRIs paroxetine, sertraline, fluoxetine, citalopram and fluvoxamine has revolutionized the approach to and treatment of PE. These drugs block axonal re-uptake of serotonin from the synaptic cleft of central and peripheral serotonergic neurons by 5-HT transporters, resulting in enhanced 5-HT neurotransmission and stimulation of post-synaptic membrane 5-HT2C autoreceptors. Although the methodology of the initial drug treatment studies was poor, later double blind and placebo-controlled studies confirmed the ejaculation-delaying effect of clomipramine and SSRIs.

a) Daily treatment with Selective Serotonin Reuptake Inhibitors (SSRIs)

Daily treatment with paroxetine 10-40 mg, clomipramine 12.5-50 mg, sertraline 50-200 mg, fluoxetine 20-40 mg, and citalopram 20-40 mg is usually effective in delaying ejaculation [244-249] [242, 245-269] (Table 10) A meta-analysis of published data suggests that paroxetine exerts the strongest ejaculation delay, increasing IELT approximately 8.8 fold over baseline [244]. However, the use of these drugs is limited by the lack of Food and Drug Administration (FDA), European Medicines Agency (EMEA) or other regulatory agency approval and therefore by the need to prescribe “off-label” [270]. Ejaculation delay usually occurs within 5-10 days of starting treatment, but the full therapeutic effect may require 2-3 weeks of treatment and is usually sustained during long-term use (Figure 8) [271]. Although tachyphylaxis is uncommon, some patients report a reduced response after 6-12 months of treatment.
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**Figure 8:**
Selective serotonin re-uptake inhibitors produce ejaculatory delay within 5-10 days. [246]
Adverse effects are usually minor, start in the first week of treatment, gradually disappear within 2-3 weeks and include fatigue, yawning, mild nausea, diarrhea or perspiration. Hypoactive desire and ED are infrequently reported and appear to have a lower incidence in non-depressed PE men compared to depressed men treated with SSRIs [272]. This effect may be related to the protective action of increased oxytocin release in men with lifelong PE [88].

Neurocognitive adverse effects include significant agitation and hypomania in a small number of patients, and treatment with SSRIs should be avoided in men with a history of bipolar depression [273]. Systematic analysis of randomized controlled studies indicates no statistical evidence of an increased risk of suicide with SSRIs in adults [274, 275]. However, an FDA meta-analysis of all pediatric randomized clinical trials (RCTs) of antidepressants suggested a small increase in the risk of suicidal ideation or suicide attempts in youth [275]. This effect is quite variable across SSRIs and it is not clear if that variance is a measurement error or represents a real difference between medications. Furthermore, systematic questionnaire data, epidemiological and autopsy studies, recent cohort surveys, and the negligible number of suicides that occur in youth taking antidepressants at the time of death do not support the hypothesis that SSRIs induce suicidal acts and suicide, raising concerns over ascertainment artifacts in the adverse event report method [274]. However, it would seem prudent not to prescribe SSRIs to young men aged 18 years or less, and to men with a depressive disorder, particularly when associated with suicidal thoughts. Patients should be advised to avoid sudden cessation or rapid dose reduction of SSRIs which may be associated with a SSRI Withdrawal Syndrome, characterized by dizziness, headache, nausea, vomiting and diarrhoea and occasionally agitation, impaired concentration, vivid dreams, depersonalization, irritability and suicidal ideation [276, 277]. Platelet serotonin release has an important role in haemostasis [278] and SSRIs, especially with concurrent use of aspirin and non-steroidal anti-inflammatory drugs, which is associated with increased risk of upper gastro-intestinal bleeding [279, 280]. Priapism is a rare adverse effect of SSRIs and requires urgent medical treatment [281-283]. Long term SSRI use may be associated with weight gain and an increased risk of type-2 diabetes mellitus. [284].

**Level 1 evidence to support the efficacy and safety of off-label daily dosing of SSRIs (paroxetine, sertraline, citalopram, fluoxetine, and the serotonergic tricyclic, clomipramine) and off-label on-demand dosing of clomipramine for the treatment of PE**

**Grade A Recommendation**

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**b) Daily treatment with a1-adrenoceptor antagonists**

Ejaculation is a sympathetic spinal cord reflex which could theoretically be delayed by a1- adrenergic blockers. Several researchers have reported their experience with the selective a1 adrenergic blockers, alfuzosin and terazosin, in the treatment of PE. **(Table 11)** Both drugs are approved only for the treatment of lower urinary tract symptoms (LUTS) in men with obstructive benign prostatic hyperplasia (BPH). In a double blind placebo-controlled study, Cavallini reported that both alfuzosin (6 mg/day) and terazosin (5 mg/day) were effective in delaying ejaculation in approximately 50% of the cases [54]. Similarly, Basar reported that terazosin was effective in 67% of men [55]. However, both studies were limited by the use of subjective study endpoints of patient impression of change and sexual satisfaction, and they did not evaluate actual ejaculatory latency. Additional controlled studies are required to determine the role of a1-blockers in the treatment of PE.

**Level 2 evidence to support the efficacy and safety of off-label daily dosing of a1-adrenoceptor antagonists in the treatment of PE. Further evidence-based research is encouraged**

**Grade D Recommendation**

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**c) On-demand treatment with Selective Serotonin Reuptake Inhibitors**

Administration of clomipramine, paroxetine, sertraline and fluoxetine 4-6 hours before intercourse is modestly efficacious and well tolerated but is associated with substantially less ejaculatory delay than daily treatment [70, 285-287]. **(Table 12)** Following acute on-demand administration of an SSRI, increased synaptic 5-HT levels are down-regulated by presynaptic 5-HT1A and 5-HT1B/1D autoreceptors to prevent over-stimulation of postsynaptic 5-HT2C receptors. However, during chronic daily SSRI administration, a series of synaptic adaptive processes which may include presynaptic 5-HT1A and 5-HT1B/1D receptor desensitization greatly enhances synaptic 5-HT levels, resulting in superior fold increases in IELT compared to on-demand administration. [86] On-demand treatment may be combined with either an initial trial of daily treatment or concomitant low dose daily treatment [70, 285, 286].

The assertion that on-demand drug treatment of PE is preferable to daily dosing parallels the rationale for the treatment of ED but is contrary to the results of the only PE drug preference study [65]. The methodology of this trial was not ideal as it involved comparison of preference for daily paroxetine, on-demand clomipramine, or topical anesthetic based only on subject information/questionnaires and not on actual use of the drug/s. Well-designed preference trials will provide additional insight into the role of on-demand...
dosing. While many men suffering from PE who engage in sexual intercourse infrequently may prefer on-demand treatment, many men in established relationships prefer the convenience of daily medication.

d) On-demand treatment with Dapoxetine

Dapoxetine is an investigational SSRI with a pharmacokinetic profile suggesting a role as an on-demand treatment for PE [288-291]. Dapoxetine has a Tmax of 1.4-2.0 hours and a mean half-life of 0.5-0.8 hours with a rapid decline of plasma levels to about 5% of Cmax at 24 hours, ensuring rapid absorption and achievement of peak plasma concentration with minimal accumulation [292]. Both plasma concentration and area under the curve (AUC) are dose dependent up to 100 mg, and are unaffected by repeated daily dosing, food or alcohol [293-295]. No drug-drug interactions associated with dapoxetine, including phosphodiesterase inhibitor drugs, have been reported [296].

In randomized, double-blind, placebo-controlled, multicenter, phase III 12 week clinical trials involving 2,614 men with a mean baseline IELT ≤ 2 minutes, dapoxetine 30 mg or 60 mg was more effective than placebo for all study endpoints (Figure 9) [291] (Table 12). Arithmetic mean IELT increased from 0.91 minutes at baseline to 2.78 and 3.32 minutes at study end with dapoxetine 30 and 60 mg respectively compared to a 1.75 minutes with placebo. However, as IELT in subjects with PE is distributed in a positively skewed pattern, reporting IELTs as arithmetic means may over-estimate the treatment response, and the geometric mean IELT is more representative of the actual treatment effect [66, 260, 271, 297, 298]. Pooled data from 4 phase 3 dapoxetine studies report arithmetic and geometric mean IELTs of 1.9 and 1.2 for placebo, 3.1 and 2.0 for dapoxetine 30 mg, and 3.6 and 2.3 for dapoxetine 60mg respectively. This represents a 1.6, 2.5, and 3.0 fold increase over baseline geometric mean IELT for placebo, and dapoxetine 30 and 60 mg respectively Dapoxetine treatment is also associated with significant improvements in patient reported outcomes (PROs) of control, distress and sexual satisfaction (Figure 9). Mean patient rating of control-over-ejaculation as fair, good, or very good increased from 2.8% at baseline to 51.8% and 58.4% at study end with dapoxetine 30 and 60 mg respectively. Treatment related side effects were uncommon, dose dependent, included nausea, diarrhea, headache, and dizziness, and were responsible for study discontinuation in 4% (30mg) and 10% (60mg) of subjects. There was no indication of an increased risk of suicidal ideation or suicide attempts and little indication of withdrawal symptoms with abrupt dapoxetine cessation [299].

There have been 3 independent studies of the efficacy of dapoxetine administered on a daily basis, inconsistent with the manufacturer’s prescribing information. [300-302]

Dapoxetine, despite its modest effect upon ejaculatory latency, has a major place in the management of PE which will eventually be determined by market forces once the challenges of global regulatory approval have been met.

Level 1 evidence to support the efficacy and safety of on-demand dosing of dapoxetine for the treatment of PE

Grade A Recommendation

The decision to treat PE with either current off-label SSRI daily dosing or on-demand dosing of dapoxetine must be based on the treating physician’s assessment of individual patient requirements.

e) On-demand treatment with Tramadol

Tramadol is a centrally acting synthetic opioid analgesic with an unclear mode of action which is thought to include binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of re-uptake
Figure 9. A. Dapoxetine increased intravaginal ejaculatory latency time (IELT) from 0.91 minutes at baseline to 2.78 and 3.32 minutes at study end with dapoxetine 30 and 60 mg respectively. B. % of subjects rating Control over Ejaculation as fair, good, or very good increased from 3.1% at baseline to 51.8% and 58.4% at study end with dapoxetine 30 and 60 mg respectively. C. % of subjects rating Sexual Satisfaction as fair, good or very good increased from 53.6% at baseline to 70.9% and 79.2% with dapoxetine 30mg and 60mg respectively. (rating scale 0-5 scale, 0=very poor & 5=very good) [507]
of GABA, norepinephrine, and serotonin [303]. The efficacy of on-demand tramadol in the treatment of PE was recently reported in 2 RCTs [304, 305]. (Table 13) Both studies were limited by methodological considerations, and although tramadol is reported to have a lower risk of dependence than traditional opioids, its use as an on-demand treatment for PE is limited by the potential risk of addiction [306].

In community practice, dependence does occur but appears minimal [307]. Adams et al reported abuse rates of 0.7% for tramadol compared to 0.5% for non-steroidal anti-inflammatory drugs and 1.2% for hydrocodone based upon application of a dependency algorithm as a measure of persistence of drug use [308]. Additional flexible dose, long term follow-up studies to evaluate efficacy, safety and in particular, the risk of opioid addiction are required.

**Level 2 evidence to support the efficacy and safety of off-label daily dosing of off-label tramadol in the treatment of PE. Further evidence-based research is encouraged**

**Grade D Recommendation**

### f) Topical anesthetics

The use of topical local anesthetics such as lignocaine and/or prilocaine as a cream, gel, or spray is well established and is moderately effective in retarding ejaculation. [309-321] (Table 14)

Their use may be associated with significant penile hypo-anesthesia and possible transvaginal absorption, resulting in vaginal numbness and resultant female anorgasmia unless a condom is used. A recent study reported that a metered-dose aerosol spray containing a eutectic mixture of lidocaine and prilocaine (TEMPE®) produced a 2.4 fold increase in baseline IELT and significant improvements in ejaculatory control and both patient and partner sexual quality-of-life [320]. The physiochemical characteristics of this eutectic mixture and the spray delivery system have been designed to both optimize and limit tissue penetration to the mucosa of the glans penis and minimize penetration of the keratinized skin of the penile shaft [322]. Penile hypoanesthesia was reported by 12% of subjects; skin irritation or burning was not observed.

**Level 1 evidence to support the efficacy and safety of off-label on-demand current off-label topical anaesthetics in the treatment of PE**

**Grade B Recommendation**

### g) Intracavernous injection of vasoactive drugs

Intracavernous self-injection treatment of PE has been reported but is currently without any evidence-based support for efficacy or safety [323]. Fein reported an open study of 8 men treated with a combination of papaverine and phentolamine administered by intracavernous auto-injection where treatment success was defined as prolongation of erection after ejaculation and not by any measure of ejaculatory latency. In the absence of well-controlled studies, treatment of PE by intracavernous auto-injection cannot be routinely recommended but may be of value in treatment refractory informed subjects.

**Level 2 evidence to support the efficacy and safety of off-label penile injection therapy in the treatment of PE. Further evidence-based research is encouraged**

**Grade D Recommendation**

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**Table 13: Level of Evidence - Drug Treatment for Premature Ejaculation – Tramadol**

<table>
<thead>
<tr>
<th>Author/s</th>
<th>Drug/s</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safarinejad MR et al. [304]</td>
<td>Tramadol</td>
<td></td>
</tr>
<tr>
<td>Salem EA et al [305]</td>
<td>Tramadol</td>
<td></td>
</tr>
</tbody>
</table>

**Table 14: Level of Evidence - Drug Treatment for Premature Ejaculation – Topical Local Anaesthetics**

<table>
<thead>
<tr>
<th>Author/s</th>
<th>Drug/s</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi HK, Jung GW, Moon KH. et al. [312]</td>
<td>SS-Cream</td>
<td>1</td>
</tr>
<tr>
<td>Atikeler, M. K., Gecit, I., Senol, F. A [313]</td>
<td>Prilocaine-lidocaine</td>
<td>1</td>
</tr>
<tr>
<td>Damru, F [314]</td>
<td>Ethyl aminbenzoate</td>
<td>1</td>
</tr>
<tr>
<td>Berkovitch, M., Keresteci, A. G., Koren, G [309]</td>
<td>Prilocaine-lidocaine</td>
<td>1</td>
</tr>
<tr>
<td>Sahin et al [315]</td>
<td>Prilocaine-lidocaine</td>
<td>3</td>
</tr>
<tr>
<td>Busato W, Galindo CC, [311]</td>
<td>Prilocaine-lidocaine</td>
<td></td>
</tr>
<tr>
<td>Xin, Z. C., Choi, Y. D., Choi, H. K [317]</td>
<td>SS Cream</td>
<td>3</td>
</tr>
<tr>
<td>Xin, Z. C., Choi, Y. D., Lee, S. H. et al [318]</td>
<td>SS Cream</td>
<td>1</td>
</tr>
<tr>
<td>Xin, Z. C., Choi, Y. D., Seong, D. H. et al [319]</td>
<td>SS Cream</td>
<td>1</td>
</tr>
<tr>
<td>Xin, Z. C., Choi, Y. D., Choi, H. K[310]</td>
<td>SS Cream</td>
<td></td>
</tr>
<tr>
<td>Dinsmore W et al. [320]</td>
<td>TEMPE</td>
<td></td>
</tr>
<tr>
<td>Dinsmore W et al. [321]</td>
<td>TEMPE</td>
<td></td>
</tr>
<tr>
<td>Henry R, Morales A et al. [322]</td>
<td>TEMPE</td>
<td></td>
</tr>
</tbody>
</table>
h) Phosphodiesterase inhibitors

Phosphodiesterase type-5 isoenzyme (PDE5) inhibitors, sildenafil, tadalafil, and vardenafil, are effective treatments for ED. Several authors have reported experience with PDE-5 inhibitors alone or in combination with SSRIs as a treatment for PE [212, 213, 316, 324-338]. (Table 15) The putative role of PDE-5 inhibitors as a treatment for PE is speculative and based only upon the role of the NO/cGMP transduction system as a central and peripheral mediator of inhibitory non-adrenergic, non-cholinergic nitricergic neurotransmission in the urogenital system [339]. A recent systematic review of 14 studies (n=1,102) on the PDE5i drug treatment of PE failed to provide robust empirical evidence to support a role of PDE-5 inhibitors in the treatment of PE with the exception of men with PE and co-morbid ED [180]. Only one study fulfilled the contemporary criteria of ideal PE drug trial design [340, 341], and this study failed to confirm any significant treatment effect on IELT [332]. Caution should be exercised in interpreting PDE5i and on-demand SSRI treatment data in inadequately designed studies and their results must be regarded as unreliable.

At this time, Level 4 evidence to support the efficacy and safety of off-label on-demand or daily dosing of PDE-5 inhibitors in the treatment of lifelong PE in men with normal erectile function. Further evidence-based research is encouraged to further understand conflicting data

**Grade D Recommendation**

i) Premature ejaculation and co-morbid ED

Recent data demonstrate that as many as one third to one half of subjects with ED also experience PE [104, 105]. There is evidence to suggest that PDE5i’s alone or in combination with a SSRI may have a role in the management of acquired PE in men with co-morbid ED [324, 329, 333]. In 45 men with PE and co-morbid ED treated with flexible doses of sildenafil (50-100mg) for periods of 1-3 months, Li et al reported improved erectile function in 40 men (89%) and reduced severity of PE in 27 men (60%) [329]. In a group of 37 men with primary or acquired PE and a baseline IIIEF EF domain score of 20.9 consistent with mild ED, Sommer et al reported and a 9.7 fold IELT increase and normalization of erectile function (IIIEF EF 26.9) with vardenafil treatment as opposed to lesser 4.4 fold IELT increase with on-demand sertraline [333].

The high correlation between improved erectile function with sildenafil and reduced severity of PE reported by Li [329] and the superior IELT fold-increase observed with vardenafil compared to sertraline reported by Sommer et al indicates that the PDE5i-related reduced PE severity is due to improved erectile function [333]. The IELT fold-increase observed by Sommer et al with on-demand sertraline (4.4) is less than that reported in reviewed studies on men with normal erectile function (mean 5.57, range 3.0-8.5) [213, 324, 330, 331], suggesting that men with PE and co-morbid ED are less responsive to on-demand SSRIs and are best managed with a PDE5i alone or in combination with an SSRI. The proposed mechanism of action of PDE5i’s as monotherapy or in combination with a SSRI in the treatment of acquired PE in men with co-morbid ED includes a reduction in performance anxiety due to better erections, down-regulation of the erectile threshold to a lower level of arousal so that increased levels of arousal are required to achieve the ejaculation threshold and reduction of the erectile refractory period [332, 342, 343], and reliance upon a second and more controlled ejaculation during a subsequent episode of intercourse.

**Table 15: Level of Evidence - Drug Treatment for Premature Ejaculation – Phosphodiesterase Type 5 Inhibitors**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Drug/s</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chia SJ. [324]</td>
<td>Sildenafil</td>
<td>2</td>
</tr>
<tr>
<td>Salonia, A., Maga, T., Colombo, R. et al. [325]</td>
<td>Sildenafil</td>
<td>1</td>
</tr>
<tr>
<td>Chen, J., Mabjeesh, N. J., Matzkin, H. et al. [328]</td>
<td>Sildenafil</td>
<td>2</td>
</tr>
<tr>
<td>Zhang XS et al. [331]</td>
<td>Sildenafil</td>
<td>3</td>
</tr>
<tr>
<td>Tang W et al. [212]</td>
<td>Sildenafil</td>
<td>3</td>
</tr>
<tr>
<td>McMahon CG et al. [332]</td>
<td>Sildenafil</td>
<td>1</td>
</tr>
<tr>
<td>Li X et al. [329]</td>
<td>Sildenafil</td>
<td>3</td>
</tr>
<tr>
<td>Atan A et al. [514]</td>
<td>Sildenafil</td>
<td>2</td>
</tr>
<tr>
<td>Aversa A et al. [337]</td>
<td>Vardenafil</td>
<td>1</td>
</tr>
<tr>
<td>Sun XZ et al. [335]</td>
<td>Vardenafil</td>
<td>3</td>
</tr>
<tr>
<td>Mathers, MJ et al. [338]</td>
<td>Vardenafil</td>
<td>3</td>
</tr>
<tr>
<td>Mattos RM et al. [336]</td>
<td>Tadalafil</td>
<td>2</td>
</tr>
</tbody>
</table>
penis augmentation in the treatment of lifelong PE refractory to behavioural and/or pharmacological treatment. [344-346] The role of surgery in the management of PE remains unclear until the results of further studies have been reported.

**Level 4 evidence i.e. no evidence, to suggest that selective dorsal nerve neurotomy or hyaluronic acid gel glans penis augmentation are effective treatments for PE. Surgery may be associated with permanent loss of sexual function and is contraindicated in the management of PE**

**Grade D Recommendation**

3. THE FUTURE OF PE DRUG DEVELOPMENT

Several in-vitro and animal studies have demonstrated that the desensitization of 5-HT1A receptors, increased activation of postsynaptic 5-HT2C receptors, and the resultant higher increase in synaptic 5-HT neurotransmission seen in daily dosing of SSRI class drugs can be acutely achieved by blockade of these receptors by administration of an on-demand SSRI and a 5-HT1A receptor antagonist [347-349]. One study reports that PE men refractory to daily paroxetine can be salvaged by the addition of high dose daily pindolol, a non-selective ß-blocker with partial beta-agonist activity and a 5-HT1A receptor antagonist [350].

An increasing number of studies report the involvement of central oxytocinergic neurotransmission in the ejaculatory process. In human males, plasma oxytocin levels are elevated during penile erection and at the time of orgasm [351, 352]. Electrical stimulation of the dorsal penile nerve produced excitation in about half of the oxytocin cells in the PVH and SON of rats [353, 354]. In a rat model, systematic administration of oxytocin facilitated ejaculation by reducing the number of intromissions required for ejaculation, ejaculation latencies, and post-ejaculation intervals [355, 356]. The use of oxytocin or vasopressin receptor antagonists may also have a role but there have been no reports of their efficacy in the treatment of PE [357].

Drug combinations of on-demand rapid acting SSRI and 5-HT1A receptor antagonist and/or oxytocin receptor antagonists, or single agents that target multiple receptors may form the foundation of more effective future on-demand medication.

**4. THE OFFICE MANAGEMENT OF PREMATURE EJACULATION: A BRIEF SUMMARIZATION**

Men with premature ejaculation should be evaluated with a detailed medical and sexual history, a physical examination, and appropriate investigations to establish the true presenting complaint, identify obvious biological causes such as medication or recent pelvic surgery, and uncover sufficient detail to establish the optimal treatment plan. **(Figure 10)**

Relevant information to obtain from the patient includes:

1. A basic medical history, including the use of prescribed and recreational medications
2. The cultural context and developmental history of the disorder, including whether the premature ejaculation is global or situational, lifelong or recent in its development,
3. Measures of the quality of each of the three phases of the sexual response cycle: desire, arousal, and ejaculation, since the desire and arousal phases may impact the ejaculatory response,
4. Details about the ejaculatory response, including the patient’s subjective assessment of his intravaginal ejaculatory latency time (IELT) and sense of ejaculatory control, the level of sexual dissatisfaction and distress, the frequency of sexual activity, and so on,
5. The partner’s assessment of the situation, including whether the partner suffers from female sexual dysfunction (FSD), and
6. Assessment of the sexual and overall relationship

**Level 3 evidence to suggest that evaluation of men presenting with self reported PE should include a full medical/sexual history, a focused physical examination, inventory assessment of erectile function and any investigations suggested by these findings**

**Grade C Recommendation**

Comprehensive and helpful decision trees that incorporate inclusion and exclusion criteria and that address most of the above points have recently been published in several sources [63, 358]. Several paper and pencil instruments that enable the health provider to tap into some or most of the specific domains above are also available [237, 359]. Although more typically used in the experimental study of PE, psychophysiological and/or electrophysiological evaluation can sometimes play a limited secondary role in the evaluation of early ejaculation. For example, visual sexual and penile stimulation administered in the laboratory elicits ejaculation in nearly 60% of men self-identified as having PE, compared with only about 8% of men having no ejaculatory disorder [69, 360]. The former group also reports a greater proximity to ejaculation and less ejaculatory control in response to such stimulation. In addition, PE men tend to exhibit stronger event-related potentials (ERP’s) to stimulation of the afferent pudendal nerves and shorter latencies in the efferent processes involved in bulbocavernosal contractions.
eliciting seminal expulsion [361-363]. Although most such evaluations can aid in the understanding of potential causes or mediators of PE, because they are time-consuming, labor intensive, and not yet reliably discriminating at an individual level, it is too early to assume a role for these procedures in the verification of a PE diagnosis.

Men with premature ejaculation secondary to erectile dysfunction, other sexual dysfunction, or genitourinary infection should receive appropriate etiology specific treatment. Men with lifelong premature ejaculation are usually best managed with pharmacotherapy. Men with significant contributing psychogenic or relationship factors may benefit from concomitant cognitive-behavioral therapy. [210-212] Recurrence of premature ejaculation is highly likely to occur following withdrawal of treatment. Men with acquired premature ejaculation can be treated with pharmacotherapy and/or cognitive-behavioral therapy according to patient/partner preference. [210-212] Restoration of ejaculatory control in men with acquired premature ejaculation is likely to occur following completion of treatment but this result appears to be the exception in men with lifelong PE. Cognitive-behavioral therapy may augment pharmacotherapy to enhance relapse prevention.

V. DELAYED EJACULATION, ANEJACULATION, AND ANORGASMIA: DEFINITION, EPIDEMIOLOGY, & PATHOPHYSIOLOGY

Any psychological or medical disease or surgical procedure which interferes with either central control of ejaculation or the peripheral sympathetic nerve supply to the vas and bladder neck, the somatic efferent nerve supply to the pelvic floor, or the somatic afferent nerve supply to the penis can result in delayed ejaculation, anejaculation and anorgasmia. As such, the causes of delayed ejaculation, anejaculation and anorgasmia are manifold (Table 16).

The progressive loss of the fast conducting peripheral sensory axons which begins to be apparent in the third decade of life, and the dermal atrophy, myelin collagen infiltration, and pacinian corpuscle degeneration observed in older men may result in a degree of age related degenerative penile hypo-anesthesia and difficulty in achieving the ejaculatory threshold. This is anecdotally exaggerated in men with ED treated with intracavernous pharmacotherapy and is often compounded by the loss of pelvic floor muscle tone seen in the similar aged, post-menopausal and often multiparous sexual partners of these men.

Figure 10. Management algorithm for premature ejaculation
1. DEFINITION, TERMINOLOGY, AND CHARACTERISTICS OF DELAYED EJACULATION

Delayed (DE), Retarded Ejaculation (RE), or Inhibited Ejaculation (IE) are probably the least common, least studied, and least understood of the male sexual dysfunctions. Yet its impact is significant in that it typically results in a lack of sexual fulfillment for both the man and his partner, an effect further compounded when procreation is among the couple’s goals of sexual intercourse.

Problems with “difficulty” in ejaculating may range from varying delays in the latency to ejaculation to complete inability to ejaculate (anejaculation). Reductions in the volume, force, and sensation of ejaculation may occur as well. At the extremes are anejaculation (time) and retrograde ejaculation (direction), but more commonly encountered is Inhibited or Retarded ejaculation (DE). Partially retarded ejaculation (PRE) is sometimes observed in men who attempt to control ejaculation by suppressing the muscular contractions associated with ejaculation. These men experience diminished pleasure and sensation as semen is released during emission, and the ejaculatory sensations are dulled through attempted suppression of striate muscle response. PRE is sometimes observed in men with PE as they first attempt to consciously delay their orgasm. A final disorder, anorgasmia, refers to a perceived absence of the orgasm experience, independent of whether or not any or all of the physiologic concomitants of ejaculation have taken place.

a) Terminology and definition

The terminology for difficulties achieving ejaculation is far from precise. Retarded ejaculation, delayed ejaculation, inadequate ejaculation, inhibited ejaculation, idiopathic anejaculation, primary impotence ejaculations, and psychogenic anejaculation have all been used synonymously to describe a delay or absence of male orgasmic response. If a distinction is to be made, usually inhibited ejaculation is characterized by the complete absence of ejaculation, although even here no clear consensus exits. In this review, the terminology Retarded Ejaculation (RE) or the preferred Delayed Ejaculation (DE) is meant to describe any and all of the ejaculatory disorders resulting in a delay or absence of ejaculation.

The DSM-IV-TR defines DE as the persistent or recurrent delay in, or absence of, orgasm after a normal sexual excitement phase during sexual activity that the clinician, taking into account the person’s age, judges to be adequate in focus, intensity, and duration. The disturbance causes marked distress or interpersonal difficulty; it should not be better accounted for by another Axis I (clinical) disorder or caused exclusively by the direct physiologic effects of a substance or a general medical condition [364]. Similarly, the World Health Organization 2nd Consultation on Sexual Dysfunction defines DE as the persistent or recurrent difficulty, delay in, or absence of attaining orgasm after sufficient sexual stimulation, which causes personal distress [75].

There are no clear criteria as to when a man actually meets the conditions for DE, as operationalized criteria do not exist. Given that most sexually functional men ejaculate within about 4-10 minutes following intromission [193], a clinician might assume that men with latencies beyond 25 or 30 minutes (21-23 min represents about two standard deviations above the mean) who report distress or men who simply cease sexual activity due to exhaustion or irritation qualify for this diagnosis. Such symptoms, together with the fact that a man and/or his partner decide to seek help for the problem, are usually sufficient for a DE diagnosis.

b) The prevalence of retarded or delayed ejaculation

The prevalence of ejaculatory disorders is unclear, partly because of the dearth of normative data for defining the duration of “normal” ejaculatory latency, particularly regarding the right “tail” of the distribution (i.e., beyond the mean latency to orgasm). Furthermore, larger epidemiologic studies have not subdivided various types of ejaculatory disorders (e.g., delayed vs. absent), further limiting our knowledge of the prevalence of DE. In general,
DE is reported at low rates in the literature, rarely exceeding 3% [85, 365, 366]. Since the beginning of sex therapy, DE was seen as a clinical rarity, with Masters and Johnson [224] initially reporting only 17 cases. Apfelbaum [367] reported 34 cases and Kaplan [368] fewer than 50 cases in their respective practices. However, based on clinical experiences, some urologists and sex therapists are reporting an increasing prevalence of DE [366, 369, 370]. The prevalence of DE appears to be moderately and positively related to age, which is not surprising in view of the fact that ejaculatory function as a whole tends to diminish as men age.

c) Characteristics of men with delayed ejaculation

Failure of ejaculation can be a lifelong primary event or an acquired or secondary problem. It may be global and happen in every sexual encounter or it may be intermittent or situational. Normative descriptive data from large samples of DE men have not been available, but a recent analysis identified 25% of a clinical sample suffering from primary DE, with the remainder reporting a secondary problem [365]. While coital anorgasmia is frequently the treatment driver (especially for extremely religious individuals referred for fertility problems), heterosexual men also seek treatment when distressed by their inability to achieve orgasm in response to manual, oral, or vaginal stimulation by their partner. Data available on homosexual men are limited, but distress/frustration associated with not being able to ejaculate by any desired/chosen mode of stimulation remains fairly constant across all men, regardless of sexual orientation [371].

Many men with secondary DE can masturbate to orgasm, whereas others, for multiple reasons, will or can not. Loss of masturbatory capacity secondary to emotional or physical trauma is also seen. Approximately 75% of one clinical sample [365] could reach orgasm through masturbation, while the remainder either would not or could not. Interestingly, correlational evidence suggests that masturbatory frequency and style may be predisposing factors for DE, since a substantial portion of men who present with coital DE report high levels of activity with an idiosyncratic masturbatory style [372, 373].

Similar to men with other types of sexual dysfunction, men with DE indicate high levels of relationship distress, sexual dissatisfaction, anxiety about their sexual performance, and general health issues—significantly higher than sexually functional men. In addition, along with other sexually dysfunctional counterparts, men with DE typically report lower frequencies of coital activity [373]. A distinguishing characteristic of men with DE—and one that has implications for treatment—is that they usually have little or no difficulty attaining or keeping their erections—in fact they are often able to maintain erections for prolonged periods of time. But despite their good erections, they report low levels of subjective sexual arousal, at least compared with sexually functional men [374].

2. PATHOPHYSIOLOGIES COMMONLY LEADING TO EJACULATORY DISORDERS, INCLUDING DE

a) Congenital disorders

1) Mullerian Duct Obstruction

As the male fetus develops, the Mullerian ducts normally disappear from above downwards under the influence of Mullerian inhibitory factor (MIF), which is produced by the Sertoli cells in the primitive testis. Failure of complete absorption may leave a small Mullerian duct remnant at the lower end that lies between the ejaculatory ducts. The Wolffian (mesonephric) ducts are composed of three distinct areas. The upper part forms the epididymis and distal vas deferens, while the proximal vas deferens, seminal vesicle, and ejaculatory duct are derived from the middle area. The most caudal part is the common mesonephric duct, from which the ureteric bud springs at approximately 4 weeks of development: this becomes the ureter and will induce the metanephric blastema to form the kidney. The urogenital sinus reabsorbs the lower end of this structure, and the ureteric orifices are thus separated from the vasa deferentia, seminal vesicles and ejaculatory ducts. Several complex anomalies may occur in this area leading to ectopic opening of the vas deferens and sometimes associated with anorectal anomalies [375]. If too much of the proximal vas precursor is absorbed, a variable amount of the proximal vas, seminal vesicle, and/or ejaculatory duct may be absent. There may also be coexisting abnormalities in the ipsilateral kidney or ureter.

Persistence of a small remnant of the Mullerian duct may lead to a cyst forming between the ejaculatory ducts which can become obstructed and cause diminution of the volume of the ejaculate and infertility. Haemospermia is not uncommon in these patients. Seminal analysis shows the changes characteristic of ejaculatory duct obstruction with a small volume (less than 1.5 ml), acid pH, and little or no fructose. Both vasa are palpable and the epididymes usually feel distended. The diagnosis is established by transrectal ultrasound scan (TRUS), and the lesion can be delineated by percutaneous puncture of the cyst with instillation of radio opaque medium. The cyst can be incised or deroofed endoscopically after delineating its extent by injection of blue dye (see below). Improvement in ejaculate volume and seminal quality follows in most cases [376].

2) Wolffian Duct abnormalities

Congenital anomalies may be either sporadic, with
a localized defect in the proximal part of the vas deferens, or a more generalized maldevelopment due to a systemic genetic abnormality. Local Wolffian duct abnormality involves loss of a variable amount of the vas deferens, seminal vesicle, and/or ejaculatory duct, and sometimes part of the ipsilateral urinary system as well. This may be associated with maldevelopment of the bladder neck and trigone, which fails to close effectively and thereby produces retrograde ejaculation. Bilateral abnormalities are often associated with carriage of the cystic fibrosis gene [377]. Unilateral absence of the vas deferens has been observed in 5%, and bilateral absence in 18% of 370 azoospermic males with normal serum FSH levels investigated by the author [378].

3) PRUNE BELLY SYNDROME

Patients with prune belly syndrome have normal libido, erections, and orgasms. Most have abnormal ejaculation and probably emission. In a study involving nine patients, seven had retrograde ejaculation and two produced ejaculates [379]. Five patients provided semen or urine passed after masturbation. Two produced ejaculated semen. One of the ejaculated specimens consisted of 4.5 cc of fluid indistinguishable from urine and one was 2.5 cc of fluid with the appearance of watery semen. Post masturbation urine specimens were of normal urinary appearance. None of the specimens contained sperm and no mention was made of the fructose content. Abnormal ejaculation thus appears to be present in the vast majority of patients with prune belly syndrome. Whether the primary abnormality is retrograde ejaculation or lack of emission is not clear.

b) Traumatic damage

1) IMPERFORATE ANUS

Ejaculatory duct obstruction may follow correction of imperforate anus. The pull through procedure passes close to the posterior aspect of the prostate, and damage is most likely if there has been closure of a recto urethral fistula. Analysis of 20 subfertile males who had repair of imperforate anus in infancy indicated that 7 had no ejaculate, 11 were azoospermic, 1 was severely oligozoospermic, and only 1 had a normal sperm concentration in a very small volume ejaculate [380]. Both vasa were blocked in 5 men and one vas in a further 8 patients, apparently as a result of the original operative procedure.

2) OPERATIONS ON THE PROSTATE

Antegrade (normal) ejaculation requires a closed bladder neck (and proximal urethra). Surgical procedures that compromise the bladder neck closure mechanism may result in retrograde ejaculation. Transurethral incision of the prostate (TUIP) results in retrograde ejaculation in 5% [381] to 45% [382] of patients and is probably related to whether one or two incisions are made and whether or not the incision includes primarily the bladder neck or extends to the level of the verumontanum. The importance of contraction of the urethral smooth muscle at the level of the verumontanum has been hypothesized to be important in preventing retrograde ejaculation [383]. Transurethral resection of the prostate (TURP) carries a higher incidence of retrograde ejaculation than does TUIP. The reported incidence of retrograde ejaculation following TURP ranges from 42% [384] to 100% [385]. Although these men may have some antegrade ejaculation and usually experience orgasmic sensation, both events may be reduced as part of the changes that occur in the male sexual response as a man ages. Retrograde ejaculation and failure of emission can be distinguished by examination of a post masturbatory specimen of urine for the presence of spermatozoa and fructose. After radical prostatectomy, ejaculation is bound to be lost since the seminal vesicles are removed with the prostate gland. Erectile impotence was common until detailed anatomical studies showed where the parasympathetic nerves ran on the surface of the prostate gland, and a nerve sparing operative technique was developed [386]. A sensation of orgasm is often preserved despite loss of ejaculation.

Retrograde ejaculation can be surgically treated with bladder neck reconstruction but results remain consistently poor [386]. Drug treatment is the most promising approach. As mentioned earlier, alpha-adrenergic sympathetic nerves mediate both bladder neck closure and emission. Several sympathomimetic agents have been described as useful with mixed results [387]. These drugs include pseudoephedrine and ephedrine, and phenylpropanolamine. These agents work by stimulating the release of noradrenaline from the nerve axon terminals but may also directly stimulate both alpha- and beta-adrenergic receptors. The most useful is pseudoephedrine which is administered at a dose of 120 mg 2-2.5 hours precoital. The tricyclic antidepressant, Imipramine, which blocks the reuptake of noradrenaline by the axon from the synaptic cleft, is also occasionally useful [388]. The usual dose is 25mg twice daily. Current thinking is that long-term treatment with imipramine is likely to be more effective. While medical treatment may not always produce normal ejaculation, it may result in some prograde ejaculation. In patients who do not achieve antegrade ejaculation with surgery or medication, sperm retrieval and artificial insemination is an alternative approach. The basic method of sperm retrieval involves recovery of urine by either catheter or voiding after masturbation, and then centrifugation and isolation of the sperm.

3) INFECTIVE DISORDERS

Genital infection such as gonorrhoea or non specific
urethral strictures can produce stricture formation in any part of the male reproductive tract, especially if treatment is delayed. Urinary infection, especially if complicated by epididymitis, can also produce obstruction that may be situated at ejaculatory duct level.

Routine vasography in subfertile men with azospermia and normal serum FSH levels revealed post-infective vasal blocks in 8% and acquired ejaculatory duct obstruction in 4% [378]. Schistosomiasis is endemic in large parts of Africa and is seen with increasing frequency in tourists returning from Africa who have contracted the disease while enjoying water sports: Lake Malawi has acquired an evil reputation in this respect. The disease may present with haemospermia [389], and fibrosis and calcification may lead to genital obstruction. Genito urinary tuberculosis can cause great damage to the male reproductive tracts, and since healing occurs with calcification, the lesions may be irreparable. Plain X ray will often show the extent of the disease.

Haemospermia is seldom as ominous a symptom as haematuria, but this complaint should not be ignored. Analysis of the findings in 81 patients revealed that an inflammatory cause could be defined in most men under 30 years of age; however, there were a few (8%) with more serious disease including carcinoma of prostate and bladder [390]. It should be remembered, also, that schistosomiasis and tuberculosis could present in this way. Routine investigation of haemospermia by TRUS not uncommonly reveals the presence of small stones in the ejaculatory ducts, which may be associated with obstruction and dilatation of the seminal vesicles. Such stones usually pass spontaneously.

c) Neurological disorders

1) **Spinal cord injury**

The ability to ejaculate is severely impaired by spinal cord injury (SCI). Bors and Comarr highlighted the impact of the level and completeness of SCI on the post-injury erectile and ejaculatory capacity (Table 17) [391, 392]. Unlike erectile capacity, the ability to ejaculate increases with descending levels of spinal injury. Less than 5% of patients with complete upper motor neuron lesions retain the ability to ejaculate. Ejaculation rates are higher (15%) in patients with both lower motor neuron lesions and an intact throracolumbar sympathetic outflow. Approximately 22% of patients with an incomplete upper motor neuron lesion and almost all men with incomplete lower motor neuron lesions retain the ability to ejaculate. In those patients capable of successful ejaculation, the sensation of orgasm may be absent and retrograde ejaculation often occurs.

Several techniques for obtaining semen from spinal cord injured men with ejaculatory dysfunction have been reported. The intrathecal administration of the anticholinesterase inhibitors neostigmine and subcutaneous physostigmine to induce ejaculation is more of historical interest and is no longer used due to a 60% risk of autonomic dysreflexia, especially in men with injuries above the T5 level [393, 394]. Vibratory stimulation is successful in obtaining semen in up to 70% of men with spinal cord injury [395]. This technique induces a reflexogenic ejaculation via the sacral roots and the ejaculatory coordination center in the upper thoracolumbar spinal cord. The use of electro-ejaculation to obtain semen by electrical stimulation of efferent sympathetic fibers of the hypogastric plexus is an effective and safe method of obtaining semen. Brindley et al have reported that 71% of men with spinal cord injury who underwent electro-ejaculation achieved ejaculation [396]. However, both are associated with a significantly higher risk of autonomic dysreflexia than electro-ejaculation. Pre-treatment with a fast acting vasodilator such as nifedipine minimizes the risk of severe hypertension, should autonomic dysreflexia occur with either form of treatment [397].

Several authors have reported the use of midodrine in spinal cord injured patients. In recent studies, antegrade or retrograde ejaculation occurred in 22-64.6% of spinal cord injured patients who had previously failed to respond to penile vibratory stimulation, following treatment with midodrine 30–120 min before a new stimulation. [398, 399]

If the spinal reflex arc is intact, a hypogastric plexus stimulator can provide ejaculation in the comfort and security of the patients’ home [400]. Percutaneous aspiration of semen from the vas deferens has also been reported as a means of harvesting semen for use with artificial reproductive techniques [401].

Semen collected from men with spinal cord injury is often initially senescent and of poor quality with a low sperm count and reduced sperm motility but may improve with subsequent ejaculations. This poor semen quality may be due to chronic urinary tract infection, sperm content with urine, chronic use of various medications, elevated scrotal temperature due to prolonged sitting, and stasis of prostatic fluid. Testicular biopsies in spinal cord injured men demonstrate a wide range of testicular dysfunction including hypospermatogenesis, maturation arrest, atrophy of seminiferous tubules, germinal cell hypoplasia, interstitial fibrosis, and Leydig cell hyperplasia. In addition, prostatitis secondary to prolonged catheterization, epididymitis, and epididymo-orchitis can precipitate obstructive ductal lesions and testicular damage. Ohl et al reported that sperm density and motility were higher in those with incomplete lesions [402]. In a recent collective analysis of 40 paraplegic patients, 22 successfully produced pregnancies by natural insemination or assisted reproductive techniques [403].

2) **Para-aortic lymphadenectomy**

This operation is usually done to clear lymph node me-
tastases from testicular tumors, when the sympathetic nerves and ganglia may also be removed leading to loss of ejaculation. Early studies showed that up to three quarters of patients lost antegrade ejaculation after full bilateral retroperitoneal lymph node dissection. As a result of careful anatomical studies, the technique of retroperitoneal lymph node dissection has been modified with nerve sparing so that antegrade ejaculation is now maintained in 70-90% of patients.

One quarter of the patients who complete chemotherapy for advanced testicular tumor have residual masses in the para aortic region [404]. Among 231 consecutive patients undergoing para aortic lymphadenectomy after chemotherapy at the Royal Marsden Hospital, there was persistent undifferentiated tumor in 21% [405]. In an experience of 186 patients, a nerve sparing operative technique introduced in 1984 led to a significant reduction in ejaculatory dysfunction from 37% to 19% [406]. Loss of ejaculation occurred significantly more often after bilateral (46%) compared to unilateral (14%) dissection, and was related to the size of the excised mass (<4 cm 4%; 4-8 cm 19%; >8 cm 60%).

It is important to anticipate this complication in young men with testicular tumors who may need chemotherapy or node dissection, and arrangements should be made for sperm storage before treatment commences. Excellent results can be obtained with artificial insemination using cryopreserved spermatozoa [407].

d) Functional disorders

1) Seminal Megavesicles

Adult polycystic kidney disease has been found in association with pathological dilatation of the seminal vesicles in 6 patients [408]. TRUS and percutaneous puncture of the seminal vesicles before and after resection of the ejaculatory ducts has revealed that the gross dilatation of the seminal vesicles was not caused by obstruction, but appeared to be due to atonicity (megavesicles). These ultrasonic appearances, when described previously, were incorrectly thought to be due to seminal vesicle cysts. Pathological dilatation of the seminal vesicles in the absence of obstruction has been described previously, although the etiology remains obscure [409].

e) Radiotherapy for male pelvic cancer

Quality of Life (QoL) in general and sexual functioning in particular have become very important in the well being of cancer patients. Due to modern surgical techniques, improved quality of drugs for chemotherapy, and modern radiation techniques, more patients can be successfully treated without largely compromising sexual functioning.

1) Prostate cancer

Prostate cancer (PC) has become the most common non-skin malignancy in men in Western countries. External-beam radiotherapy (EBRT) and brachytherapy (BT) are, together with the radical prostatectomy (RP), the most common and effective treatments for localized PC. Regardless of the introduction of very modern radiotherapy (RT) techniques, sexual functioning after PC treatment remains problematic for many patients. Self-administered questionnaires have widely been used to evaluate sexual functioning in patients after RT of PC. Nevertheless, such instruments are highly variable and largely unvalidated. These questionnaires elicit limited information about aspects of sexuality other than erectile function. Although a deterioration of sexual activity has been associated with the severity of ejaculatory dysfunction, particularly a decrease in volume or absence of semen [410], only a few questionnaires included items related to ejaculation and orgasm.

Already in the 1980s ejaculatory disturbances following RT of PC were reported [411]. (Table 18) In the 1990s more studies included items related to desire, ejaculation, and orgasm. After EBRT, a decline in sexual desire was reported by 43% of 64 patients and a decreased frequency of orgasm by 57%; all men reported a decrease in ejaculate volume[412]. Using a validated questionnaire, Borghede and Sullivan [413] reported a decrease in the ability to ejaculate in 56% of the patients. Good prognostic factors for sexual functioning preservation following RT were low age and higher frequency of intercourse.

Early BT studies also assessed sexual functioning. Herr [414] reported already in 1979 on 51 patients treated with retropubic iodium-125 seeds, with loss of ejaculate experienced by 6% of the patients. In a later study, dry ejaculation was reported by 16%

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Table 17: Correlation of erection, ejaculation and intercourse with level and severity of spinal cord injury [509]

<table>
<thead>
<tr>
<th>Cord Lesion</th>
<th>Reflexogenic Erections (%)</th>
<th>Psychogenic Erections (%)</th>
<th>Successful Coitus (%)</th>
<th>Ejaculation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Motor Complete</td>
<td>92</td>
<td>9</td>
<td>66</td>
<td>1</td>
</tr>
<tr>
<td>Neuron Lesion Incomplete</td>
<td>93</td>
<td>48</td>
<td>86</td>
<td>22</td>
</tr>
<tr>
<td>Lower Motor Complete</td>
<td>0</td>
<td>24</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Neuron Lesion Incomplete</td>
<td>0</td>
<td>1</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

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[Table 18]
of the patients after BT [415]. In both studies, all patients had previously undergone a trans-urethral resection of the prostate (TURP). For the first time a discomfort with ejaculation was mentioned in two studies (up to 25% of the patients) [416, 417]. This result is quite common in clinical practice after BT, due to edema of the prostate possibly reducing the elasticity of the urethra and inducing discomfort with ejaculation. In some patients discomfort with ejaculation did not disappear even 18-24 months after BT [418]. Also, decreased interest in sex, sexual desire, and libido was mentioned in up to 50% of the patients evaluated [413, 417-419].

Several studies on the etiology of post-RT decreased libido and ejaculatory disorders have been reported. Daniell et al [420] studied retrospectively levels of testosterone (TST) and other hormones after RT of PC. TST was found to be low 3 to 8 years after EBRT with lower levels found in older patients. Although testes are very sensitive to radiation, spermatogenesis is more easily affected than androgen productions. The radiation dose calculated in the testes of men irradiated for PC is only 3-8% of the dose that could possibly affect androgen production and explain a decrease in TST. A TURP carries a high incidence of retrograde ejaculation because it is thought to disrupt the closure mechanism of the vesical neck; this could explain ejaculatory disturbances in most patients following RT with previous TURP.

2) RECTAL CARCINOMA

Not much is known about sexual functioning following RT of rectal carcinoma. Pre-operative RT for rectal cancer has been associated with a reduction in the rate of local relapse and possibly an advantage in survival. Pre-operative RT with the total mesorectal excision (TME) in low stage rectal cancer has become a common procedure in Europe. A sharp dissection of the mesorectum associated with visualization and preservation of the pelvic autonomic nerve leads to excellent results regarding erectile and ejaculatory functioning. Only one study has specifically studied the effects of pre-operative RT for rectal carcinoma on male sexual functioning and concluded that it may impair male sexual functioning [421]. However, numbers were too small to draw final conclusion.

3) TESTICULAR CANCER

Germ cell tumors of the testis are relatively rare, accounting for about 1% of all male cancers. The long-term survival for early disease approaches 100%. Because testicular cancer affects mainly young men in their sexual and fertile life, sexual functioning and ejaculatory disorders are particularly important. The side effects of retroperitoneal lymph node dissection (RPLND) for residual mass after chemotherapy for non-seminomatous cancer are better documented than sexual sequelae of elective abdominal RT for seminoma. Dry ejaculation occurs in the majority of the patients in non-nerve sparing techniques. As a result of careful anatomical studies, the technique of RPLND has been modified with nerve sparing so that antegrade ejaculation is now maintained in 80 100% of patients [422]. Libido and orgasm seem to be normal in these patients.

Following RT, deterioration in sexual functioning has been reported between 1% and 25% of the patients [423-427]. Tinkler et al reported on 237 patients after orchiectomy and abdominal RT and compared these data to 402 age-matched controls [425]. In almost all parameters studied including erection, ejaculation, and libido, patients scored less than controls (reduction in orgasm, in libido, and interest in sex). Specifically, there was no difference in the ability to ejaculate during sexual activity but the RT patients reported a noticeable reduction in the amount of semen compared to before treatment [425]. Caffo et al evaluated toxicity and QoL of 143 patients treated for early-stage testicular cancer. Twenty-three per cent reported a decreased libido, 27% problems with getting an orgasm, and 38% ejaculation disturbances, including premature ejaculation. A decrease in sexual desire, in orgasm, and volume or semen was negatively correlated with age [423]. Jonker-Pool et al [424] reported on three groups of patients, after RT, wait and see, and chemotherapy. RT patients reported decreased libido in 22% compared to 12% in the wait and see group and 30% in the chemotherapy group. Decrease of absence of ejaculate was reported in 15%, 7% and 21% in the three groups, respectively; decreased orgasm in 15%, 12% and 30%, respectively. Although the differences were not statistically significant, in the RT group ejaculation and orgasm disturbances were higher than in the wait and see group. Similar results were reported by Arai et al [410]. PE was reported in up to half of the patients [410, 427], but it was the same as recalled before treatment [427].

The superior hypogastric plexus is responsible for ejaculation and it is mediated by the sympathetic system; it is a fenestrated network of fibers anterior of the lower abdominal aorta. The hypogastric nerves exit bilaterally at the inferior pole of the superior hypogastric plexus, and have connections with the S1-S2 roots. Normal emission requires integrity of this system. During RPLND these nerves are difficult to recognize and might be damaged, resulting in decreased semen volume or dry ejaculation. Pathways for ejaculation are included in the RT fields for rectal and prostate carcinomas. Damage of the sympathetic nerves could be caused by radiation, but the dose does not seem enough to completely explain the dysfunction. Orgasm is even more complex than ejaculation since it is also affected by cortical input. Drug treatment for loss of ejaculation is not very successful but electroejaculation can
produce spermatozoa for insemination. It is important to anticipate this complication in young men with testicular tumors who may need chemotherapy or node dissection. Arrangements should be made for sperm collection and storage at the earliest opportunity before treatment commences. Excellent results can be obtained with artificial insemination using cryopreserved spermatozoa [407].

3. PSYCHOLOGICAL ETIOLOGIES OF DELAYED EJACULATION

Like most other sexual dysfunctions, unless a clear pathophysiology has been identified, DE may be best understood as an interaction of organic and psychogenic factors. That is, a biological set point for ejaculatory latency is affected by multiple organic and psychogenic factors in varying combinations over the course of a man's life cycle. Appropriate assessment requires an appreciation of how these factors combine to determine the inhibited ejaculatory response for any particular individual.

Among those factors that are psychogenic and/or behavioral, a number of possibilities have been proposed. Although none has been identified or accepted as the primary determinant of DE, some explanations have received more support than others, and some appear more plausible than others.

a) Psychodynamic approaches

Psychodynamic interpretations emphasize psychosexual development issues and have attributed life-long DE to a wide range of conditions, including fear, anxiety, hostility and relationship difficulties [225, 428, 429]. Many different manifestations of anxiety and fear have been hypothesized, including fear of death and castration, fear of loss of self resulting from loss of semen, fear of castration by the female genitals, fear that ejaculation would hurt the female, fear of being hurt by the female, performance anxiety, unwillingness to give of oneself as an expression of love, fear of impregnating the female, and guilt secondary to a strict religious upbringing [430]. Although some of these factors may contribute to the etiologies of individual men with DE, no well controlled studies provide broad support, at this point, for any of the various hypotheses for mentioned above [430].

b) Religious/culture

Masters and Johnson were the first to suggest that DE was associated with orthodoxy of religious belief [224]. Beliefs may limit the sexual experience necessary for learning to ejaculate or may result in an inhibition of normal function. Regardless of specific religion involved (Muslim, Hindu, Jewish, etc.), many devoutly religious men have masturbated only minimally or not at all. Some of these men masturbated for a period of years like their secular counterparts, but guilt and anxiety about “spilling seed” may have led to idiosyncratic masturbatory patterns, which in turn resulted in DE. These men often had little contact with women prior to marriage (which may have been arranged after a few chaperoned dates) and, although these men may have dated, they were less likely than their secular counterparts to experience orgasm with a partner, especially through intercourse. Some of these men did sexually experiment with women who they did not marry; however, their cognitions about these women often reflected a «Madonna-whore» split.

Table 18: Level of Evidence - Radiotherapy for male pelvic cancer

<table>
<thead>
<tr>
<th>Author/s</th>
<th>Cancer</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helgason AR, Fredriksen M, Adolfsen J, et al.[516]</td>
<td>Prostate</td>
<td>1</td>
</tr>
<tr>
<td>Borghede G, Hedelin H [413]</td>
<td>Prostate</td>
<td>1</td>
</tr>
<tr>
<td>Herr [517]HW</td>
<td>Prostate</td>
<td>2</td>
</tr>
<tr>
<td>Kwong EWH, Huh SH, Nobler MP, et al.[518]</td>
<td>Prostate</td>
<td>2</td>
</tr>
<tr>
<td>Kleinberg L, Wallner K, Roy J, et al. [519]</td>
<td>Prostate</td>
<td>1</td>
</tr>
<tr>
<td>Danieli HW, Clark JC, Pereira SE, et al. [420]</td>
<td>Prostate</td>
<td>1</td>
</tr>
<tr>
<td>Bonnel C, Parc YR, Pocard M, et al. [521]</td>
<td>Rectal</td>
<td>3</td>
</tr>
<tr>
<td>van Basten JP, Jonker-Pool G, van Driel MF, et al. [522]</td>
<td>Testicular</td>
<td>1</td>
</tr>
<tr>
<td>Schover LR, Gonzales M, von Eschenbach AC. [523]</td>
<td>Testicular</td>
<td>2</td>
</tr>
<tr>
<td>Tinkler SD, Howard GCW, Kerr GR [525]</td>
<td>Testicular</td>
<td>2</td>
</tr>
<tr>
<td>Caffo O, Amichetti M [526]</td>
<td>Testicular</td>
<td>2</td>
</tr>
<tr>
<td>Scammell GE, White N, Stedronska J et al. [527]</td>
<td>Testicular</td>
<td>2</td>
</tr>
</tbody>
</table>
c) Insufficient sexual arousal

An excellent critical review of the psychological etiology of DE has been provided by Apfelbaum [367], who first noted the sexual politic surrounding DE and female anorgasmia: “Like the woman who has inappropriately been castigated for willfully depriving her husband of the pleasure of bringing her to orgasm, the delayed ejaculator’s own belief that he is withholding is widely endorsed, understandably by his partners and less justifiably by most therapists” (p. 182). Not only psychoanalysts, but sex therapists and behavior therapists as well, seemed to assume the DE patient’s orgasm is blocked, rather than the patient’s level of arousal being insufficient.

Apfelbaum observed that some males appear able to achieve erections sufficient for intercourse despite a relative absence of subjective arousal [367]. He felt these “automatic erections” were taken as erroneous evidence by both the man and his partner that he was ready for sex and capable of achieving orgasm. This same process is the likely cause of increased anecdotal clinical reports of DE for patients using popular urologic-based treatments for ED [2, 431, 432]. Urologists received a few early complaints of RE secondary to successful penile prosthesis surgery and ICI. However, the introduction of sildenafil brought increased numbers of patients to physician’s offices, many of whom experienced restored erections and coitus with ejaculation. A subset of men on sildenafil, however, experienced erection without adequate psychoemotional arousal and, as a result, experienced difficulty achieving orgasm, as they did not experience sufficient erotic stimulation before and during coitus. These men confused their erect state as an indication of sexual arousal when it merely indicated vasocongestive success [2, 431].

d) Masturbation

Apfelbaum coined “autosexual” orientation to describe men with DE who prefer masturbation to partnered sex [367]. Many men with RE engage in self-stimulation that is idiosyncratic in the speed, pressure, duration, and intensity necessary to produce an orgasm, yet dissimilar to what they experienced with a partner. Thus, they precondition themselves to possible difficulty attaining orgasm with a partner and, as a result, experience secondary DE. Disparity between the reality of sex with the partner and the use of sexual fantasy (whether unconventional or not) during masturbation is another potential cause of DE. This disparity may take any number of forms: body type, orientation, and sex activity performed. Although many men and women are inhibited about using their masturbatory fantasies when with their partner, like their female counterparts, when men with DE integrate their masturbation fantasies into sex with their partner, orgasm is more likely attained [431].

In summary, delayed or absent ejaculation can be a lifelong (primary) or an acquired (secondary) problem. Many psychodynamic explanations have been offered for DE and these may account for the problem in specific individual cases. More likely, however, men with DE derive greater arousal and enjoyment from masturbation than from intercourse, an “auto-sexual” orientation that may involve an idiosyncratic and vigorous masturbation style that ultimately interferes with the ability to attain orgasm [372, 433-437]. In fact, masturbatory frequency and style may be predisposing factors for DE, since a substantial portion of men who present with coital DE report high levels of idiosyncratic masturbatory activity [372, 434-437]. Disparity between the reality of sex with the partner and the sexual fantasy used during masturbation may represent another contributor to DE [431, 438]. And finally, the evaluative/performance aspect of sex with a partner often creates “sexual performance anxiety,” a factor that may contribute to DE. Specifically, anxiety surrounding the inability to ejaculate may draw the man’s attention away from erotic cues that normally serve to enhance arousal [433].

VI: EVALUATION OF DELAYED EJACULATION, ANEJACULATION AND ANORGASMIA

1. EVALUATION AND ASSESSMENT OF DE

Treatment should be etiology specific and address the issue of infertility in men of a reproductive age. If a man has difficulty with ejaculation, or has a small volume or absent ejaculate, it must first be established whether the problem is congenital or acquired, and whether organic factors are implicated. Assessment begins by reviewing the conditions under which the man is able to ejaculate, for example, during sleep, with masturbation, with partner’s hand or mouth stimulation or infrequently with varying coital positions. The course of the problem is documented, and variables that improve or worsen performance are noted. Questions concerning the man’s ability to relax, sustain, and heighten arousal and the degree to which he can concentrate on sensations are posed [439]. If orgasmic attainment had been possible previously, the life events/circumstances temporarily related to orgasmic cessation are reviewed. The events in question maybe pharmaceutical, congenital problems, illness, trauma, or a variety of life stressors and other psychological factors, for example, following his wife’s mastectomy: the man is afraid of hurting her and therefore only partially aroused. Societal/religious attitudes that may interfere with excitement are noted, such as the spilling of seed as a sin. Finally, questions concerning the quality of the nonsexual relationship are posed and
problems explored. This assessment in conjunction with appropriate physical examination and laboratory results will provide understanding and determine an appropriate treatment path.

2. INVESTIGATING AND ALLEVIATING ORGANIC FACTORS IN DE OR ANEJACULATION

a) General investigation

A careful clinical history should be taken, and physical examination will establish whether the testicles and epididymes are normal, and whether the vasa are present or absent, on each side. Next, it is essential to establish whether there is retrograde or completely absent ejaculation, by examination of a deposit of urine after centrifugation. The presence of spermatozoa indicates retrograde ejaculation. These facts will allow the patient to be placed into one of several broad categories, after which more detailed evaluation can take place.

If the etiology is unclear, organic factors such as haemospermia may require full investigation. Culture of expressed prostatic secretion and urine will define the nature of an infective process such as prostatitis [440] and urine cytology and serum prostate specific antigen should be assayed to exclude bladder or prostatic cancer. Ultrasound scan of the testicles and epididymes should define any local disease. TRUS will demonstrate structural abnormality in the prostate or seminal vesicles, or may show up a stone in the ejaculatory duct or even a Mullerian duct cyst. Cystoscopy is seldom helpful.

Patients with ejaculatory duct obstruction usually present with infertility. Seminal analysis may simply be reported as showing azospermia or oligospermia, but the characteristic biochemical changes should be sought. There should be absence of part or the entire component of the ejaculate that comes from the vasa and seminal vesicles via the ejaculatory ducts. The volume is low (usually less than 1.5 ml), the pH is low (less than 7) and the fructose content is either low (less than 120 mg/100ml) or absent. If both vasa are palpable, a diagnosis of ejaculatory duct obstruction is very likely.

When there is absence of the vasa, it is important to establish whether the condition is unilateral or bilateral. With unilateral absence of the vasa deferens, the urinary system must also be checked by ultrasound scanning, as coexisting renal anomalies may be present [441]. With bilateral absence or malformation of the vasa, it is essential to consider whether the anomaly may be part of a genetic defect associated with carriage of the potentially harmful cystic fibrosis chromosome anomaly [377].

b) Imaging in ejaculatory duct obstruction

A lesion or obstruction may be suspected by finding distended seminal vesicles on transrectal ultrasound scanning. However, the exact site of obstruction should be defined radiologically by vasography or percutaneous puncture of the seminal vesicles. Subsequently, methylene blue dye may be instilled to outline the ejaculatory system so that it can be recognized after it has been entered at transurethral resection [442].

c) Electrophysiological evaluation of the nervous pathways controlling ejaculation

Neurophysiological tests allow objective evaluation of the nervous pathways controlling ejaculation and are occasionally of use in the evaluation of delayed ejaculation or anejaculation. Four tests are routinely used.

d) Pudendal Somatosensory Evoked Potentials (Pudendal SEPs)

Somatosensory evoked potentials (SEPs) are defined as a transient alteration of the EEG following peripheral nerve stimulation. They provide objective information concerning the afferent volley from the dorsal nerve of penis to the cortex. The technique consists of electrical stimulation of the dorsal nerve of penis with recording of the evoked responses over the spine and the scalp (2 cm behind the central vertex). First the sensibility threshold is measured. By definition, the sensibility threshold is the lowest perceivable sensation of the electrical current at the point of stimulation. The latency of the response is measured both at the onset of the response and the peak of the first reproducible deflection. By recording the response at two different levels, three different transit times are obtained: a total transit time (from penis to brain), a peripheral transit time (from penis to spine), and a central transit time (which is obtained by subtracting the peripheral from the total transit time). The peripheral transit time is approximately 13.5 msec. The total transit time is approximately 34 msec (onset) and 43 msec (top of P1 deflection) [443, 444].

e) Pudendal Motor Evoked Potentials (Pudendal MEPs)

Motor Evoked Potentials (MEPs) explore the efferent pathways (pyramidal tracts) from brain to target muscle (bulbocavernosus muscles). This technique consists of stimulating the motor cortex and sacral roots by means of a magneto electric stimulator. For brain stimulation, the coil is applied 2 cm behind the vertex. For sacral root stimulation, the coil is applied laterally to the spine. The response is picked up from the bulbocavernosus muscles with co axial EMG needle electrodes. Brain stimulation is performed, first at rest, and then during a voluntary contraction of the pelvic floor (facilitation procedure). Sacral root stimulation is performed only at rest. The response is measured at the onset of the first reliable deflec-
tion. By stimulating the central nervous system at 2 levels, 3 different transit times will be obtained: a total transit time (from brain to target muscle), a peripheral transit time (from sacral roots to target muscle) and a central transit time (obtained by subtracting the peripheral from the total transit time). The total transit time measured in the bulbocavernous muscles is respectively 28 msec (brain stimulation patient at rest) and 23 msec (brain stimulation patient contracting the pelvic floor). The peripheral transit time is 7 msec (sacral root stimulation) [445].

f) Sacral Reflex Arc Testing: the Somatic somatic Reflex Arc

This test allows the investigation of the sensory and motor branch of the pudendal nerve and of the sacral segments S2, S3, S4. The technique consists in stimulating the dorsal nerve of the penis and recording the response from the bulbocavernous muscles. The response consists usually of 2 deflections. The mean latency of the first deflection is 35 msec, although a late deflection is often observed at 80 msec [444, 446].

g) Sympathetic Skin Responses (SSRs)

Electrical activity from the sympathetic nerve terminals controlling the sweat glands of the skin can be recorded following electrical stimulation of any peripheral nerve trunk. The test allows evaluation of the sympathetic efferent outflow to the skin of the genital organs which may impact ejaculatory function. The dorsal nerve of the penis is stimulated using 2 ring electrodes wrapped around the penile shaft, the cathode being proximal. The stimulation consists of single electrical pulses applied at a rate of 0.05 Hz. Sympathetic skin responses are recorded from hand, foot, and perineum using disc electrodes affixed to the skin. Two tracings are superimposed to check the reproducibility of the response. The right median nerve is then stimulated, and SSRs are recorded from the hand, foot, perineum, and penis. The mean latency of hand, foot, and perineum SSRs following dorsal nerve of the penis stimulation are, respectively, 1.40 sec, 2 sec, and 1.4 sec. Following median nerve stimulation, the latency of penile SSRs is 1.50 sec [447, 448].

VII: TREATMENT OF DELAYED EJACULATION, ANEJACULATION AND ANORGASMIA

1. PSYCHOLOGICAL STRATEGIES IN THE TREATMENT OF DELAYED EJACULATION

a) General considerations and approaches

As indicated above, before considering a psychological/behavioral approach toward the treatment of DE, clinicians first need to exclude probable iatrogenic and pathophysiological causes. They should, for example, be alert to various medical conditions as well as medications that might delay ejaculation and, in the case of antidepressants, consider a reduction in dose or use of antidote [449]. Vascular or neuropathic damage that causes DE is usually irreversible and therefore the patient might be counseled to seek alternative methods to achieve mutual sexual satisfaction with his partner. Androgen deficiency—another potential cause for DE—requires appropriate testosterone replacement therapy. Whether a clear pathophysiological cause is present or absent, patients might be counseled to consider lifestyle changes, including enjoying more time together to achieve greater intimacy, minimizing alcohol consumption, making love when not tired, and practicing techniques that maximize penile stimulation such as pelvic floor training [430]. Patient education regarding existing factors that can exacerbate their delayed ejaculation is an important first step and may represent a segue into either short-term or long-term counseling.

Beneficial effects through psychotherapy depend on the severity of the DE and the individual's receptiveness to engage in counseling and adhere to the counselor's recommendations. Indeed, for DE that has its probable roots in psychological and behavioral issues, psychotherapy appears to be the only effective treatment, as effective drug treatment is limited and poorly tested. The man who presents with DE, in whom organic and pharmacologic causes have been eliminated, requires thorough psychosocial assessment. His partner and the quality of the relationship also warrant exploration. Numerous psychotherapeutic processes are described for the management of delayed or inhibited ejaculation [224, 225, 367, 450] and some appear to be effective, but none has been properly evaluated in large scale samples [451]. Among these strategies are: (1) sex education; (2) reduction of goal-focused anxiety; (3) increased, more genitally-focused stimulation; (4) patient role-playing an exaggerated ejaculatory response on his own and in front of his partner; (5) masturbatory retraining; and (6) re-alignment of sexual fantasies and arousal strategies.

Treatment strategies for DE have typically been based upon the etiologies previously described, and most benefit from cooperation of the sexual partner. Successful treatment approaches typically begin by recognizing the importance of de-stigmatizing the dysfunction, providing appropriate sex-response education to the couple, and defusing dyadic tension that might have evolved in response to the dysfunction. For example, discussion of a potential biologic predisposition is often helpful in reducing patient and partner anxiety and mutual recriminations, while simultaneously assisting the formation of a therapeutic alliance with the health care professional [365].

Most current sex therapy approaches to DE empha-
size the importance of masturbation in the treatment of DE, with most of the focus on “masturbatory retraining” integrated into sex therapy [365, 368]. Masturbation retraining is, however, only a means to an end, and the true goal of most current therapeutic techniques for DE (either primary or secondary) is to both provide more intense stimulation and induce higher levels of psychosexual arousal so the man can attain orgasm within the framework of a satisfying partnered experience. A number of strategies have been utilized to achieve the endpoints of increased arousal and satisfaction.

Men with primary anorgasmia (a complete lack of ejaculatory response), like their female counterparts, typically need help determining their sexual arousal preferences through self-exploration and then in communicating that knowledge to their partner. Masturbation training may use a modification of the model described by Barbach [452] for women, although the use of vibrators, sometimes recommended by urologists, is rare. Progressing from neutral sensations to the ability to identify and experience pleasurable sensations is encouraged whether or not ejaculation should occur.

Typically, self-stimulation techniques incorporating fantasy can be used to achieve incremental increases in arousal that eventually enable orgasm. Fantasy can serve the purpose of increasing arousal and blocking inhibiting thoughts that might otherwise interfere. Once the man’s ejaculatory ability is established through masturbation, the same skill set can be incorporated into sex with the partner. Although some cultures and religions forbid masturbation, temporary religious dispensation is sometimes available, especially when procreation is a goal of treatment.

An important component in the treatment of any type of DE is the removal of the “demand” (and thus anxiety-producing) characteristics of the situation [367]. "Ejaculatory performance” anxiety can interfere with the erotic sensations of genital stimulation and may result in levels of sexual excitement insufficient for climax (although they may be more than adequate to maintain an erection). To reduce anxiety, treatment may include recognition of DE men’s over-eagerness to please their partners, validation of (though not necessarily encouragement of) the man’s autosexual orientation, removal of stigmas suggesting hostility or withholding toward their partner, and general anxiety reduction techniques such as relaxation and desensitization. By normalizing the anorgasmia, therapy can then explore factors that increase the man’s arousal (similar to treatment of anorgasmia in women). Finally, like a previously anorgasmic woman, the man is taught to effectively communicate his preferences to his partner so that both their needs are incorporated into the sexual experience.

b) Issues related to counseling
As with counseling for other kinds of problems, men with DE may resist the recommendations of the therapist. For example, a therapeutic suggestion to temporarily discontinue masturbation may be met with resistance by the patient. Nevertheless, the therapeutic benefit of temporarily discontinuing self-stimulation can be an important part of the therapeutic process to increase overall sexual arousal, when it does occur. Such recommendations must be balanced with maintenance of a therapeutic rapport and alliance with the patient, and therefore the issue of masturbation interruption may be negotiated. For example, a man who continues to masturbate may be encouraged by the therapist to alter the style of masturbation to approximate (in terms of speed, pressure, and technique) the stimulation likely to be experienced through manual, oral, or vaginal stimulation by his partner [371].

In addition to suspending masturbation, the patient might be encouraged to use fantasy and bodily movements during coitus that help approximate the thoughts and sensations previously experienced in masturbation. This process is facilitated and resistance minimized when the man’s partner is supported by the practitioner and understands that the alteration in coital style is part of a series of steps designed to reach a long term goal of coital harmony and satisfaction for them both.

The partner also needs to collaborate in the therapeutic process, finding ways that not only enhance the man’s arousal, but to accept the use of erotica and various (harmless) sexual fantasies that also might be incorporated into the couple’s lovemaking. Because fantasy plays an important role in arousal, sexual fantasies may have to be realigned so that thoughts experienced during masturbation better match those occurring during intercourse with the partner. The attractiveness and seductive/arousing capacity of the partner might also be increased to reduce the disparity between the man’s fantasy and the actuality of coitus with his partner.

Because interventions used in the treatment of DE may be experienced by the female partner as mechanistic (e.g., using a step wise program) and insensitive to her sexual needs, many women may initially respond negatively to the impression that the man is essentially masturbating himself with her various body parts, as opposed to engaging in connected lovemaking. This response may be exacerbated for the female when her partner needs actual pornography/erotica instead of mere fantasy to distract himself from negative thoughts and emotions that might interfere with arousal. The therapist must help the partner accept postponement of her
needs until the patient has progressed to a level of functionality, which then allows for encouragement and development of a greater sensitivity and sharing between them. The therapeutic challenge is to facilitate the rapport between the partners, while maintaining a therapeutic alliance with both partners and simultaneously optimizing his response to her manual, oral, and vaginal stimulation.

Finally, issues surrounding reproduction/conception may need to be addressed, as this issue is often an initial driver for treatment. This issue may require special sensitivity, particularly if the couple’s stated or unstated goals regarding family size and constitution (boys, girls, or no children at all) do not coincide. In such instances, the practitioner must find an acceptable way to refocus the treatment, at least temporarily, on the underlying issues responsible for the discordant goals of the couple in order for DE treatment to succeed. This process may require individual sessions with the man and occasionally with the partner as well.

Patients with psychogenic inhibited ejaculation (IE) are a challenging to treat population. Level 4 evidence to support that all require patient/couple psycho-education and/or psychosexual therapy which may be long term.

**Grade C Recommendation**

c) Treatment efficacy

The success of treating DE is difficult to assess from the literature [451] as the available evidence on the effectiveness of various treatments is limited [220, 430], and both successful and unsuccessful case reports have been cited [367, 372]. Heiman and Meston’s summary of sex therapy treatments concluded that “inadequate data” on the topic of delayed orgasm in men prevented any conclusion regarding efficacy of treatment [220]. Although many treatments for DE have been suggested in the psychotherapy literature, including early psychodynamic and sex therapy approaches [224, 225, 442, 453-456], few have been subject to rigorous testing. Masters and Johnson[224] reported a low failure rate of 17.6% using a treatment combination of sensate focus, vigorous non coital penile stimulation and modifications of intercourse technique. In the Ohl et al. study [457], 81% of men who were anorgasmic prior to fertility treatment were successful in reaching orgasm through vibrator stimulation. Apfelbaum treated almost all of his DE cases with «body work» using sexual surrogates [367]. And Perelman reported retrospective chart review success rates of over 80% in treating DE using various forms of cognitive-behavioral sex therapy [431]. However, these analyses represent, for the most part, uncontrolled reports with treatment ranging from a few brief sessions of sex education to nearly two years of multiple-modality treatment in more complex multiple etiologic cases.

2. DRUG TREATMENT FOR DELAYED AND INHIBITED EJACULATION

Treatment of delayed or inhibited ejaculation with pharmaceuticals has met with limited success. No drugs have been approved by regulatory agencies for this purpose, and most drugs that have been identified for potential use have limited efficacy, impart significant side effects, or are yet considered experimental in nature. (Table 19) In some instances, the drugs may only indirectly affect ejaculatory latency by affecting other components of the sexual response cycle; in other instances, the drugs have been used primarily to counter effects of other pharmaceuticals that iatrogenically induce delayed or inhibited ejaculation.

There are multiple reports in the literature of the use of a variety of drugs in the treatment of delayed ejaculation or anejaculation. Typically, these drugs facilitate ejaculation by either a central dopaminergic or anti-serotonergic mechanism of action. Most studies do not use placebo controlled designs and most are anecdotal case reports/series dealing with the treatment of SSRI induced ejaculatory dysfunction. (Table 20)

Several authors have reported that the cerebral serotonergic system exerts an inhibitory role on ejaculation and male sexual activity in the rat model and that the dopaminergic system, particularly that in the anterior hypothalamus, has a facilitatory role [458, 459]. The ejaculatory dysfunction commonly associated with the anti-hypertensive alphamethyl dopa which reduces cerebral monoamine levels by suppressing the cerebral dopaminergic system is consistent with these reports. The occurrence of paradoxical hypersexuality, for example, spontaneous orgasm with clomipramine and fluoxetine, however, suggests that this balance is more complex and that different 5-HT receptor subtypes may have opposing effects on sexual function [460-462].

a) Alpha-1 Adrenergic Receptor Agonists

Alpha-1 adrenergic receptor agonists such as imipramine, ephedrine, pseudoephedrine and midodrine may have a role in the pharmacological treatment of inhibited ejaculation. Midodrine is used in the treatment of various hypotensive disorders and is associated with causes less frequent and less severe adrenergic effects than ephedrine and other sympathomimetic agents. Midodrine is used in the treatment of various hypotensive disorders and is associated with causes less frequent and less severe adrenergic effects than ephedrine and other sympathomimetic agents. Several authors have reported the use of midodrine in spinal cord injured patients. In recent studies, antegrade or retrograde ejaculation occurred in 22-64.6% of spinal cord injured patients.
who had previously failed to respond to penile vibratory stimulation, following treatment with midodrine 30–120 min before a new stimulation. [398, 399]

Safarinejad recently reported that midocrine reverses organic anejaculation in non-SCI subjects in more than 50% of patients. In a placebo controlled study of 128 patients, stepwise titration of oral midodrine 7.5–15mg/day resulted in antegrade, retrograde and combined antegrade/retrograde ejaculation occurred in 18 (29.5%), 8 (13.1%) and 9 (14.8%) patients respectively. [463]

b) Cyproheptadine

The antihistamine cyproheptadine, which increases cerebral serotonin levels, has been shown to increase male sexual activity in the rat [458]. The literature contains several anecdotal case reports and other small case series of the use of cyproheptadine to reverse the anorgasmia induced by the SSRI antidepressants but no controlled studies are known [464-469]. These studies suggest an effective dose range of 2-16mg., with administration on a chronic or «on demand» basis. McCormick reported the use of cyproheptadine to reverse the anorgasmia induced by the SSRI luoxetine in 2 patients [464]. Ashton et al also reported improvement in 12 of 25 men with SSRI induced sexual dysfunction with a mean dose of 8.6 mg, with efficacy limited by sedation and potential reversal of antidepressant effect [465]. A role for cyproheptadine in the treatment of both delayed ejaculation and anejaculation may be limited to a degree by its sedative effect.

<table>
<thead>
<tr>
<th>Author/s</th>
<th>Drug/s</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCormick, S., Olin, J., Brozman, A. W[464]</td>
<td>Cyproheptadine</td>
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<tr>
<td>Ashton, K., Hamer, R., Rosen, R [465]</td>
<td>Cyproheptadine</td>
<td>2</td>
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<tr>
<td>Feder, R [466]</td>
<td>Cyproheptadine</td>
<td>4</td>
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<tr>
<td>Lauerna, H[467]</td>
<td>Cyproheptadine</td>
<td>4</td>
</tr>
<tr>
<td>Balon, R [472]</td>
<td>Amantadine</td>
<td>4</td>
</tr>
<tr>
<td>Shrivastava, R., Shrivastava, S., Overweg, N. et al. [473]</td>
<td>Amantadine</td>
<td>4</td>
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<tr>
<td>Valevski, A., Modai, I., Zbarski, E. et al. [475]</td>
<td>Amantadine</td>
<td>4</td>
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<tr>
<td>Gitlin, M. J [474]</td>
<td>Amantadine</td>
<td>4</td>
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<tr>
<td>Balogh, S., Hendricks, S., Kang, J [476].</td>
<td>Amantadine</td>
<td>4</td>
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<tr>
<td>Price, J., Grunhaus, L. J [477]</td>
<td>Yohimbine</td>
<td>4</td>
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<tr>
<td>Jacobsen, F. M. [478]</td>
<td>Yohimbine</td>
<td>4</td>
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<tr>
<td>Hollander, E., McCarley, A.[479]</td>
<td>Yohimbine</td>
<td>4</td>
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<tr>
<td>Othmer, E., Othmer, S. C [481]</td>
<td>Buspirone</td>
<td>4</td>
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<tr>
<td>Ashton, A., Rosen, R. [483]</td>
<td>Bupropion</td>
<td>4</td>
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<tr>
<td>Aizenberg ], D., Gur, S., Zemishlany, Z. et al. [485]</td>
<td>Mianserin</td>
<td>4</td>
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<tr>
<td>Ishak WW et al. [494]</td>
<td>Oxytocin</td>
<td>4</td>
</tr>
<tr>
<td>Safarinejad et al. [463]</td>
<td>Midocrine</td>
<td>1</td>
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</tbody>
</table>
c) Amantadine

Central dopamine activity can be increased by a variety of mechanisms ranging from the provision of dopamine synthesis precursors, for example, L-dopa, to use of substitute neurotransmitters to directly stimulate central dopamine receptors (Table 21). Amantadine, an indirect stimulant of dopaminergic nerves both centrally and peripherally which is used in the treatment of Parkinson’s disease and has a limited role as an anti-viral agent, has been reported to stimulate sexual behaviour, ejaculation, and other sexual reflexes in rats [470, 471]. Several authors have reported a place for amantadine in the reversal of SSRI antidepressant induced anorgasmia [465, 472-476]. Ashton et al reported improvement in SSRI induced sexual dysfunction in 8 of 19 men with mean dose of 200mg [465]. Balon reported some efficacy with «on demand» amantadine (100mg) administered 5-6 hrs before coitus in a similar group of patients [472].

d) Yohimbine

Several authors have reported their experience with Yohimbine, a derivative of the bark of the Yocon tree, in the management of SSRI induced sexual dysfunction [477-479]. Yohimbine is an alpha-2 antagonist, an alpha-1 agonist, and a calcium channel blocker that inhibits platelet aggregation. Price and Grunhaus reported reversal of clomipramine-induced anorgasmia with a dose of 10mg administered 90 minutes prior to coitus [477]. In a placebo-controlled study of 15 patients with fluoxetine-induced anorgasmia, Jacobsen reported a 73% response rate to yohimbine [478]. Hollander reported that yohimbine reversal of anejaculation in 5 of 6 men with intercourse and/or masturbation [479]. The response to yohimbine is typically delayed, taking up to 8 weeks, and is often associated with adverse effects including nausea, headache, dizziness, and anxiety. Careful dose titration is important as the extremes of dose have less pro-sexual effect.

e) Buspirone

Buspirone is a benzodiazepine class anxiolytic which possesses 5HT-1A receptor agonist activity [480]. Othmer et al reported normalization of sexual function in 8 of 10 men with a generalized anxiety disorder and associated sexual dysfunction using a dose range of 15-60mg daily [481]. Bupropion is a novel antidepressant which prolongs the action of dopamine by reducing its uptake from the synaptic cleft [482]. Ashton and Rosen described reversal of SSRI induced anorgasmia in 66% of patients studied. [483]

f) Apomorphine

Several authors have reported induction of «early ejaculation» in rats following administration of apomorphine, a central and peripheral DA-2 receptor agonist, at a dose of 50 mg/kg. DA receptor antagonists block this effect [44, 484]. Aizenberg et al examined the effect of the 5-HT2a/2c and alpha 2 antagonist mianserin in the treatment of patients with sexual dysfunction induced by serotonin reuptake inhibitors (SSRIs) [485]. Nine of the 15 subjects reported a marked improvement in their sexual functioning in the areas of orgasm and satisfaction usually within the first and second week of mianserin treatment. The authors suggested that co-administration of low-dose mianserin might be an additional option in the treatment of sexual dysfunction induced by SSRIs.

g) Quinelorane

Quinelorane is a highly selective, potent DA-2 agonist which was extensively studied in animals in the early part of this decade. Foreman and Hall observed increased mounting, intromission and ejaculation in both sexually inactive and sluggish rats following administration of quinelorane [486]. Prior administration of a dopamine antagonist eliminated these stimulatory effects, confirming that these sexual effects were due to stimulation of DA receptors. These investigators reported that many rats failed to ejaculate at the extremes of doses, with low doses causing sedation and high doses causing hyperactive behaviour such as chewing or sniffing. Animals appear to become more sensitive to dopamine agonists with increased use, suggesting that abuse may eliminate any sexual benefits. Eaton et al. injected quinelorane directly into the rat paraventricular nucleus and medial preoptic area and reported different response with different doses [487]. At extremes, quinelorane could cause paradoxical PE, reduced sexual desire, and ED. The reduced sexual response observed at low doses is due to stimulation of dopamine «auto-receptors» which decrease dopamine activity and respond to lower doses than do dopamine

Table 21: Mechanism of Action of Drugs which increase Dopamine Neurotransmission

<table>
<thead>
<tr>
<th>Mechanism of Increasing Dopamine Neurotransmission</th>
<th>Drug</th>
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</thead>
<tbody>
<tr>
<td>Prolong action by decreasing uptake</td>
<td>bupropion, cocaine</td>
</tr>
<tr>
<td>Prolong action by decreasing metabolism</td>
<td>L-deprenyl</td>
</tr>
<tr>
<td>Increased release of dopamine</td>
<td>amphetamine</td>
</tr>
<tr>
<td>Direct stimulation of DA receptors with substitute neurotransmitters</td>
<td>bromocriptine, quinelorane, apomorphine</td>
</tr>
<tr>
<td>Increase Dopamine synthesis by providing precursors</td>
<td>L-dopa</td>
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</table>
the stimulatory DA-2 receptors. In theoretical clinical use, lowering the dose to avoid excess excitement may result in worse sexual dysfunction than prior to treatment. Human double blind placebo controlled clinical studies of quinelorane were commenced in the late 1980s involving multiple sites and more than 500 men and women with ED, reduced sexual desire, and reduced arousal. The United States Food and Drug Administration review of the trial data was inconclusive and concern was expressed over the more than 50% incidence of nausea and hypotension and the indirect negative sexual adverse effects. Clinical studies were terminated and the results remain confidential and unpublished.

**h) Oxytocin**

Oxytocin is a peptide hormone made of nine amino acids. It is released by the human posterior pituitary gland, and has been associated with the Letdown reflex in lactating mothers, uterine contractions during the second and third stages of labor, in addition to increased levels at orgasm in both men and women. [488] Oxytocin has been used to facilitate labor induction, for initiation of lactation in women after delivery [489], and more recently in the treatment of autism [490]. More recently, a study on humans published in Nature has shown its value in social bonding, increasing trust, and enhancing the sense of well-being. Studies on attachment, social bonding, and sexual behaviors in the animal models have pointed to oxytocin as an important mediator [491]. Animal studies pointed to the role of oxytocin receptors in selective serotonin reuptake inhibitors-induced ejaculation delays [492], with evidence of successful reversal using oxytocin in the male rat [493].

Ishak et al recently reported a single case effectiveness of administering intranasal oxytocin intracoitaly in a case of treatment-resistant anorgasmia. Oxytocin (20–24 IU) was effective in restoring ejaculation at the point when ejaculation was sought. Following its use, the patient ejaculated regularly (multiple times per week) after sexual intercourse, an effect that is persisting consistently for 8 months until the time of submission of this report. Both the patient and his wife reported a high degree of satisfaction with this intervention. [494] Whether oxytocin works in anorgasmia by increasing the ability to “fully share oneself” or more plausibly through promoting rhythmic contracility of the penile and pelvic musculature, the exact mechanism of action is awaiting to be discovered.

Finally, some men may exhibit retrograde ejaculation rather than delayed ejaculation or anejaculation. Retrograde ejaculation can be surgically treated with bladder neck reconstruction, although no surgical procedure exists for the treatment of failed emission. Drug treatment also offers a promising approach for retrograde ejaculation. Thus, while medical treatment may not always produce normal ejaculation it may convert a patient with lack of emission into one with retrograde ejaculation and may result in small amounts of viable sperm both of which can be combined with standard artificial insemination techniques to produce a pregnancy.

**Level 4 evidence to support the treatment of DE/anejaculation with pharmacotherapy**

**Grade D Recommendation**

**3. OFFICE MANAGEMENT OF DELAYED EJACULATION AND ANEJACULATION: A SUMMARY**

Men with delayed ejaculation, anejaculation and/or anorgasmia should be evaluated with a detailed medical and sexual history, a physical examination, and appropriate investigations to establish the true presenting complaint, identify obvious biological causes such as medication or recent pelvic surgery, and uncover sufficient detail to establish the optimal treatment plan (Figure 11).

Relevant information to obtain from the patient includes:

1. A basic medical history, including use of prescribed and recreational medications
2. The cultural context and developmental history of the disorder, including whether the ejaculatory dysfunction is global or situational, lifelong or recent in its development,
3. Measures of the quality of each of the three phases of the sexual response cycle: desire, arousal, and ejaculation, since the desire and arousal phases may impact the ejaculatory response,
4. Details about the ejaculatory response, including the presence or absence of orgasm, the prodromal sensation of ejaculatory inevitability and prograde ejaculation, the level of sexual dissatisfaction and distress, the frequency of sexual activity, and so on,
5. A careful physical examination to establish whether the testicles and epididymes are normal, and whether the vasa are present or absent, on each side
6. The partner’s assessment of the situation, including whether the partner is suffers from female sexual dysfunction (FSD), and
7. Assessment of the sexual and overall relationship

**Level 4 evidence to suggest that evaluation of men presenting with DE/anejaculation should include a full medical/sexual history, a focused physical examination, determination of serum testosterone levels and any investigations suggested by these findings**

**Grade C Recommendation**
Treatment should be etiology specific and address the issue of infertility in men of a reproductive age. Men, who never achieve orgasm and ejaculation, are suffering from either a biogenic failure of emission and/or psychogenic inhibited ejaculation may require fairly extensive medical evaluation. Men who occasionally achieve orgasm and ejaculation are usually suffering from psychogenic inhibited ejaculation or penile hypoanaesthesia secondary to age related degeneration of the afferent penile nerves and may respond well to various cognitive-behavioral strategies that include education and sexual techniques designed to maximize arousal.

Level 4 evidence to suggest that treatment of DE/anejaculation should be etiology specific, and may include patient/couple psycho-education and/or psychosexual therapy, pharmacotherapy or integrated treatment. Men/partners of reproductive age should be informed of the risk of infertility due to anejaculation following pelvic surgery and the need for sperm harvesting and assisted reproductive techniques.

**Grade C Recommendation**

The majority of men who always achieve orgasm but never experience prograde ejaculation or have a greatly reduced prograde ejaculatory volume should be investigated for retrograde ejaculation. The presence of spermatozoa and fructose in centrifuged post-ejaculatory voided urine confirms the diagnosis. Management involves education and reassurance of the patient, pharmacotherapy or, in rare cases, bladder neck reconstruction. The absence of spermatozoa suggests congenital absence or agenesis of the testis or vas/vasa or acquired ejaculatory duct obstruction. Management involves investigation by ultrasonic or radiological imaging to identify the site of obstruction and disease specific treatment.

**4. THE FUTURE**

Combined treatment—need for integrated pharmacotherapy and sex therapy approaches—has been gaining acceptance within both medical and counseling circles, and although evidence is yet limited, preliminary research suggests that the patient has much to gain from this more holistic approach.[4] It seems likely that the most effective treatments for PE and DE will follow the pattern seen in the treatment of ED, where an integration of pharmacotherapy and sex therapy is becoming the treatment of choice [462, 495-505]. These recent articles by urologists and sex therapists have advocated a multidisciplinary approach for the treatment of ED; emphasizing the importance of follow-up in providing opportunity for necessary patient education and counseling. Additionally, the integration of sexual counseling and pharmacotherapy is likely to be of assistance to patients seeking adjustment and rehabilitation from multiple medical conditions (e.g., retrograde ejaculation secondary to prostatic surgery). Furthermore, couples presenting multiple sexual dysfunctions are likely to benefit from a model incorporating additional sex therapy with pharmacotherapy. An integrated model allows for resolving and balancing significant intra and interpersonal psychological issues which otherwise may destabilize treatment success. There are published case reports integrating sex therapy and pharmacotherapy when treating a couple’s multiple dysfunc-
tions (including DE), but large controlled prospective studies are needed in order to define an appropriate treatment algorithm [506]. The development of new pharmaceuticals will only refine such an algorithm and improve our opportunity for enhancing orgasmic function.

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Implants, Mechanical Devices, & Vascular Surgery for Erectile Dysfunction

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Implants, Mechanical Devices, & Vascular Surgery for Erectile Dysfunction

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1. INTRODUCTION

A satisfactory erection has been the pursuit of mankind for millennia. Historically, numerous potions and superstitions have been employed to improve erectile function, often with a placebo benefit.

The introduction of penile prostheses for the treatment of men suffering with erectile dysfunction (ED) has opened new avenues of basic research, introduced the concept of related medical comorbidities, established an epidemiology for this condition, and stimulated a variety of successful less-invasive treatment options. Indeed, recent advances in the science and clinical management of sexual dysfunction can largely be attributed to the introduction of the modern day penile prosthesis.

Early implants were wooden splints that supported the penis in a semi-rigid state. The French surgeon Ambrose Pare’ suggested an “artificial penis” made of a wood pipe constructed for patients after traumatic penile amputation in order to facilitate urination in the standing position. Although not intended for sexual intercourse, one may refer to this 16th century device as an early “penile prosthesis.”

The first real implant using autologous materials was the use of rib cartilage in conjunction with a tubed phalloplasty by Russian surgeon Bogoraz in 1936 [2]. Future endeavors by this far-sighted surgeon utilized rib cartilage in morphologically intact penises in men suffering from ED. Unfortunately, long term success with this method was limited by natural resorption.

The use of alloplastic materials originates from experimental materials developed in laboratories and resulted in the first acrylic subcutaneous penile implants in 1949 [3]. Another major innovation was the intracavernosal implantation of acrylic rods by Egyptian surgeon G.E. Beheri [4]. After the clinical acceptance of malleable and semi-rigid implants, Scott et al introduced the 3-piece inflatable device in 1973 [5]. Besides progress in the design and durability of the penile implant, a whole industry focusing on ED diagnosis and treatment has evolved. Diagnostic measurement devices became more sophisticated, but with time have largely been supplanted by more specialized validated subjective questionnaires.

While the newer medical treatments are considered first and second lines of therapy, penile implants still remain a popular and important option for men with medication-resistant ED. Additionally, implants are appropriate when medical therapy is contraindicated, causes severe side effects, vacuum erection therapy has proven unsatisfactory or unacceptable, and/or in men with end organ failure (e.g. diabetes mellitus), severe structural abnormalities (e.g. Peyronie’s disease), or cavernosal fibrosis (e.g. after prolonged priapism or infection).

2. INDICATIONS FOR SURGERY

A variety of penile prosthesis designs are currently available for implantation, but not all patients with ED are candidates for penile prosthesis implantation. Penile prostheses are indicated for the treatment of organic erectile dysfunction in men who fail or reject more conservative measures, such as oral PDE5 inhibitors, vacuum erection devices (VED), urethral alprostadil suppositories, and intracavernosal injection therapy. For those men, in whom penile prostheses are suggested, careful counseling before penile implant procedures will limit many of the problems with postoperative dissatisfaction. Once the discussion and demonstration of penile implant varieties has been carried out, patients may
then choose a specific prosthetic type based on their needs and preferences [6]. Younger patients with normal manual dexterity and patients who wear form-fitting clothing or who shower in public (e.g., health club) often choose a three-piece inflatable penile prosthesis because appearance in the flaccid position is better than other designs. For these patients, implantation of a semirigid rod penile prosthesis requires a significant lifestyle change and they are better served with an inflatable-type prosthesis.

Similarly, patients with Peyronie’s disease, secondary implantation, or neurological disease are best served with an inflatable penile prosthesis considering interior tissue pressures are diminished between uses and the possibility of extrusion is diminished [7]. For patients in whom the convenience of inflation and deflation are not important, the risks of mechanical malfunctions may outweigh the concealment disadvantage of a malleable penile prosthesis. Such patients as paraplegics – who require external urinary collection device, those with inadequate manual dexterity, or those with significant obesity may be better served with a malleable penile prosthesis.

3. TYPES OF PENILE IMPLANTS

There are three classes of penile implants, hydraulic, semi-rigid, and soft silicone (Table 1) [5, 8, 9]. The hydraulic consists of two types, the three-piece inflatable and the two-piece inflatable. Two companies manufacture the three-piece variety; American Medical Systems (AMS) (Minnetonka, MN) and Coloplast (Minneapolis, MN).

**TABLE 1. Available Penile Prostheses**

<table>
<thead>
<tr>
<th>Semirigid rods</th>
<th>Inflatable</th>
</tr>
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<tbody>
<tr>
<td>AMS 600 (AMS)</td>
<td>700 CX (AMS)</td>
</tr>
<tr>
<td>Malleable (Coloplast)</td>
<td>700 LGX (AMS)</td>
</tr>
<tr>
<td>Dura II (AMS)</td>
<td>Alpha 1 (Coloplast)</td>
</tr>
<tr>
<td></td>
<td>Titan (Coloplast)</td>
</tr>
<tr>
<td></td>
<td>Ambicor (AMS)</td>
</tr>
</tbody>
</table>

Both companies market two widths of inflatable cylinders. AMS calls its standard cylinder the CX and its narrow cylinders the CXR. Coloplast titles its standard cylinder the Titan and its narrow-base model the Titan NB. The narrow cylinders are appropriate for the thin penis and for the penis with scar tissue where dilation to a large caliber corporal body is not easily accomplished. All of these cylinders expand in girth, but not in length. AMS also manufactures the LGX cylinder that expands in girth and length. Cylinder construction is quite different for the two manufacturers. AMS cylinders are composed of three layers. The inner layer is silicone, the middle layer is a fabric of woven Dacron and Lycra, and the outer layer is silicone. The CX and CXR have a unidirectional weave to their fabric allowing only girth expansion, whereas the LGX has a bidirectional weave permitting expansion both in length and girth. In late 1999 AMS added a Parylene coating to the surfaces of the silicone not in contact with the body tissues. This micropolymer increases the lubricity of the silicone and in bench testing by the manufacturer makes the silicone much more wear-resistant. The AMS pump and reservoir are also made from silicone and Parylene has not been added to their construction at this time.

The Coloplast cylinders and reservoir are made of Bioflex, a material similar to polyurethane, and silicone is used for the pump and the tubing to connect the components. Bioflex and silicone do not bond to each other chemically and the process used to bond the components to the silicone tubing is proprietary and undisclosed by Coloplast. Coloplast Bioflex cylinders in lab testing are more abrasion-resistant than silicone cylinders and clinical studies prior to Parylene introduction bore this out, as the studies of non-Parylene AMS devices had worse 5-year freedom from mechanical revision than did the Coloplast implants [10]. It is notable that a very large series of Coloplast devices had virtually no failures from the Bioflex component; most revisions were necessitated by silicone tubing failure adjacent to the pump [11].

Coloplast devices are all pre-connected between the cylinders and pump (Figure 1). The cylinders are available in 2 cm increments from 10-22 cm – longer lengths are available by special order. Reservoir sizes are 75 cc and 100 cc. AMS devices are available pre-connected and also as separate components. Cylinder length for AMS is in 3 cm increments from 12-21 cm for the standard size CX and LGX, but 2 cm increments for the downsized CXR. Reservoir sizes available are 65 and 100 cc. Rear tip extenders (RTE) are 1-3 cm for the Coloplast implants and are stackable to allow rear tips to equal 6 cm in total. RTE for AMS CX and LGX are similar except that a 0.5 cm is also available. The CXR has non-stackable, snap-on RTE available from 0.5 cm to 6 cm.

**FIGURE 1: Coloplast Titan Alpha 1**
Infections are the most disastrous complications of any implantable device. Both companies have taken steps to decrease the incidence of these problems by applying coatings to the prosthesis designed to retard bacterial growth. In May 2001 AMS introduced InhibiZone™, a patented antibiotic surface treatment that impregnates minocycline and rifampin into the external silicone surfaces of all the components, except the RTE, resulting in a mottled orange external appearance (Figure 2).

FIGURE 2 – AMS 700CX InhibiZone Device

The antibiotics elute into the implant space over 7-10 days and all traces are gone by 12 days. Concentrations of the antibiotics represent less than a common oral dose, but seem effective in preventing early colonization and the development of a bacterial biofilm layer [12]. The mechanism of minocycline (inhibits protein synthesis) and rifampin (inhibits DNA-dependent RNA polymerase) may help reduce the likelihood of developing bacterial resistance to either agent [13]. In-vitro and in-vivo studies have demonstrated minocycline’s effectiveness in retarding the emergence of staphylococcal strains that are resistant to rifampin [14]. Short-term follow up for this prosthesis enhancement shows statistical improvement in infection reduction for first time implant patients by a single surgeon [15] and the manufacturer’s data bank studies [16].

Coloplast also coats their Alpha 1 and Alpha NB with a hydrophilic coating. Initially this coating was called Resist; this title was subsequently dropped in the United States and the prosthesis was renamed Titan and Titan NB. The hydrophilic coating absorbs 23 times its weight in water and the theory is that when a coated implant is soaked in an antibiotic-containing solution, the antibiotics adhere to the surface of the device. No clinical studies are available as of yet, however, a manufacturer data bank study shows a decreased rate of implant infection when compared to non-coated Coloplast devices [17]. Coincident with the introduction of the new-coated Titan prosthesis, the tips of the cylinders were changed to a more physiologic tapered shape rather than the former blunt appearance.

The only two-piece device presently available in the United States is the AMS Ambicor (Figure 3). This device has cylinders similar to the obsolete AMS self-contained implant, the Dynaflex. In this 2-piece model the pump mechanism has been moved from the tip of each cylinder to a separate scrotal pump attached to the two cylinders. Depression of the pump causes fluid to move from a 3-5 cc reservoir in the base of the cylinder to the middle of the penile shaft achieving marked rigidity. Detumescence is obtained by bending the penis 90° from the horizontal position for 12 seconds. Flaccidity and erection are compromised with this model when compared to the 3-piece multi-component device, mainly because the reservoir volume is so severely restricted. The device is not available with Parylene or InhibiZone™ coatings as of yet, but has a popular following and good short-term mechanical reliability [18].

FIGURE 3: AMS Ambicor

Coloplast previously marketed a two-piece device as the Mentor Mark II. This device had a pump/reservoir (Resipump) that contained 25cc but delivered approximately 15-20 cc to Bioflex standard sized cylinders. The device was not popular and Coloplast withdrew it from the marketplace. Coloplast developed a similar device called the Excel that has narrow based cylinders attached to a smaller (20cc) combined pump reservoir. This device is currently approved in a number of markets outside the USA.

There are two types of semi-rigid rod prostheses, the malleable and the mechanical. Coloplast’s Genesis is a malleable device composed of a braided silver wire surrounded by a silicone hydrophilic coat. The AMS 650 and 600 implants have similar construction of silicone surrounding a stainless steel woven core (Figure 4).
The Jonas prosthesis manufactured in Germany for over 20 years also has a silver core and silicone covering [19]. The AMS Dura II is a unique semi-rigid rod that features articulating segments of polyethylene held together by a central spring (Figure 5). The articulating segments resembling a ball and socket are covered by a polytetrafluoroethylene sleeve and surrounded by a silicone jacket to prevent ingrowth of tissue into the mechanical parts.

Finally there are soft silicone rods that were originally manufactured in France by Subrini [20]. Currently, these inexpensive devices are sold under various names in several countries, mostly in Europe and Mainland China. This implant has been promoted to aid the partially impotent man who has tumescence, but not rigidity. The soft silicone implants are used less often because many of these men with partial ED now respond to oral medication. There are other rods manufactured locally throughout the world, but few of these find their way out of their native countries (Table 2). Currently only one semi-rigid rod model is available with a coating to retard infection, the Mentor Genesis.

Table 2. Various semi-rigid penile prostheses

<table>
<thead>
<tr>
<th>Prosthesis Name</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promedon Tube Prosthesis</td>
<td>Argentina</td>
</tr>
<tr>
<td>HR Penile Prosthesis</td>
<td>Brazil</td>
</tr>
<tr>
<td>Silimed Penile Prosthesis</td>
<td>Brazil</td>
</tr>
<tr>
<td>Jonas (ESKA) Prosthesis</td>
<td>Germany</td>
</tr>
<tr>
<td>Shah Implant</td>
<td>India</td>
</tr>
<tr>
<td>Virilis I and II Implants</td>
<td>Italy</td>
</tr>
</tbody>
</table>

For patients with complex anatomic issues such as kidney transplant or neobladder, the surgeon might consider placing a more simple prosthesis than the 3-piece. Another solution might be to place the reservoir outside of its usual location behind the pelvic bone in the space of Retzius. Coloplast manufactures a reservoir suited for these complicated patients. The reservoir has a lock-out valve that prevents transfer of fluid from the reservoir into the cylinders (Figure 7). Fluid is only transferred from the reservoir to the cylinders upon creation of negative pressure from the pump, not in response to positive pressure on the reservoir.
The reason the space of Retzius is chosen for reservoirs without this auto-inflation modification is due to its potential capacity. Three months after reservoir implantation the new capsule formation around the reservoir usually prevents increased abdominal pressure from milking fluid from the reservoir into the cylinders. The Coloplast reservoir with lockout valve allows placement of the reservoir in locations that would normally cause auto-inflation (e.g. anterior to the transversalis fascia, but posterior to the abdominal wall muscles) [23]. Many skilled surgeons continue to use the traditional reservoir position, even in anatomically compromised patients, but others resort to ectopic locations, such as mentioned above, or even place the reservoir in an intraperitoneal location. The tubing caliber for the AMS and Coloplast products is similar. This permits the surgeon in specialized situations to combine manufacturer’s components.

4. PATIENT SELECTION

When selecting a prosthesis for a particular patient the surgeon considers the three choices of semi-rigid, 2-piece inflatable, and 3-piece inflatable. All things being equal and cost not being a factor, the 3-piece is considered the gold standard in most industrialized countries. The semi-rigid rod implants are easy to insert and usually easy to manipulate. The rods are especially bendable and with minimal exertion can easily be maneuvered in the upward or downward position. The wire devices will sometimes spring back and may not be perfectly positionable for erection or in a straight downward position [24]. Sitting and standing may require surreptitious manipulation of the device to promote concealment. Cystoscopy with a rigid instrument was formerly a problem, but flexible cystoscopy has eliminated this problem with semi-rigid rod implants. Patients with spinal cord injury have been more prone to have erosion of semi-rigid rod cylinders through the glans because of cylinder pressure and the absence of sensation. The patient lacking cutaneous sensation may not appreciate when rods are eroding through the tissues of the penis. Most authorities recommend inflatable implants for spinal cord injury patients even if the implant is used only to facilitate condom catheter urinary drainage [25]. When considering choices of semi-rigid rods, the mechanical model, AMS Dura II, is more expensive than the devices using internal wires, but is “the prosthesis of choice for patients lacking manual or mental ability to manipulate other devices” [26]. The two-piece prosthesis is advantageous if the surgeon desires to avoid intra-abdominal reservoir placement since the functional result is better than a rod implant. The Ambicor can deliver good rigidity and fair flaccidity, or fair rigidity and good flaccidity, but rarely good rigidity and flaccidity simultaneously. There are other compromises when compared to the three-piece prosthesis. The long proximal segment between the proximal end of the implant and the input tube (5 cm) tends to make this tube palpable on the shaft of the penis in thin patients resembling what some call “tailpipe penis.” Finally, as mentioned above, deterioration in erection with time may occur. The three-piece “gold standard” accounts for 70% of implants implanted in the United States, while 20% are two-piece inflatable (Ambicor) devices. The remaining 10% are semi-rigid rods. Outside the United States, where reimbursement by third parties is less frequent, and the cost of the rods is considerably less, the split is 50% inflatable and 50% rods.

Outcome studies published in the medical literature indicate higher satisfaction from implants than pills, injections, or VEDs [27]. In 2005 the majority of well-informed patients elected surgical correction rather than pursing a trial of intracavernosal injections or VED. Many educated individuals seek out an urologist who specializes in prosthetic urology [28]. It is imperative that physicians with a focus on prosthetic urology profess their qualifications on internet search sites to enable patient connection with qualified implanters.

Today a patient would be considered a good candidate for a penile prosthesis if he had failed medical therapy or if medical therapy were contraindicated and the other therapies such as penile injections, intraurethral therapy, and VED have also failed or do not satisfy the patient. Patients who eventually opt for an implant are usually highly motivated to continue with sexual activity.

In many instances, the physician helps the patient decide which prosthesis type to choose. This decision is usually based on the physician’s comfort with the surgical approach, assessment of body habitus, and manual dexterity of the patient and overall cost. Patients with a larger penis will be best served by a three-piece inflatable device, as these devices deliver the best rigidity. Similarly, patients with shorter penises often choose the three-piece device, since semi rigid rods and two-piece implants are more difficult to conceal. Patients with limited manual dexterity or those who have difficulty manipulating hydraulic devices are directed towards a semi-rigid rod. An exception to this rule is when a motivated partner manipulates the hydraulic device for the patient.

It is important for the patient receiving a 3-piece inflatable implant to understand that the post implant size of his penis will invariably be slightly shorter than his natural erection when he was fully potent. Also, unlike a normal erection, the prosthetic erection does not result in an increase in the size of the glans. Preoperative consultation with the implant candidate should explain this loss of length, but emphasize that girth of the penis may be greater than a natural erection, and girth, not length is responsible
for penile rigidity. To continue along this line of reasoning, rigidity is what produces maximum sexual satisfaction in the female, as the area for maximal female stimulation resides just inside the introitus.

Sensitivity of the penis, ejaculatory abilities, and sexual drive are for the most part unchanged following placement of a prosthesis. The patient needs to clearly understand that penile implants only restore the ability to penetrate. They do not restore any special sensitivity or sexual drive that may have been present in earlier years. If the cylinders are removed at a later date, the capsule remains and the empty space will partially fill with proliferating scar tissue. This may make it difficult for the patient to respond adequately to other treatments such as medication or a VED. It is important that the patient have a realistic expectation of his penile prosthesis.

There are a number of possible complications associated with penile prosthesis implantation, as with any surgical procedure. The most common complications necessitating reoperation are infection (1-4%) [12] and mechanical dysfunction (5-13% in first 5 years) [10, 11]. A preoperative consultation needs to include a discussion of these potential causes of a return to the operating theatre. The patient and his physician need to be mutually satisfied they have covered the major risks and rewards of the surgical event and this needs to be noted in the clinical record.

5. PRE-OPERATIVE PREPARATION AND POSTOPERATIVE CARE

Most penile implants are placed in patients with an organic etiology to ED, and have failed to respond, did not tolerate, or are unwilling to consider more conservative options [29]. Oral therapy often fails in men with severe ED due to diabetes mellitus or after radical pelvic surgery. Men with severe Peyronie's disease associated ED, severe penile fibrosis, or cases of post-priapism are more likely to be considered for implantation of a penile prosthesis. In the pre-sildenafil era it was the norm to diagnose the precise etiology of a patient's ED. Comprehensive blood testing (including cholesterol, glucose and hormone studies), vasoactive injection testing, color duplex Doppler ultrasound, and nocturnal penile tumescence studies were all routinely obtained. This extensive evaluation process is now thought to be unnecessary in the day of effective oral therapy. Many third party payers have recognized that many of these diagnostic tests do not influence ultimate patient outcome and refuse to reimburse ancillary test expenses.

Diabetes mellitus is known to be a risk factor for severe ED and the need for penile prosthesis implantation [30]. In 1992 Bishop et al suggested that patients with diabetes mellitus whose blood sugar was in better control for a period of time preoperatively, as manifested by a normal hemoglobin A1C, were less prone to develop a penile implant infection versus a group whose Hgb A1C was elevated [31]. Other larger series repeated this study and found no difference in infection rates in patients with normal or elevated Hgb A1C [32]. The presence of diabetes raises the risk of prosthetic infection from 3% to 8%, but the level of glycosylated hemoglobin, the fasting blood sugar (FBS) on day of surgery, and whether the patient was insulin-dependent were not predictive for increased rate of infection [32]. Another study, however, showed no difference in infection rates between diabetic and non-diabetic men receiving penile prosthesis [33].

Current work up consists of a history and physical, with some focus on sexual desire and enjoyment. Failure or intolerance to oral drug therapy and knowledge of penile injections, intrarethral agents, and VED is ascertained during initial history taking. If the history and physical is uncertain, further diagnostic testing may be warranted. If the patient indicates an interest, one can prescribe oral therapy, intracorporal injections, intrarethral pellets, or VED. If disinterested, or a history of unsatisfactory results with second line therapies exists, the surgeon can explain the surgical benefits of penile prosthesis surgery. Many high volume implanters are tertiary referral centers for prosthetic surgery with patients travelling from considerable distances. These patients are often seen for the first time one day and undergo surgery the next. The expedited work up consists of history, physical, and assessment of the lower urinary tract.

It is important that the lower urinary tract be evaluated prior to penile prosthesis surgery in order to avoid untoward events such as urinary tract infection, difficulty inserting a catheter, or urinary retention. It is customary to perform a urinalysis, post-void residual check, and if indicated a cystoscopy. Urinary tract infections are treated and patients who are prone to develop urinary infections (such as those with neurogenic bladders) are placed on prophylactic antibiotics preoperatively to maintain sterile urine for the day of surgery. If prostate obstruction is detected, this is treated prior to prosthesis implantation by either medication, or surgical therapy. Post-radical prostatectomy patients may have a bladder neck contracture that would prevent easy Foley catheter placement or post-operative urination. Such patients are dilated or undergo transurethral bladder neck incision. If significant urinary incontinence is encountered, prosthesis insertion is delayed to determine if concurrent artificial urinary sphincter (AUS) placement or a male sling procedure is recommended.

Patients shower with antibacterial soap for a few days prior to surgery. Shaving of the genital area
is performed in the holding area or operating room to minimize the chance of bacterial colonization. Antibiotics are initiated prophylactically one hour prior to surgery. The antibiotic choice is made by the surgeon and this decision should cover the possibility of infection by skin contaminants. There have never been any controlled studies in penile prosthesis recipients demonstrating that postoperative antibiotics decrease the incidence of surgical infections. If a scrotal incision is utilized, a catheter is inserted to facilitate urethral identification and to empty the bladder completely before reservoir placement. The catheter may be discontinued when the patient has recovered from anesthesia or remains until the following morning. Some surgeons opt to use drains at the conclusion of the procedure to reduce edema and provide an exit for corporal bleeding in the postoperative period. Such a drain is removed the following morning and has not demonstrated an increased incidence of prosthesis infection [34].

Pain following placement of a penile prosthesis is variable and individual. The pain is usually more prolonged than genital procedures without prosthetic components.

Some scrotal ecchymosis and swelling is common and a scrotal hematoma, if it forms, usually slowly resolves without operative intervention.

Patients are instructed at discharge to wear brief-type underwear for the first month and direct their penis upward if possible. Coloplast implants with a lockout valve prevent fluid transfer from the reservoir to the cylinders. A capsule has not formed around the reservoir fully until three months postoperatively and in the early period in patients without a lockout valve, any increase in intrabdominal pressure may cause fluid to leak from the reservoir into the cylinders causing partial tumescence. In such cases, the patient should either deflate his device or return to the office for deflation. Generally at three months a capsule has formed around the reservoir and protects the patient from future auto-inflation. A new pump from AMS for the three-piece prosthesis that prevents auto-inflation has been recently introduced into the market.

Patients are taught how to operate their hydraulic devices at approximately four to six weeks. Some surgeons prefer to begin cycling of devices earlier, but in most patients pain will be a limiting factor to early cycling. At three months most patients are pain free. In some cases (e.g. diabetes mellitus) neuropathic pain may persist for longer periods of time. If prolonged pain does occur, the surgeon should suspect the possibility of a subclinical infection associated with the prosthesis.

After patients are instructed in the operation of their device they are advised to cycle regularly. When the cylinders are left semi-inflated for prolonged periods of time, a capsule forms over the reservoir in the less-than-full state that thereby restricts its expansion. Patients particularly dislike auto-inflation if they are attempting to achieve complete flaccidity. After three months it is usually no longer possible to influence reservoir capacity, and corrective capsulotomy may be necessary to correct bothersome auto-inflation [35].

6. ANESTHESIA

Three-piece penile implants are placed under general or regional anesthesia. A short acting spinal is ideal for the procedure. Local anesthesia is inadequate for reservoir placement. On the other hand, semi rigid rods may be placed with local anesthesia only. A penile block with 1% lidocaine is utilized before a tourniquet is placed around the base of the penis and approximately 25 cc of anesthetic is instilled into either corpus cavernosum and held in place for one minute. The tourniquet is released allowing the local anesthetic to diffuse into the proximal portion of the corpora. Infiltration of the skin incision site completes the anesthetic block. Some surgeons inject the corpora with a small amount of long acting anesthetic such as marcaine to keep the patient pain-free in the immediate post-operative period.

7. OPERATIVE TECHNIQUE

Surgical implantation of penile prostheses can be carried out using a variety of surgical approaches and incisions. Semirigid and malleable prostheses can be implanted through a distal penile approach. Multiple-component prostheses, however, can be implanted by the infrapubic or penoscrotal approach. While individual surgeons have a variety of rationales for each of these approaches, there does not appear to be any clear advantage in patient satisfaction or outcome of the two approaches. There is no difference in infection rates between either infrapubic or scrotal incisions [30]. Patient anatomy may dictate appropriate choice. Patients with previous abdominal surgical procedures where reservoir placement is difficult may be better served with an infrapubic approach while patients with massive obesity may be better approached through a penoscrotal incision. Two-piece devices, because there is no separate reservoir, are best implanted through a penoscrotal incision.

a) Distal Penile Approach

A distal penile approach is usually the best approach for insertion of a semirigid or malleable penile prosthesis. This incision heals well, allows complete corporeal dilation, and facilitates rod placement. After placement of a Foley urethral catheter, a circumcoronal incision is carried out over 180 degrees of the subcoronal region of the penis. Dissection is carried down to the layer of Buck’s fascia, taking care to avoid the dorsal penile nerves, which course within Buck’s fascia. After Buck’s fascia is identified, stay
sutures are placed in the two corpora through the tunica albuginea lateral to the penile nerves. These longitudinal incisions can be extended as much as is necessary for dilatation and cylinder insertion. The corporal dilatation is commenced with large scissors to establish a track in the corporal tissue. Dilation then follows with Hagar, Brooks, or dilamezinsert dilators from 9 to 14 depending upon required cylinder girth (Figure 8). Once the corpora are sized using a Furlow or other dilator, the cylinders can be placed (Figure 9 and 10). A small vein retractor can be used to facilitate placement of the distal end of the cylinder. The corporotomy is closed with 2-0 absorbable, synthetic sutures. With noninlatable cylinders, a penile block can be performed and a noncompression dressing is applied.

b) Infrapubic Approach

The infrapubic approach allows better visualization of the reservoir placement than the penoscrotal approach. However, due to the proximity of the dorsal neurovascular bundle in the infrapubic approach, nerve injury is possible, resulting in decreased distal penile sensation in some patients. The infrapubic approach is carried out with a horizontal or vertical incision approximately one finger breadth below the symphysis pubis, allowing implantation with an easily concealed incision once the pubic hair regrows (Figure 9 and 10). After incision of the subcutaneous tissue, the dissection is continued to the rectus fascia. The rectus fascia is incised and dissected cephalad for approximately 2 to 3 cm. A midline separation of the rectus muscles is carried out using sharp and blunt dissection. A pouch is created bluntly beneath the rectus muscles to comfortably insert the inflatable reservoir without compression.

Dissection is then carried out over the corpora cavernosa. Sharp and blunt dissection is performed on either side of the fundiform ligament, identifying the dorsal neurovascular bundle. Note that the dorsal nerves of the penis lie approximately 2 to 3 mm lateral to the deep dorsal vein. Once Buck’s fascia has been dissected free from the tunica albuginea, the shiny white tunica albuginea is fixed with longitudinal traction sutures. A corporotomy incision is then carried out between the traction sutures and the corpora cavernosa is entered (Figure 12). The corporotomy incision can be carried out with scalpel or electrocautery. Large scissors are then used to carefully initiate the tunneling of the corpora cavernosa. Hagar dilators from size 9 to 14 or alternatively Brooks, Pratt, or dilamezinsert dilators can be used. If corporeal fibrosis is encountered, Rossillo cavernotomes can be used to dilate to size 12. Once dilation has been adequately carried out bilaterally, the Furlow introducer or dilamezinsert is used to measure the corpora cavernosal length using a traction suture as a central point of reference. The proximal and distal measurements are added to give total corporal length and choose appropriately sized inflatable cylinders. A length slightly less than the total measurement is usually used to permit comfortable positioning of the cylinders. Rear tip extenders of size 0.5, 1, 2, 3 cm, or combinations thereof are placed on the proximal cylinder end to adjust length. Once measurement has been obtained, interrupted sutures can be placed for later corporotomy closure. The advantage to this technique is the elimination of suture needles close to the area of the inflatable cylinder, diminishing the possibility of cylinder damage during corporotomy closure. Other methods of corporotomy closure include running sutures with or without a locking technique. Once the corporotomy sutures are placed, cylinders are positioned in the dilated straight corpora cavernosa using the Furlow inserting tool with distal needle to pull the cylinders into position. Once positioned, it is essential to ensure that there is no kinking and complete proximal and distal seating of the cylinders has taken place. The corporal incision should be placed proximal enough to allow easy exit of the input tube and minimize cylinder/input tube contact. Closure of the corpora cavernosum is carried out with traction on the cylinder placement suture to maintain it in a flat, nonkinking position and ensure adequate seating. Following placement of cylinders and closure of the corporotomy incision, cylinder inflation can be tested by pumping fluid to identify any abnormalities in position, curvature, or related problems.

A finger is placed beneath Scarpa’s fascia down into the scrotum on one side to develop a sub dartos pouch for the pump. The pump is then positioned in the previously constructed subrectus pocket and filled with an appropriate volume of normal saline or water/radiographic contrast media. Before connection, it is important to release pressure on the filling syringe and determine if any backfilling is observed. This backfilling or backpressure may predict an autoinflation problem in the future. Tubing connection is then carried out using quick connectors or suture tie plastic connectors. Snap-on connectors are used for Coloplast prostheses. The tubing is tailored to eliminate excessive length but to allow for adequate pump positioning. Shodded clamps are used to compress the tubing and the ends of the tubing, once tailored, are flushed with inflation fluid to eliminate small particles and blood clots. After the tubing is connected, the adequacy of the connection is tested by gently pulling on the connectors. All shodded clamps are removed and the device is inflated and deflated on multiple occasions to ensure adequate location, placement, and erection.

Following testing, thorough irrigation with antibiotic solution is carried out and the rectus fascia closed with interrupted sutures. The wound is then closed in
the standard fashion with two layers of subcutaneous tissue and a subcuticular skin suture. A dry sterile dressing is applied, a Foley catheter placed if necessary, and an ice pack applied. Suction drains may be used at the surgeon’s discretion.

Postoperatively, patients are instructed to maintain their penis in a dependent position for 4 to 6 weeks. Tight underwear and athletic supporters are not used in an effort to maintain the pump in its most dependent position.

c) Penoscrotal Approach

Three-piece inflatable penile prostheses, as well as, semirigid and two-piece prostheses can be implanted by a transverse or vertical penoscrotal incision. This approach has distinct advantages in obese patients and is the most common approach for routine penile prosthesis implantation. Because the penoscrotal approach requires differentiation of corpora cavernosa from the corpus spongiosum during resection, initial placement of a Foley catheter is preferred for this approach. The incision, usually horizontal, is placed in the upper portion of the scrotum one finger breadth below the penoscrotal junction. The Scott/Lone Star retractor (Lone Star Medical Products, Stafford, TX) facilitates exposure with this incision. Once the skin incision has been carried out, dissection is continued lateral to the corpus spongiosum and urethra to expose the corpora cavernosa. Incision, dilation, and closure of the corpora cavernosa are similar to that described previously for the infrapubic incision, but synthetic absorbable sutures should be used with this approach because the suture line may be palpable postoperatively (Figure 15). Cylinder sizing and placement are as described above. Pump placement is likewise in the most dependent portion of the scrotum just below the dartos fascia.

Dissection for reservoir placements can be carried out with a second separate infrapubic incision, but is more commonly performed through the penoscrotal incision (Figure 16). The scrotal skin incision is retracted to the area of the external inguinal ring and dissection is carried out medial to the spermatic cord. It is important to drain the bladder completely at this point. The transversalis fascia is then identified and incised sharply using large scissors pushed firmly through the medial aspect of the external inguinal ring. Dilation is carried out with the index finger after incision of the transversalis fascia. The reservoir balloon is then positioned over the index finger and placed in the perivesical space. Inflation of the reservoir is carried out with care that no backpressure is observed. If refilling of the syringe occurs, pocket enlargement must be carried out to help prevent autoinflation occurring down the line. Once the reservoir is placed, inflated, and tubing connected as previously described, the device is tested in inflation and deflation modes (Figure 17).

Closure is carried out with a subcuticular suture in the standard fashion. In men with a penoscrotal skin web, the horizontal skin incision can be closed in a midline fashion or employing a Z-plasty technique to enhance functional penile length.

8. PENILE PROSTHESIS COMPLICATIONS

a) Infection

Periprosthetic infection, infection in the space around a penile prosthesis, is the bane of genitourinary prosthetic surgery. While men with these infections are seldom seriously ill, eradication of the infection invariably requires complete device removal. Subsequent penile prosthesis reimplantation is difficult due to scarring of the corporeal smooth muscle, which leads to decreased penile length and girth as well as difficult cylinder implantation.

The use of prophylactic broad spectrum antibiotics is widespread in penile prosthetic surgery; however, the timing of the administration of these antibiotics varies. Guidelines suggest that “infusion of the first antimicrobial dose should begin within 60 minutes before surgical incision and that prophylactic antimicrobials should be discontinued within 24 hours after the end of surgery [36].”

Traditionally infection rates in revision penile prosthesis have been higher than with primary implant surgery. When at the time of revision surgery the entire device is removed and the implant spaces are lavaged with a series of antiseptic solutions before implantation of a new device, the infection rate is similar to that with first time (primary) penile prosthesis implantation [37]. Earlier however, it had been shown that when the old implant is entirely removed and replaced with a new device, lavage with only one antibiotic solution was enough to achieve an infection rate equivalent to that seen with primary penile prosthesis implantation [33].

In 1996 Brant and Mulcahy introduced the concept of penile prosthesis salvage for infected implants [38]. With this procedure, the entire infected device is removed and the implant spaces are lavaged with a series of antiseptic solutions. A new prosthesis is then implanted. This series was updated in 2000 [39] and again in 2003 at which time the success rate of salvage in a series of 101 infected implants was 84% [1]. After inflatable penile prosthesis implantation, infection usually first becomes evident by tissue changes around the pump. It is now generally accepted that the entire penile prosthesis is infected. Whether a salvage procedure is performed or the device is removed with planned later reimplantation, it is mandatory to remove all the prosthetic material including, if present, polytetrafluoroethylene tubing coverings and rear tip extenders (Table 3) [1].

Unfortunately some surgeons still remove only the
pump; with subsequent removal of the rest of the device becoming necessary because of infection. Superficial wound separation and / or infection is more common than periprosthetic infection. If the entire penile prosthesis is implanted below the fascia, routine wound care will result in wound healing without device infection. With inflatable penile prostheses, where the pump and cylinders are often available as a unit, surgeons using a penoscrotal approach often employ a technique that results in tubing being present under the scrotal skin and subcutaneous tissue. This is not only undesirable from a cosmetic standpoint but it also greatly increases the chance of device infection should a superficial wound infection or separation occur. Routing the pump through an opening in the back wall of the scrotal pouch for the pump buries the tubing beneath the fascia, thus avoiding these problems.

In 2001 American Medical Systems (Minnetonka, MN, USA) introduced a dual antibiotic coating, minocycline and rifampin, for their three-piece inflatable penile prosthesis product line. This was shown to decrease the infection rate 180 days after implant from 1.61% to 0.68% [16]. Mentor Corporation (now Coloplast) soon after introduced a hydrophilic coating, polyvinylpyrrolidone (PVP), for their three-piece inflatable penile prostheses. This coating allows the implanting surgeon to immerse the device in an antibiotic solution of his or her choosing. This resulted in a decrease in the infection rate one year after implant from 2.07% to 1.06% [17].

b) AUTO-INFLATION

Partial spontaneous inflation of a three-piece inflatable penile prosthesis sometimes occurs and may be bothersome to the patient. In one study the rates of auto-inflation in men implanted with three-piece inflatable prostheses after prostatectomy was 3% and in men with erectile dysfunction due to other causes it was 5%. (p>0.99) [40] Mentor introduced a lock-out valve in the reservoir stem which resulted in a 1.3% rate of auto-inflation compared to an 11% rate in historical controls [23]. American Medical Systems recently introduced a lock out valve in the top of the pump of their AMS 700MS™ device; published rates of auto-inflation with this prosthesis are not yet available.

c) GLANS PROBLEMS AFTER PENILE PROSTHESIS IMPLANTATION

Patients who are considering penile prosthesis implantation should be told about the lack of glans tumescence and that their erection may be shorter than their former natural erection. Some men who complain of lack of glans tumescence or coolness after penile prosthesis implantation may benefit from the use of a phosphodiesterase type 5 inhibitor or from the use intrarethral alprostadil (MUSE, Vivus, Mountain View, CA) [41].

Other patients may complain of poor support of the glans penis by the tips of the prosthesis. This downward drooping of the distal penis is referred to as the SST deformity because of the similarity of its appearance to the supersonic transport or Concord aircraft. If the SST deformity is due to cylinders which are too short, revision with implantation of longer cylinders will correct the deformity and result in a somewhat longer penis. Sometimes this deformity occurs because of anatomic variations in the relationship of the glans penis to the corporeal tips. In this case a glanulopexy modified after that originally described by Ball [42] may be helpful [43].

d) RESERVOIR DISPLACEMENT

In three-piece inflatable penile prosthesis implantation by the penoscrotal approach, the empty reservoir is inserted blindly into the retropubic space by perforating the fascia on the medial side of the external inguinal ring or through the fascia just above the pubic tubercle. This is safely done by insure complete bladder emptying through a urethral catheter. The fascial defect created should be tight to the surgeon’s finger. Filling the reservoir with saline after placement helps maintain its retropubic position. Reservoir displacement or herniation into the inguinal canal or upper scrotum will rarely occur. One survey

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**Table 3. Mulcahy Salvage Protocol [1]**

<table>
<thead>
<tr>
<th>Steps</th>
<th>7 Antiseptic solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Removal all prosthetic parts and foreign material</td>
<td>Kanamycin and bacitracin</td>
</tr>
<tr>
<td>Irrigate wound and all compartments with 7 antiseptic solutions</td>
<td>Half strength hydrogen peroxide</td>
</tr>
<tr>
<td>Change gowns, gloves, drapes, and instruments</td>
<td>Half strength povidone iodine</td>
</tr>
<tr>
<td>Implant new prosthesis</td>
<td>Water pic pressure irrigation with 1 gm vancomycin and 80 mg gentamicin in 5 liters</td>
</tr>
<tr>
<td>Primary wound closure without drains</td>
<td>Half strength povidone iodine</td>
</tr>
<tr>
<td>Oral antibiotics as determined by culture for 1 month</td>
<td>Half strength hydrogen peroxide</td>
</tr>
<tr>
<td><strong>AFTER IMPLANTATION</strong></td>
<td>Kanamycin and bacitracin</td>
</tr>
</tbody>
</table>
found an incidence of this complication of 0.7% [44]. Correction of this complication is by revision through an inguinal incision with placement of the reservoir in its proper position and repairing the defect.

e) Distal Cylinder Erosion or Extrusion

Because of loss of sensation, erosion of a penile implant into the urethra occurs more commonly in paraplegic or quadriplegic recipients. This erosion rate was 18.1% (15 of 83) for cases of semirigid rods, 2.4% (2 of 84) for self contained inflatable prostheses, and 0% (0 of 28) for 3 piece inflatable devices [7]. Three-piece inflatable prostheses appear to be associated with less risk of this complication in these recipients. Distal cylinder extrusion laterally can be repaired by creating a new cavity for the distal cylinder behind the back wall of the fibrotic sheath containing it [45]. An alternative technique is to perform distal corporoplasty using synthetic material [46]. Proximal perforation of the cura during the implant procedure can be repaired by the constructing wind sock of vascular prosthetic material and anchoring this to the prosthesis [47].

However, perforation of the crus during dilation usually occurs with the use of narrow dilators and is recognized by the sudden passage of the dilator into the soft tissue of the perineum. When this occurs, it is usually possible to use large scissors to establish the true plane of dilation down to the attachment of the crus to the pelvic bone.

Larger dilators follow this plane, thus avoiding further dilation of the false passage. The rear tip of the cylinder can then be implanted within the crus. The small false passage heals over the tip of the cylinder. These steps eliminate the need for wind sock repair.

f) Carvernosal Fibrosis

Smooth muscle fibrosis occurs in men with ED following prolonged ischemic priapism and in men who have had removal of an infected penile prosthesis.

Dilation of the corpora can be quite difficult and limited dilation may be all that can be achieved. Smaller diameter penile prostheses are useful in these cases. If primary closure of the tunica albuginea over the prosthesis is not possible, the device may be covered by graft material. The following graft materials have been used for this purpose: human cadaveric dura mater [48], polytetrafluorethylene [49], human cadaveric pericardium [50], and porcine small intestinal submucosa [51]. The results of prosthetic surgery using narrow diameter cylinders are often satisfactory. When they are not, future upsizing to wider and sometimes longer cylinders may be helpful [52].

In cases of severe cavernosal fibrosis, corporeal excavation through extended corporotomies has been successfully performed with most of the fibrotic contents of the corpora being removed [53]. This leaves a tunica albuginea shell into which the prosthetic cylinders can be laid. Primary closure of the tunica albuginea over the cylinders is then easily accomplished without graft materials.

9. Penile Prosthesis Survival

Mechanical failure of penile prosthesis can include leakage from the cylinders, tubing fracture, reservoir malfunction, connector disruption, tube kinking, and cylinder aneurysm. Failure rates among inflatable penile prostheses (IPP) have historically been low (Table 4). A recent study from the University of Arkansas assessed the long term survival of IPP, covering both AMS and Mentor/Coloplast models (n = 2,384), and documented the overall 15 year freedom from reoperation to be about 60%, with no significant difference between models [54]. Another study evaluated the efficacy and survivability of the two-piece Ambicor inflatable penile prosthesis, finding that, due to recent revisions in rear tip extenders and pump tubing reinforcement, freedom from reoperation was 99.2%, 99.2% and 91% at 12, 36 and 48 months, respectively (n = 146). Corresponding patient and partner satisfaction were similarly 85% and 76% [55]. The AMS three-piece 700 CX was evaluated for long-term survival in a recent study including 455 patients and was found to have an overall freedom from reoperation of 74.9% and freedom from mechanical failure of 81.3% after ten years [56].

Table 4. Failure rates of various inflatable penile prostheses by type and follow-up period.

<table>
<thead>
<tr>
<th>Prosthesis type</th>
<th>Follow-up (yrs) Kaplan-Meier (KM) or mean (M)</th>
<th>Mechanical failure</th>
<th>Prosthesis type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daitch[55]</td>
<td>5 (KM)</td>
<td>9.1% 17.1%</td>
<td>CX three-piece (AMS) Ultrex (pre 1993 modification)</td>
</tr>
<tr>
<td>Wilson[51]</td>
<td>5 (KM)</td>
<td>7.4%</td>
<td>Alpha 1 (Mentor/ Coloplast)</td>
</tr>
<tr>
<td>Ferguson[50]</td>
<td>5.7 (M)</td>
<td>0</td>
<td>Malleable –Duraphase (now AMS)</td>
</tr>
<tr>
<td>Deuk Choi[54]</td>
<td>4 (M)</td>
<td>7.3%</td>
<td>700 CXM (AMS)</td>
</tr>
<tr>
<td>Levine[52]</td>
<td>3.5 (M)</td>
<td>2.3%</td>
<td>Ambicor 2-piece (AMS)</td>
</tr>
<tr>
<td>Milbank[52]</td>
<td>5 (KM)</td>
<td>6.3%</td>
<td>Ultrex post 1993 modification</td>
</tr>
</tbody>
</table>
10. PATIENT AND PARTNER SATISFACTION

Numerous studies have reported high satisfaction rates for both patients and partners after penile prosthesis implantation for the treatment of ED. In a series of 185 patients from a group of European institutions, authors reported a 98% patient and 96% partner satisfaction rate [61]. The rapid ability to produce an erection and consistent excellent rigidity with the prosthesis were two major factors contributing to this high level of satisfaction for this modality of ED treatment. Lower satisfaction rates have been noted when there is an overall loss of penile length, such as in revision surgery after infection and in prosthesis implantation for Peyronie's disease with penile shortening [62, 63]. Patient satisfaction is a complex and multifactorial issue that may include the degree of postoperative pain and swelling, occurrence of postoperative complications, cosmetic outcome, device function, ease of use, and partner acceptance. Besides shorter length of the penile erection, other reasons given for dissatisfaction include reduced sensitivity, diminished sexual drive, unnatural feeling by the partner, and the partner perception of having a diminished role in initiating erection. Another common patient complaint is the lack of glans engorgement during sexual activity. Typically the patient reports that the corpora cavernosa provide satisfactory rigidity after activating the implant, but notes a soft and mobile glans. One recent study reported on the beneficial effect of sildenafil (Viagra, Pfizer, NY, NY) on glans engorgement in patients having undergone penile implant [64]. By using the International Index of Erectile Function (IIEF), researchers documented that sildenafil caused a statistically significant improvement in implant-assisted intercourse. Similar results were reported with the on demand administration of transurethral alprostadil in patients with self-contained inflatable penile prostheses [65]. Research evaluating the efficacy and satisfaction of prosthesis implantation continues. In a recent study of 146 recipients of two-piece penile prostheses, the authors reported 85% satisfaction among the men and 76% satisfaction among their partners [55]. Even more impressive is the data from a large Italian study, which showed patient satisfaction of 97%, 81%, and 75% with the AMS 700CX, AMS Ambicor, and AMS 600-650; partner satisfaction was 92%, 91% and 75%, respectively [66]. A recent case series from China reported successful coitus in 97.6% (41 of 42) of patients after IPP placement, which was higher than previous reports [67]. Certain patient factors may be predictors of reduced satisfaction. In an Italian multi-institution study surveying patients with penile implants and Peyronie’s disease, 79% of patients and 75% of partners reported satisfaction with the result [61]. It is recognized that patients with Peyronie’s disease, radical prostatectomy, or a BMI >30 kg/m² have a statistically significant reduction in level of satisfaction compared with the general implant population [68]. It is likely that penile length issues play a large role in Peyronie’s disease and radical prostatectomy patients in this regard. It has not been clearly delineated why a BMI >30 kg/m² should be associated with reduced satisfaction, but mechanical issues relating to the pre-pubic fat pad size have been noted in many of these men. Efficacy can also be assessed in a more quantitative fashion with post-operative IIEF scores. One group reported IIEF scores 3, 6, and 12 months after placement of a Mentor/Coloplast Alpha-1 IPP. They found IIEF erectile function domain (EFD) scores to be 13, 21, and 24 and IIEF Satisfaction scores to be 9, 11, and 15 at each respective time interval (baseline in both groups = 7) [69]. A recent study assessing patient overall satisfaction with a specialized questionnaire reported patient satisfaction to be 69%, which is in general agreement with prior reports using other questionnaires [70]. Earlier studies compared inflatable and semi-rigid prostheses and found increased satisfaction in men using inflatable devices over noninflatable penile prostheses. Another study showed a corresponding higher satisfaction among female partners of men using inflatable prostheses in comparison to noninflatable prostheses [71].

Table 5. Recent publications of IPP satisfaction data

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Satisfaction</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natali et al[66]</td>
<td>2008</td>
<td>97%/81%/75%</td>
<td>AMS 700CX/Ambicor/600-650</td>
</tr>
<tr>
<td>Xuan et al[71]</td>
<td>2007</td>
<td>97.6%</td>
<td>Percent achieving coitus</td>
</tr>
<tr>
<td>Lux et al[55]</td>
<td>2007</td>
<td>85%</td>
<td>Ambicor modified 2-piece</td>
</tr>
<tr>
<td>Kava et al[72]</td>
<td>2007</td>
<td>77%</td>
<td>Only post-revision patients</td>
</tr>
<tr>
<td>Akin-Olugbade et al[66]</td>
<td>2006</td>
<td>60-86% (15 out of 20)</td>
<td>RR, obesity, and PD were negative predictors of satisfaction</td>
</tr>
<tr>
<td>Mulhall et al[66]</td>
<td>2003</td>
<td>IIEF 15 at one year (baseline 7 out of 20)</td>
<td>IIEF satisfaction domain at 1 year doubled from baseline</td>
</tr>
</tbody>
</table>

As expected, satisfaction domain scores for patients with corporal fibrosis and shortened penises who had undergone revision prosthesis surgery...
reported lower scores compared to other revision implant groups [72]. In a recent study comparing Mentor/Coloplast Alpha prostheses to the AMS series, no difference in satisfaction rates was found between the two models when employing a specialized follow-up questionnaire [70]. Comparisons between IPP and other forms of ED therapy generally reveal a higher satisfaction rate in men with ED who chose the prosthesis. A 2003 study using IIEF erectile function domain (EFD) and Erectile Dysfunction Inventory for Treatment Satisfaction (EDITS) scoring systems comparing IPP, intracavernous prostaglandin E1 injections (ICI), and sildenafil showed that IPP had significantly higher satisfaction rates compared to the other ED treatment modalities [27].

**Recommendations**

**Indications for penile prosthesis implantation**

- Penile prosthesis implantation is indicated for the treatment of organic erectile dysfunction after failure or rejection of other treatment options.
  - Level of Evidence 3, strength of recommendation C.

- The three-piece inflatable penile prosthesis is recommended for younger patients with normal manual dexterity, patients who wear form fitting clothes, or patients that shower in public.
  - Level of Evidence 3, strength of recommendation C.

- Inflatable penile prostheses are recommended for patients with Peyronie’s disease, as a secondary implantation, or patients with neurological disease.
  - Level of Evidence 3, strength of recommendation C.

- Malleable prostheses are recommended for significantly obese patients, and those with minimal manual dexterity, or when the cost of inflatable penile prostheses is prohibitive.
  - Level of Evidence 3, strength of recommendation C.

**Pre-operative Preparation and Postoperative Care**

- In order to prevent complications, it is important to obtain the patient’s medical and sexual history and perform a physical examination before the prosthesis is implanted. The physician should ensure the patient is aware of all other treatment options and get an accurate idea of what the patient hopes to achieve. This will help in choosing the appropriate prosthesis for the patient.
  - Level of Evidence 3, strength of recommendation C.

- Patients are recommended to follow-up with doctors to learn how to use their devices optimally, ensure their devices are working properly, and confirm there are no postoperative complications such as infection, fluid leaks, or autoinflation.
  - Level of Evidence 3, strength of recommendation C.

**Informed Consent**

The patient should be informed of the following possible complications related to the prosthesis prior to implantation: infection and its consequences, pain, mechanical failure, penile shortening, and autoinflation.

- Level of Evidence 3, strength of recommendation C.

**Anesthesia**

- Inflatable and semi-rigid rods are usually implanted under regional or general anesthesia. Rarely, local anesthesia can be used for malleable types of prostheses.
  - Level of Evidence 3, strength of recommendation C.

**Operative Technique**

- Distal penile, infrapubic, and penoscrotal are the three main approaches for inserting the penile prosthesis. The method chosen is based upon the prosthesis type, patient’s specific anatomy, surgical history, and surgeon preference.
  - Level of Evidence 3, strength of recommendation C.

**Penile Prosthesis Complications**

**a) Infection**

- Periprosthetic infection is an important concern for both doctors and patients, not only because it can cause serious illness, but also requires the complete removal of the devices. Subsequent reimplantation is difficult because of scar formation.
  - Level of Evidence 3, strength of recommendation C.

- A number of measures have been taken to decrease the risk of infection. Still, there is no consensus on a standardized method of minimizing infection rates. AMS and Coloplast, both manufacturers of hydraulic implants, have taken steps to decrease infection rates by applying antibiotic coatings or hydrophilic surfaces to their prosthetic devices. Initial research suggests these newer interventions decreases the rate of prosthetic infection.
  - Level of Evidence 3, strength of recommendation C.

- In addition to using an antibiotic coating on the prosthesis, prophylactic broad spectrum antibiotics...
have also been used with guidelines suggesting application within 60 minutes before surgical incision. Also, antimicrobials should be discontinued without 24 hours after the end of the surgery.

- Level of Evidence 3, strength of recommendation C.

- If the prosthesis becomes infected, it is recommended the entire prosthesis should be removed. In certain situations a salvage procedure may be performed in which the entire area is lavaged with a variety of solutions and a new device is implanted.

- Level of Evidence 3, strength of recommendation C.

b. Other Complications

- Spontaneous inflation is a potential and bothersome problem with the three-piece inflatable penile prosthesis. Additionally, lack of full glans tumescence, shorter erections, unwanted movement of the pump or reservoir, erosion into the urethra, fibrosis, and mechanical failure are other potential complications associated with penile prostheses.

- Level of evidence 3, strength of recommendation C.

Penile Prosthesis Survival

- Many studies have been conducted regarding long-term survival of inflatable penile prostheses, with failure rates of both the 2-piece and 3-piece recorded as fairly low.

- Level of Evidence 3, strength of recommendation C.

- Future studies reporting device survival should express this by using Kaplan-Meier projections which allow meaningful comparisons of various studies and patients with differing follow-ups.

- Level of Evidence 3, strength of recommendation C

Prosthesis Satisfaction

- Numerous studies have shown high satisfaction rates for both patients and partners.

- Level of Evidence 3, strength of recommendation C.

- One study demonstrated a higher satisfaction rate in men with penile prostheses over other treatments for ED such as intracavernous prostaglandin E1 injections, intraurethral alprostadil, vacuum erection devices, and oral PDE5 inhibitors.

- Level of Evidence 3, strength of recommendation C.

- Future satisfaction studies should be prospective, include partners whenever possible, and use standardized forms. A new form for satisfaction in penile prosthesis recipients needs to be developed and validated.

- Level of Evidence 3, strength of recommendation C

II. VACUUM CONSTRUCTION DEVICES

1. History

The first report on the concept of negative pressure being applied to the field of ED was by John King, an American physician who described a method of improving erections by a small vacuum pump [73] (Figure 18). In 1917, a patent was granted to Otto Lederer for his surgical device to produce erections with a combination of a vacuum and a compression ring, now known as the vacuum erection device (VED) [74]. The credit for the popularization of VED is attributed to a Georgian entrepreneur, Geddings D. Osbon who (reluctant to accept his own impotence) developed and constructed his personal VED in 1960. After perfecting the device on himself for over a decade, it became commercially available in 1974, but only in 1982 was he granted permission from the Food and Drug Administration to market the device (known as Erec-Aid), as a prescription product – the first of its kind [75]. Since that time several patents have been granted, although they all share similar device characteristics.

Figure 18. VED with pump, vacuum cylinder, and compression rings.

2. Devices and Mechanisms of Action

There are currently a number of VED commercially available, all using the same principle, but varying slightly in their method of inducing a vacuum, in their pressure-release valves, and in the shape of the rings.

The standard VED consists of suction cylinder and pump to induce an erection by increasing corporal blood flow and then a compression band placed around the base of the penis to maintain the erection-like state by decreasing corporal venous drainage after the suction device is removed (Figure 19).
Figure 19. Pump creating negative pressure in cylinder with resultant penile engorgement and decreased corporal drainage by placing a compression ring at base of penis.

Figure 20. VED with combined pump and cylinder system.

Some models combine the suction cylinder and pump into one piece and most manufacturers offer their device with a battery-driven motor to create the vacuum (Figure 20). The cylinder is usually clear plastic and must be of sufficient length and diameter to fit over the erect penis. The cylinder has a pressure release valve designed to prevent penile injury from excessive negative pressure.

The compression rings vary widely with regard to their thickness and grips, but some manufacturers have introduced shaped rings with a notch to fit over the urethra in an attempt to reduce ejaculatory difficulties and to concentrate pressure onto the corpora.

The base of the penis, the contact area of the VED and the compression rings are lubricated with copious amounts of water-soluble jelly and the rings are fed over a loading cone to the base of the cylinder. The cylinder is then placed over the flaccid penis, pressed firmly against the pubic bone to obtain an airtight seal, and suction is applied for a few minutes to effect penile engorgement [76]. Once an erection-like state has been produced, one or more bands, previously rolled onto the cylinder prior to the vacuum maneuver, are slipped from the cylinder onto the base of the penis preventing venous return and maintaining tumescence [77]. Then the vacuum is released via a valve and the cylinder is removed.

The compression rings are left in place no longer than 30 minutes to avoid ischemic damages to the cavernosal tissue; if intercourse is to be prolonged past this point, the band must be removed and after few minutes the same procedure can be repeated. The time taken to obtain an erection varies but has been reported on an average between 2 and 2.5 minutes [78, 79]. Intermittent pumping can improve penile rigidity, enabling more satisfactory penetration. Patients should be instructed to pump for 1 to 2 minutes, releasing pressure and then pump again for 3 to 4 minutes [80]. Prescription devices are advised and metal or other inelastic rings are contraindicated [76].

3. PHYSIOLOGIC EFFECTS

The erection obtained with VED is not natural and there are distinct differences in the physiology of a spontaneous erection and that of an erection following use of a VED, as outlined by Nadid and associates [81]. Although persistent reduced blood flow during compression has been described by one group using plethysmography, others using duplex Doppler sonography found maintenance of the cavernous arterial inflow [82, 83].

The VED promotes engorgement of the penis through negative pressure effects and blood is trapped in different compartments in the penis, including subcutaneous tissues and the sinusoidal spaces of the cavernous bodies whose diameters double [82]. Cavernosal blood gas analysis has confirmed that engorgement in the penis is composed of predominantly venous blood [84].

Vacuum pressures between 100 and 225 mm Hg are necessary to achieve erection [83]. Excessive negative pressure can cause bruising and hematoma, and to avoid injury to the penis only VED containing a vacuum limiter should be used [85].

It is important that patients and their partners be informed that VED-derived erections are perceived differently when compared to naturally occurring erections. All turgidity is distal to the constriction band and the crura are not involved in the erection, causing some degree of instability, leaving the potential for pivoting at the base and often requiring manual assistance to insert the penis into the vagina.

Owing to extracorporeal congestion, the VED-erect penis appears more cyanotic, is cooler, and girth is usually greater than a normal erection [78, 84].

4. RESULTS OF VED THERAPY

Although VED have proven to be effective in treating ED, even in the era of PDE-5 inhibitors, the literature
consists largely of single center observational series, and a collection of small prospective clinical trials. Efficacy rates of 67 to 90% have been reported in achieving satisfactory erections but patient satisfaction rates with the device are lower, ranging from 34 to 68% [86-90].

There is a great deal of variability in the clinical efficacy and satisfaction of VED therapy. In an evaluation of 216 consecutives patients, Cookson et al. reported regular device use in 69%, with a 90% chance of attaining good-quality erections. Patient and partner satisfaction was 82% and 89% respectively [91]. Vrijhof et al. reported their experience with 67 patients treated with VED, and adequate erections were reported by 72% [90]. In contrast, the experience of other authors with patient satisfaction using the VED has been consistently less.

In a retrospective study, Derouet et al [92] evaluated the medical and psychological outcome of the use of VED in the treatment of ED in 190 patients using a questionnaire and a clinical examination. 110 patients (57.8%) answered the questionnaire. Twenty-two (20%) rejected the device primarily and 34 (30.9%) after a period of up to 16 weeks (primary rejection rate 50.9%). A secondary drop-out rate of 8 patients (7.3%) was observed after an intermediate time of 10.5 months. Forty-two percent of patients were long-term users and were mainly subjects who did not respond to intracavernosal pharmacotherapy.

The general low acceptance of VED therapy in the treatment of mild, moderate, and severe ED was revealed in the series of Dutta et al. [93]. One hundred twenty-nine patients received a follow-up questionnaire regarding satisfaction, months of use, reasons for discontinuing, and further treatment. The overall attrition rate observed was 65% and was lowest among patients with moderate ED (55%). All patients with mild ED discontinued use, and a large number (70%) of patients with complete ED also discontinued use. Of the patients who discontinued, most stopped treatment early (median one month, mean four months) and 63% did not seek further treatment. Thirty-five percent of patients were satisfied with the device and have continued to use it long term (mean 37 months).

Earle et al. conducted a retrospective survey to assess the use, efficacy and acceptance of the VED among 60 impotent men not satisfied with intracavernosal injection therapy and found a high dissatisfaction rate with VED therapy [94]. Eighty-one percent of the men abandoned the device citing lack of efficacy.

Certainly, organic impotence as a whole responds well to VED therapy, with satisfactory erections expected in at least 70% of diabetics subjects, 93% with arteriopathy, 70% with venous leaks, and more than 90% following radical prostatectomy [86, 91, 95-99]. Patient and partner satisfaction appear to be closely correlated and also depends on successful erection [100].

5. SPECIALIZED AND COMBINED USES

In those patients in whom intracavemosal pharmacotherapy has failed, the use of VED in combination with vasoactive injection therapy may lead to an adequate erection. Chen et al. studied the effect of combining intracavernous injection and a VED in 10 men with ED who previously failed attempts at treatment with either method as monotherapy [101]. They conclude that VEDs can augment a partial response to intracavernous injection and the combination may be an alternative treatment before other more invasive treatments such as a penile prosthesis are considered.

Prostaglandin E1 (PGE1) agents delivered by intraurethral administration can significantly increase vacuum-assisted erections. Combination therapy can increase both penile length and diameter [102].

The addition of a phosphodiesterase type-5 inhibitor with VED improved sexual satisfaction and penile rigidity in patients dissatisfied with VED alone after radical prostatectomy. Raina et al. reported the efficacy of combining sildenafil citrate with a VED in men with ED after radical prostatectomy [103]. A total of 31 patients were instructed to take 100 mg of sildenafil 1 to 2 hours before VED use for the purpose of sexual intercourse. Patients used combination therapy for a minimum of 5 attempts. Of the 31 patients, 24 (77%) reported improved penile rigidity and sexual satisfaction. Of the 24 men, 7 (30%) reported a return of natural erections at 18 months using combination therapy, with 5 of 7 reporting erections sufficient for vaginal penetration.

The VED can also be used in men who either have prosthesis in place but find these erections unsatisfactory, those with fibrosis of the erectile tissue secondary to priapism, or after an explanted prosthesis [104, 105].

The VED has been used as a tissue expander following surgical correction of Peyronie’s disease in order to maintain the elasticity of the tissues [106]. More recently, there has been interest in the use of VED in early intervention protocols to augment corporeal rehabilitation of post-radical prostatectomy fibrosis. Raina et al. showed that early use of VED following prostatectomy facilitates early sexual activity and potentially an earlier return of natural erections sufficient for vaginal penetration [107]. Kohler et al. in a pilot study on the early use...
of the VED after radical retropubic prostatectomy showed that this form of treatment improved early sexual function and preserved penile length [108]. For some investigators, VED have become first-line therapy for preservation of erectile function following treatment of prostate cancer [109].

6. SIDE EFFECTS AND CONTRAINDICATIONS

Adverse effects are usually observed early in the treatment and usually decrease with continued use of the VED. Pain on ejaculation is reported in 3 – 16%, with an inability to ejaculate in 12-30% [79, 91, 110]. Pain may occur during the creation of the vacuum in 20 to 40% of users. Petechiae or ecchymosis of the penis are reported in 25-39%, with bruising (especially at the position of the ring) in 6 – 20% [86, 91]. Numbness during erection is reported as the major problem in 5% [91].

Major complications are infrequent. Rare descriptions of isolated, serious adverse effects after VED use have been published including penile skin necrosis, urethral varicosites, capture of scrotal tunica within the penile shaft, Peyronie’s disease, and Fournier’s gangrene [111-114].

There are few contraindications to this form of therapy. Patients on anticoagulant therapy and patients with bleeding disorders must use VED with caution [115]. Similarly, special attention must be given to patients with a tendency for spontaneous priapism or prolonged erections [80].

7. CONCLUSIONS

Use of a VED is a safe and effective form of therapy for men with ED. The British Society for Sexual Medicine Guidelines, an evidence-based guideline for the diagnosis and treatment of ED, concluded that oral pharmacotherapy with PDE5 inhibitors and VED are the first-line therapy for ED [116]. The importance of proper patient selection improves outcome results as confirmed by the experience of a number of authors. VED may be offered preferentially to elderly patients who partake in limited intercourse attempts versus younger patients who document lower preference for VED because of unnatural erections and cumbersome application.

Recommendations

- VEDs are ED treatment devices that employ the use of negative pressure to engorge the penis with blood and constriction rings artificially trap blood in the penis. Studies have reported the time to erection varies, but averages from 2 to 2.5 minutes. Level of Evidence 3, strength of recommendation C.

- A number of studies have reported that erections obtained with VEDs are unnatural and therefore are distinctly different from natural erections. Level of Evidence 3, strength of recommendation C.

Results of VED therapy

- Considerable variability in clinical efficacy and satisfaction has been reported, but, overall, organic impotence responds well to VED therapy, especially in those who do not respond well to intracavernosal pharmacotherapy. Level of Evidence 3, strength of recommendation C.

Specialized and combined uses

- VED use can be combined with vasoactive injection therapy, to give men adequate erections in those whom monotherapy for ED has failed. Level of Evidence 3, strength of recommendation C.

- After radical prostatectomy, VED therapy combined with a PDE5i improved sexual satisfaction in patients dissatisfied with VED alone. Level of Evidence 3, strength of recommendation C.

- VED therapy has also been used as a tissue expander to maintain elasticity following corrective surgery for patients with Peyronie’s disease. Level of Evidence 4, strength of recommendation C.

- Additionally, VED use is indicated for rehabilitation of post-radical prostatectomy patients to facilitate early sexual activity and potentially improve early return of natural erections. Level of Evidence 3, strength of recommendation C.

Side effects and contraindications

- The most common VED side effects are painful ejaculation, inability to ejaculate, generalized pain, petechiae, bruising, and numbness. Level of Evidence 3, strength of recommendation C.

- Serious complications from VED use are rare, but include penile skin necrosis, urethral varicosities, capture of scrotal tissues within the penile shaft, development of Peyronie’s disease, and Fournier’s gangrene. Level of Evidence 3, strength of recommendation C.

VED: Basic Principles

Externally applied device mechanically effects penile blood engorgement

Cylinder/pump placed over penis creates closed chamber; pump creates vacuum, drawing oxygenated blood into corpora

The ring then placed at base of penis to restrict flow of blood

Erections are unnatural

Level of Evidence 3, Recommendation C
VACUUM ERECTION DEVICES (VED)

RESULTS

- Literature:
  - Largely of single observational series
  - Small prospective clinical trials

- Efficacy and Satisfaction Rates:
  - Report by authors – 67 to 90%
  - Report by patients – 34 to 68%
  - Organic ED responds well to VED therapy
  - Patient and partner satisfaction appear to be closely equal

Level of Evidence 3, Recommendation C

Specialized & Combined Uses of VED

- Combined with vasoactive injection therapy *
- Combined with intraurethral alprostadil therapy
- Combined with PDE5 inhibitor therapy
- Rarely in men who have “inadequate” penile implant function

- To prevent penile fibrosis (after priapism or explanted prosthesis)
- After surgical correction of Peyronie’s disease **
- Corporeal rehabilitation after radical prostatectomy ***

* Level of Evidence 3, Recommendation C
** Level of Evidence 4, Recommendation C
*** Level of Evidence 3, Recommendation C

SIDE EFFECTS AND CONTRAINDICATIONS

- Pain during creation of vacuum – 20-40%
- Pain on ejaculation – 3-16 %
- Inability to ejaculate – 12-30 %
- Petechiae or ecchymosis – 12-30 %
- Bruising – 6-20 %
- Numbness during erection – 5%
- Rare side effects:
  - Penile skin necrosis
  - Urethral varicosites
  - Capture of scrotal skin
  - Peyronie’s disease
  - Fournier’s gangrene

* Level of Evidence 3, Recommendation C

III. ARTERIAL REVASCULARIZATION

1. INTRODUCTION

The prevalence of vascular disease increases with age and is a major cause of organic ED in men over the age of 50. A number of medical conditions or risk factors are associated with ED, including hyperlipidemia, atherosclerosis, smoking, diabetes, obesity and peripheral vascular disease. The pathogenesis of ED in these patients appears, in part, to be linked to endothelial dysfunction.

Arterial surgery for ED was popularized in the 1970s and 1980s. It has since become clear that ED is often associated with generalized cardiovascular disease and many of the patients undergoing revascularization surgery have intrinsic smooth muscle dysfunction throughout their body. For this reason, the efficacy of penile revascularization surgery is controversial and considered by many to still be experimental. Follow up studies vary in the procedure used and rarely document adequate long-term objective follow up data.

2. BACKGROUND

Historically, the success of bypass grafting for coronary artery disease suggested bypassing obstructed arteries could restore normal erectile function in men suffering from vasculogenic ED.

3. PATHOGENESIS OF ARTERIOGENIC ERECTILE DYSFUNCTION

It is now evident that ED in patients with cardiovascular disease is multifactorial in origin and cannot be simply attributed to only an impairment of penile blood flow due to occlusion.

A number of in vitro and in vivo studies suggest that both endothelial dysfunction and corporal smooth muscle dysfunction are the main factors leading to ED in these men.

Therefore, even if there is a reduction in blood flow through the penile vessels, there often coexists underlying smooth muscle dysfunction that limits the success of any potential penile bypass procedure. Hence, the only select group where penile revascularization surgery is likely to be successful is in young men with isolated arterial stenosis following perineal or pelvic trauma.

4. PENILE VASCULAR ANATOMY

The main source of blood supply to the penis originates from the internal pudendal artery, although accessory contributions may arise from the external iliac, obturator, vesical, and femoral arteries. The internal pudendal artery becomes the common penile artery after giving off a branch in the perineum.
The three branches from the common penile artery are named the dorsal, bulbourethral, and cavernous arteries. The cavernous artery further delivers multiple helicine arteries, which supply the cavernosal tissues and sinusoids. These helicine arteries are in a contracted state when the penis is flaccid and vasodilate during erection.

The dorsal artery of the penis runs along the dorsal surface of the penis and supplies the glans penis. The bulbourethral artery supplies both the bulb and corpus spongiosum, while distally the three branches anastomose near the glans.

**5. THE HISTORY OF PENILE REVASCULARIZATION SURGERY**

Michal [117] reported the first penile arterial revascularization, in 1973, by anastomosis of the inferior epigastric artery (IEGA) to the corpus cavernosum. This procedure produced only short-term success with ensuing fibrosis of the smooth muscle and thrombosis of the anastomosis. The Michal II procedure was then popularized where the IEGA was anastomosed in an end-to-side fashion to the dorsal penile artery. Hauri [118] proposed direct arterial anastomosis of the IEGA to the dorsal artery, but in addition, incorporating the deep dorsal vein into the anastomosis. In principle arterialization of the dorsal vein would improve arterial flow to the corpora cavernosa in a retrograde manner via the emissary veins.

Virag [119] and colleagues described a procedure in which the IEGA was anastomosed directly to the deep dorsal vein, introducing the concept of venous arterialization. Not only has Virag described modifications of his technique (Virag I-VI), but also a number of other investigators have described other variations on this basic procedure. The principles of surgery remain the same, consisting of distal or proximal ligation of the arterialized vein, windows between the artery and vein, and ligation of the circumflex vessels and destruction of the valves in the dorsal vein. In theory these modifications improve inflow, while reducing venous outflow. In concept these procedures may be attractive not only in men with pure arteriogenic ED, but also those with a venogenic component.

**6. PRINCIPLES OF SURGERY FOR ARTERIAL PATHOLOGY**

The principles of revascularization and arterialization surgery are based upon the following techniques (modified from Sohn [120]):

a. Anastomosis of the IEGA to the dorsal artery (revascularization).

b. Anastomosis of the IEGA to the deep dorsal vein (arterialization)

c. Anastomosis of the IEGA to the deep dorsal vein with venous ligation.

**7. SELECTION AND INVESTIGATION OF THE PATIENT WITH SUSPECTED ARTERIOGENIC ED**

Penile arteriography is the gold standard in assessing patient’s suitability for arterial reconstructive surgery. However, prior to embarking upon this procedure, other organic causes of ED need to be excluded. In those in whom arterial surgery is contemplated, a penile duplex Doppler study confirms vascular insufficiency and documents any venous leak. A peak systolic velocity (PSV) of less than 25cm per second suggests vascular insufficiency.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Success n (%)</th>
<th>Failure n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (2-y follow-up)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young &lt;28 y</td>
<td>19 (73)</td>
<td>7 (27)</td>
</tr>
<tr>
<td>Old &gt; 28 y</td>
<td>6 (23)</td>
<td>20 (77)</td>
</tr>
<tr>
<td>Age (5-y follow-up)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young &lt;28 y</td>
<td>10 (77)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Old ≥ 28 y</td>
<td>7 (32)</td>
<td>15 (68)</td>
</tr>
<tr>
<td>Tobacco</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>5 (29)</td>
<td>12 (71)</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>20 (57)</td>
<td>15 (43)</td>
</tr>
<tr>
<td>Venous leak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>11 (64)</td>
<td>6 (36)</td>
</tr>
<tr>
<td>Mild</td>
<td>10 (38)</td>
<td>16 (62)</td>
</tr>
<tr>
<td>Moderate</td>
<td>4 (44)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IEGA to DA</td>
<td>4 (40)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>IEGA to DV</td>
<td>12 (41)</td>
<td>17 (59)</td>
</tr>
<tr>
<td>IEGA to DA and DV</td>
<td>8 (51)</td>
<td>5 (49)</td>
</tr>
</tbody>
</table>
Cookson [121] analyzed surgical outcomes based on the preoperative etiology of impotence (pure arterial versus arterial combined with corporeal venous leak). There was a significant improvement in surgical outcome in patients with a pure arterial ED compared to those with mixed etiology (67% and 42%, respectively (p < 0.01)). The authors suggest that in patients with arteriogenic ED, concomitant corporeal veno-occlusive dysfunction should be excluded by preoperative dynamic infusion cavernosography and cavernosometry (DICC), as this may further predict postoperative success. A Rigiscan study may be considered in the young patient with suspected arterial injury. Vardi [122] demonstrated that patients under the age of 28 years showed a 73% success rate versus 23% in the older age group. Furthermore, non-smokers had a 57% success compared to 29% in smokers. They also found that the presence of venous leak and type of procedure had no significant impact on success. However, when patients without a venous leak were compared to a group with moderate venous leak, the results showed a 73.3% success versus 26.7%, respectively (P=0.32). The authors argue this conflicting result may have been proven significant with a larger number of patients in the moderate leak group.

Table 7. Odds Ratio of Success According to Risk Factor

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young vs old</td>
<td>9.05*</td>
<td>2.72–34.45</td>
</tr>
<tr>
<td>Young vs old (5-y follow-up)</td>
<td>7.14*</td>
<td>0.24–1.85</td>
</tr>
<tr>
<td>Tobacco</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker vs smoker</td>
<td>3.2**</td>
<td>1.00–11.9</td>
</tr>
<tr>
<td>Venous leak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None vs any leak</td>
<td>2.75**</td>
<td>0.85–9.65</td>
</tr>
<tr>
<td>None vs moderate</td>
<td>2.29</td>
<td>0.44–12.75</td>
</tr>
<tr>
<td>Mild vs (moderate and none)</td>
<td>2.18</td>
<td>0.73–6.80</td>
</tr>
<tr>
<td>Moderate vs (mild and none)</td>
<td>1.19</td>
<td>0.28–5.40</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IEA to DA vs all</td>
<td>1.36</td>
<td>0.34–5.99</td>
</tr>
<tr>
<td>IEA to DV vs all</td>
<td>1.55</td>
<td>0.51–4.73</td>
</tr>
<tr>
<td>IEA to DA and DV vs all</td>
<td>2.30</td>
<td>0.65–8.86</td>
</tr>
</tbody>
</table>

* **Statistically significant as determined by Wald’s test (p≤0.05)
** Statistical trend determined by Wald’s test as 0.05<p<0

In a further study [123], success in diabetics and older patients was lower (43% for diabetics, 39% for those older than 50 years at surgery). Based upon their experience, Zumbe [124] recommended the following important factors in case selection for arterial surgery: (i) non-responder to ICI (intracavernous injection); (ii) age less than 55 years; (iii) non-diabetic; (iv) cavernous venous leak excluded; (v) stenosis in the internal pudendal artery.

Therefore, based upon the literature, the following appear to be inclusion criteria in selecting patients for arterial surgery:

- Age less than 55 years
- Non-smoker
- Non-diabetic
- Absence of venous leakage
- Stenosis of the internal pudendal artery

8. COMPLICATIONS FROM PENILE REVASCULARIZATION SURGERY

A number of authors have described complications following penile revascularization procedures [123, 125, 126]. The most frequent complication is glans hyperaemia. In a series reported by Manning [123] glans hyperemia developed in 13% of patients, shunt thrombosis in 8%, and inguinal hernias in 6.5%.

9. OUTCOMES FROM PENILE REVASCULARIZATION SURGERY IN MEN WITH ARTERIOGENIC ED

Surprisingly, there has only been one retrospective case series published in the literature since 2003 [131]. The lack of further studies may reflect consensus opinion, such as guidelines [85] which state that, “Treatment of vasculogenic ED by penile arterial revascularization has been performed using a variety of microvascular procedures for the past 30 years. The efficacy of this surgery is unproven and controversial largely because, in most reported studies, selection and outcome criteria have not been objective and because a variety of surgical techniques have been used.”

The 2005 guidelines are based upon the 1996 guidelines report following a meta-analysis of this literature. The 1996’s, stated arterial surgery was not justified to be performed routinely, although, arterial revascularization procedures appeared to have the highest efficacy in young men with ED secondary to arterial injury from pelvic or perineal trauma. Only four articles with a total of 50 patients met the Panel’s inclusion criteria (Table 8). These studies were retrospective with small numbers of patients (Table 9). Objective outcome was not measured uniformly and follow up interval in most studies was short.
Table 8. Outcomes from penile revascularization surgery (adapted from Sohn [120] Clinical Guidelines Panel, in

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Procedure</th>
<th>FU (months)</th>
<th>Overall intercourse success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jarow 1996 [127]</td>
<td>11</td>
<td>DDVA</td>
<td>50</td>
<td>92</td>
</tr>
<tr>
<td>Lukkarinen 1997 [126]</td>
<td>24</td>
<td>Hauri F-F14</td>
<td>N/A</td>
<td>77</td>
</tr>
<tr>
<td>Manning 1998 [123]</td>
<td>62</td>
<td>Virag Hauri</td>
<td>41</td>
<td>54</td>
</tr>
<tr>
<td>Manning 1998 [123]</td>
<td>42</td>
<td>DDVA</td>
<td>N/A</td>
<td>57</td>
</tr>
<tr>
<td>Sarramon 1997 [129]</td>
<td>114</td>
<td>Dorsal Art DDVA</td>
<td>17</td>
<td>63</td>
</tr>
<tr>
<td>Sarramon 2001 [130]</td>
<td>38</td>
<td>DDVA</td>
<td>61</td>
<td>N/A</td>
</tr>
<tr>
<td>Vardi 2002 [122]</td>
<td>61</td>
<td>N/A</td>
<td>60</td>
<td>N/A</td>
</tr>
<tr>
<td>Kawanishi 2004 [125]</td>
<td>51</td>
<td>Haunt Furlow</td>
<td>36-60</td>
<td>85.9</td>
</tr>
</tbody>
</table>

Table 9. Penile arterial surgery: Criteria for article selection by the AUA guidelines committee 1996 (updated 2005)

**Exclusion criteria**
- Diabetes mellitus
- Cigarette smoking

**Length of follow-up**
- 12 month minimum

**Inclusion criteria**
- Normal serum testosterone
- Failed pharmacologic erection test or documentation of organicity by either abnormal nocturnal penile tumescence or abnormal penile blood flows (duplex Doppler ultrasonography (DICC))
- Abnormal penile arteriogram
- Artery to artery or artery to dorsal vein anastomosis employed in surgical technique
- Objective follow-up data reported by either duplex Doppler ultrasonography, penile arteriogram, or validated outcome questionnaire

Table 10. Original studies fulfilling the AUA 1996 guidelines committee inclusion criteria.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Surgery</th>
<th>Nbr of Patients</th>
<th>Months of Follow-up Overall: Range (Mean)</th>
<th>Success Rate% (N) Success</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ang and Lim(1997) [132]</td>
<td>Dorsal vein</td>
<td>6</td>
<td>8 to 37 (20)</td>
<td>66 (4)</td>
<td>NPT, Doppler</td>
</tr>
<tr>
<td>DePalma et al (1995) [133]</td>
<td>Dorsal artery</td>
<td>11</td>
<td>12 to 48</td>
<td>60% (7)</td>
<td>Doppler</td>
</tr>
<tr>
<td>Grasso et al (1992) [134]</td>
<td>Dorsal artery</td>
<td>22</td>
<td>1 y for all</td>
<td>68 (15) 36 (8)</td>
<td>NPT Doppler</td>
</tr>
<tr>
<td>Jarow and DeFranzo (1996) [127]</td>
<td>Mixed</td>
<td>11</td>
<td>12 to 84 (50)</td>
<td>91 (10)</td>
<td>Doppler DUS</td>
</tr>
</tbody>
</table>
One of the largest contemporary retrospective series is that of Kawanishi [125]. Although published in 2004 and using the 1996 guidelines, this study on 51 men with arteriogenic ED stands out from other retrospective series in terms of objective outcome data reported by color Doppler duplex studies and a longer follow-up period. Prior to surgery all patients had a full assessment of their ED, which included intracavernosal pharmacological erection tests, penile duplex Doppler, DICC, and digital subtraction angiography. The etiology of the arterial lesions was blunt perineal trauma in 33 and unknown in 35. Either the Hauri or Furlow-Fischer procedure was used for penile revascularization. The patency of the neoarterial blood flow was assessed objectively by color flow duplex Doppler. The mean (SD) subjectively estimated efficacy rate was 85.9 ± 6.3%, after 3 and 67.5 ± 10.7% after 5 years of follow-up. The objectively estimated efficacy rate was 84.9 ± 7.3% at 3 and 65.5 ± 13.5% after 5 years of follow-up.

In the second Paris consultation in 2003, the literature from 1993 to 2003 was evaluated. Table 6 summarizes these studies and another two studies [135] questioned the role of arterial surgery in men with vascular ED. They compared the sexual satisfaction rate in 130 patients with arterial and/or venous impotence treated with four surgical techniques with long-term follow up. Arterialization of the deep dorsal penile vein was performed in 39 (30%) and 78 (60%) were treated with penile implants. Sexual satisfaction, defined as the possibility of satisfactory sexual intercourse without any additional treatment or pain, was evaluated by patient interview.

Of the evaluable patients, the sexual satisfaction rate was 12% for arterialization compared to 93% for penile prosthesis (Mean follow-up was 46 and 54 months respectively). The success rate for young patients with traumatic arterial lesions was 100%. It is apparent from this 2003 study that patient outcome is poor in men undergoing arterialization compared to other treatment modalities.

Despite the negative opinion by the AUA consensus panel on penile revascularization surgery and the poor outcome from the comparative study by Wespes [135], Kayigil recently published a paper that supported the efficiency of deep dorsal vein arterialization (DDVA) in carefully selected healthy elderly patients [131]. Forty-three patients with a mean age of 59.7±4.6 years underwent corpus cavernosum electromyography, DICC, and penile duplex Doppler ultrasonography. Risk factors including hypertension, diabetes, hyperlipidemia, smoking, psychiatric or neurologic disorders, liver or kidney failure, and a history of major trauma were excluded. All patients underwent DDVA using the Furlow-Fisher technique. Surgical outcome was tested postoperatively using the IIEF-15. A surgical success was achieved if the score in the five-item version of the IIEF (IIEF-5) had increased by at least five points. The mean follow-up interval was 22.1+/-7.1 months. Veno-occlusive dysfunction was found in 21 patients, 13 had arteriogenic disease, and 9 had both caverno-venous and arteriogenic disease. The operation was deemed successful in 26 cases (60.5%) according to IIEF-5 criteria. The authors concluded that DDVA can be performed in carefully selected older patients as long as the major risk factors for ED are excluded. This latest paper adds little to the previous retrospective series, as there is a short follow-up period and no objective data analyzing pre and post-operative erectile function with the exception of the IIEF questionnaire.

10. OUTCOMES FROM PENILE REVASCULARIZATION SURGERY IN MEN FOLLOWING PERINEAL TRAUMA.

Evidence supporting the traditional concept that young men who undergo revascularization appear to have better outcomes compared to other groups is still limited. However, the group of patients who appear to have definite improved outcomes from arterial revascularization remains young men who have sustained blunt perineal or pelvic trauma.

In the study by Vardi [122], 10 patients had documented pelvic trauma with a mean age of 30 years. In this group, all regained satisfactory erectile function at a two year follow-up. The younger traumatic patients had an 80% success rate compared to 20% in the older men (P=0.04). The higher success rates in younger men was also confirmed by Wespes where the success rate for young men with traumatic arterial lesions was 100% [135].

More recently Babaei [136] performed a meta-analysis and systematic review to determine the subjective and objective outcomes of penile revascularization surgery in patients with arteriogenic ED. Published articles were searched up to May 2008 in the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and Biological Abstracts. Data on participants’ characteristics, study quality, population, intervention, cure and adverse events were collected and analyzed. Not surprisingly, the results in men younger than 30 years old were better than older men. The authors conclude that ‘inconsistent measurements of outcomes limited the findings, and none of the studies were randomized controlled trials’.

Recomendations

- There are a large number of retrospective studies reporting outcome data for penile revascularization surgery for arteriogenic ED. Level 3 evidence.
- These studies are limited by variable inclu-
tion and exclusion criteria, short length of follow-up, and lack of objective follow-up data. Level 3 evidence.

- Young men who have sustained traumatic arterial lesions appear to have better outcomes compared to elderly patients. Level 3 evidence.

- There are no comparative prospective randomized studies assessing outcome of penile revascularization surgery for arteriogenic ED. Based upon the evidence within the literature, this surgery may be offered to men less than 55 years of age who are non-smokers, non-diabetic, with absence of venous leakage and demonstrate an isolated stenosis of the internal pudendal artery. Level 3 evidence, recommendation C.

IV. SURGERY FOR CORPORAL VENO-OCCULSIVE DYSFUNCTION (CVOD)

“Venous surgery was performed by stubborn surgeons to a high degree around the end of the nineteenth century, and recommended by similarly stubborn urologists until some years ago.”

Dieter Hauri, 2003 [137]

1. HISTORY

(from ancient times until the Second International Consultation on Sexual Dysfunctions, Paris, 2003)

Although ED was known to Aristotle (364-322 B.C.) and has been described by Sushruta in the eighth century [138], its identification as a vascular event occurred only in the Common Era. Galen (129-200), Avicenna (980-1037), and da Vinci (1452-1519) have all been credited with this [139]. Francesco Parona [140] was the first to suggest a specific role of veins in the causation of ED. In 1873, he conjectured that varicose superficial dorsal veins of the penis could cause ED by excessive blood run-off, and reported good results with saline sclerotherapy. Towards the end of the nineteenth century, superficial, and later, deep dorsal vein ligations were reported by Raymond [141], Duncan [142], Wooten [143], and Lydston [144] (100 cases). In the twentieth century, between 1936 and 1953, Oswald Lowsley [145] introduced the concepts of bulbocavernosum and ischiocavernosus plication and suspensory ligament tightening [146], in addition to reporting an experience with more than 1000 patients, including 273 who were assiduously followed up over 17 years [147]. There was a lull in the development of venous surgery during the middle (1940s to 1960s) of the twentieth century. However, venous shunt surgery for priapism made strides during this time. The 1970s and 80s witnessed a renewal of interest in vascular ED. In 1973, Malvar [148] described the use of a Doppler device to study penile arterial blood flow, and Michal [117] reported direct arterialization surgery of the corpora cavernosa. Around the same time, Fitzpatrick performed spongiosograms, cavernosograms [149], and deep dorsal vein venography [150]. In 1979, Ebbehej and Wagner [151] described the successful correction of a venous fistula causing ED. By this time, microsurgery in urology [152] had also arrived.

In 1980-1, Virag[153, 154]described cavernosometry, arterialization of the deep dorsal vein of the penis (DDV) and also its ligation. In that same year, Shirai and Ishii [155] used cavernosography during visual sexual stimulation (VSS) to study the hemodynamics of erection. In 1982 [156], Virag induced a pharmacologic erection in a clinical setting by injecting papaverine into the corpora cavernosa. Flow [157] and post-papaverine [158] cavernosometry-cavernosography, high-resolution ultrasonography, pulsed Doppler spectrum analysis after papaverine [159], and duplex ultrasound [160] were all performed by Lue in 1984-86. Puech-Leão [161] drew attention to the role of the penile crura in CVOD. The neural control of erection became better understood [162], and the importance of cavernosal smooth muscle pathology in the etiology of CVOD [163] was recognized. The mechanism [164, 165] and pathophysiology [166] of CVOD became more widely understood.

Soon, a classification [167] of CVOD, a diagnostic algorithm [168], the indications for surgery [169, 170], criteria for case selection for surgery [171], lists of post-operative complications [172], and post-operative follow-up guidelines [173, 174] began to appear in the literature. Unfortunately, there was no standard surgical procedure recommended for all patients with CVOD. Hence, different workers in the field employed different operative techniques based on their own convictions and logic. Also, nonsurgical treatments such as oral drugs, vasoactive injections, and VED were employed. Even if not effective by itself, surgery was used as an adjunct to convert penile injection [175] non-responders to responders and later, oral drug non-responders to responders.

A number of different and innovative surgical options were offered to patients with CVOD. These included deep dorsal vein arterialization [130, 176-178], cavernosal vein arterialization [179], deep dorsal vein ligation-excision [180, 181], spongiosotomy [182], pericavernoplasty [183], ligation of multiple venous systems [184], crural vein ligation and/or crural plication [185-188], antegrade and retrograde therapeutic embolization [189-195], and combined

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ligation-embolization [196] of penile veins using different agents. Over time, many researchers reported their results [173, 197-200] with CVOD surgery and published CVOD reviews [201-203].

However, contrary opinions began to appear, such as Sharlip's 1991 article titled “The Incredible Results of Vascular Surgery,” [204]

'Since the end of the 1970s, many investigators have reported success of 70-80 % or more with various forms of penile vascular surgery. Few investigators have reported surgical success less than this. While the results of penile vascular surgery may actually be this good, there are five reasons I find these reports hard to believe and, therefore, incredible. First, our methods of patient selection for this surgery have been imprecise and unreliable because of unstandardized and inaccurate diagnostic testing for vasculogenic impotence. Second, we have used follow-up methods which are not objective, not controlled and not standardized. Third, some of our surgical techniques are not rational. Fourth, a sham or placebo effect of surgery may account for a large number of successful operations. Fifth, we have not taken care to eliminate author prejudice in the reporting of surgical results.'

In December 1992, the NIH held a Consensus Development Conference [205] on impotence and suggested that arterial revascularization procedures havea very limited role.

Similarly, in 1996, the AUA released its guidelines [76] on the management of ED, wherein it stated that: “Venous surgery and arterial surgery in men with arteriosclerotic disease are considered investigational and should be performed only in a research setting with long-term follow-up available.”

The proceedings of the First Paris International Consultation on Erectile Dysfunction [206] (1999) state, “...the immediate results are satisfactory but relapse can be observed a few months later...these patients must be evaluated by specialized testing and should be treated at centers capable of providing longitudinal follow-up, if possible within research protocols.”

The Second International Consultation on Sexual Dysfunctions [207](2003) was much less optimistic:

“Revascularization and venous ligation procedures have not demonstrated the necessary surgical simplicity and reproducibility of results to make them a widely applicable treatment option for erectile dysfunction...[201, 208]...There is still a need for further study with well defined diagnostic criteria, surgical techniques, and standardized patient and partner outcome assessment.......It is the conclusion of this committee that with the current review of evidence based analysis there are no additional outcomes data of sufficient quality or quantity to supersede this recommendation (viz. that of the NIH, 1993, and the AUA, 1996)."

2. THE PRESENT

(from the Second International Consultation on Sexual Dysfunctions [209], 2003, to the 3rd International Consultation on Sexual Medicine, 2009)

The important guideline publications in this time period have been the AUA Update on the Management of ED, 2005 [85], and the ISSM's Standard Practice in Sexual Medicine [120] textbook:

'Penile Venous Reconstructive Surgery Recommendation: Surgeries performed with the intent to limit the venous outflow of the penis are not recommended. [Based on review of the data and panel consensus.]

Since the publication of the 1992 NIH Consensus Statement and subsequently the 1996 Report, there has been no new substantial evidence to support a routine surgical approach in the management of veno-occlusive ED. While the hemodynamics of veno-occlusive ED are recognized, it is difficult to distinguish functional abnormalities (smooth muscle dysfunction) from anatomical defects (tunical abnormality). It also is difficult to determine what percentage of ED is due to veno-occlusive ED independent of general arterial hypofunction, how to accurately diagnose this condition, how often arterial insufficiency coexists, and whether or not there exists a subset of patients with this disorder who would benefit from surgical intervention. Currently, there is no evidence from randomized controlled trials documenting a standardized approach to diagnosis or the efficacy of treatment for veno-occlusive ED. This lack of new evidence suggests that no changes in the previous guideline statement are warranted.' (Chapter 1-25)

The ISSM's Standard Practice in Sexual Medicine states:

Further research should focus on diagnostic possibilities to differentiate isolated venous leakage from systemic intracavernosal disease. Results of evidence-based medicine meta-analyses in surgery of the venous system should be integrated in our future approaches. Basic research on intracorporal hemodynamics should be pursued. For future clinical studies, validated survey instruments such as the IIEF should be administered both pre- and post-operatively to determine long-term success. However, in spite of all these admonitions, a review of the recent literature on this subject between 2003 and the present time of this writing shows there have been several publications on virtually every aspect of CVOD: basic science and hemodynamics [210-213], pathogenesis [214-218], investigations [213, 219], surgery [131, 220-226], prognosis [227, 228], and post-operative changes [229]. It must be conceded that not all workers in the field continue with the same old techniques of deep
dorsal vein arterialization and penile vein ligation, or minor modifications of the same any longer (the recent description of an otherwise innovative extraperitoneal laparoscopic approach to the ligation of the dorsal penile venous system is an exception). Today, it is agreed by most that venous leakage is an effect rather than a cause, and newer pathogenetic mechanisms that cause CVOD, and therapeutic possibilities that might address these causes, are being examined. The hunt for an effective surgical cure is still on.

3. AND THE FUTURE

It would be utopian to have an oral pill for all CVOD, engineered healthy cavernous smooth muscle, or maybe an injectable endoluminal vein sealant. An aspect of CVOD that needs study is the phenomenon of crural compression. The observation that compression of the crura of an erect penis increases intracavernosal pressures in its distal cylinders and improves erection was first made by Puech-Leão et al in 1987. Since then, although there have been experimental and animal studies [51, 230-233], its therapeutic potential in humans with CVOD has not been exploited [234].

4. APPENDIX

(The bullet points in these lists have been culled from various publications in the literature, collated and merely presented as guidelines to workers in the field of CVOD.)

A) CVOD Surgery – types of interventions

1) Superficial dorsal vein ligation
2) Deep dorsal vein ligation/ excision
3) Crural vein ligation
4) Crural plication/ ligation
5) Deep dorsal vein arterialization
6) Cavernosal vein arterialization
7) Spongiolysis
8) Pericavernoplasty
9) Therapeutic embolization
10) Combinations of the above
11) Extraperitoneal laparoscopic penile vein ligation

B) CVOD Surgery – complications / side effects

1) Glandular hypo/ anesthesia
2) Skin necrosis
3) Wound infections
4) Penile curvature
5) Penile shortening
6) Glans hyperemia
7) Hematomas after DDV arterialization
8) Inguinal hernias
9) Penile edema
10) ‘Vascular’ pain after embolization procedures

C) CVOD – causes

1) Congenital vascular anomalies
2) Trauma
3) Arterial disease, e.g. hypercholesterolemia
4) Arteriosclerosis
5) Alterations in cavernosal smooth muscle, trabeculae, or tunica albuginea
6) ? Psychogenic
7) Post-priapism
8) Unknown

Levels of Evidence and Recommendations

1. At the time of this writing, CVOD surgery in the management of ED remains controversial. Level of Evidence 3, strength of recommendation C.
2. The weight of available evidence is contrary to routine use as a treatment option for ED. Level of Evidence 3 strength of recommendation C.
3. CVOD surgery, as it is practiced today, does not conform to the desiderata of good clinical practice (GCP) or evidence-based medicine (EBM). The normal diagnostic values for available tests, universal diagnostic criteria for case selection for surgery, consensus on choice of operation in a given patient, etc. have not been unequivocally established. There is a need to establish a Standard Operating Procedure (SOP) for CVOD. Level of Evidence 3, strength of recommendation C. While CVOD surgery is still considered investigational, it may be offered in special situations. Level of Evidence 1, strength of recommendation C.

i) With informed consent in writing in a teaching hospital or an investigational or research setting. Level of Evidence 3, strength of recommendation C.

ii) If CVOD is undertaken, it should be required to follow an operated patient longterm (48 months post-operatively). Level of Evidence 3, strength of recommendation C.

iii) Post-operative follow-up should include objective evaluation of the penile vascular and erectile status. Level of Evidence 3, strength of recommendation C.

iv) Penile color duplex Doppler ultrasound after
complete cavernosal smooth muscle relaxation is the gold standard investigation of choice for both pre-op and post-op objective assessment.

v) Young patients with site-specific congenital, post-traumatic or post-inflammatory leaks may also be considered for vein ligation surgery with informed consent. The choice of operation offered should be decided on available wisdom and infrastructure, the experience and preference of the operating surgeon, and the basis of the site, nature, and size of the leak. Level of Evidence 3, strength of recommendation C.

vi) Validated measuring instruments (e.g. IIEF) should be used both pre-and post-operatively. Level of Evidence 1, strength of recommendation C.

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Pharmacotherapy for Erectile Dysfunction

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Pharmacotherapy for Erectile Dysfunction

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INTRODUCTION

For most men with erectile dysfunction, pharmacotherapy provides the initial form of therapy. Historically, locally active agents were used, such as injectable papaverine, phentolamine and prostaglandin. In the late 1990s, the first effective oral agent, namely sildenafil, became available and it was soon followed by other similar drugs such as vardenafil and tadalafil. While all these agents acted peripherally within the penis, drugs that work within the central nervous system to improve erectile function have proven more difficult to develop, with apomorphine currently the only licensed agent.

This chapter seeks to initially place these agents within the physiological and pharmacological context. Brief resumes of the relevant physiology are supplemented by short sections outlining the mechanisms of action and relevant basic science that underpins the most commonly used and investigated agents.

The major portion of this chapter provides an evidence based review of the clinical data that relates to the available orally active agents. The efficacy, tolerability and safety of the drugs are reviewed, with much of the data being presented in tables which summarise the many large controlled trials that have been published. We have not included unpublished data, since it will not have undergone peer review. On the basis of this data we have been able to make a number of recommendations in relation to these agents.

The final portion of the chapter deals with locally active agents, and where possible seeks to present data relating to the efficacy and safety of these agents. The volume of good quality data relating to such agents is small, and our recommendations are accordingly less strong.

Two groups are drugs are also worthy of mention. The first group contains drugs that have been reviewed in previous consultations (notably yohimbine and trazodone). For these drugs, which are not commonly used, and for which there is no new data, we have not included any comments. Interested readers are referred to the publications that have followed previous Consultations. The second group of drugs includes those that are currently under clinical development. Inevitably there is less published data relating to these drugs and we have reviewed that which is available, although much of it is published only in abstract form. This inevitably restricts our ability to make significant recommendations regarding these drugs.

We would regard this chapter as a reference source. It should be the starting point for interested readers and researchers, and hopefully summarises the medical literature in this area at a point in time.

Overall we are able to make the following general recommendations:

1. PDE5 inhibitors are effective, safe and well tolerated therapies for the treatment of men with erectile dysfunction. Almost all currently available evidence relates to sildenafil, tadalafil and vardenafil (Grade A)

2. PDE5 inhibitors are first line therapy for most men with erectile dysfunction who do not have a specific contraindication to their use (Grade C)

3. There is no evidence of significant differences in efficacy, safety and tolerability between the PDE5 inhibitors (Grade A)

4. Apomorphine is an effective and well tolerated treatment for men with erectile dysfunction (Grade A)

5. Sildenafil has superior efficacy to apomorphine in the treatment of men with erectile dys-
function (Grade A). There are no trials comparing the other PDE5 inhibitors and apomorphine.

6. We recommend some standardisation of the assessment of psychosocial outcomes within clinical trials in the field of erectile dysfunction (Grade C)

7. Intracavernosal injection therapy with alprostadil is an effective and well tolerated treatment for men with erectile dysfunction (Grade A)

8. Intracavernosal injection therapy with alprostadil should be offered to patients as second line therapy for erectile dysfunction. (Grade C)

9. Intraurethral alprostadil is an effective and well tolerated treatment for men with erectile dysfunction (Grade A)

10. Intraurethral alprostadil is a less effective treatment than intracavernosal alprostadil for the treatment of men with erectile dysfunction (Grade A)

More detailed recommendations are made throughout the chapter.

A. MECHANISMS OF ACTION

I. CENTRALLY ACTING DRUGS

Although the mechanisms underlying erectile function are not fully understood, some advances have been made regarding the interplay of central and peripheral mechanisms. It is now widely agreed that central disinhibition plays a crucial role in the induction of erectile responses and this has led to the development of a number of centrally acting agents, most notably the dopaminergic substance apomorphine and the melanocortin analogue PT-141.

The current state of knowledge of the central mechanisms involved in the development of and control of penile erection are discussed in Chapter [x]. In short, erections are initiated, in large part, by central stimuli. It is thought that stimuli from higher centers pass via the medial preoptic area (MPOA), and the paraventricular nucleus (PVN), both of which lie within the hypothalamus. The role of the MPOA is to recognise sensory stimuli from the higher brain centres and integrate them with sexual motivation and copulatory motor programmes. The PVN seems to integrate the input from higher centers [1,2] and contains premotor neurones that project directly onto spinal autonomic preganglionic neurones. The PVN plays a key role in the erectile response and stimulation of this nucleus results in seminal discharge in anaesthetised rats [3] and erection and ejaculation in anaesthetised rats [4]. Dopaminergic neurones are the main components of the PVN which is believed to be the nucleus where apomorphine acts as a dopaminergic substance. From the PVN, signals are transmitted to the brainstem nuclei and then to the periphery of the erectile axis [5,6,7].

Dopamine is one among a number of important central neurotransmitters involved in the initiation of erection. It is the main transmitter within the PVN [3,8] and plays an important role in the central control of erection. Dopamine receptors are divided into two main families D1 and D2-like receptors that are in turn further subdivided into D1 to D5 receptor subtypes. Apomorphine has a higher affinity for the D2-like receptors [9] that are thought to be the main site for the induction of erections in the PVN [10]. Apomorphine is therefore postulated to increase erectile responses by acting as a conditioner in the PVN, increasing the response to sexual stimuli resulting in enhanced erections induced in the periphery [11].

Apomorphine is an agonist of the D1-and D2-receptor subtypes that are mainly located in the paraventricular nucleus of the hypothalamus. Oxytocinergic neurones in this nucleus are responsive to the administration of apomorphine via activation of both the D1-and D2-receptor subtypes, which subsequently induces a cascade of events that reach the periphery to elicit penile erection. It has been suggested that nitric oxide acts as a cofactor at the level of the paraventricular nucleus of the hypothalamus with regards to the activation of the oxytocinergic neurones [12]. In this scenario, the presence of nitric oxide is thus mandatory in order to allow for the action of apomorphine. A sublingual formulation of Apomorphine has been approved for the treatment of erectile dysfunction in several parts of the world at the doses of 2 and 3 mg. The erectile effects are usually seen within 20 minutes of its administration.

Melanocortins are implicated in the regulation of sexual behaviour including penile erection, sexual motivation and in the female rat the secretion of sexual attractants from the preputial gland [13, 14]. Through cloning techniques five types of melanocortin receptors (MC1, MC2, MC3, MC4, and MC5) have been characterized [15]. Bremelanotide (PT-141) is a synthetic peptide analogue of α-melanocyte stimulating hormone (α-MSH) activating melanocortin receptors 3 and 4 (MC3R and MC4R). It is an active metabolite of melanotan II. The effects of α-MSH on sexual behaviour, including grooming, stretching, yawning and penile erection, have been demonstrated in laboratory animals, and it is believed to act downstream from dopamine and oxytocin in hypothalamic centres near the third ventricle at the
MC4R [16]. When subcutaneously administered has been reported to initiate penile erection in normal men as well as men with psychogenic and organic erectile dysfunction [17-19]. It is also noted to significantly increase sexual desire. The frequent side effects associated with melanotan II administration are nausea and stretching/yawning. Although clinical trials have been undertaken to assess the potential use of an intranasal formulation of this compound for the treatment of men with erectile dysfunction, it has not yet been licensed, and at the time of writing, development of bremelanotide for men with ED appears to have ceased.

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II. PERIPHERALLY ACTING AGENTS

The normal physiology and pharmacology of penile erection is discussed more fully in Chapter [x]. However, a resume of the relevant physiology and pharmacology of the corpus cavernosum is presented here, in order to understand the mechanisms of action of the peripherally acting agents, whether they be orally active, as in the case of the PDE5 inhibitor or whether they be locally active.

1. PDE5 INHIBITORS

In summary, the normal pathway for penile erection is initiated by sexual arousal, which stimulates release of nitric oxide at nerve endings in the penis (Fig. 1). Another source of nitric oxide is vascular endothelial cells. Nitric oxide diffuses into vascular smooth muscle cells in the penile corpus cavernosum to cause stimulation of guanlyl cyclase and elevation of cGMP in these cells. This leads to activation of cGMP-dependent protein kinase (PKG), phosphorylation of several proteins, and lowering of cell calcium or reduction in sensitivity to calcium, which results in smooth muscle relaxation. The increased accumulation of blood in corpus cavernosum caused by this relaxation is the underlying basis for penile erection. Lack of proper cGMP elevation could be due at least in part to insufficient release of nitric oxide from nerve endings or endothelium. PDE5 inhibitors enhance erectile function during sexual stimulation by penetrating into smooth muscle cells and inhibiting PDE5, which is an enzyme.
that degrades cGMP. This results in decreased degradation of cGMP, which maintains higher cellular levels of cGMP in both corpus cavernosum and the vessels supplying it. This increases relaxation of the smooth muscle, which dilates the corporeal sinusoids resulting in increased blood flow, allowing an erection to occur. The pathway shown in (Fig. 1) may not work properly if the cGMP level in corpus cavernosum smooth muscle cells is not elevated sufficiently or if relaxation of smooth muscle in the tissue is deficient/incomplete [1,2].

PDE5 inhibitors do not increase the nitric oxide level, but they potentiate the nitric oxide effect to stimulate erection. Without sexual arousal, which triggers the nerve-nitric oxide pathway, these inhibitors are ineffective. The same type of synergistic effect between PDE5 inhibitors and nitric oxide was found at the time of discovery of the caffeine inhibitory effect on PDEs more than forty years ago [3], whereby caffeine, which is a PDE inhibitor, was shown to be synergistic with epinephrine to elevate cAMP in dog liver. In other words, caffeine alone had little if any effect on metabolism of several isolated tissues, but when added together with a stimulator (such as epinephrine or glucagon) of cAMP production, which also had minimal effect when added alone, caffeine had a pronounced effect to increase cAMP as well as the tissue metabolic response to cAMP. This same principle also applies to the combination of PDE5 inhibitor and nitric oxide (sexual arousal) in the cGMP pathway that causes penile erection. PDE5 was discovered by Corbin and colleagues [4,5]. A cartoon depicting the PDE5 structure is shown in (Fig. 2). The enzyme is a homodimer containing two identical subunits with molecular weight of about 100,000 daltons per subunit. Each of the two subunits has a catalytic domain and a regulatory domain. The catalytic domain, but not the regulatory domain, is the target of PDE5 inhibitors. The catalytic domain contains a single binding site for cGMP. When cGMP occupies this site the catalytic machinery, which is located very near the catalytic cGMP-binding site,
breaks the cyclic phosphate bond of cGMP to form linear 5'-GMP. This dampens or terminates cGMP action. The catalytic machinery has been shown to utilize divalent cations such as Zn$$^{2+}$$ [6]. Because they have similar structures as cGMP, sildenafil or other PDE5 inhibitors can also occupy the catalytic site, thus blocking access to cGMP. In fact, sildenafil occupies the site about 1000 times more avidly than does the natural substrate, cGMP. However, the PDE5 inhibitors are not broken down by the catalytic machinery. Occupation of the catalytic site by these inhibitors competitively inhibits cGMP breakdown since cGMP cannot bind to gain access to the catalytic machinery. Inhibition of cGMP breakdown leads to elevation of cGMP in smooth muscle cells of the penile corpus cavernosum, resulting in relaxation of the muscle and penile erection.

Major research efforts have led to the production and development of compounds that are selective and potent in inhibiting particular PDEs [7]. Sildenafil (Viagra, Pfizer) was the first commercialized compound in the class that inhibits PDE5. This class has been joined by vardenafil (Levitra, Bayer Schering Pharma/Schering Plough) and tadalafil (Cialis, Lilly) in most countries of the world, and by udenafil (Zydena, Dong-A Pharmaceutical) and mirodenafil (SK Chemical Co., Ltd.) in Asia [8]. Other PDE5 inhibitors are in the pipeline. Some of these inhibitors have a similar overall structure as sildenafil and some, such as tadalafil, have significantly different structures (Fig. 3). A part of the structure of each PDE5 inhibitor also resembles the structure of cGMP (see circled component). This is important since these drugs are competitive inhibitors (antagonists) of cGMP for PDE5, and they are believed to form some of the same molecular interactions (hydrogen bonds, hydrophobic stacking interactions, van der Waals contacts, ionic interactions, etc) as cGMP forms with amino acids in PDE5. Based on x-ray crystal structures of PDE5 inhibitors co-crystallized with PDE5 [9,10] and studies using site-directed mutagenesis [11], sildenafil, for example, forms at least seventeen contacts with amino acids in PDE5. Combination of the numerous contacts between inhibitor and PDE5, and the strength of each contact, confer high affinity (low IC$_{50}$) for inhibitor. Three of these amino acids (Tyr-612, Gin-817, and Phe-820 in human PDE5) have been shown to be the most critical contacts for both cGMP and the PDE5 inhibitors that have been studied to date. The fact that PDE5 inhibitors form stronger contacts with PDE5 compared with other PDEs underlies selectivity of PDE5 inhibitors.

Although the catalytic domain of PDE5 is the direct target of PDE5 inhibitors, certain features of the regulatory domain impact PDE5 inhibitor actions on

![Figure 3. Molecular structures of PDE5 inhibitors as compared with that of cGMP. Circled component represents the part of each structure that is believed to mimic the structure of cGMP.](image)
the enzyme [12]. The regulatory domain of PDE5 contains two GAF domains (GAF A and GAF B) and a site for phosphorylation by PKG. The inhibitors do not bind to the regulatory domain. Binding of cGMP to GAF A of the regulatory domain stimulates breakdown of cGMP at the catalytic site, and this process also stimulates phosphorylation of the enzyme. PKG phosphorylates this site (Ser-102 in human PDE5A1) about 10 times faster than cAMP-dependent protein kinase (PKA) does, and PKG is thought to be the main physiological catalyst for this phosphorylation reaction. When cGMP binds to the allosteric site, cGMP is not degraded as it is in the catalytic site, but PDE5 enzyme activity is stimulated by this binding reaction. Phosphorylation also activates PDE5 enzyme functions. The two stimulatory actions together represent a physiological negative feedback process for the cGMP pathway, i.e., when cGMP increases in cells the breakdown of cGMP is stimulated [13]. This negative feedback dampens the cGMP signaling leading to penile erection or other effects of cGMP. Whether or not irregularities in this negative feedback system could partly explain erectile dysfunction, priapism, or other afflictions is unknown. However, in the presence of PDE5 inhibitor the negative feedback is blocked and inhibitor binding to the catalytic site not only elevates cGMP, which stimulates the catalytic site by binding to the regulatory domain, but it also stimulates the catalytic site by inducing phosphorylation of PDE5. Therefore, the PDE5 inhibitor stimulates its own binding to the catalytic site, which turns the negative feedback process of the physiological cGMP pathway into a positive feedback process for the PDE5 inhibitors. This means that when cGMP is elevated in smooth muscle cells after a patient takes a PDE5 inhibitor tablet, this should stimulate the catalytic site to bind more of the inhibitor. That is, the PDE5 inhibitor stimulates its own efficacy. For example, were it not for this built-in enzyme mechanism, a 200-mg dose rather than a 100-mg dose of a particular PDE5 inhibitor might be required to induce penile erection in a particular patient.

An interesting feature of PDE5 is that the catalytic site is an important regulatory site in addition to its catalytic function of breaking down cGMP [13,14]. A result of this regulation is physiological enhancement of both negative feedback of the cGMP pathway and positive feedback of the PDE5 inhibitor effect as follows. When cGMP is elevated and interacts with the catalytic site, both binding of cGMP to the allosteric site and phosphorylation of the enzyme are stimulated. Thus, these two stimulatory effects are reciprocal. Since cGMP binding to the allosteric site stimulates phosphorylation and vice versa, these two stimulatory effects also demonstrate reciprocity. Therefore, all three functional sites (catalytic site, allosteric cGMP-binding site, phosphorylation site) are reciprocally stimulated. The combined result of these interactions represents a powerful negative feedback system for the cGMP pathway, i.e., when cGMP increases, cGMP breakdown is stimulated. Apparently, cells cannot tolerate excess cGMP and have evolved an intricate negative feedback control system to dampen cGMP elevation and facilitate termination of cGMP effects. Again, the PDE5 inhibitors inadvertently exploit the physiological feedback system by substituting for cGMP in binding to the catalytic site to stimulate their own effects in a positive feedback manner.

Assuming all other factors are equal, the higher the affinity (potency) of a PDE5 inhibitor for PDE5, the lower the expected dose of the inhibitor that will be

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>IC 50 for PDE5</th>
<th>PDE Selectivity</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Udenafil</td>
<td>8.2 nM</td>
<td>Low activity against PDE3, PDE6</td>
<td>Doh H et al [15]</td>
</tr>
<tr>
<td>SLx-2101</td>
<td>0.24 nM</td>
<td>-</td>
<td>Sweetnam et al, [16]</td>
</tr>
<tr>
<td>Avanafil</td>
<td>1 nM</td>
<td>“Highly” selective</td>
<td>Kotera J et al [17]</td>
</tr>
<tr>
<td>Mirodenafil</td>
<td>0.33 nM</td>
<td>Similar to sildenafil</td>
<td>Lee et al, [18]</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>3.5-10 nM</td>
<td></td>
<td>Francis SH et al, [19]</td>
</tr>
<tr>
<td>Sildenafil *</td>
<td>3.7 nM</td>
<td>Low activity against PDE6</td>
<td>Francis SH and Corbin JD [20]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Very low activity against PDE1</td>
<td></td>
</tr>
<tr>
<td>Vardenafil</td>
<td>0.14-1 nM</td>
<td></td>
<td>Francis SH et al, [19]</td>
</tr>
<tr>
<td>Vardenafil *</td>
<td>0.091 nM</td>
<td>Low activity against PDE6</td>
<td>Francis SH and Corbin JD [20]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Very low activity against PDE1</td>
<td></td>
</tr>
<tr>
<td>Tadalafil</td>
<td>1.8-10 nM</td>
<td>-</td>
<td>Francis SH et al, [19]</td>
</tr>
</tbody>
</table>

* DONE HEAD TO HEAD
needed [7]. This concept of potency can be assessed by measuring the concentration of a particular PDE5 inhibitor in vitro that inhibits PDE5 activity by 50%, and is known as the IC50 (Table 1).

Highly potent drugs are expected to have affinities (IC50 values) in the nanomolar (nM) range. Vardenafil, SLX-2101 (Surface Logix, Inc.), and mirodenafil are within a class of biochemically high-affinity PDE5 inhibitors as compared with sildenafil, tadalafil, and udenafil, and avanafil has an intermediate potency. However, as discussed below, factors such as pharmacokinetics have strong impact on the dose required. Higher potency does not mean that a PDE5 inhibitor has a greater clinical effect, but that less of it is needed for the desired effect. For the PDE5 inhibitors, less vardenafil is required than sildenafil or tadalafil to achieve the same degree of in vitro PDE5 inhibition. Vardenafil is therefore more biochemically potent than are sildenafil and tadalafil, although not necessarily more efficacious (as evidenced by head-to-head trials). Based on in vitro potencies, it would be predicted that a lower dosage of vardenafil than sildenafil would be required to cause penile erection in men. This appears to be the case since 5-20 mg doses of vardenafil are recommended compared with 25-100 mg doses of sildenafil. The dose of vardenafil required would be predicted to be even lower were it not for the bioavailability of vardenafil being only 15% vs 40% for sildenafil. The recommended doses of tadalafil are also lower than those of sildenafil, but since these two drugs have similar biochemical potencies, a partial explanation for lower dosage could be higher bioavailability or slower body metabolism of the drug.

Debates over degree of penile rigidity caused by particular PDE5 inhibitors have continued, and head-to-head trials have been inconclusive. Many years of investigations of cAMP and cGMP pathways, which are similar to each other in many respects, may offer insight on this important question. In most body tissues a two- to three-fold elevation in cAMP or cGMP is adequate to produce maximum stimulation of these pathways that lead to numerous physiological responses [22, 23]. This could be due to the likelihood that this rise in cAMP or cGMP causes sufficient stimulation of the next step, e.g., PKA or PKG activation, to maximally stimulate the downstream steps leading to the physiological responses. If this is the case, elevation of cGMP by more than three-fold by increasing the biochemical potency or dose of PDE5 inhibitor would theoretically not be productive to further improve penile rigidity. Therefore, there is a threshold level of cGMP in corpus cavernosum that produces optimum penile rigidity given the conditions of the patient. At sufficient dose, each inhibitor would be predicted to cause enough increase in cGMP to produce equal penile rigidity.

There are methods in addition to classical IC50 to measure potency of a drug. It can be done by assessing the strength of binding of radiolabeled PDE5 inhibitors to PDE5, and the value obtained by this method is termed Kd instead of IC50 [12]. As compared with IC50, measurement of Kd is a more direct method of determining potency. The Kd of a PDE5 inhibitor obtained using this approach should approach the IC50 of the same PDE5 inhibitor. In fact, our results show that the Kd for sildenafil, vardenafil, or tadalafil approximates the IC50 for each compound. The finding that the value of Kd approaches the value of IC50 for each inhibitor suggests that these compounds do not bind to an appreciable extent to sites on PDE5 other than the catalytic domain. The approach of determining Kd not only provides another tool to measure PDE inhibitor potency but has also revealed new properties of PDE5 and PDE5 inhibitors which were not possible to study previously. These include the PDE5 on-rates and off-rates of PDE5 inhibitors, which should help to predict time of onset and duration of inhibitor action in patients. The radiolabeled inhibitors could also be used to search for the presence of non-PDE PDE5 inhibitor-binding proteins of high affinity in body tissues, which might suggest the potential for side effects of a particular PDE5 inhibitor. So far, no such proteins have been found.

Based on comparative IC50 values, the potency of sildenafil is about 1 million times higher than that of the non-selective PDE inhibitor caffeine [24]. Other experimental PDE inhibitors have intermediate potencies. According to literature values, the in vitro biochemical potencies of the commercial PDE5 inhibitors are within the same range of each other—least from a clinically meaningful equipotent range of IC50 values 0.1-10 nM. The in vitro potency of a PDE5 inhibitor is not the same as efficacy. As discussed below, efficacy is based on the actual in vivo (clinical), effects of the inhibitor.

The biochemical selectivity of an inhibitor for PDE5 is a key factor in determining its side-effect profile [7]. Once a large enough separation exists between the affinity (IC50) of the inhibitor for PDE5 and its affinity for non-target PDEs (or other proteins), the less likely it is that it can achieve sufficient plasma concentrations to activate the non-target site at therapeutic doses. For PDE5 inhibitors, selectivity is usually expressed in terms of potency (IC50) to inhibit PDE5 as opposed to inhibiting any others in the PDE family. Selectivity is computed by dividing the IC50s of the two compounds that are compared. PDEs are comprised of 11 families of enzymes that catalyze the termination of second messenger activity in cells by breaking the phosphodiester bond of either cAMP, cGMP, or both. These families (PDE1 to PDE11) are known or implicated in a broad range of cellular functions. Within some families, more than a single gene exists, for a total of at least 21 PDE genes, and some of these genes have multiple prod-
ucts brought about by alternative mRNA splicing, resulting in a grand total of at least 100 PDE forms [25]. PDE5, which is cGMP-specific, exhibits only one gene, although its mRNA can be spliced to yield at least three isoforms. However, it should be noted that these isoforms may not differ significantly in their catalytic domains, which is the site of action of PDE5 inhibitors. PDE5 is present in high concentrations in the smooth muscle of corpora cavernosa of the penis. Sildenafil and vardenafil cross-react slightly with PDE6, i.e., their IC₅₀ₐₕ values for PDE6 are only 4-10 fold lower than those for PDE6. This may explain the complaint of some patients that sildenafil or vardenafil causes visual disturbances since PDE6 predominates in the retina. Tadalafil cross-reacts with PDE11 to some extent, but the consequences of this effect are unknown. PDE11 is found in the heart (cardiac myocytes), testes (germinal cells and Leydig cells), and anterior pituitary. Neither of the PDE5 inhibitors cross-reacts to a large extent with any of the other PDEs except for PDE6 and PDE11, i.e., the IC₅₀ₐₕ values of these compounds for PDE5 are more than 1000 times lower than those for most of the other PDEs. Except for visual disturbances, the other reported side effects of PDE5 inhibitors (headaches, flushing, slight lowering of blood pressure, etc) are likely caused by PDE5 inhibition in smooth muscle and other tissues outside the penile corpus cavernosum.

In addition to biochemical properties discussed above, pharmacokinetic properties of PDE5 inhibitors (ingestion/food interaction, movement in the circulation, tissue uptake, elimination) have great impact on efficacy [7]. There are several common pharmacokinetic parameters that can be measured and quantified that describe distribution of a PDE5 inhibitor. The bioavailability, maximum plasma concentration (Cₘₐₓ), time (tₘₐₓ) required for attaining Cₘₐₓ, and time (t₁/₂) required for elimination of one-half of the inhibitor from plasma are all important factors (Table 2). Bioavailability is the ultimate percentage of an orally administered drug that is found in the circulation compared to an injected dose. It is a reflection of intestinal absorption and the effects of first-pass hepatic metabolism.

Sildenafil, vardenafil, udenafil, and avanafil have broadly similar tₘₐₓ, which predicts a similar time of onset of action. The t₁/₂ values of tadalafil and udenafil are longer than those of the other two PDE5 inhibitors, which could be due to slower intestinal absorption and/or slower degradation of this drug by the liver, or it could be due to other factors. The extended t₁/₂ of tadalafil provides a longer therapeutic effect [32], and this may also be the case for udenafil [26,27] and SLx-2101 [28]. This may be preferred by patients who prefer spontaneous sexual activity. The Cₘₐₓ of udenafil is significantly lower than that for sildenafil and tadalafil, which might be expected based on its lower bioavailability.

PDE5 inhibitors are believed to be degraded in the liver. Therefore, since they are not degraded by PDE5 or any other enzyme in smooth muscle cells of corpus cavernosum, they must dissociate from PDE5, exit the smooth muscle cells and then be transported to the liver via the bloodstream before they can be degraded (Fig. 1). The rate of exit of a PDE5 inhibitor from smooth muscle cells should be considered when comparing PDE5 inhibitors since this could affect its duration of action. Disappearance

Table 2: Pharmacokinetics of the PDE5 inhibitors

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Cₘₐₓ (ng/ml)</td>
<td>378</td>
<td>450</td>
<td>20.9</td>
<td>416.2</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>157</td>
</tr>
<tr>
<td>Tₘₐₓ (hr)</td>
<td>2</td>
<td>0.8</td>
<td>0.7-0.9</td>
<td>1-1.5</td>
<td>1</td>
<td>0.5-1.5</td>
<td>1.25</td>
<td>1.2</td>
</tr>
<tr>
<td>T₁/₂ (hr)</td>
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<td>3.5</td>
<td>4.5</td>
<td>11-13</td>
<td>9-14</td>
<td>&lt;1.5</td>
<td>2.5</td>
<td>2.4</td>
</tr>
</tbody>
</table>
of the inhibitor from plasma may imply, but does not prove, its disappearance, or clearance, from the cells in which it produces its effects. Since the inhibitor binds tightly to PDE5 in these cells, as portrayed in cartoon form in Fig. 1 this could significantly retard its exit from these cells and prolong effects of PDE5 inhibitors in patients. It is conceivable that PDE5 inhibitors with higher affinities for PDE5 would dissociate from the enzyme more slowly, resulting in a more retarded clearance from corpus cavernous cells. Studies of clearance of PDE5 inhibitors from plasma are documented, but studies of clearance of these inhibitors from smooth muscle cells are rare.

CONCLUSIONS

The first potent and selective PDE5 inhibitor, sildenafil citrate, has had a revolutionary effect on the management of male erectile dysfunction. Newer inhibitors, including some still in the development pipeline, have different profiles of dosage, side effects, onset of action, duration of action, and other features. This translates into greater physician and patient flexibility.

REFERENCES

antagonist with similar affinity for alpha 1- and alpha 2-adrenoceptors. Both types of receptors are present in corpus cavernosum and penile vascular smooth muscle [1-4]. Pre-junctional alpha 2 adrenoceptors in the corpus cavernosum modulate stimulus-evoked release of noradrenaline from sympathetic nerves in the erectile tissue [1], whereas those in the horse penile resistance arteries regulate the release of nitrergic transmitter [4].

Phentolamine mesylate induced relaxation of corpus cavernosum erectile tissue is thought to occur by direct antagonism of alpha 1- and alpha 2-adrenoceptors, as well as by indirect functional antagonism via a non-adrenergic, endothelium-mediated mechanism suggesting nitric oxide synthase activation [5, 6]. The clinical utility of phentolamine is presumably a reflection of the contribution of adrenergic neurotransmission to the maintained rugosity of the penis, and thus, inhibition of α-adrenoceptor activity alone may be sufficient for erection to commence [7].

Oral/intracavernosal phentolamine therefore may facilitate penile erection by inhibiting the functional predominance of alpha 1- alpha adrenoceptor activity that maintains erectile tissues in a non-erect state. Attenuation of the opposing adrenergic contractile response enhances NO-mediated corpus cavernosum relaxation. Furthermore, phentolamine may delay detumescence, which is mediated by noradrenaline, contributing to the maintenance of penile erection.

b) Vasoactive intestinal polypeptide

Vasoactive intestinal peptide (VIP) is a naturally occurring neurotransmitter. VIPergic nerves are most densely concentrated in the penis around the pudendal arteries and in the erectile tissue of the corpus cavernosum. VIP is known to exert regulatory actions on blood-flow, secretion, and muscle tone. Its presence in considerable amounts in the male genital tract suggests that this peptide neurotransmitter may be important in the nervous control of male external genitalia [8]. VIP co-localizes with NOS within the perivascular and trabecular nerve fibres innervating the penis [9]. Most of these NO- and VIP-containing nerves appear to be cholinergic, since they also contain vesicular acetylcholine transporter, a specific marker for cholinergic neurons [10]. The effects of VIP are mediated by a specific membrane-bound receptor linked to adenylyl cyclase via a stimulatory G-protein. VIP has been shown to elevate cAMP concentrations in cavernosal tissues without affecting cGMP levels [11,12]. Though VIP is a potent relaxant of both the corpus cavernosum and penile vascular smooth muscle in vitro, in vivo evidence suggest that it is not likely to be the primary neurotransmitter mediating penile erection in man [13, 14].

c) Prostaglandin E1

PGE1 produced relaxation of human corpus cavernosum smooth muscle and this relaxant activity was first described by [15] Karim and Adaikan (1975). PGE1 mediates relaxation of corpus cavernosum smooth muscle via activation of EP prostaglandin receptors (EP2/4) which results in an increase in the intracellular concentration of cAMP in corpus cavernosum smooth muscle [16-19]. PGE1 may also act by inhibiting the release of noradrenaline from sympathetic nerves [20] and suppressing angiotensin II secretion in the cavernosal tissues [21].

PGE1 is metabolised by the 15-hydroxydehydrogenase present in the corpus cavernosum [22]. The ability of human corpus cavernosum to degrade PGE1 probably aids in regulating the activity of PGE1 and reducing the risk of undesirable side effects such as prolonged erection and priapism. PGE1 suppressed the induction of collagen synthesis by TGF-beta-1 in cultured human corpus cavernosum suggesting that PGE1 and TGF-beta-1 may play a key role in modulation of collagen synthesis and in the regulation of fibrosis of the corpus cavernosum [23]. This suppressant effect seems to correlate with the low incidence of local fibrotic lesions reported in PGE1 treated ED patients [24].

d) Papaverine

Intracavernosal papaverine injection was the first clinically effective pharmacological therapy for ED. It is a smooth muscle relaxant. In vitro, papaverine evokes relaxation of isolated corpus cavernosum smooth strips, penile arteries, cavernous sinusoids and the
penile veins and attenuated contractions induced by stimulation of adrenergic nerves and exogenous noradrenaline [25, 26]. It acts as a nonspecific phosphodiesterase inhibitor that initiates an increase in intracellular CAMP and cGMP leading to corporal smooth muscle relaxation and penile erection. Papaverine may also regulate cavernosal smooth muscle tone via inhibition of voltage-dependent L-type Ca²⁺ channels independent of cAMP as demonstrated in tracheal smooth muscle and suppression of angiotensin II secretion in cavernosal tissue [21,27].

e) Combinations

Phentolamine, papaverine, PGE1 and VIP are the vasoactive agents most commonly used in combination therapy to treat erectile dysfunction. Combination therapy is not only predictably more efficacious as a result of well-planned strategies based on sound pharmacological principles but it is also associated with a reduction in incidence of side effects and cost per dose.

In vitro studies on human and rabbit cavernosal strips demonstrated that phentolamine significantly potentiated relaxation induced by sildenafil, VIP and PGE₁. These vasodilators also significantly enhanced relaxation induced by phentolamine in the cavernosal tissue strips. The enhancement by phentolamine of VIP and PGE₁-induced relaxation (cAMP-mediated) suggests a synergistic interaction while the interaction between phentolamine and sildenafil (cGMP-mediated) appears to be additive [28]. The same investigators also show that sildenafil and PGE₁ has additive and synergistic effect respectively with phentolamine-induced relaxation.

Hence, in combination therapy employing phentolamine as an adjunct, reducing the predominance of adrenergic tone through the blockade of oc-adrenoceptors, increases the efficacy of vasodilators that initiate erection via other independent relaxatory pathways.

REFERENCES


B. ORAL THERAPIES FOR ERECTILE DYSFUNCTION

I. PHOSPHODIESTERASE INHIBITORS

In most countries, the phosphodiesterase inhibitors are the initial form of pharmacotherapy for men with erectile dysfunction. Three such drugs, sildenafil, tadalafl and vardenafil, are licensed for use around the world. A number of phosphodiesterase inhibitors are available in a few countries (udenafil, mirodenafil) and others (avanafil, lodenafil, SLX-2101) are currently under development.

1. SILDENAFIL

A comprehensive review of the literature has identified a number of publications which attest to the efficacy, tolerability and safety of sildenafil in men with erectile dysfunction. The salient features of the level 1 publications have been tabulated in Tables 3a-3e, which outline the trial design, the patients randomized, the efficacy outcome and the side effect profiles of the studies.

For assessment of efficacy we have not included pooled studies or analyses of pooled studies, and we have attempted to ensure that no dataset is reported more than once. For assessment of safety and tolerability, we have included pooled analyses in an attempt to identify relatively infrequent tolerability or safety issues.

a) EFFICACY IN THE BROAD POPULATION OF MEN WITH ERECTILE DYSFUNCTION

Overall we can recommend that there is clear evidence that sildenafil is efficacious in the treatment of erectile dysfunction in the broad population when taken on demand at doses of 25mg, 50mg and 100mg. There are multiple level 1 studies with consistent outcomes [1-24]. The overall grade of recommendation is grade A.

b) EFFICACY IN SPECIAL POPULATIONS OF MEN WITH ERECTILE DYSFUNCTION

Overall we can recommend that there is clear evidence that sildenafil is efficacious in the treatment of erectile dysfunction in a number of special populations of men with erectile dysfunction. These populations include:

- Men with diabetes and ED [25-28] (Consistent level 1 studies with an overall grade of recommendation = A)
- Men with depression and ED [29-32] (Consistent level 1 studies with an overall grade of recommendation = A)
- Men with spinal cord injury and ED [33,34] (Single level 1 publication with an overall grade of recommendation = A)
- Men with multiple sclerosis and ED [35,36] (Consistent level 1 studies with an overall grade of recommendation = A)
- Men with cardiovascular disease and ED [37, 38, 40, 41] (Consistent level 1 studies with an overall grade of recommendation = A)
- Men with hypertension and ED [39] (Single level 1 studies with an overall grade of recommendation = A)
- Men with lower urinary tract symptoms and ED [42] (Single level 1 study with an overall grade of recommendation = A)

c) TOLERABILITY AND SAFETY

Overall, we can recommend that although side effects do occur with sildenafil (most notably headache, flushing, indigestion, nasal congestion and occasional visual changes), providing that the drug is used in line with the labeling recommendations, there is no convincing evidence in the literature of any significant safety issue, including cardiovascular, visual and aural safety [1-111] (Consistent level 1 studies, Overall grade of recommendation is grade A).

REFERENCES

Efficacy and Tolerability in Broad population


Table 3a: Level 1 studies demonstrating efficacy of sildenafil in men with erectile dysfunction

<table>
<thead>
<tr>
<th>Senior Author Year</th>
<th>Patient group</th>
<th>Patients Randomised</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein, 1998</td>
<td>Broad</td>
<td>532</td>
<td>Multicenter, randomized, double blind, placebo controlled, 4 arm parallel group, fixed dose (placebo, 25mg, 50mg, 100mg), 24 weeks</td>
</tr>
<tr>
<td>and Padma Nathan,</td>
<td>Broad</td>
<td>329</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 12 weeks</td>
</tr>
<tr>
<td>1998</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dinsmore, 1999</td>
<td>Broad</td>
<td>111</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 12 weeks</td>
</tr>
<tr>
<td>Montorsi, 1999</td>
<td>Broad</td>
<td>514</td>
<td>Multicenter, randomized, double blind, placebo controlled, 4 arm parallel group, fixed dose (placebo, 25mg, 50mg, 100mg), 12 weeks</td>
</tr>
<tr>
<td>Tan, 2000</td>
<td>Broad</td>
<td>254</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 12 weeks</td>
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<tr>
<td>Christiansen, 2000</td>
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<td>205</td>
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<td>Multicentre, randomized, double blind, placebo controlled, 2 arm dose escalation, 12 weeks</td>
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<td>940</td>
<td>Flexible dose pooled data</td>
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<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 12 weeks</td>
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<td>Boulton, 2001</td>
<td>Type 2 diabetes</td>
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<td>Seidman, 2001</td>
<td>Depression</td>
<td>152</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 12 weeks</td>
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<td>Giuliano, 1999</td>
<td>Spinal cord injury</td>
<td>178</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm crossover study, flexible dose, 6 weeks each arm</td>
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<td>and Hultling, 2000</td>
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<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 12 weeks</td>
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<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 12 weeks</td>
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<td>Gomez, 2002 [14]</td>
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<td>Stuckey, 2003 [27]</td>
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<td>Nurnberg, 2003 [30]</td>
<td>ED associated with treated depression</td>
<td>90</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 6 weeks</td>
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<tr>
<td>DeBusk, 2004 [38]</td>
<td>Stable coronary artery disease</td>
<td>151</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 12 weeks</td>
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<td>Tignol, 2004 [31]</td>
<td>Men in remission from depression</td>
<td>??</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 12 weeks</td>
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<tr>
<td>Webster 2004 [40]</td>
<td>Heart Failure</td>
<td>35</td>
<td>Single centre randomized, double blind, placebo controlled, 2 arm fixed dose (placebo, 50mg), 12-week, crossover study</td>
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<tr>
<td>Safarinejad, 2004 [28]</td>
<td>Diabetes</td>
<td>282</td>
<td>Single centre, randomized, double blind, placebo controlled, two arm fixed dose (sildenafil 100mg) study, 16 week study</td>
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<tr>
<td>Pickering, 2004 [39]</td>
<td>Treated hypertension</td>
<td>568</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, 2 arm flexible-dose, 6 week study</td>
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<td>Katz, 2005 [41]</td>
<td>Stable Heart failure</td>
<td>137</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 12 weeks</td>
</tr>
<tr>
<td>Fowler, 2005 [35]</td>
<td>Multiple sclerosis</td>
<td>218</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 12 weeks</td>
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<td>O’Leary, 2006 [16]</td>
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<td>256</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 12 weeks</td>
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<tr>
<td>Fava, 2006 [32]</td>
<td>SSRI related ED</td>
<td>142</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 6 weeks</td>
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<td>Althof, 2006 [17]</td>
<td>Broad</td>
<td>300</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 12 weeks</td>
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<tr>
<td>Heiman, 2007 [18]</td>
<td>Broad</td>
<td>180</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 12 weeks</td>
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<tr>
<td>McVary, 2007 [42]</td>
<td>ED and LUTS</td>
<td>369</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 12 weeks</td>
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### Table 3a: Level 1 studies demonstrating efficacy of sildenafil in men with erectile dysfunction

<table>
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<tr>
<th>Senior Author Year</th>
<th>Patient group</th>
<th>Number Randomised</th>
<th>Study design</th>
</tr>
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<tbody>
<tr>
<td>Burankitjaroen, 2007 [19]</td>
<td>Broad (Thai)</td>
<td>150</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 6 weeks</td>
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<tr>
<td>Seftel, 2007 [20]</td>
<td>Broad (Pooled)</td>
<td>1270</td>
<td>Pooled analysis of 5 multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 12 weeks</td>
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<td>Hundertmark, 2007 [21]</td>
<td>Broad</td>
<td>98</td>
<td>Single centre, randomized, double blind, placebo controlled, 2 arm flexible dose, 6 months</td>
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<tr>
<td>Kadioglu, 2008 [22]</td>
<td>Broad</td>
<td>307</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 6 weeks</td>
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<tr>
<td>Zonanca Fraca, 2008 [23]</td>
<td>Broad</td>
<td>95</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 12 weeks</td>
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<tr>
<td>Jones, 2008 [24]</td>
<td>Broad</td>
<td>209</td>
<td>Multicentre, randomized, double blind, placebo controlled, 2 arm flexible dose, 10 weeks</td>
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<tr>
<td>Safarinejad, 2009 [36]</td>
<td>Multiple Sclerosis</td>
<td>203</td>
<td>Single Centre, randomized, placebo controlled, two arm, flexible dose trial for 24 doses</td>
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### Table 3b: Level 1 studies demonstrating efficacy of sildenafil in men with erectile dysfunction

<table>
<thead>
<tr>
<th>Senior Author Year</th>
<th>IIEF EF Domain Score</th>
<th>GAQ</th>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Sildenafil 25mg</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>End</td>
</tr>
<tr>
<td>Goldstein, 1998 [1]</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dinsmore, 1999 [3]</td>
<td>9.3</td>
<td>10.1</td>
</tr>
<tr>
<td>Montorsi, 1999 [4]</td>
<td>approx 13</td>
<td>approx 13</td>
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</table>
Table 3b: Level 1 studies demonstrating efficacy of sildenafil in men with erectile dysfunction Senior author, IIEF domain score and GAQ (continued)

<table>
<thead>
<tr>
<th>Senior Author Year</th>
<th>IIEF EF Domain Score</th>
<th>GAQ</th>
<th>Sildenafil</th>
<th>Placebo</th>
<th>Sildenafil 25mg</th>
<th>Placebo</th>
<th>Sildenafil 50mg</th>
<th>Placebo</th>
<th>Sildenafil 100mg</th>
<th>Placebo</th>
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<td>Baseline</td>
<td>End</td>
<td>Baseline</td>
<td>End</td>
<td>Baseline</td>
<td>End</td>
<td>Baseline</td>
<td>End</td>
<td>Baseline</td>
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<tr>
<td>Tan, 2000 [5]</td>
<td>13.3</td>
<td>15.5</td>
<td>Baseline 13.3: End 25.1</td>
<td>32.7%</td>
<td>87%</td>
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<td>NR</td>
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<td>NR</td>
<td>NR</td>
<td>26%</td>
<td>82%</td>
<td></td>
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<td>Olsson, 2000 [7]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>38%</td>
<td>64% (10mg)</td>
<td>79% (25mg)</td>
<td>88% (50mg)</td>
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<tr>
<td>Meuleman, 2001 [8]</td>
<td>11.8</td>
<td>13.3</td>
<td>Baseline 11.1; End 21.9</td>
<td>23%</td>
<td>79%</td>
<td></td>
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<tr>
<td>Chen, 2001 [9]</td>
<td>13.5</td>
<td>18.1</td>
<td>Baseline 13.5; End 24.3</td>
<td>38.4%</td>
<td>88.2%</td>
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<td>Rendell, 1999 [25]</td>
<td>9.2</td>
<td>10.4</td>
<td>Baseline 9.5; End 17.5</td>
<td>10%</td>
<td>56%</td>
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<td>Boulton, 2001 [26]</td>
<td>10.4</td>
<td>11.5</td>
<td>Baseline 10.4; End 20.4</td>
<td>11%</td>
<td>65%</td>
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<tr>
<td>Seidman, 2001 [29]</td>
<td>9.3</td>
<td>12.4</td>
<td>Baseline 9.3; End 23.4</td>
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<td>91%</td>
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<td>Giuliano, 1999 [33] and Hultling, 2000 [34]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>4%</td>
<td>76%</td>
<td></td>
<td></td>
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<td>71%</td>
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<td>Lewis, 2001 [11]</td>
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<td>NR</td>
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<td>70%</td>
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<td>Becher, 2002 [12]</td>
<td>14.5</td>
<td>15.9</td>
<td>Baseline 14.5, End of trial 20.5</td>
<td>33.8</td>
<td>77.3</td>
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<tr>
<td>Glina, 2002 [13]</td>
<td>EF domain scores showed improvement for sildenafil compared with placebo, but actual numbers not reported</td>
<td>NR</td>
<td>NR</td>
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Table 3b: Level 1 studies demonstrating efficacy of sildenafil in men with erectile dysfunction
Senior author, IIEF domain score and GAQ (continued)

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<tr>
<th>Senior Author Year</th>
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<td>13.6</td>
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<tr>
<td>Stuckey, 2003[27]</td>
<td>Approx 12</td>
<td>Approx 14</td>
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<td>Nurnberg, 2003[30]</td>
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<td>17.1</td>
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<td>Levinson et al, 2003 [15]</td>
<td>Approx 12</td>
<td>Approx 15</td>
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<td>DeBusk, 2004 [38]</td>
<td>10.5</td>
<td>15</td>
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<tr>
<td>Tignol, 2004 [31]</td>
<td>10.5</td>
<td>15</td>
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<tr>
<td>Webster 2004 [40]</td>
<td>Baseline EF domain score 9. Crossover design confirmed efficacy of sildenafil 50mg with score at end of sildenafil phase 15-16 and score at end of placebo phase 9-10</td>
<td>NR</td>
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<td>Safarinejad, 2004 [28]</td>
<td>10.1</td>
<td>11.4</td>
</tr>
<tr>
<td>Pickering, 2004 [39]</td>
<td>Approx 12.5</td>
<td>Approx 15</td>
</tr>
<tr>
<td>Katz, 2005 [41]</td>
<td>9.9</td>
<td>15.9</td>
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<td>Fowler, 2005 [35]</td>
<td>EF domain scores reported as percentage improvements over baseline</td>
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<td>12.6</td>
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Table 3b: Level 1 studies demonstrating efficacy of sildenafil in men with erectile dysfunction. Senior author, IIEF domain score and GAQ (continued)

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<td>13.2 15.1</td>
<td>Baseline 13.4, End of Trial 22.6</td>
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<td>Baseline 14.3; End of Trial 23.1</td>
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<td>15.9 17.3</td>
<td>Baseline 15.4; End of Trial 24.1</td>
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<td>14.7 16.9</td>
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<td>Baseline 14.4; End of Trial 21.8</td>
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<td>Sildenafil</td>
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<tr>
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<td>Baseline</td>
<td>End</td>
</tr>
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<td>Goldstein, 1998 [1]</td>
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<td>NR</td>
</tr>
<tr>
<td>Dinsmore, 1999 [3]</td>
<td>NR</td>
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<td>Montorsi, 1999 [4]</td>
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<td>Sildenafil</td>
</tr>
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<tr>
<td></td>
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</tr>
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<td>29%</td>
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<td>Webster 2004 [40]</td>
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<tr>
<td>Pickering, 2004 [39]</td>
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<td>O’Leary, 2006 [16]</td>
<td>NR</td>
<td>19% improvement from baseline</td>
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<td>Fava, 2006 [32]</td>
<td>NR</td>
<td>31%</td>
</tr>
<tr>
<td>Althof, 2006 [17]</td>
<td>NR</td>
<td>31% improvement from baseline</td>
</tr>
<tr>
<td>Senior Author Year</td>
<td>Placebo Baseline</td>
<td>Placebo End</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Heiman, 2007 [18]</td>
<td>NR</td>
<td>49%</td>
</tr>
<tr>
<td>McVary, 2007 [42]</td>
<td>23%</td>
<td>39%</td>
</tr>
<tr>
<td>Burankitjaroen, 2007 [19]</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Seftel, 2007 [20]</td>
<td>Efficacy results reported within individual studies</td>
<td></td>
</tr>
<tr>
<td>Hundertmark, 2007 [21]</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Kadioglu, 2008 [22]</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Zonanca Fraca, 2008 [23]</td>
<td>NR</td>
<td>50.5%</td>
</tr>
<tr>
<td>Jones, 2008 [24]</td>
<td>35.9%</td>
<td>60.8%</td>
</tr>
<tr>
<td>Safarinejad, 2009 [36]</td>
<td>21% (SEP3)</td>
<td>38.2% (SEP3)</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Senior Author Year</th>
<th>Treatment emergent adverse events</th>
<th>Dropouts due to adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein, 1998 [1]</td>
<td>100mg: Headache 30%, Flushing 20%, Dyspepsia 16%, Rhinitis 11%, Visual Aes 9% 50mg: Headache 21%, Flushing 27%, Dyspepsia 11%, Rhinitis 3%, Visual Aes 6% 25mg: Headache 14%, Flushing 13%, Dyspepsia 3%, Rhinitis 1%, Visual Aes 2%</td>
<td>Placebo &lt; 1%  Sildenafil 100mg: 2.0%  Sildenafil 50mg: 1%  Sildenafil 25mg: 1%</td>
</tr>
<tr>
<td>Dinsmore, 1999 [3]</td>
<td>Headache 12%, flushing 9%, Dyspepsia 7%, Abnormal vision 4%</td>
<td>Placebo: 0%  Sildenafil: 0%</td>
</tr>
<tr>
<td>Montorsi, 1999 [4]</td>
<td>100mg: Headache 21%, Flushing 20%, Dyspepsia 11%, Nausea 6%, Altered vision 11% 50mg: Headache 17%, Flushing 19%, Dyspepsia 5%, Nausea 2%, Altered vision 1% 100mg: Headache 20%, Flushing 13%, Dyspepsia 2%, Nausea 1%, Altered vision 0%</td>
<td>Placebo: 1.0%  Sildenafil: 4.0%</td>
</tr>
<tr>
<td>Tan, 2000 [5]</td>
<td>Headache 9.4%, Flushing 7.1%, Rhinitis 3.1%, Visual Aes 3.1%</td>
<td>Placebo: 0.0%  Sildenafil: 3.0%</td>
</tr>
<tr>
<td>Christianson, 2000 [6]</td>
<td>Headache 6%, Dyspepsia 5%, Flushing 7%</td>
<td>N/A</td>
</tr>
<tr>
<td>Olsson, 2000 [7]</td>
<td>Sildenafil 50mg: Headache 19.8%, Flushing 8.6%, Myalgia 7.4%, Dyspepsia 6.2%, Sildenafil 25mg: Headache 23.5%, Flushing 8.2%, Myalgia 3.5%, Dyspepsia 10.6%  Sildenafil 10mg: Headache 13.3%, Flushing 4.4%, Myalgia 1.1%, Dyspepsia 4.4%</td>
<td>Placebo: 4.2%  Sildenafil 50mg: 6.2%  Sildenafil 25mg: 4.7%  Sildenafil 10mg: 1.1%</td>
</tr>
<tr>
<td>Meueleman, 2001 [8]</td>
<td>Flushing 11%, Headache 9%, Dyspepsia 7%, Flu syndrome 7%, Rhinitis 6%</td>
<td>Placebo: &lt;1.0%  Sildenafil: 3.0%</td>
</tr>
<tr>
<td>Chen, 2001 [9]</td>
<td>Flushing 25%, Dizziness 6.7%, Headache 5.9%, Abdominal pain 3.4%, Palpitation 3.4%</td>
<td>Placebo: 1.0%  Sildenafil: 1%</td>
</tr>
<tr>
<td>Rendell, 1999 [25]</td>
<td>Headache 11%, Dyspepsia 9%, Respiratory tract disorder 6%, Flushing 4%, Rhinitis 4%, Visual Aes 4%</td>
<td>Placebo: 1.0%  Sildenafil: 1.0%</td>
</tr>
<tr>
<td>Boulton, 2001 [26]</td>
<td>Headache 18.2%, Flushing 14.5%, Dyspepsia 1.8%, Visual Aes 4.5%</td>
<td>Placebo: 0%  Sildenafil: 0%</td>
</tr>
<tr>
<td>Seidman, 2001 [29]</td>
<td>Headache 20.3%, Flushing 14.9%, Dyspepsia 14.9%, Visual Aes 8.1%</td>
<td>NR</td>
</tr>
<tr>
<td>Giuliano, 1999 [33] and Hultling, 2000 [34]</td>
<td>Headache 17%, Flushing 7%, Dyspepsia 3%</td>
<td>Placebo: 1.0%  Sildenafil: 2.0%</td>
</tr>
<tr>
<td>Olsson, 2001 [37]</td>
<td>Flushing 17%, Headache 15%, Dyspepsia 5%</td>
<td>Placebo: 1.0%  Sildenafil: 1%</td>
</tr>
</tbody>
</table>
Table 3d: Level 1 studies demonstrating efficacy of sildenafil in men with erectile dysfunction Senior author, treatment emergent adverse events, dropouts due to adverse events (Continued)

<table>
<thead>
<tr>
<th>Senior Author Year</th>
<th>Treatment emergent adverse events</th>
<th>Dropouts due to adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seidman, 2001 [29]</td>
<td>Headache 20.3%, Flushing 14.9%, Dyspepsia 14.9%, Visual Aes 8.1%</td>
<td>NR</td>
</tr>
<tr>
<td>Giuliano, 1999 [33] and Hultling, 2000 [34]</td>
<td>Headache 17%, Flushing 7%, Dyspepsia 3%</td>
<td>Placebo: 1.0% Sildenafil: 2.0%</td>
</tr>
<tr>
<td>Olsson, 2001 [37]</td>
<td>Flushing 17%, Headache 15%, Dyspepsia 5%</td>
<td>Placebo: 1.0% Sildenafil: 1%</td>
</tr>
<tr>
<td>Becher, 2002 [12]</td>
<td>Headache 24%, Flushing 22.2%</td>
<td>Sildenafil 0% Placebo 0%</td>
</tr>
<tr>
<td>Glina, 2002 [13]</td>
<td>Headache 8.9%, Flushing 8.9%, Dyspepsia 6.5%, Rash 3.2%</td>
<td>Sildenafil 1% Placebo 0%</td>
</tr>
<tr>
<td>Gomez, 2002 [14]</td>
<td>Headache 25%, Vasodilatation 11.8%, Dyspepsia 6.6%</td>
<td>Sildenafil 1% Placebo 0%</td>
</tr>
<tr>
<td>Stuckey, 2003 [27]</td>
<td>Headache 20%, Flushing 17.9%, Dyspepsia 8.4%</td>
<td>Placebo: 4.0% Sildenafil: 2.2%</td>
</tr>
<tr>
<td>Nurnberg, 2003 [30]</td>
<td>Headache 40.5%, Flushing 16.7%</td>
<td>Placebo 2% Sildenafil 2%</td>
</tr>
<tr>
<td>Levinson et al, 2003 [15]</td>
<td>Headache 20.3%, Dyspepsia 9.4%, Abnormal vision 7.8%, Flushing 6.3%, Rhinitis 5.5%, Flu syndrome 3.9%</td>
<td>Sildenafil 2.3% Placebo 0 %</td>
</tr>
<tr>
<td>DeBusk, 2004 [38]</td>
<td>Headache 8.1% (drug related 8.1%), Chest pain 5.4% (Drug related 1.4%), Hypertension 5.4% (Drug related 0), Flushing 8.1% (drug related 6.8%), Leg cramps 4.1% (drug related 0), Respiratory infection 5.4% (drug related 0)</td>
<td>Sildenafil: 1.3%</td>
</tr>
<tr>
<td>Tignol, 2004 [31]</td>
<td>Headache 12%, Flushing 12%, Nasal congestion 2.4%</td>
<td>Placebo 0% Sildenafil 1%</td>
</tr>
<tr>
<td>Webster 2004 [40]</td>
<td>No AEs reported</td>
<td>Placebo 0% Sildenafil 0%</td>
</tr>
<tr>
<td>Safarinejad, 2004 [28]</td>
<td>Headache 20%, Flushing 19%, Dyspnoea 9%, Rhinitis 6%, cardiovascular 7%</td>
<td>Sildenafil 5.5% Placebo 0%</td>
</tr>
<tr>
<td>Pickering, 2004 [39]</td>
<td>Headache 10.1%, Flushing 6.1%, Dyspepsia 5.4%, Dizziness 4%, Nasal congestion 2.5%, abnormal vision 2.5%</td>
<td>Placebo 1% Sildenafil 1%</td>
</tr>
</tbody>
</table>
Table 3d: Level 1 studies demonstrating efficacy of sildenafil in men with erectile dysfunction Senior author, treatment emergent adverse events, dropouts due to adverse events (Continued)

<table>
<thead>
<tr>
<th>Senior Author Year</th>
<th>Treatment emergent adverse events</th>
<th>Dropouts due to adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katz, 2005 [41]</td>
<td>Headache 13%, Respiratory infection 8%, Asthenia 8%, Oedema 5%, Rhinitis 3%, Back pain 3%, Chromatopsia 3%</td>
<td>Sildenafil 3% Placebo 3%</td>
</tr>
<tr>
<td>Fowler, 2005 [35]</td>
<td>Headache 21%, Flushing 13%, Rhinitis 4%, Chromatopsia 4%, dyspepsia 3%</td>
<td>Placebo 1% Sildenafil 0%</td>
</tr>
<tr>
<td>O'Leary, 2006 [16]</td>
<td>Headache 10%, Rhinitis 6%, Vasodilation 6%, Dyspepsia 6%, Chromatopsia 2%, photophobia 2%, Dry mouth 2%, Nausea 2%</td>
<td>Placebo 0% Sildenafil 0%</td>
</tr>
<tr>
<td>Fava, 2006 [32]</td>
<td>Headache 9%, Dyspepsia 9%, Anxiety 6%, Abnormal vision 3%</td>
<td>Placebo 0% Sildenafil 0%</td>
</tr>
<tr>
<td>Althof, 2006 [17]</td>
<td>Headache 14%, Flushing 10%, Dyspepsia 5%</td>
<td>Placebo 0% Sildenafil 1%</td>
</tr>
<tr>
<td>Heiman, 2007 [18]</td>
<td>Headache 7%, Vasodilation 7%, Rhinitis 7%, Dyspepsia 2%, Abnormal vision 3.5%</td>
<td>Placebo 0% Sildenafil 0%</td>
</tr>
<tr>
<td>McVary, 2007 [42]</td>
<td>Headache 11%, Flushing 5%, Dyspepsia 6%, Rhinitis 4%</td>
<td>Placebo 1% Sildenafil 5%</td>
</tr>
<tr>
<td>Burankitjaroen, 2007 [19]</td>
<td>Dizziness 7.7%, Tinnitus 2.9%</td>
<td>Sildenafil 0.5% Placebo 1%</td>
</tr>
<tr>
<td>Seftel, 2007 [20]</td>
<td>Safety results reported within individual studies</td>
<td></td>
</tr>
<tr>
<td>Hundertmark, 2007 [21]</td>
<td>Not reported</td>
<td>Placebo 0% Sildenafil 0%</td>
</tr>
<tr>
<td>Kadioglu, 2008 [22]</td>
<td>Headache 8%, Vasodilation 3%</td>
<td>Placebo 0% Sildenafil 0%</td>
</tr>
<tr>
<td>Zonanca Fraca, 2008 [23]</td>
<td>Headache 10%, Rhinitis 4%, Dyspepsia 4%</td>
<td>Placebo 0% Sildenafil 0%</td>
</tr>
<tr>
<td>Jones, 2008 [24]</td>
<td>Headache 13.5%, Flushing 15.4%, Nasal congestion 4.8%, Dizziness 2.9%</td>
<td>Placebo 0% Sildenafil 1%</td>
</tr>
<tr>
<td>Safarinejad, 2009 [36]</td>
<td>Headache 14.7%, Flushing 9.8%, Visual disturbances 9.8%, Nausea 6.9%, Rhinitis 6.9%</td>
<td>Placebo 2% Sildenafil 5.9%</td>
</tr>
</tbody>
</table>
### Table 3: Level 1 studies demonstrating efficacy of sildenafil in men with erectile dysfunction

<table>
<thead>
<tr>
<th>Study</th>
<th>Assessment tool</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein, 1998 [1]</td>
<td>IIEF</td>
<td>Improvement in all domains IIEF for sildenafil versus placebo</td>
</tr>
<tr>
<td>Dinsmore, 1999 [3]</td>
<td>IIEF</td>
<td>Improvement in all domains IIEF for sildenafil versus placebo</td>
</tr>
<tr>
<td>Montors, 1999 [4]</td>
<td>IIEF</td>
<td>Improvement in all domains IIEF for sildenafil versus placebo</td>
</tr>
<tr>
<td>Tan, 2000 [5]</td>
<td>IIEF</td>
<td>Improvement in all domains IIEF for sildenafil versus placebo</td>
</tr>
<tr>
<td>Meuleman, 2001 [8]</td>
<td>IIEF</td>
<td>Improvement in all domains IIEF for sildenafil versus placebo</td>
</tr>
<tr>
<td>Chen, 2001 [9]</td>
<td>IIEF</td>
<td>Improvement in all domains IIEF for sildenafil versus placebo</td>
</tr>
<tr>
<td>Giuliano, 2001 [10]</td>
<td>1. IIEF Q13 and 14 2. Impact erectile problem on Quality of life questionnaire 3. Broad based psychometric questionnaires</td>
<td>1. Improvement in Overall satisfaction for sildenafil versus placebo 2. Improvement over baseline of 31% for sildenafil versus 8% for placebo 3. Minor changes in the broad based questionnaires for sildenafil versus placebo</td>
</tr>
<tr>
<td>Rendell, 1999 [25]</td>
<td>IIEF</td>
<td>Improvement in orgasmic function, Intercourse satisfaction, Sexual desire and Overall satisfaction for sildenafil versus placebo</td>
</tr>
<tr>
<td>Boulton, 2001 [26]</td>
<td>1. IIEF 2. Life satisfaction checklist</td>
<td>1. Improvement in all domains IIEF for sildenafil versus placebo 2. Sildenafil improved QOL sexual life domain, but no effect upon other domains</td>
</tr>
<tr>
<td>Seidman, 2001 [29]</td>
<td>1. IIEF 2. Beck Depression inventory, Hamilton Depression rating, Life satisfaction checklist</td>
<td>1. Improvement in all domains IIEF for sildenafil versus placebo 2. Improved score with response to therapy (whether sildenafil or placebo user) compared with non-responder for both both Depression scales and for the sexual function domain of the life satisfaction checklist</td>
</tr>
<tr>
<td>Giuliano, 1999 [33] and Hultling, 2000 [34]</td>
<td>1. IIEF 2. Life satisfaction checklist</td>
<td>1. Improvement in all domains IIEF for sildenafil versus placebo 2. Sildenafil improved QOL sexual life domain cw with placebo, but no effect upon other domains</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patient: Sildenafil 73.6%; Placebo 48.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Partner: Sildenafil 63.9%; Placebo 33.3%</td>
</tr>
</tbody>
</table>
# Table 3e: Level 1 studies demonstrating efficacy of sildenafil in men with erectile dysfunction

<table>
<thead>
<tr>
<th>Study</th>
<th>Assessment tool</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurnberg, 2002 [30]</td>
<td>1. IIEF</td>
<td>1. Improvement in all domains IIEF except desire for sildenafil versus placebo</td>
</tr>
<tr>
<td></td>
<td>2. Arizona Sexual Experience Scale (ASEX) and Massachusetts General Hospital-Sexual Functioning Questionnaire (MGH SFQ)</td>
<td>2. Mean scores of ASEX and MGH SFQ showed greater improvement with sildenafil than with placebo</td>
</tr>
<tr>
<td></td>
<td>3. Hamilton Rating Scale for Depression (HAM-D)</td>
<td>3. No significant changes in HAM-D</td>
</tr>
<tr>
<td>Becher, 2002 [12]</td>
<td>IIEF</td>
<td>Improvement in all domains IIEF for sildenafil versus placebo</td>
</tr>
<tr>
<td>Glina, 2002 [13]</td>
<td>IIEF</td>
<td>Improvement in all domains IIEF for sildenafil versus placebo</td>
</tr>
<tr>
<td>Gomez, 2002 [14]</td>
<td>IIEF</td>
<td>Improvement in all domains IIEF except desire and orgasmic function for sildenafil versus placebo</td>
</tr>
<tr>
<td>Levinson et al, 2003 [15]</td>
<td>IIEF</td>
<td>Improvement in all domains IIEF for sildenafil versus placebo</td>
</tr>
<tr>
<td>DeBusk, 2004 [38]</td>
<td>1. EDITS</td>
<td>1. Significant benefit cw placebo. Patient: Sildenafil 63.6%; Placebo 41.4%</td>
</tr>
<tr>
<td></td>
<td>2. Life Satisfaction checklist</td>
<td>2. Sildenafil improved QOL sexual life domain cw placebo, but no effect upon other domains</td>
</tr>
<tr>
<td>Tignol, 2004 [31]</td>
<td>1. IIEF</td>
<td>1. Improvement in all domains IIEF for sildenafil versus placebo</td>
</tr>
<tr>
<td></td>
<td>2. Life satisfaction checklist</td>
<td>2. No benefit for Life satisfaction checklist</td>
</tr>
<tr>
<td>Webster 2004 [40]</td>
<td>1. Centre for Epidemiological studies Depression scale (CES-D) and Beck Depression inventory (BDI)</td>
<td>1. Sildenafil demonstrated significant improvements in both depression scales when compared with placebo</td>
</tr>
<tr>
<td></td>
<td>2. Minnesota Living With Heart Failure Questionnaire (QOL)</td>
<td>2. Sildenafil demonstrated significant improvements in the QOL scale when compared with placebo</td>
</tr>
<tr>
<td>Safarinejad, 2004 [28]</td>
<td>IIEF</td>
<td>Improvement in all domains IIEF for sildenafil versus placebo</td>
</tr>
</tbody>
</table>
Table 3e: Level 1 studies demonstrating efficacy of sildenafil in men with erectile dysfunction

Senior author, psychosocial outcomes including satisfaction, quality of life, impact, bother (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Assessment tool</th>
<th>Results</th>
</tr>
</thead>
</table>
2. EDITS  
3. Life satisfaction checklist | 1. Improvement in all domains IIEF for sildenafil versus placebo  
2. Improvement in all EDITS questions for sildenafil versus placebo  
3. Improved Sexual life question for sildenafil. Other questions showed no significant change |
| Katz, 2005 [41]    | 1. IIEF  
2. EDITS | 1. Improvement in all domains IIEF except orgasmic function for sildenafil versus placebo  
2. EDITS index: Significant benefit vs placebo: placebo 47.8, sildenafil 75.1 |
| Fowler, 2005 [35]  | 1. IIEF  
2. Life satisfaction checklist  
3. Erection distress scale | 1. Improvement in all domains IIEF for sildenafil versus placebo  
2. Improvement in 5 out of 8 items for sildenafil compared with placebo (life as a whole, sexual life, partner relation, family life, social contact)  
3. EDS: 43% improvement over baseline for sildenafil compared with 13% for placebo |
| O’Leary, 2006 [16] | 1. IIEF  
2. SEAR | 1. Improvement in all domains IIEF for sildenafil versus placebo  
2. Improvement in all domains SEAR for sildenafil versus placebo |
| Fava, 2006 [32]    | 1. IIEF  
2. EDITS  
3. Depression Scales | 1. Improvement in all domains IIEF for sildenafil versus placebo  
2. Improvement in all EDITS questions for sildenafil versus placebo  
3. No change in depression scale scores |
| Althof, 2006 [17]  | 1. IIEF  
2. SEAR | 1. Improvement in all domains IIEF for sildenafil versus placebo  
2. Improvement in all domains SEAR for sildenafil versus placebo |
| Heiman, 2007 [18]  | 1. IIEF  
2. SEAR  
3. EDITS  
4. Dyadic Adjustment scale  
5. FSFI (partner)  
6. SFQ (Partner) | 1. Improvement in all domains IIEF except orgasmic and desire for sildenafil versus placebo  
2. Improvement in all domains SEAR except overall relationship subscale for sildenafil versus placebo  
3. EDITS: Significant benefit vs placebo Patient: Placebo 43.4; Sildenafil 64.1; Partner: Placebo 38.7, Sildenafil 57.7  
4. DAS: No change was found in relationship functioning  
5. FSFI: Improvement in satisfaction, arousal, orgasm and pain domains for sildenafil versus placebo  
6. SFQ: Improvement in enjoyment domain for sildenafil versus placebo. No significant differences in other domains |
| McVary, 2007 [42]  | 1. IIEF  
2. SEAR  
3. EDITS | 1. Improvement in all domains IIEF for sildenafil versus placebo  
2. Improvement in all domains SEAR for sildenafil versus placebo  
3. EDITS: Significant benefit vs placebo: Patient: Placebo 41.7; Sildenafil 71.2 |
| Burankitjaroen, 2007 [19] | 1. IIEF  
2. EDITS | 1. Improvement in all domains IIEF for sildenafil versus placebo  
2. EDITS: Significant benefit vs placebo: Patient: Placebo 53.5; Sildenafil 72.9 |
Table 3e: Level 1 studies demonstrating efficacy of sildenafil in men with erectile dysfunction

<table>
<thead>
<tr>
<th>Study</th>
<th>Assessment tool</th>
<th>Results</th>
</tr>
</thead>
</table>
| Seftel, 2007 [20]            | Erectile distress scale (EDS) (Bother)               | Placebo baseline value 53.3; end of trial 58.4  
Sildenafil baseline value 54; end of trial 72.7  
This represents a significant advantage for sildenafil over placebo |
| Hundertmark, 2007 [21]       | 1. Dyadic Adjustment scale (DAS)  
2. EDITs, WHO brief QOL questionnaire, Centre for Marital and Sexual Health Sexual Functioning Questionnaire | 1. No change was found in relationship functioning as assessed by the DAS scores  
2. Factor analysis of all questions from all questionnaires for patient confirmed effectiveness of treatment, but no effect upon Relationship with partner, Physical QOL, Satisfaction with intercourse, quality of erection or quality of sexual activity for sildenafil versus placebo. Factor analysis of all questions from all questionnaires for female partner demonstrated no significant changes in any domain for sildenafil versus placebo |
| Kadioglu, 2008 [22]          | 1. IIEF  
2. EDITs  
3. SEAR  
4. QEQQ  
5. Erection hardness scale Grade 3 or 4 | 1. Improvement in all domains IIEF for sildenafil versus placebo  
2. EDITs results not explicitly reported  
3. Improvement in all domains SEAR for sildenafil versus placebo  
4. Baseline; Placebo 37, Sildenafil 34; End of trial; Placebo 44, Sildenafil 75  
5. Baseline; Placebo 46%, Sildenafil 45%; End of trial; Placebo 57%, Sildenafil 85% |
| Zonanca Fraca, 2008 [23]     | 1. IIEF  
2. SEAR                                            | 1. Improvement in all domains IIEF except desire domain for sildenafil versus placebo  
2. Improvement in all domains SEAR for sildenafil versus placebo |
| Jones, 2008 [24]             | 1. IIEF  
2. EDITs  
3. SEAR  
4. SEX-Q  
5. QEQQ  
6. Erection hardness scale | 1. Improvement in all domains IIEF except desire domain for sildenafil versus placebo  
2. EDITs: Significant benefit cw placebo: Placebo 49.6%, Sildenafil 66.5%  
3. Improvement in all domains SEAR for sildenafil versus placebo  
4. Improvement in all domains SEX-Q for sildenafil versus placebo  
5. Baseline; Placebo 28.8, Sildenafil 29.3; End of trial; Placebo 37.1, Sildenafil 63.4  
6. Baseline; Placebo 47.9%, Sildenafil 44.3%; End of trial; Placebo 52.1%, Sildenafil 79.0% |
| Safarinejad, 2009 [36]       | 1. IIEF  
2. EDITs                                          | 1. Improvement in orgasmic function, Intercourse satisfaction and overall satisfaction for sildenafil versus placebo  
2. EDITs: Significant benefit cw placebo: Placebo 48.6%, Sildenafil 64.4% |


[15] Levinson IP, Khalaf IM, Shaeer KZM, Smart DO. Efficacy and safety of sildenafil citrate for the treatment of erectile dysfunction in men in Egypt and South Africa. IJIR, 2003, 15, supplement 1, S25-S29


Efficacy and Tolerability in Diabetes


[28] Safarinejad MR. Oral sildenafil in the treatment of erectile

Efficacy and Tolerance in Depression


Efficacy and Tolerance in Spinal cord injury and Multiple Sclerosis


Efficacy and Tolerance in Cardiovascular disease and Hypertension


Efficacy and Tolerance in men with Lower urinary tract symptoms


Additional references for Tolerability and Safety General safety


Ocular safety


Cardiovascular safety

[86] Zusman RM. Cardiovascular data on sildenafil citrate: introduction. Am J Cardiol 1999;83:1C-2C.


2.TADALAFIL

A comprehensive review of the literature has identified a number of publications which attest to the efficacy, tolerability and safety of tadalafil in men with erectile dysfunction. The salient features of the level 1 publications have been tabulated in Tables 4a-4e, which outline the trial design, the patients randomized, the efficacy outcome and the side effect profiles of the studies.

For assessment of efficacy we have not included pooled studies or analyses of pooled studies, and we have attempted to ensure that no dataset is reported more than once. For assessment of safety and tolerability, we have included pooled analyses in an attempt to identify relatively infrequent tolerability or safety issues.

a) Efficacy in the Broad Population of Men with Erectile Dysfunction

Overall we can recommend that there is clear evidence that tadalafil is efficacious in the treatment of erectile dysfunction in the broad population when taken on demand at a dose of 10mg and 20mg. There are multiple level 1 studies with consistent outcomes [1-10, 12-15]. The overall grade of recommendation is grade A.

In addition there are two level 1 studies that confirm that tadalafil is also efficacious when taken daily [11,16]. Although several doses have been tested, the doses that have been licensed are 2.5mg and 5mg. The overall grade of recommendation is grade A.

b) Efficacy in Special Populations of Men with Erectile Dysfunction

Overall we can recommend that there is clear evidence that tadalafil is efficacious in the treatment of erectile dysfunction in a number of special populations of men with erectile dysfunction. These populations include:

• Men with diabetes and ED (A single level 1 study using on demand dosing [17] and a single study using regular dosing [18]. The overall grade of recommendation = A)

• Men with ED who have undergone bilateral nerve sparing radical prostatectomy (A single level 1 study using on demand dosing [19]. The overall grade of recommendation = A)

• Men with ED who have undergone external beam radiotherapy for prostate cancer (A single level
1 study using on demand dosing [20]. The overall grade of recommendation = A)

- Men with ED secondary to spinal cord injury (A single level 1 study using on demand dosing [21]. The overall grade of recommendation = A)
- Men with lower urinary tract symptoms and ED (Two level 1 studies using regular dosing [22,23] with an overall grade of recommendation = A)

c) Tolerability and Safety

Overall, we can recommend that although side effects do occur with tadalafil (most notably headache, flushing, indigestion, nasal congestion and back or girdle pain), providing that the drug is used in line with the labeling recommendations, there is no convincing evidence in the literature of any significant safety issue, including cardiovascular, visual and aural safety (Consistent level 1 studies [1-47], Overall grade of recommendation is grade A).

REFERENCES

Efficacy in the broad population of men with erectile dysfunction


Efficacy in ED secondary to diabetes


Efficacy in men with ED secondary radical prostatectomy


Efficacy in men with ED secondary to external beam radiotherapy


Efficacy in ED secondary to spinal cord injury

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient group</th>
<th>Patient numbers</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Padma-Nathan, 2001 [1]</td>
<td>Broad population</td>
<td>179</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, parallel group, fixed dose, 3 weeks</td>
</tr>
<tr>
<td>Saenz de Tejada, 2002 [17]</td>
<td>Diabetes</td>
<td>216</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, parallel group, fixed dose, 12 weeks</td>
</tr>
<tr>
<td>Montorsi, 2004 [19]</td>
<td>BNSRRP*</td>
<td>303</td>
<td>Multicenter randomized, double-blind, placebo-controlled, parallel group, fixed dose, 12 weeks</td>
</tr>
<tr>
<td>Eardley, 2004 [4]</td>
<td>Broad population</td>
<td>220</td>
<td>Multicenter randomized, double-blind, placebo-controlled, parallel group, fixed dose, 12 weeks</td>
</tr>
<tr>
<td>Skoumal, 2004 [5]</td>
<td>Broad population</td>
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<td>Multicenter randomized, double-blind, placebo-controlled, parallel group, fixed dose, 12 weeks</td>
</tr>
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<td>Seftel, 2004 [6]</td>
<td>Broad population</td>
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<td>Multicenter randomized, double-blind, placebo-controlled, parallel group, fixed dose, 12 weeks</td>
</tr>
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<td>McMahon, 2005 [7]</td>
<td>Broad population</td>
<td>152</td>
<td>Multicenter randomized, double-blind, placebo-controlled, parallel group, flexible dose, 6 months</td>
</tr>
<tr>
<td>Carrier, 2005 [8]</td>
<td>Broad population</td>
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<td>Multicenter randomized, double-blind, placebo-controlled, parallel group, fixed dose, 12 weeks</td>
</tr>
<tr>
<td>Young, 2005 [9]</td>
<td>Broad population</td>
<td>483</td>
<td>Multicenter randomized, double-blind, placebo-controlled, parallel group, fixed dose, 4 phases 1st 4 weeks, 2nd 2-4 weeks, 3rd 4-6 weeks, 4th 6 months open label</td>
</tr>
<tr>
<td>Guo, 2006 [10]</td>
<td>Broad population</td>
<td>367</td>
<td>Multicenter randomized, double-blind, placebo-controlled, parallel group, fixed dose, 12 weeks</td>
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<tr>
<td>Incrocci, 2006 [20]</td>
<td>3DCRT#</td>
<td>60</td>
<td>Randomized, double-blind, placebo-controlled, cross over, fixed dose, 12 weeks</td>
</tr>
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Table 4a: Level 1 studies demonstrating efficacy of tadalafil in men with erectile dysfunction

<table>
<thead>
<tr>
<th>Study</th>
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<th>Patient numbers</th>
<th>Study design</th>
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<tr>
<td>Nagao, 2006 [12]</td>
<td>Broad population</td>
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<td>Multicenter randomized, double-blind, placebo-controlled, parallel group, fixed dose, 12 weeks</td>
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<td>McMahon, 2006 [13]</td>
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<td>Saylan, 2006 [14]</td>
<td>Broad population</td>
<td>132</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, parallel group, fixed dose, 12 weeks</td>
</tr>
<tr>
<td>Yip, 2006 [15]</td>
<td>Broad population</td>
<td>242</td>
<td>Multicenter randomized, double-blind, placebo-controlled, parallel group, fixed dose, 12 weeks</td>
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<tr>
<td>Rajfer, 2007 [16]</td>
<td>Broad population</td>
<td>287</td>
<td>Multicenter randomized, double-blind, placebo-controlled, parallel group, fixed dose, 24 weeks</td>
</tr>
<tr>
<td>McVary, 2007 [22]</td>
<td>ED and LUTS</td>
<td>281</td>
<td>Multicenter randomized, single-blind, placebo-controlled, parallel group escalating dose, 12 - 24 weeks</td>
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<tr>
<td>Giuliano, 2007 [21]</td>
<td>Spinal cord Injury</td>
<td>186</td>
<td>Multicenter randomized, double-blind, placebo-controlled, parallel group, flexible dose, 12 weeks, maintained or titrated at 4 or 8 weeks</td>
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<tr>
<td>Roerborn, 2008 [23]</td>
<td>ED and LUTS</td>
<td>1058</td>
<td>Multicenter randomized, double-blind, placebo-controlled, parallel group flexible dose, 12 weeks</td>
</tr>
<tr>
<td>Hatzichristou, 2008 [18]</td>
<td>Diabetes</td>
<td>298</td>
<td>Multicenter randomized, double-blind, placebo-controlled, parallel group, fixed dose, 12 weeks</td>
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* BNSRRP: Bilateral nerve sparing radical retropubic prostatectomy  
# 3DCRT: Three-dimentional conformal external-beam radiotherapy
<table>
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<th>Study</th>
<th>IIEF EF domain score</th>
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<td>Saenz de Tejada, 2002 [18]</td>
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<td>Chen, 2004 [3]</td>
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<td>Eardley, 2004 [4]</td>
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<td>McMahon, 2005 [7]</td>
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<td>12.7</td>
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<td>Carrier, 2005 [8]</td>
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<td>Young, 2005 [9]</td>
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<td>Guo, 2006 [10]</td>
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<td>Incrocci, 2006 [20]</td>
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Table 4b: Level 1 studies demonstrating efficacy of tadalafil in men with erectile dysfunction
Senior author, IIEF domain score and GAQ. (Continued)

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<td>19.5</td>
<td>GAQ 2</td>
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<td>Change 4.8</td>
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<td>NA</td>
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<td>NA</td>
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<td>22.1</td>
<td>70</td>
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<td>19.4 # 26.1 *</td>
<td>17.5 # 25.5 *</td>
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Table 4c: Level 1 studies demonstrating efficacy of tadalafil in men with erectile dysfunction Senior author, SEP3 scores. (Continued)

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<td>Yip, 2006 [15]</td>
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NA: non available/non applicable
Ca: circa (about)
# All randomized patients
* Subgroup with evidence of postoperative tumescence
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment emergent adverse events</th>
<th>Dropouts due to adverse events</th>
</tr>
</thead>
</table>
| Padma-Nathan, 2001 [1] | Headache: 2mg(5.7%), 5mg(2.7%), 10mg(16.7%), 25mg(13.9%)  
Dyspepsia: 5mg(8.1%), 10mg(2.8%), 25mg(8.3%)  
Back pain: 2mg(2.9%), 10mg(8.3%), 25mg(2.8%) | 10mg: 2 patients |
| Saenz de Tejada, 2002 [18] | Dyspepsia: 10mg(11%), 20mg(11.1%)  
Headache: 10mg(9.6%), 20mg(8.3%)  
Myalgia: 10mg(5.5%), 20mg(4.2%)  
Flu syndrome: 10mg(4.1), 20mg(4.2%)  
Back pain: 10mg(1.4%), 20mg(5.6%)  
Flushing: 10mg(2.7%), 20mg(4.2%) | NA |
| Porst, 2003 [2] | Headache: 8%, Flushing: 5.7%, Dyspepsia: 5.1%, Myalgia: 3.4% | Placebo: 1 (0.5%)  
Tadalafil: 3 (2%) |
20mg: 1 (1.5%) |
| Montorsi, 2004 [19] | Headache: 20.9%, Dyspepsia: 13.4%, Myalgia: 6.5%, Back pain: 4.5%, Nasal congestion: 4.5%, Fatigue: 3.5%, Flushing: 3.5%, Sinus congestion: 2.5%, Cough: 2%, Gastroesophageal reflex: 2% | Placebo: 2%  
Tadalafil: 5.5% |
Tadalafil: 3% |
| Skoumal, 2004 [5] | Headache: 7.2%, Flushing: 4.6%, Back pain: 2.3%, Influenza: 2% , Nasal congestion: 2% | Placebo: 0 (0%)  
Tadalafil: 1 (0.8%) |
| Seftel, 2004 [6] | Headache: 15.7%, Back pain: 8.8%, Dyspepsia: 7.5% | Placebo: 1 (2.1%)  
Tadalafil: 8 (5%) |
Tadalafil: 4 (4.3%) |
| Young, 2005 [9] | Headache: 5.6-10.6%, Back pain: 6.2-6.8%, Dyspepsia: 3.7-5%, Nasopharyngitis: 3.1-5%, Nasal congestion: 1.9-3.7%, Upper respiratory tract infection: 2.5-3.1%, Myalgia: 1.2-3.1%, Influenza: 1.2-2.5% | Placebo: 0.6%  
Tadalafil: 1.8% |
| Guo, 2006 [10] | Headache: 4.8-5%, Back pain: 0.8-4%, Dizziness: 1.6-2.5%, Dyspepsia: 1.7-2.4%, Chest pain: 0.8-2.5%, Cough: 2.5% | Tadalafil: 4 patients |
Table 4d: Level 1 studies demonstrating efficacy of tadalafil in men with erectile dysfunction. Senior author, Treatment emergent adverse events and dropout rates reported in clinical studies on Tadalafil. (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment emergent adverse events</th>
<th>Dropouts due to adverse events</th>
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</thead>
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<tr>
<td>Porst, 2006 [11]</td>
<td>Dyspepsia: 5mg (5.5%) 10mg (11.4%), Headache: 5mg (6.4%) 10mg(10.5%), Back pain: 5mg(3.7%) 10mg(9.5%), per abdominal pain: 5mg(2.8%) 10mg(8.6%), Myalgia: 5mg(2.8%) 10mg(6.7%)</td>
<td>Tadalafil: 9 patients</td>
</tr>
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<td>Nagao, 2006 [12]</td>
<td>Headache: 5mg(5.9%) 10mg(11.6%) 20mg(18.6%), Nasopharyngitis: 5mg(8.1%) 10mg(3.5%) 20mg(5.8%), Flushing: 5mg(4.7%) 10mg(4.7%) 20mg(5.8%), Hot flush: 10mg(7%) 20mg(3.5%), Back pain: 5mg(3.5%) 10mg(1.2%) 20mg(3.5%), Diarrhea: 5mg(1.2%) 10mg(2.3%) 20mg(2.3%), Dyspepsia: 5mg(1.2%) 10mg(1.2%) 20mg(4.7%), Pyrexia: 10mg(1.2%) 20mg(4.7%), Malaise: 5mg(1.2%) 10mg(3.5%) 20mg(2.3%), Nasal congestion: 5mg(1.2%) 10mg(1.2%) 20mg(3.5%) Abdominal pain: 5mg(1.2%), Contact dermatitis: 5mg(3.5%), Occular hyperaemia: 20mg(3.5%)</td>
<td>Tadalafil: 3-6%</td>
</tr>
<tr>
<td>Yip, 2006 [15]</td>
<td>Headache: 11.3%, Back pain: 7.5%, Dizziness: 3.8%, Dyspepsia: 3.1%, Myalgia: 3.1%</td>
<td>Placebo: 1.2%</td>
</tr>
<tr>
<td>Rajfer, 2007 [16]</td>
<td>Nasopharyngitis: 2.5mg(6.2%) 5mg(6.1%), Influenza: 2.5mg(5.2%) 5mg(3.1%), Gastroenteritis: 2.5mg(3.1%) 5mg(5.2%), Back pain: 2.5mg(5.2%) 5mg(2.1%), Upper respiratory tract infection 2.5mg(3.1%) 5mg(4.1%), Dyspepsia: 2.5mg(4.2%) 5mg(1%), Nasal congestion: 5mg(4.1%), Gastrooesophageal reflux: 2.5mg(3.1%) 5mg(2.1%), Myalgia: 2.5mg(4.2%) 5mg(1%), Headache: 2.5mg(3.1%) 5mg(1%), Hypertension: 2.5mg(1%) 5mg(3.1%), Bronchitis: 2.5mg(3.1%), Sinus congestion: 5mg(3.1%)</td>
<td>Placebo: 2(2.1%) 2.5mg: 6(6.3%) 5mg: 4(4.1%)</td>
</tr>
<tr>
<td>McVary, 2007 [22]</td>
<td>Dyspepsia: 2.2%, Back pain: 2.2%, Headache: 2.2%, Nasopharyngitis: 1.4%, Upper respiratory tract infection: 1.4%</td>
<td>Placebo: 1.4% Tadalafil: 3.6%</td>
</tr>
<tr>
<td>Roerborn, 2008 [23]</td>
<td>Headache: 2.4 – 3.4%, Dyspepsia: 1-3.3%, Back pain: 1.4 – 3.2%, Myalgia: 1.4 – 2.1%, Nasopharyngitis: 3.3 – 2.1%, Diarrhea: 1 _ 1.7%, Gastroesophageal reflux: 1 – 1.5%, Extremity pain: 1.4 – 1.5%, Influenza: 1.9 – 1.3%, Bronchitis: 1.4 – 1.1%, Muscle spasm: 1 – 1.1%</td>
<td>Placebo: 2.4% Tadalafil: 1.9 – 4.8%</td>
</tr>
<tr>
<td>Hatzichristou, 2008 [18]</td>
<td>NA</td>
<td>Placebo: 4% 2.5mg: 4% 5mg: 3.1%</td>
</tr>
</tbody>
</table>

NA: non available/non applicable
Table 4e: Level 1 studies demonstrating efficacy of tadalafil in men with erectile dysfunction

<table>
<thead>
<tr>
<th>Study</th>
<th>Assessment tool</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Padma-Nathan, 2001 [1]</td>
<td>IIEF intercourse satisfaction domain score</td>
<td>Change from baseline: Placebo: 1.3, 2mg: 2.5, 5mg: 3.4, 10mg: 3.2, 20mg: 4.2</td>
</tr>
<tr>
<td></td>
<td>IIEF overall sexual satisfaction domain score</td>
<td>Placebo: 0.3, 2mg: 1.8, 5mg: 2.5, 10mg: 2.5, 20mg: 2.5</td>
</tr>
<tr>
<td>Saenz de Tejada, 2002 [18]</td>
<td>IIEF intercourse satisfaction domain score</td>
<td>Significant improvement for 10, 20mg vs placebo</td>
</tr>
<tr>
<td></td>
<td>IIEF overall sexual satisfaction domain score</td>
<td>Significant improvement for 10, 20mg vs placebo</td>
</tr>
<tr>
<td>Chen, 2004 [3]</td>
<td>IIEF intercourse satisfaction domain score</td>
<td>Change from baseline: Placebo: 1.8, 10mg: 3.6, 20mg: 3.9</td>
</tr>
<tr>
<td></td>
<td>IIEF overall sexual satisfaction domain score</td>
<td>Placebo: 1.7, 10mg: 2.0, 20mg: 2.1</td>
</tr>
<tr>
<td></td>
<td>IIEF overall satisfaction domain score</td>
<td>Placebo: 4%, Tadalafil: 24%</td>
</tr>
<tr>
<td></td>
<td>IIEF overall sexual satisfaction domain score</td>
<td>Placebo: 2.5, Tadalafil: 2.8</td>
</tr>
<tr>
<td></td>
<td>SEP 4 (hardness of erection)</td>
<td>Placebo: 21.4, Tadalafil: 37.2</td>
</tr>
<tr>
<td></td>
<td>SEP 5 (overall satisfaction)</td>
<td>Placebo: 20.5, Tadalafil: 37</td>
</tr>
<tr>
<td></td>
<td>IIEF overall satisfaction domain score</td>
<td>Change from baseline: Placebo: 0.7, Tadalafil: 3.7</td>
</tr>
<tr>
<td>Seftel, 2004 [6]</td>
<td>IIEF intercourse satisfaction domain score</td>
<td>Change from baseline: Placebo: 0.8, Tadalafil: 4</td>
</tr>
<tr>
<td></td>
<td>IIEF overall sexual satisfaction domain score</td>
<td>Placebo: 0.0, Tadalafil: 3.1</td>
</tr>
<tr>
<td></td>
<td>3. SEP 4 (hardness of erection)</td>
<td>Placebo: 5.6, Tadalafil: 43.8</td>
</tr>
<tr>
<td>McMahon, 2005 [7]</td>
<td>IIEF intercourse satisfaction domain score</td>
<td>Change from baseline: Placebo: -0.5, Tadalafil: 2.6</td>
</tr>
<tr>
<td></td>
<td>IIEF overall sexual satisfaction domain score</td>
<td>Placebo: -0.1, Tadalafil: 2.5</td>
</tr>
</tbody>
</table>
Table 4E: Level 1 studies demonstrating efficacy of tadalafil in men with erectile dysfunction Senior author, psychosocial outcomes including satisfaction, quality of life, impact, bother. (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment emergent adverse events</th>
<th>Change from baseline</th>
<th>Dropouts due to adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier, 2005 [8]</td>
<td>IIEF intercourse satisfaction domain score IIEF overall sexual satisfaction domain score</td>
<td>Change from baseline: Placebo: 0.4, 10mg: 2.6, 20mg: 3.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24-hr assigned time</td>
<td>Change from baseline: 24-hr assigned time Placebo: 5.9, 10mg: 29.2, 20mg: 44.7</td>
<td></td>
</tr>
<tr>
<td>Young, 2005 [9]</td>
<td>IIEF intercourse satisfaction domain score IIEF overall sexual satisfaction domain score</td>
<td>Change from baseline: Placebo: 2.1, 10mg: 4.3, 20mg: 4.1</td>
<td></td>
</tr>
<tr>
<td>Guo, 2006 [10]</td>
<td>IIEF intercourse satisfaction domain score IIEF overall sexual satisfaction domain score</td>
<td>Change from baseline: Baseline: 8.4, Tadalafil: 8.2, Placebo: 5.6</td>
<td></td>
</tr>
<tr>
<td>Porst, 2006 [11]</td>
<td>% of patients reporting no ED at end point</td>
<td>Baseline: 8.3, 5mg: 51.5, 10mg: 50.5</td>
<td></td>
</tr>
<tr>
<td>Nagao, 2006 [12]</td>
<td>IIEF intercourse satisfaction domain score IIEF overall sexual satisfaction domain score</td>
<td>Baseline: 8.4, Tadalafil: 8.2, Placebo: 5.6</td>
<td></td>
</tr>
<tr>
<td>McMahon, 2006 [13]</td>
<td>NA</td>
<td>Change from baseline: Placebo: 1.4, 5mg: 3.2, 10mg: 3.2, 20mg: 4.1</td>
<td></td>
</tr>
<tr>
<td>Saylan, 2006 [14]</td>
<td>IIEF intercourse satisfaction domain score IIEF overall sexual satisfaction domain score</td>
<td>Change from baseline: Placebo: 2.3, Tadalafil: 4.8</td>
<td></td>
</tr>
</tbody>
</table>
Table 4e: Level 1 studies demonstrating efficacy of tadalafil in men with erectile dysfunction Senior author, psychosocial outcomes including satisfaction, quality of life, impact, bother. (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment emergent adverse events</th>
<th>Dropouts due to adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rajfer, 2007 [16]</td>
<td>IIEF intercourse satisfaction domain score IIEF overall sexual satisfaction domain score SEP 4 (hardness of erection) SEP 5 (overall satisfaction) PAIRS Sexual self- confidence, change Spontaneity, change</td>
<td>Change from baseline Placebo: 1, 2.5mg: 2.2, 5mg: 2.8 Placebo: 0.9, 2.5mg: 2.1, 5mg: 2.4 Placebo: 11.6, 2.5mg: 33.4, 5mg: 37.2 Placebo: 11.2, 2.5mg: 32.9, 5mg: 36.1 Placebo: 0.2, 2.5mg: 0.6, 5mg: 0.6 Placebo: 0.1, 2.5mg: 0.1, 5mg: 0.1</td>
</tr>
<tr>
<td>McVary, 2007 [22]</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Roerborn, 2008 [23]</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hatzichristou, 2008 [18]</td>
<td>IIEF intercourse satisfaction domain score IIEF overall sexual satisfaction domain score SEP 4 (hardness of erection) SEP 5 (overall satisfaction)</td>
<td>Change from baseline Placebo:0.7, 2.5mg:2, 5mg: 1.6 Placebo: 0.5, 2.5mg: 1.8, 5mg: 1.9 Placebo: 10, 2.5mg: 24.5, 5mg: 26.1 Placebo: 9.8, 2.5mg: 23.3, 5mg: 25.6</td>
</tr>
</tbody>
</table>

NA: non available/non applicable
Safety and tolerability of tadalafil


3. VARDENAFIL

A comprehensive review of the literature has identified a number of publications which attest to the efficacy, tolerability and safety of vardenafil in...
men with erectile dysfunction. The salient features of the level 1 publications have been tabulated in Tables 5a-5e, which outline the trial design, the patients randomized, the efficacy outcomes and the side effect profiles of vardenafil in those studies.

For assessment of efficacy we have not included pooled studies or analyses of pooled studies, and we have attempted to ensure that no dataset is reported more than once.

For assessment of safety and tolerability, we have included pooled analyses in an attempt to identify relatively infrequent tolerability or safety issues.

b) Efficacy in the Broad Population of Men with Erectile Dysfunction

Overall we can recommend that there is clear evidence that vardenafil is efficacious in the treatment of erectile dysfunction in the broad population at doses of 10mg and 20mg taken in an on demand fashion. There are multiple level 1 studies with consistent outcomes [1-12]. The overall grade of recommendation is grade A.

References

Efficacy in the Broad Population


Diabetes

### Table 5a: Level 1 studies demonstrating efficacy of vardenafil in men with erectile dysfunction

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient group</th>
<th>Patient numbers</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porst, 2001 [1]</td>
<td>Broad population</td>
<td>601 randomized&lt;br&gt;580 included in ITT analysis&lt;br&gt;506 included in efficacy analysis&lt;br&gt;590 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, 4-arm, parallel group, fixed dose, 12 weeks</td>
</tr>
<tr>
<td>Hellstrom, 2002 [2]</td>
<td>Broad population</td>
<td>805 randomized&lt;br&gt;749 included in ITT analysis&lt;br&gt;762 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, 4-arm, parallel group, fixed dose, 26 weeks</td>
</tr>
<tr>
<td>Goldstein, 2003 [13]</td>
<td>Diabetes</td>
<td>452 randomized&lt;br&gt;430 included in ITT analysis&lt;br&gt;439 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, 3-arm, parallel group, fixed dose, 12 weeks</td>
</tr>
<tr>
<td>Brock, 2003 [16]</td>
<td>Radical prostatectomy</td>
<td>440 randomized&lt;br&gt;423 included in ITT analysis&lt;br&gt;427 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, 3-arm, parallel group, fixed dose, 12 weeks</td>
</tr>
<tr>
<td>Nagao, 2004 [4]</td>
<td>Broad population</td>
<td>283 randomized&lt;br&gt;279 included in ITT analysis&lt;br&gt;280 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, 4-arm, parallel group, fixed dose, 12 weeks</td>
</tr>
<tr>
<td>Hatzichristou, 2004 [3]</td>
<td>Broad population</td>
<td>323 randomized&lt;br&gt;309 included in ITT analysis&lt;br&gt;321 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, flexible dose, 12 weeks</td>
</tr>
<tr>
<td>Carson, 2004 [17]</td>
<td>Broad population Sildenafil non-responders</td>
<td>463 randomized&lt;br&gt;454 included in ITT analysis&lt;br&gt;457 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, flexible dose, 12 weeks</td>
</tr>
<tr>
<td>Stief, 2004 [5]</td>
<td>Broad population</td>
<td>1020 randomized&lt;br&gt;566 included in ITT analysis&lt;br&gt;566 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, double dummy, 2-arm, parallel group, fixed dose, 2 years</td>
</tr>
</tbody>
</table>
Table 5a: Level 1 studies demonstrating efficacy of vardenafil in men with erectile dysfunction Senior author, patient group, number of patients randomized and study design. (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient group</th>
<th>Patient numbers</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher, 2005 [6]</td>
<td>Broad population of men with ED and female partners</td>
<td>229 randomized 225 included in ITT analysis 227 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, flexible dose, 12 weeks</td>
</tr>
<tr>
<td>Van Ahlen, 2005 [18]</td>
<td>Arterial hypertension</td>
<td>388 randomized 354 included in ITT analysis 388 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, flexible dose, 12 weeks</td>
</tr>
<tr>
<td>Edwards, 2006 [7]</td>
<td>Broad population Sildenafil naïve patients</td>
<td>260 randomized 254 included in ITT analysis 259 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, flexible dose, 12 weeks</td>
</tr>
<tr>
<td>Giuliano, 2006 [19]</td>
<td>Spinal cord injury</td>
<td>418 randomized 394 included in ITT analysis 401 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, flexible dose, 12 weeks</td>
</tr>
<tr>
<td>Ishi, 2006 [14]</td>
<td>Diabetes</td>
<td>790 randomized 778 included in ITT analysis 778 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, 3-arm parallel group, fixed dose, 12 weeks</td>
</tr>
<tr>
<td>Ziegler, 2006 [15]</td>
<td>Diabetes type 1</td>
<td>318 randomized 302 included in ITT analysis 318 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, flexible dose, 12 weeks</td>
</tr>
<tr>
<td>Rosen, 2006 [20]</td>
<td>Depression</td>
<td>280 randomized 259 included in ITT analysis 265 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, flexible dose, 12 weeks</td>
</tr>
<tr>
<td>Chen, 2007 [8]</td>
<td>Broad population</td>
<td>306 randomized 306 included in ITT analysis 306 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel group, fixed dose, 12 weeks</td>
</tr>
<tr>
<td>Ralph, 2007 [10]</td>
<td>Broad population</td>
<td>611 randomized 584 included in ITT analysis 605 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, flexible dose, 26 weeks</td>
</tr>
<tr>
<td>Martin Morales, 2007 [9]</td>
<td>Broad population</td>
<td>129 randomized 121 included in ITT analysis 125 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, flexible dose, 12 weeks</td>
</tr>
<tr>
<td>Tan, 2008 [11]</td>
<td>Broad population</td>
<td>358 randomized 334 included in ITT analysis 348 included in safety analysis</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel group, fixed dose, 12 weeks</td>
</tr>
</tbody>
</table>
Table 5a: Level 1 studies demonstrating efficacy of vardenafil in men with erectile dysfunction Senior author, patient group, number of patients randomized and study design. (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient group</th>
<th>Patient numbers</th>
<th>Study design</th>
</tr>
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<tbody>
<tr>
<td>Miner, 2008 [21]</td>
<td>Dyslipidemia</td>
<td>395 randomized</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel group, flexible dose, 12 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>386 included in ITT analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>395 included in safety analysis</td>
<td></td>
</tr>
<tr>
<td>Rosenberg, 2009 [12]</td>
<td>Broad population</td>
<td>201 randomized</td>
<td>Multicenter, randomized, double-blind, placebo-controlled, crossover, fixed dose, 2 treatment phases (4 weeks each)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>191 included in ITT analysis</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>191 included in safety analysis</td>
<td></td>
</tr>
</tbody>
</table>

ITT: Intend To Treat

Table 5b: Level 1 studies demonstrating efficacy of vardenafil in men with erectile dysfunction Senior author, IIEF domain score and GAQ

<table>
<thead>
<tr>
<th>Study</th>
<th>IIEF EF domain score</th>
<th>GAQ</th>
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<td>Placebo</td>
<td>5mg</td>
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<tr>
<td></td>
<td>Baseline</td>
<td>End</td>
</tr>
<tr>
<td>Porst, 2001 [1]</td>
<td>14</td>
<td>15.6</td>
</tr>
<tr>
<td>Hellstrom, 2002 [2]</td>
<td>13.6</td>
<td>14.8</td>
</tr>
<tr>
<td>Van Ahlen, 2005 [18]</td>
<td>NA</td>
<td>18.1</td>
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<tr>
<td>Ishi, 2006 [14]</td>
<td>13.6</td>
<td>15.72</td>
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<tr>
<td>Chen, 2007 [8]</td>
<td>13.3</td>
<td>15.9</td>
</tr>
<tr>
<td>Ralph, 2007 [10]</td>
<td>9.5</td>
<td>11.4</td>
</tr>
<tr>
<td>Martin Morales, 2007 [9]</td>
<td>15.6</td>
<td>17.3</td>
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NA: non available/non applicable
Table 5c: Level 1 studies demonstrating efficacy of vardenafil in men with erectile dysfunction Senior author, intercourse success

<table>
<thead>
<tr>
<th>Study</th>
<th>SEP3</th>
<th>Placebo</th>
<th>5mg</th>
<th>10mg</th>
<th>20mg</th>
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<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>End</td>
<td>Baseline</td>
<td>End</td>
</tr>
<tr>
<td>Porst, 2001 [1]</td>
<td>23.7</td>
<td>39.5</td>
<td>28.9</td>
<td>71.1</td>
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<tr>
<td>Hellstrom, 2002 [2]</td>
<td>14.8</td>
<td>32.7</td>
<td>14</td>
<td>51.7</td>
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<td>Brock, 2003 [16]</td>
<td>6</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
<td>7</td>
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<tr>
<td>Nagao, 2004 [4]</td>
<td>9</td>
<td>33.4</td>
<td>13.1</td>
<td>63.5</td>
<td>7.8</td>
</tr>
<tr>
<td>Carson, 2004 [17]</td>
<td>12.4</td>
<td>19.9</td>
<td></td>
<td></td>
<td>Baseline: 10.5</td>
</tr>
<tr>
<td>Stief, 2004 [5]</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>15.9</td>
</tr>
<tr>
<td>Van Ahlen, 2005 [18]</td>
<td>18</td>
<td>35</td>
<td></td>
<td></td>
<td>Baseline: 18</td>
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<td>Ishi, 2006 [14]</td>
<td>NA*</td>
<td>NA*</td>
<td>NA</td>
<td>NA</td>
<td>NA*</td>
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<tr>
<td>Chen, 2007 [8]</td>
<td>7.2</td>
<td>22.9</td>
<td>NA</td>
<td>NA</td>
<td>7.7</td>
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<tr>
<td>Ralph, 2007 [10]</td>
<td>NA</td>
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<td>Baseline: NA</td>
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<tr>
<td>Miner, 2008 [21]</td>
<td>15.93</td>
<td>33.83</td>
<td></td>
<td></td>
<td>Baseline: 17.95</td>
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<tr>
<td>Rosenberg, 2009 [12]</td>
<td>16.7</td>
<td>38.54</td>
<td>NA</td>
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NA: non available/non applicable
NA*: data presented only in graphs with no specific values presented
Table 5d: Level 1 studies demonstrating efficacy of vardenafil in men with erectile dysfunction Senior author, treatment emergent adverse events, dropouts due to adverse events

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment emergent adverse events</th>
<th>Dropouts due to adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porst, 2001 [1]</td>
<td>Headache: 6.8-15.3%, Flushing: 10.2-11.3%, Dyspepsia: 0.7-6.7%, Rhinitis: 2.8-7.3%</td>
<td>Placebo: 2 (1.3%) 5mg: 7 (4.8%) 10mg: 2 (1.4%) 20mg: 1 (0.7%)</td>
</tr>
<tr>
<td>Hellstrom, 2002 [2]</td>
<td>Headache: 10-22%, Rhinitis: 9-17%, Flushing: 5-13%, Dyspepsia: 1-6%, Sinusitis: 3-5%, Accidental injury: 4-6%, Flu syndrome: 2-5%</td>
<td>Placebo: 4 (2.2%) 5mg: 8 (4.1%) 10mg: 7 (3.5%) 20mg: 15 (8%)</td>
</tr>
<tr>
<td>Brock, 2003 [16]</td>
<td>Headache: 16-22%, Flushing: 19-21%, Rhinitis: 16-20%, Sinusitis: 6-7%, Dyspepsia: 4-5%, Nausea: 1-5%</td>
<td>Placebo: 1 (0.7%) 10mg: 5 (3.6%) 20mg: 5 (3.4%)</td>
</tr>
<tr>
<td>Nagao, 2004 [4]</td>
<td>Flushing: 21-36%, Headache: 7-12%, Rhinitis: 4-9%, Palpitation: 3-5%, Dyspepsia: 0-3%</td>
<td>Placebo: 4 (6%) 5mg: 2 (3%) 10mg: 2 (3%) 20mg: 3 (4%)</td>
</tr>
<tr>
<td>Hatzichristou, 2004 [3]</td>
<td>Flushing: 11%, Headache: 10%, Rhinitis: 5%, Dyspepsia: 3%, Dizziness: 2%</td>
<td>Placebo: 3 (2%) Vardenafil: 5 (3%)</td>
</tr>
<tr>
<td>Carson, 2004 [17]</td>
<td>Flushing: 6.9%, Headache: 6.9%, Nasal congestion: 5.6%</td>
<td>Placebo: 3 (0.7%) Vardenafil: 5 (1.1%)</td>
</tr>
<tr>
<td>Stief, 2004 [5]</td>
<td>Headache: 16% (10mg), 20% (20mg), Flushing: 14% (10mg), 20% (20mg), Rhinitis: 10% (10mg), 14% (20mg), Nausea: 2% (10mg), 2% (20mg), Dyspepsia: 4% (10mg), 9% (20mg), Sinusitis: 1% (10mg), 2% (20mg), Conjunctivitis: 2% (10mg), 1% (20mg)</td>
<td>10mg: 5 (1.8%) 20mg: 6 (2%)</td>
</tr>
<tr>
<td>Fisher, 2005 [6]</td>
<td>Flushing: 11%, Nasal congestion: 8%, Headache: 4%, Dyspepsia: 4%</td>
<td>Placebo: 0 (0%) Vardenafil: 1 (0.9%)</td>
</tr>
<tr>
<td>Van Ahlen, 2005 [18]</td>
<td>Flushing: 7.3%, Headache: 5.2%, Influenza:14%</td>
<td>Placebo: 2 (1%) Vardenafil: 4 (2.1%)</td>
</tr>
<tr>
<td>Edwards, 2006 [7]</td>
<td>Headache: 3.1%, Flushing: 1.6%</td>
<td>Placebo: 2 (1.5%) Vardenafil: 3 (1.5%)</td>
</tr>
</tbody>
</table>
Table 5d: Level 1 studies demonstrating efficacy of vardenafil in men with erectile dysfunction Senior author, treatment emergent adverse events, dropouts due to adverse events. (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment emergent adverse events</th>
<th>Dropouts due to adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giuliano, 2006 [19]</td>
<td>Headache: 15%, Flushing: 6%, Nasal congestion: 5%, Dyspepsia: 4%, Dizziness: 2%</td>
<td>Placebo: 2 (0.9%) Vardenafil: 4 (1.9%)</td>
</tr>
<tr>
<td>Ishi, 2006 [14]</td>
<td>Headache: 4% (10mg), 6% (20mg), Flushing: 9% (10mg), 13% (20mg), Nasal congestion: 3% (10mg), 2% (20mg), Nasopharyngitis: 9% (10mg), 5% (20mg), Palpitations: 4% (10mg), 2% (20mg)</td>
<td>Placebo: 1% Vardenafil 10mg: 1% Vardenafil 20mg: 2%</td>
</tr>
<tr>
<td>Ziegler, 2006 [15]</td>
<td>Headache: 3%, Flushing: 2.5%, Bronchitis: 1.8%, Nasopharyngitis: 1.2%</td>
<td>Placebo: 2 (1.3%) Vardenafil: 3 (1.8%)</td>
</tr>
<tr>
<td>Chen, 2007 [8]</td>
<td>Vasodilatation: 25.8%, Rhinitis: 11.6%, Headache: 9.7%, Pharyngitis: 4.5%, Palpitation: 3.9%</td>
<td>Placebo: 2 (1.3%) Vardenafil: 2 (1.3%)</td>
</tr>
<tr>
<td>Ralph, 2007 [10]</td>
<td>Headache: 17.4%, Flushing: 2%, Dyspepsia: 2%, Nasal congestion: 0.7%</td>
<td>Placebo: 2 (1.3%) Vardenafil: 5 (1.1%)</td>
</tr>
<tr>
<td>Tan, 2008 [11]</td>
<td>Headache: 7.2%, Flushing: 6.2%, Nasal congestion: 3.37%, Gastrointestinal disorders: 2.5%, Musculoskeletal disorders: 3.6%, Dizziness: 2.2%</td>
<td>Placebo: 0 (0%) Vardenafil: 6 (2.2%)</td>
</tr>
<tr>
<td>Rosenberg, 2009 [12]</td>
<td>Flushing: 5%, Headache: 3%, Nasal congestion: 2%</td>
<td>Placebo: 0 (0%) Vardenafil: 1 (0.5%)</td>
</tr>
</tbody>
</table>

NA: non available
Table 5: Level 1 studies demonstrating efficacy of vardenafil in men with erectile dysfunction
Senior author, psychosocial outcomes including satisfaction, quality of life, impact, bother

<table>
<thead>
<tr>
<th>Study</th>
<th>Assessment tool</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porst, 2001 [1]</td>
<td>Fugl-Meyer QoL questionnaire (question on sexual life satisfaction, scale 1-6)</td>
<td>Improvement in sexual life satisfaction from baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo: 0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5mg: 1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10mg: 1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20mg: 1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo: 2.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5mg: 3.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10mg: 4.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20mg: 4.33</td>
</tr>
<tr>
<td>Donatucci, 2004 [27]</td>
<td>1. ‘Were you satisfied with the hardness of your erection?’ 2. ‘Were you satisfied overall with this sexual experience?’ 3. Fugl-Meyer QoL questionnaire (question on sexual life satisfaction, scale 1-6)</td>
<td>1. Placebo: 18%, 5mg: 38%, 10mg: 52%, 20mg: 58%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Placebo: 23%, 5mg: 45%, 10mg: 58%, 20mg: 62%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Placebo: 2.9, 5mg: 3.5, 10mg: 3.9, 20mg: 4.1</td>
</tr>
<tr>
<td>Stief, 2004 [5]</td>
<td>1. Fugl-Meyer Life Satisfaction Checklist</td>
<td>1. Improvement from baseline in the score for ‘sexual life’: 2.2 (10mg), 2.2 (20mg)</td>
</tr>
<tr>
<td></td>
<td>2. Center for Epidemiologic Studies Depression (CESD) scale</td>
<td>Improvement from baseline in the score for ‘sexual satisfaction’: 2.3 (10mg), 2.4 (20mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. -2.4 (10mg), -0.9 (20mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo: 32 Vardenafil: 66 (partners)</td>
</tr>
<tr>
<td>Study</td>
<td>Assessment tool</td>
<td>Results</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Hatzichristou, 2005 [38] | 1. ‘Were you satisfied with the hardness of your erection?’
2. ‘Were you satisfied overall with this sexual experience?’
3. Global Confidence question (*To what extent did your level of sexual functioning affect your self-confidence?’*)
4. Center for Epidemiologic Studies Depression (CES-D) scale | 1. Placebo: 23%, Vardenafil: 63%
2. Placebo: 28%, Vardenafil: 65%
3. Placebo: 17%, Vardenafil: 50% (moderately or significantly increased)
4. Overall change: 0.2 (placebo), -2 (vardenafil)
Change in patients with depression (CESD≥16): 1.2 (placebo), -8.1 (vardenafil) |
| Nehra, 2005 [3]  | 1. IIEF intercourse satisfaction domain score
2. IIEF orgasmic function domain score
3. IIEF overall sexual satisfaction domain score
4. Satisfaction with hardness of erection | Change from baseline:
1. Placebo: -0.1, 10mg: 2.3, 20mg: 2.2
2. Placebo: -0.1, 10mg: 1.5, 20mg: 1.1
3. Placebo: 0.1, 10mg: 1.9, 20mg: 1.7
4. Placebo: 7.5, 10mg: 26.9, 20mg: 22.5 |
| Edwards, 2006 [7] | Treatment Satisfaction Scale (TSS) – 6 domains                                                                 | Change from baseline:
1. Satisfaction with orgasm: -1 (placebo), 31 (vardenafil)
2. Ease with erection: 2.5 (placebo), 28.5 (vardenafil)
3. Confidence: 0.4 (placebo), 32.4 (vardenafil)
4. Pleasure: 2.7 (placebo), 26.4 (vardenafil)
5. Erectile function satisfaction: 3.7 (placebo), 41.4 (vardenafil)
6. Satisfaction with medication: 24.3 (placebo), 59.8 (vardenafil) |
2. Satisfaction with sexual experience
3. Hamilton Depression (HAM-D) score
4. Center for Epidemiologic Studies Depression (CES-D) scale
5. Rosenberg self-esteem scale | 1. Placebo: 25%, Vardenafil: 55.2%
2. Placebo: 27.5%, Vardenafil: 60%
3. Placebo: 10.1, Vardenafil: 7.9
4. Overall change: -6.8 (placebo), -8.4 (vardenafil)
5. Overall change: 3 (placebo), 2.7 (vardenafil) |
Table 5e: Level 1 studies demonstrating efficacy of vardenafil in men with erectile dysfunction
Senior author, psychosocial outcomes including satisfaction, quality of life, impact, bother. (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Assessment tool</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosen, 2007 [58]</td>
<td>Treatment Satisfaction Scale (TSS) – 6 domains</td>
<td>1. Satisfaction with orgasm: 27.82 (placebo), 60.81 (vardenafil)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Ease with erection: 35.01 (placebo), 61.18 (vardenafil)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Confidence: 26.01 (placebo), 59.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Pleasure: 38.08 (placebo), 65.2 (vardenafil)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Erectile function satisfaction: 10.48 (placebo), 53.17 (vardenafil)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Satisfaction with medication: 9.16 (placebo), 53.84 (vardenafil)</td>
</tr>
<tr>
<td>Ralph, 2007 [10]</td>
<td>1. IIEF overall satisfaction</td>
<td>1. 4.7 (placebo), 7.6 (vardenafil)</td>
</tr>
<tr>
<td></td>
<td>2. ED-EqoL</td>
<td>2. 24.8 (placebo), 22.1 (vardenafil)</td>
</tr>
<tr>
<td></td>
<td>3. Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) – patient</td>
<td>3. 34.08 (placebo), 74.07 (vardenafil)</td>
</tr>
<tr>
<td></td>
<td>4. EDITS – partner</td>
<td>4. 28.71 (placebo), 70.16 (vardenafil)</td>
</tr>
<tr>
<td></td>
<td>5. Center for Epidemiologic Studies Depression (CES-D) scale</td>
<td>5. 12.5 (placebo), 10.1 (vardenafil)</td>
</tr>
<tr>
<td>Martin Morales, 2007 [9]</td>
<td>1. Rosenberg self-esteem scale</td>
<td>Change from baseline:</td>
</tr>
<tr>
<td></td>
<td>2. Johnson-McCoy self confidence score (attitudes and belief domain)</td>
<td>1. 3.54 (placebo), -1.51 (vardenafil)</td>
</tr>
<tr>
<td></td>
<td>3. Medical Outcome Short Form (SF-36)</td>
<td>2. 1.12 (placebo), 0.08 (vardenafil)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. 18.17 (placebo), 18.58 (vardenafil)</td>
</tr>
<tr>
<td>Giuliano, 2008 [63]</td>
<td>1. Global Confidence Question</td>
<td>1. Change from baseline: 0.3 (placebo), 1 (vardenafil)</td>
</tr>
<tr>
<td></td>
<td>2. Center for Epidemiologic Studies Depression (CES-D) scale</td>
<td>2. 9.4 (placebo), 9.7 (vardenafil)</td>
</tr>
<tr>
<td></td>
<td>3. Rosenberg self-esteem scale</td>
<td>3. 33 (placebo), 33.3 (vardenafil)</td>
</tr>
<tr>
<td></td>
<td>4. Psychosocial General Well Being Index (PGWBI)</td>
<td>4. Change from baseline: -0.8 (placebo), 3.3 (vardenafil)</td>
</tr>
<tr>
<td></td>
<td>5. Mental Health Domain of SF-36</td>
<td>5. 78.2 (placebo), 79.2 (vardenafil)</td>
</tr>
</tbody>
</table>
Radical prostatectomy


Sildenafil non-responders


Hypertension


Spinal cord injury


Depression


Dyslipidaemia


Safety and tolerability


erection dysfunction following nerve sparing radical prosta-

[44] Brison TE, Broderick GA, Thiel DD, Heckman MG, Pinkstaff DM. Vardenafil rescue rates of sildenafil nonre-
sponlers: objective assessment of 327 patients with erec-

[45] Thadani U, Smith W, Nash S, Bittar N, Glasser S, Na-
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selective phosphodiesterase-5 inhibitor for the treat-
ment of erectile dysfunction, on the cardiovascular response to
exercise in patients with coronary artery disease. J Am Coll

on endothelial function of brachial and cavernous arteries.

[47] Mazo EB, Gamidov SI, Iremashvili VV. Does the clinical
efficacy of vardenafil correlate with its ef-
efect on the endothelial function of cavernosal ar-

and safety of vardenafil in renal transplant recipients with

[49] Porst H, Sharlip ID, Hatzichristou D, Rubio-Aurioles E,
Khelifa C et al. Relationship between vascular damage degrees
and endothelial progenitor cells in patients with erectile
dysfunction following nerve sparing radical prostate-

[50] Valiquette L, Montorsi F, Auerbach S. First-dose success with
vardenafil in men with erectile dysfunction and associated

[51] McMahon C, Lording D, Stuckey B, Tan V, Gillman M,
Valiquette L, Montorsi F, Auerbach S. Vardenafil restores erectile

and safety of vardenafil in renal transplant recipients with

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treatment of erectile dysfunction-results from 30,010 U.S.

Landen H. The real-life safety and efficacy of vardenafil: an
international post-marketing surveillance study of 2824 pa-

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zi C et al. Relationship between vascular damage degrees
and endothelial progenitor cells in patients with erectile
dysfunction: effect of vardenafil administration and PDE5
expression in the bone marrow. Eur Urol 2007;51:1411-7; dis-
cussion 7-9.

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safety of vardenafil among patients with erectile dysfunction

[57] Padma-Nathan H, Montorsi F, Giuliano F, Meuleman E,
Auerbach S, Eardley I et al. Vardenafil restores erectile
function to normal range in men with erectile dysfunction.

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Velty LG. Efficacy of vardenafil for the treatment of erectile
dysfunction in men with hypertension: a meta-analysis of

T. The COUPLES-project: a pooled analysis of patient
and partner treatment satisfaction scale (TSS) outcomes

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on-demand vardenafil in men with mild-to-moderate erec-
tile dysfunction: findings of the RESTORE study. Eur Urol
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[61] Mitsonou CI, Mitropoulos PA, Dimopoulos NA, Karazicou
EG, Psarra VV, Tsakiris FE et al. Vardenafil in the treat-
mence of erectile dysfunction in outpatients with chronic
schizophrenia: a flexible-dose, open-label study. J Clin

[62] Ng CF, Wong A, Cheng CW, Chan ES, Wong HM,
Hou SM. Effect of vardenafil on blood pressure profile of
patients with erectile dysfunction concomitantly treated with
doxazosin gastrointestinal therapeutic system for benign

ED, Finkbeiner AE et al. Vardenafil improves ejaculation
success rates and self-confidence in men with erectile

II. NEWER PDE5 INHIBITORS

1. UDENAFIL

Udenafil is a new PDE5 inhibitor currently available in
Korea, Russia and Saudi Arabia. The time to reach maximum concentration (Tmax) is 0.76 – 1.25
hours while the plasma elimination half-life (T1/2) is
9.88 – 12.13 hours (100 and 200 mg, single dose
study) [1]. During multiple dosing, a steady state was
reached at 5 days and little accumulation occurred after repeated dosing for 7 days. Preclinical studies
revealed that udenafil’s PDE5 selectivity is similar to
sildenafil [2].

A phase III study evaluated the efficacy and safety of oral udenafil in ED patients in Korea (level of
evidence: 1) [3]. This was a randomized, double-
blind, parallel-group, placebo-controlled, fixed-dose,
multicentre trial. 167 men with ED of broad aetiology
and severity received udenafil 100 mg (mean age:
53.6 years), 200 mg (mean age: 54.6 years), or
placebo (mean age: 55.7 years), for 12 weeks. More
than 70% of patients had previous PDE5 inhibitor
experience before entering the study. Results are
shown in Table 6: The safety analysis of udenafil
included 164 patients. The most common adverse
events were facial flushing (10.5-23.2%), nasal
congestion (3.5-7.1%), ocular hyperemia (3.5-7.1%) and
headache (1.8-8.9%). Most adverse events were
mild or moderate in severity and no serious adverse
events were reported. Only 2 patients (both in the
udenafil 200 mg group), withdrew from the study due
to adverse events (one for flushing and headache
and one for chest pain).

At the time of writing, much of the data relating to
udenafil is available in abstract form only. One study
investigating the duration of action of udenafil dem-
onstrated efficacy up to 12 hours post dosing [4]
while another Phase 3 study investigated the efficacy in men with diabetes [5]. The change from baseline to endpoint in IIEF-EF domain scores was 7 for udenafil 100 mg and 8.21 for udenafil 200 mg compared with 1.2 for placebo (p < 0.0001). The mean SEP3 rates were 53.13% (100 mg), 63% (200 mg) and 22.6% (placebo, p < 0.0001). Overall, improved erections (GAQ) were reported by 65.5% (100 mg), 83.9% (200 mg) and 30.9% (placebo, p < 0.0001).

The most frequently reported adverse events were flushing and headache, and all were mild. Finally, a third study assessed the efficacy and safety of udenafil 50 mg taken once daily [6]. After 12 weeks of treatment, the IIEF-EF domain score increased significantly (p<0.001) in the udenafil group compared to placebo (12.93 vs 1.57).

### 2. MIRODENAFIL

Mirodenafil is a new PDE5 inhibitor already available in Korea (approved in November 2007). The time to reach maximum concentration (Tmax) is 1.25 hours while the plasma elimination half-life (T1/2) is 2.5 hours. Preclinical studies suggest that mirodenafil’s selectivity toward PDE5 is 10-fold higher than that of sildenafil, whereas its inhibitory effects on other PDEs are much lower than those of sildenafil [7-9].

Preliminary results from a phase II clinical study provided evidence for the efficacy and safety of mirodenafil (level of evidence: 1) [10]. The optimal doses in terms of efficacy and safety were determined from this study to be 50 mg and 100 mg. A 12 week phase III, randomized, double-blind, parallel-group, placebo-controlled, fixed-dose, multicentre clinical trial was conducted at fifteen sites in Korea to evaluate the efficacy and safety of the drug (level of evidence: 1) [11]. 223 men were randomized. About half of these patients were not treatment naive to PDE5 inhibitors. Results are shown in Table 7.

The safety analysis of mirodenafil included all 223 patients. The most common adverse events were facial flushing (9.46-16.22%), headache (8.1-10.81%), nausea (2.7-4.05%) and eye redness (2.7-4.05%). Most adverse events were mild, resolving spontaneously by the end of treatment. Only 4 patients (all from mirodenafil 50 mg group), withdrew from the study because of mild to moderate

### Table 6: Efficacy of udenafil [3]

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Udenafil 100mg</th>
<th>Udenafil 200mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF domain score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.93</td>
<td>14.68</td>
<td>14.26</td>
</tr>
<tr>
<td>End of Trial</td>
<td>13.13</td>
<td>22.2</td>
<td>24.19</td>
</tr>
<tr>
<td>SEP3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.67</td>
<td>17.14</td>
<td>9.26</td>
</tr>
<tr>
<td>End of Trial</td>
<td>15.44</td>
<td>70.08</td>
<td>75.7</td>
</tr>
<tr>
<td>GAQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of Trial</td>
<td>25.9%</td>
<td>81.5%</td>
<td>88.5%</td>
</tr>
</tbody>
</table>

### Table 7: Efficacy of mirodenafil [11]

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Mirodenafil 50mg</th>
<th>Mirodenafil 100mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF domain score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>13.6</td>
<td>14.5</td>
<td>14</td>
</tr>
<tr>
<td>End of Trial</td>
<td>17.0</td>
<td>22.1</td>
<td>25.6</td>
</tr>
<tr>
<td>SEP3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.59</td>
<td>8.63</td>
<td>5.87</td>
</tr>
<tr>
<td>End of Trial</td>
<td>26.77</td>
<td>52.83</td>
<td>73.2</td>
</tr>
<tr>
<td>GAQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of Trial</td>
<td>31.51%</td>
<td>66.67%</td>
<td>89.04%</td>
</tr>
<tr>
<td>Life satisfaction checklist</td>
<td>Change from baseline</td>
<td>1.61</td>
<td>3.41 (NS compared to placebo)</td>
</tr>
</tbody>
</table>
No alterations of color vision and no clinically significant changes in laboratory values, electrocardiographic findings, or vital signs were reported.

Recently, the results in men with ED secondary to diabetes were reported in abstract form. This was a double-blind, fixed dose, controlled trial [12]. The IIEF-EF domain score changes from baseline were significantly higher for mirodenail compared to placebo (9.31 vs 1.37, p<0.0001). SEP3 success rates increased significantly after mirodenail treatment compared to placebo (68.99% vs 22.25%). A positive response to the General Assessment Question (GAQ) reported by 76.92% of patients in the mirodenail group. Most treatment-emergent adverse events were of mild intensity, recovering spontaneously.

3. LODENAFIL CARBONATE

Lodenail carbonate is another new PDE5 inhibitor under development in Brazil. It is a dimer formed by two lodenail molecules linked by a carbonate bridge. After ingestion, the bridge is broken delivering the active compound lodenail. Lodenail carbonate has been shown to be more potent as an inhibitor of cGMP hydrolysis in PDE extracts than lodenail and sildenafil [13]. The time to reach maximum concentration (Tmax) was 1.2 hours while the plasma elimination half-life (T1/2) was 2.4 hours.

Recently, a phase II clinical trial has been completed in Brasil (level of evidence: 2) [14]. This was a randomized, double-blind, placebo-controlled, parallel group, multicentre trial. 72 men with ED of various aetiologies and an IIEF –EF domain score between 7 and 24 were randomized to receive placebo, 20, 40 or 80mg of lodenail for 4 weeks. Results are shown in Table 8. for the EF domain score and SEP3 only lodenail 80mg was superior to placebo (p=0.007) but the treatment groups were not homogeneous regarding basal IIEF-EF scores.

Lodenail was well tolerated. Adverse reactions were mild and self-limited and included headache (15-22.2%), dyspepsia (5-22.2%), rhinitis (5-11.1%), flushing (5-5.9%) and color visual disorders (0-5.9%). The drop-out rate was about 5%. However, no details are provided on adverse events that resulted in discontinuation in the different treatment groups. These preliminary findings suggest that lodenail is an efficacious and well tolerated treatment but remains to be confirmed from a phase III clinical trial.

4. AVANAFIL

Avanail is a pyrimidine derivative synthesized as a PDE5 inhibitor [15]. It is rapidly absorbed (Tmax approximately 35 minutes) and has a short plasma elimination half-life (T1/2) of < 1.5 hours without any significant accumulation of the drug with either once or twice daily administration [16]. It is a strong (50% inhibitory concentration [IC50] = 5.2 nmol/L) and highly selective inhibitor of PDE5. Avanail showed higher selectivity (120-fold) against PDE6 than sildenafil (16-fold) and vardenail (21-fold).

Data relating to avanail is currently only available in abstract form. A 12 week phase II, randomized, double-blind, placebo-controlled, parallel group, multicentre, study explored the efficacy and tolerability of avanail at doses of 50, 100, 200 or 300 mg, taken 30 minutes before initiation of sexual activity [17]. 284 men aged 32–70 years were enrolled. The majority (87%) of the subjects had used PDE5 inhibitors experience before entering the study. After 12 weeks, the IIEF-EF domain scores were 16, 19.9, 21.3, 22 and 22.7 for the placebo, avanail 50 mg, 100 mg, 200 mg and 300 mg group, respectively (p<0.001 vs placebo for all avanail groups). SEP3 success rates were 28%, 53.9%, 58.6%, 62.1% and 64.3% for the placebo, avanail 50 mg, 100 mg, 200 mg and 300 mg group, respectively (p<0.001 vs placebo for all avanail groups). The most common adverse event was headache.

Further studies, again only available in abstract form, have explored the efficacy and safety of avanail compared to both placebo and sildenafil 50 mg using a rigiscan methodology [18] and the haemodynamic effects of co-administration of avanail and glyceryl trinitrate (NTG) [19]. Currently, phase III clinical trials are running to assess efficacy and safety of avanail in general ED population and diabetic men with ED. The results are expected in early 2010.

Table 8: Efficacy of Lodenail [14]

<table>
<thead>
<tr>
<th>EF domain score</th>
<th>Placebo</th>
<th>Lodenail</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20mg</td>
</tr>
<tr>
<td>Baseline</td>
<td>11.9</td>
<td>15.8</td>
</tr>
<tr>
<td>End of Trial</td>
<td>12.6</td>
<td>18.9</td>
</tr>
</tbody>
</table>

| SEP3            |         |          |          |
|-----------------|---------|----------|
| Baseline        | 23.3    | 32.3     | 39.7     | 17.2     |
| End of Trial    | 33.6    | 51.2     | 46.7     | 74.3     |
5. SLX-2101

SLX-2101 is a new PDE5 inhibitor that it is converted to an M1 metabolite, SLX-2081, which continues to be active. In preclinical studies, SLX-2101 demonstrated excellent potency at the molecular, cellular, ex vivo and in vivo levels, and pharmacokinetic studies revealed the drug to be long lasting, maintaining therapeutic levels for >24 hours in rats [20]. Again, only abstract data is currently available. A randomized, double-blind, single-dose study in healthy male volunteers was conducted to assess preliminary safety, tolerability, pharmacokinetics and endothelial function [21, 22]. Five different doses (5, 10, 20, 40 and 80 mg) were used, with six subjects receiving active doses and two receiving placebo at each dose level (mean: 35±6.4 years). The Tmax was 1 hour (SLX-2101) and 2.8 hours (SLX-2081); T1/2 was 6–13 hours (SLX-2101) and 9–14 hours (SLX-2081). This pharmacokinetic profile predicts inhibition of PDE5 for at least 36–48 h at all doses tested. RigiScan® data showed positive effects at 24–24.5 hours post-administration with VSS for 20, 40 and 80 mg doses. No clinically significant effects on blood pressure, heart rate or ECG were noted. SLX-2101 was well tolerated in single doses up to 40 mg with headache being the most common adverse event while visual effects were noted at 80 mg. At this time, four Phase 2a clinical studies have been completed in hypertension, Reynaud’s disease and erectile dysfunction but no new clinical trials are registered for SLX-2101.

REFERENCES FOR NEW PDE5 INHIBITORS


III. CENTRALLY ACTING AGENTS

1. APOMORPHINE

A review of the literature identified a number of publications which attest to the efficacy, tolerability and safety of apomorphine in men with erectile dysfunction. For assessment of efficacy we have not included pooled studies or analyses of pooled studies, and we have attempted to ensure that no dataset is reported more than once. For assessment of safety and tolerability, we have included pooled analyses in an attempt to identify relatively infrequent tolerability or safety issues.

a) Efficacy in the broad population of men with erectile dysfunction

Overall there is evidence that apomorphine is efficacious in the treatment of erectile dysfunction in the broad population at doses of 2mg and 3mg taken sublingually in an on demand fashion. There are two level 1 studies [1,2] and two level 2 studies [3,4] with consistent outcomes. The overall grade of recommendation is grade A.

b) Efficacy in special populations of men with erectile dysfunction

There is a single level 2 study suggesting efficacy in the treatment of erectile dysfunction in men with erectile dysfunction secondary to diabetes [5].

c) Tolerability and Safety

There are several publications attesting to the tolerability of apomorphine at a dose of 2mg and 3mg [1-9]. The most common side effects are nausea, headache and dizziness, with small numbers of patients developing syncope. This latter side effect was particularly noted at doses higher than those licensed for use in Europe. Overall providing the drug is used in line with labeling we could find no evidence of significant tolerability of safety issues. (Consistent level 1 studies. The overall grade of recommendation is grade A.)

APOMORPHINE REFERENCES

2. BREMELANOTIDE

Double-blind, placebo-controlled phase I and phase II studies evaluated intranasal bremelanotide in healthy males and patients with mild-to-moderate ED who had been treated successfully with sildenafil for at least the last 6 months using a Rigiscan methodology [1]. Median time to (C max) was 0.5 hours and mean half-life (t½) ranged from 1.85 to 2.09 hours. In both studies, an erectile response induced by bremelanotide administration was statistically significant at doses >7 mg compared with placebo. The onset of the first erection occurred in approximately 30 minutes. Bremelanotide was safely administered and well tolerated in both studies. Flushing and nausea were the most common adverse events reported in both studies (up to 33.3% using the 20 mg dose).

Similar double-blind, placebo-controlled phase I and phase II studies were designed to evaluate the safety, pharmacokinetic properties and pharmacodynamic effects of subcutaneous bremelanotide in healthy males and in patients with ED who had an inadequate response to sildenafil [2]. An inadequate response was defined by a patient report indicating that achievement of an erection suitable for vaginal penetration occurred ≤50% of the time while taking sildenafil 100 mg. Median t max ranged from 0.5 to 1 hour and mean t½ ranged from 1.9 to 2.7 hours. A >2-fold increase in the duration of base rigidity ≥60% compared with the response of individual patients to placebo was observed in 82% and 84% of ED patients who received 4 mg or 6 mg of bremelanotide, respectively. In the phase II study, nausea (36.4%), headache (27.3%), flushing (9.1%), diaphoresis (9.1%), lower back pain (9.1%) and vomiting (9.1%) were the most common adverse events at the 6-mg dose. Subsequent studies have only been published in abstract form. In phase Iib studies bremelanotide was delivered intranasally in non-diabetic patients (726 men) who were randomized to receive placebo or one of five doses (5, 7.5, 10, 12.5 or 15 mg). The mean change in IIEF-EF domain score was 1.8 for placebo, 4.2 for 5 mg, 5.7 for 7.5 mg, 6.4 for 10 mg, 6.1 for 12.5 mg and 8.4 for 15 mg (statistically significant from placebo for all doses except 5 mg). Similarly, mean intercourse completion rates (question 3 of SEP [SEP3]) improved and were statistically significant from placebo for all doses except 5 mg. Major adverse events included nausea, emesis and blood pressure increases, and the discontinuation rates were dose-related and ranged from 4% in the placebo group to 49% in the 15-mg group [3]. In a second study in diabetic men the mean change in IIEF-EF domain score was 2.3 or placebo, 3.7 for 10 mg, 5.9 for 12.5 mg and 7.1 for 15 mg (statistically significant from placebo for all doses except 10 mg. SEP2 and SEP3 rates were improved, but none reached statistical significance. Major adverse events included nausea, emesis and blood pressure increases, and the discontinuation rates were dose-related and ranged from 4% in the placebo group to 49% in the 15-mg group [4]. A third study explored the efficacy of bremelanotide in combination with sildenafil using a rigiscan methodology. Nineteen patients with ED who were responders to either sildenafil or vardenafily by self-report were given sildenafil 25 mg plus intranasal bremelanotide 7.5 mg, sildenafil 25 mg plus an intranasal placebo spray, or a placebo tablet plus an intranasal placebo spray in a randomized, crossover design. A statistically significant difference was demonstrated between combination therapy and sildenafil (p<0.05), combination therapy and placebo (p<0.001) and sildenafil monotherapy and placebo (p<0.05). The combination treatment did not result in new adverse events or in an increase in the frequency or severity of adverse events compared with sildenafil or historical data of intranasal bremelanotide alone. Four patients (21%) experienced flushing, and one of these patients also reported nausea after combination therapy [5].

REFERENCES


IV. COMPARATOR STUDIES

A number of studies have compared the efficacy and safety of the oral medications used in the treatment of men with erectile dysfunction. A careful review of the published trials was undertaken and the salient features of the studies are shown in tables 9 a-e. The trial designs used was variable with many studies demonstrating inadequate design resulting in clear bias. Almost all the studies were pharmaceutically sponsored.
Table 9a: Comparator trials Senior author, drugs compared, patients randomised and trial design

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Drugs compared</th>
<th>Numbers patients randomised</th>
<th>Trial design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Govier et al, 2003 [2]</td>
<td>Sildenafil and Tadalafil</td>
<td>215</td>
<td>Multicentre, double blind, fixed dose (Tadalafil 20mg, sildenafil 50mg), crossover study, each drug treatment period of 4 weeks, with 1-2 week washout</td>
</tr>
<tr>
<td>Eardley, 2004 [9]</td>
<td>Sildenafil and apomorphine</td>
<td>139</td>
<td>Multicentre, open label, flexible dose, crossover study, each drug treatment period of 8 weeks, with 2 week washout</td>
</tr>
<tr>
<td>Perimenis, 2004 [14]</td>
<td>Sildenafil and apomorphine</td>
<td>40 men with arterial flow greater than 25 cm/sec</td>
<td>Single centre, open label, flexible dose, crossover study, each drug treatment period of 6 weeks, with 1 week washout</td>
</tr>
<tr>
<td>Perimenis, 2004 [15]</td>
<td>Sildenafil and apomorphine</td>
<td>43 men with arterial flow less than 25 cm/sec</td>
<td>Single centre, open label, flexible dose, crossover study, each drug treatment period of 6 weeks, with 1 week washout</td>
</tr>
<tr>
<td>Pavone, 2004 [13]</td>
<td>Sildenafil and apomorphine</td>
<td>62</td>
<td>Single centre, open label, fixed dose (sildenafil 50mg and apomorphine 3mg) crossover study, each drug treatment period 4 weeks with 4 week washout</td>
</tr>
<tr>
<td>von Keitz et al, 2004 [4]</td>
<td>Sildenafil and Tadalafil</td>
<td>219</td>
<td>Multicentre, double blind, fixed dose tadalafil (20mg) versus flexible dose sildenafil 50mg (although maximum 35% of patients allowed to titrate up to 100mg), 2 period crossover study, each drug treatment period of 12 weeks, with 1-2 week washout</td>
</tr>
<tr>
<td>Eardley et al, 2005 [1]</td>
<td>Sildenafil and Tadalafil</td>
<td>367 treatment naïve</td>
<td>Multicentre, open label, flexible dose, crossover study, each drug treatment period of 12 weeks, with 1-2 week washout</td>
</tr>
<tr>
<td>Tolra et al, 2006 [5]</td>
<td>Sildenafil, tadalafil, vardenafil</td>
<td>132</td>
<td>Single centre, open label, randomised, fixed dose, 6 arm crossover study, with sildenafil 100mg, tadalafil 20mg, vardenafil 20mg. 6 doses of treatment each treatment arm, with washout of 1 week between arms</td>
</tr>
<tr>
<td>Rubio-Aurioles et al, 2006 [6]</td>
<td>Sildenafil and vardenafil</td>
<td>Pooled analysis of two trials with total of 1057 men</td>
<td>Multicentre, double blind, fixed dose (sildenafil 100mg, vardenafil 20mg), 2 treatment period crossover study, each 4 weeks with 1 week washout</td>
</tr>
</tbody>
</table>
Table 9a: Comparator trials Senior author, drugs compared, patients randomised and trial design

<table>
<thead>
<tr>
<th>Trial</th>
<th>EF Domain score</th>
<th>Successful intercourse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porst et al, 2007 [10]</td>
<td>Sildenafil and apomorphine</td>
<td>Multicentre, randomised, open label, 2 arm comparison trial of flexible dose sildenafil and apomorphine</td>
</tr>
<tr>
<td>Afif Abdo, 2008 [11]</td>
<td>Sildenafil and apomorphine</td>
<td>Multicentre, open label, flexible dose, crossover study, each drug treatment period of 8 weeks, with 2 week washout</td>
</tr>
<tr>
<td>Giammusso et al, 2008 [12]</td>
<td>Sildenafil and apomorphine</td>
<td>Multicentre, open label, randomised, flexible dose, crossover study, each drug treatment period 8 weeks, with 4 week washout</td>
</tr>
</tbody>
</table>

Table 9b: Comparator trials Efficacy comparisons

<table>
<thead>
<tr>
<th>Trial</th>
<th>EF Domain score</th>
<th>Successful intercourse</th>
<th>GAQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Govier et al, 2003 [2]</td>
<td>No efficacy measures reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eardley, 2004 [9]</td>
<td>Baseline: Not reported</td>
<td>Baseline: Not recorded</td>
<td>End of treatment with Sildenafil: 94.1% End of treatment with Apomorphine: 51.7%</td>
</tr>
<tr>
<td></td>
<td>End of treatment with Sildenafil: 25.2</td>
<td>End of treatment with Apomorphine: 15.9</td>
<td>This reached statistical significance</td>
</tr>
<tr>
<td></td>
<td>Baseline: 17.0</td>
<td>Baseline: Not measured</td>
<td>Sildenafil: 73.1% Apomorphine: 63.7%</td>
</tr>
<tr>
<td></td>
<td>Sildenafil: Not measured</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apomorphine: Not measured</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perimenis, 2004 [14]</td>
<td>Baseline: 7.9</td>
<td>Baseline: Not measured</td>
<td>Sildenafil: 63.7% Apomorphine: 32.1%</td>
</tr>
<tr>
<td></td>
<td>Sildenafil: Not measured</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apomorphine: Not measured</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perimenis, 2004 [15]</td>
<td>Baseline: 7.9</td>
<td>Baseline: Not measured</td>
<td>Sildenafil: 63.7% Apomorphine: 32.1%</td>
</tr>
<tr>
<td></td>
<td>Sildenafil: Not measured</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pavone, 2004 [13]</td>
<td>Baseline 14.1, end of treatment 24.6</td>
<td>Baseline 26% Sildenafil 81% Apomorphine 43%</td>
<td>Not recorded</td>
</tr>
<tr>
<td></td>
<td>Apomorphine: Baseline 14.4, end of treatment 16.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial</td>
<td>EF Domain score</td>
<td>Successful intercourse</td>
<td>GAQ</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>--------------</td>
</tr>
</tbody>
</table>
Tadalafil: Baseline 14.2, end of treatment 24.3  
No statistical difference between responses | Sildenafil: Baseline 19.4%, end of treatment 72.2%  
Tadalafil: Baseline 19.4%, end of treatment 76.9%  
This reached statistical significance in favour of tadalafil | NR           |
Vardenafil improvement over baseline 10.0  
The response to vardenafil was statistically superior | Sildenafil end of treatment 71.6%  
Vardenafil end of treatment 74.4%  
The response to vardenafil was statistically superior | Not reported |
Apomorphine: baseline 12.8, end of treatment 16.1                                  | Not reported                                                                          | Sildenafil 90%  
Apomorphine 46% |
| Afif Abd, 2008 [11]           | Response to sildenafil was 6.72 points greater than for apomorphine  
Baseline not reported  
This reached statistical significance                                                                 | Sildenafil 83.3%  
Apomorphine 40.3%  
This reached statistical significance                                                                 | Sildenafil: 88.9%  
Apomorphine: 52.0%  
This reached statistical significance |
Apomorphine: Baseline 14.2, End of trial 16.8                                      | Sildenafil: Baseline 18.2%, End of trial 75.7%  
Apomorphine: Baseline 24.2%, End of Trial 34.6%                      | Sildenafil 96.6%  
Apomorphine 45.7% |
### Table 9c: Comparator trials Preference

<table>
<thead>
<tr>
<th>Trial</th>
<th>Preference results</th>
<th>Reasons for preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Govier et al, 2003 [2]</td>
<td>66.3% men who expressed a preference preferred tadalafil and 33.7% preferred sildenafil</td>
<td>Not explored</td>
</tr>
<tr>
<td>Eardley, 2004 [9]</td>
<td>96.6% men who expressed a preference, preferred sildenafil and 3.4% preferred apomorphine</td>
<td>Not explored</td>
</tr>
<tr>
<td>Perimenis, 2004 [14]</td>
<td>Not measured</td>
<td>N/A</td>
</tr>
<tr>
<td>Perimenis, 2004 [15]</td>
<td>Not measured</td>
<td>N/A</td>
</tr>
<tr>
<td>Pavone, 2004 [13]</td>
<td>88.2% men who expressed a preference preferred sildenafil and 11.8% preferred apomorphine</td>
<td>Not explored</td>
</tr>
<tr>
<td>von Keitz et al, 2004 [4]</td>
<td>73% men who expressed a preference preferred tadalafil and 27% preferred sildenafil</td>
<td>Not explored in this publication</td>
</tr>
<tr>
<td>Tolra et al, 2006 [5]</td>
<td>52.2% preferred tadalafil, 27.8% preferred sildenafil, 20% preferred vardenafil</td>
<td>Reasons for preferences explored qualitatively. The ability to achieve an “intense and long lasting” erection was the main driver for preference for all three drugs</td>
</tr>
<tr>
<td>Dean et al, 2006 [7]</td>
<td>See Eardley et al, 2005</td>
<td>The drug attributes most important in determining preference related to the duration of action of the medication, and the rigidity of the erection that was achieved</td>
</tr>
<tr>
<td>Rubio-Aurioles et al, 2006 [6]</td>
<td>34.5% men preferred sildenafil, 38.9% men preferred vardenafil, 26.6% had no preference</td>
<td>Not explored in this publication</td>
</tr>
<tr>
<td>Eardley et al, 2007 [8]</td>
<td>See Eardley et al, 2005</td>
<td>Patient differences in time concerns, dosage choice, intercourse satisfaction, treatment tolerability, number of sexual attempts and satisfaction with erection hardness were the set of factors most significantly associated with treatment preference</td>
</tr>
</tbody>
</table>
### Table 9c: Comparator trials Preference. (Continued)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Preference results</th>
<th>Reasons for preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porst et al, 2007 [10]</td>
<td>95% men who expressed a preference preferred sildenafil and 5% preferred apomorphine</td>
<td>Not explored</td>
</tr>
<tr>
<td>Afif Abdo, 2008 [11]</td>
<td>87.6% men who expressed a preference preferred sildenafil and 12.4% preferred apomorphine</td>
<td>Not explored</td>
</tr>
<tr>
<td>Giammusso et al, 2008 [12]</td>
<td>88.6% men who expressed a preference, preferred sildenafil and 11.4% preferred apomorphine</td>
<td>No explored</td>
</tr>
</tbody>
</table>

### Table 9d: Comparator trials Safety and tolerability

<table>
<thead>
<tr>
<th>Trial</th>
<th>Side effect</th>
<th>Dropouts due to Adverse events</th>
</tr>
</thead>
</table>
| Govier et al, 2003 [2]       | Sildenafil: Headache 8.8%, Dyspepsia 4.2%, Nasopharyngitis 2.8%, Flushing 4.7%, Myalgia 0%, Nasal congestion 3.3%  
Tadalafil: Headache 11.2%, Dyspepsia 6.0%, Nasopharyngitis 4.7%, Flushing 2.8%, Myalgia 2.3%, Nasal congestion 2.3% | Sildenafil 0.5%  
Tadalafil 0.5% |
| Eardley, 2004 [9]            | Sildenafil: Flushing 9.6%, Headache 16%, Dizziness 3.2%, Dyspepsia 4.8%, Nausea 3.2%, Abnormal vision 4.8%  
Apomorphine: Flushing 0%, Headache 4.8%, Dizziness 0%, Dyspepsia 0.8%, Nausea 5.6%, Abnormal vision 0.8% | Sildenafil: 0%  
Apomorphine: 0% |
| Perimenis, 2004 [14]         | Not recorded                                                                 | Not recorded                 |
| Perimenis, 2004 [15]         | Sildenafil: Headache 7.5%, Dyspepsia 7.5%  
Apomorphine: not recorded | Sildenafil: 0%  
Apomorphine: 5% |
Apomorphine: Nausea 12%, Headache 6%, Somnolence 6%, Dizziness 12% | Sildenafil: 0%  
Apomorphine: 0% |
| von Keitz et al, 2004 [4]     | Sildenafil: Headache 7.8%, dyspepsia 4.6%, Back pain 1.8%, Myalgia 0.5%, Flushing 3.7%, Nasal congestion 4.6%  
Tadalafil: Headache 11.9%, Dyspepsia 6.4%, Back pain 4.1%, Flushing 2.7%, Nasal congestion 2.7% | Sildenafil 1.4%  
Tadalafil 1.8% |
<table>
<thead>
<tr>
<th>Trial</th>
<th>Side effect</th>
<th>Dropouts due to Adverse events</th>
</tr>
</thead>
</table>
| Eardley et al, 2005 [1] | Sildenafil: Headache 9.3%, Flushing 7.4%, Backache 2.5%, Dyspepsia 3%, Nasal congestion 4.1%  
Tadalafil: Headache 8.4%, flushing 2.5%, Backache 4.6%, Dyspepsia 4.1%, Nasal congestion 3.5% | Sildenafil 1.4%  
Tadalafil 1.4% |
Vardenafil: Headache 12.2%, Flushing 3.3%, Dyspepsia 5.6%, Vision disorders 3.3%  
Tadalafil: Headache 8.9%, Flushing 4.4%, Dyspepsia 3.3%, Myalgia 4.4%, Vision disorders 3.3% | |
Dizziness 1%  
Vardenafil: Headache 10%, Flushing 7%, Nasal congestion 3%, Dyspepsia 2%, Cyanopsia <1%,  
Dizziness 2% | Sildenafil 0.3%  
Vardenafil 0.3% |
| Porst et al, 2007 [10] | Not reported                                                                                  |                               |
Apomorphine: Nausea 4.8%, Headache 4%, Dizziness 3.8%, abnormal taste 3.8% | Sildenafil 0%  
Apomorphine 0.8% |
| Giammusso et al, 2008 [12] | Not reported                                                                                 | Sildenafil 0.8%  
Apomorphine 0.8% |
<table>
<thead>
<tr>
<th>Trial</th>
<th>Instruments used</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eardley, 2004 [9]</td>
<td>IIEF domains</td>
<td>Sildenafil produced significantly greater improvements in all domains IIEF than apomorphine Sildenafil 82.5: Apomorphine 46.8</td>
</tr>
<tr>
<td>Eardley, 2005 [1]</td>
<td>IIEF domains</td>
<td>Statistical advantage for tadalafil in orgasmic domain, desire domain and overall satisfaction domain IIEF. No difference in other domains</td>
</tr>
<tr>
<td></td>
<td>SEP questionnaire</td>
<td>Statistical advantage for tadalafil in SEP5 (Overall satisfaction)</td>
</tr>
<tr>
<td>Dean et al, 2007 [7]</td>
<td>PAIRS</td>
<td>The PAIRS questionnaire demonstrated that tadalafil had statistical superiority over sildenafil in relation to the Sexual self confidence domain, the Spontaneity domain, the Time concerns domain</td>
</tr>
<tr>
<td>Porst et al, 2008 [10]</td>
<td>IIEF EDITS</td>
<td>Significant advantages for sildenafil in intercourse satisfaction and overall satisfaction domains Apomorphine EDITS index 45.7, Sildenafil EDITS index 94.2</td>
</tr>
<tr>
<td>Afif Abdo, 2008 [11]</td>
<td>IIEF domains</td>
<td>Sildenafil produced significantly greater improvements in all domains IIEF except desire and orgasm than apomorphine Sildenafil 86.7: Apomorphine 56.9</td>
</tr>
<tr>
<td>Giamusso et al, 2008 [12]</td>
<td>IIEF EDITS index</td>
<td>Sildenafil produced significantly greater improvements in all domains IIEF except desire and orgasm than apomorphine Sildenafil 53.8: Apomorphine 80.4 (reported in this study that lower values favoured sildenafil)</td>
</tr>
</tbody>
</table>
1. COMPARISONS OF PDE5 INHIBITORS

The authors consider that one trial comparing sildenafil and tadalafil could be considered a Level 1 study [1,7,8] with the other published studies suffering from biases such as inadequate duration, inadequate washout, and biased dosing [2-6]. The single level 1 study was an open label study, but in other respects was well conducted and of adequate size. Overall, there was no evidence of superiority for any one of the PDE5 inhibitors over the others in terms of efficacy or safety (Grade A recommendation).

2. COMPARISONS OF SILDENAFIL AND APOMORPHINE

The authors consider that several trials comparing the efficacy and tolerability of apomorphine and sildenafil could be considered level 1 trials [9-12] with other published studies suffering from design limitations [13-15]. All Level 1 studies were all open label studies, but all were otherwise well designed trials, with adequate numbers of patients randomized. Overall there was clear evidence that sildenafil has greater efficacy in the treatment of men with ED than apomorphine (Grade A recommendation).

COMPARATOR REFERENCES

[8] Eardley I, Montorsi F, Jackson G et al. Factors associated with preference for sildenafil citrate and tadalafil for treating erectile dysfunction in men naïve to phosphodiesterase 5 inhibitor therapy: post hoc analysis of data from a multicentre, randomized, open-label, crossover study. BJU Int 2007; 100: 122–9

C.LOCAL THERAPIES

The dawn of the age of pharmacologic treatment began 25 years ago with the recognition that vasoactive drugs when injected into the penile erectile tissue were capable of initiating and maintaining erection [1,2]. Currently there are three main agents for intracavernosal injection (ICI) therapy (one of which is approved by prominent national drug approval agencies (i.e. FDA, European Agencies) for the treatment of erectile dysfunction (ED)). Additionally one agent for intravesical therapy of ED has also received approval.

These were relegated to second line therapy after the appearance of effective oral phosphodiesterase-5 inhibitors (PDE5Is). However, the local delivery of medications remain useful for the treatment of men with ED since PDE5Is are ineffective in about 25-32% of men [3], secondly a significant proportion will ultimately fail to respond to oral therapy secondary to progression of their disease and thirdly are a small number of men have contraindications to PDE5Is. The result is a large number of men who are unable to utilize oral treatments for ED.
I. INTRACAVERNOSAL

1. INTRACAVERNOSAL PROSTAGLANDIN E1 (ALPROSTADIL)

Intracavernosal prostaglandin E1 is licensed for the treatment of men with erectile dysfunction. Linet and Ogrinc reported three multi-centered, randomized prospective clinical trials and a six month open label extension examining the efficacy of intracavernosal alprostadil [4]. The initial trial was a dose-response study of 296 men randomized between increasing doses of alprostadil (2.5 micrograms to 20 micrograms) and placebo. All doses of alprostadil were better than placebo in producing an erectile response and there was a significant dose-response relation, resulting in higher response rates with increasing doses PGE1. In the second study of 201 men with erectile dysfunction of neurogenic, vasculogenic, psychogenic, or mixed causes, alprostadil also demonstrated significant efficacy. In a six-month open label flexible dose self-injection study in 683 men, 94 percent of patients had better erections after the injections. Sexual activity was rated as satisfactory by 87% of the males and 86 percent of their partners. Penile pain was the most commonly reported adverse event, occurring in 50 percent of the men at some time but was usually mild. Prolonged erections occurred in 5 percent of the men.

In an open-label, multi-center study, 67 ED patients who had failed previous PDE5 inhibitor therapy, Shabsigh et al reported successful rescue with prostaglandin E1 [5]. After an in-office titration phase to determine the optimal dose, these patients used alprostadil (up to 40 µg) at home for up to 6 weeks. Erections adequate for sexual intercourse during the 6-week at-home trial were reported by approximately 88% (57) of patients. Headache was the most commonly reported side effect with sildenafil use, and penile pain was the most frequent complaint with alprostadil alfadex. A recent meta-analysis reported intracavernosal injections of alprostadil has an efficacy >70% [6].

We are able to conclude, on the basis of this evidence that intracavernosal prostaglandin E1 is an effective treatment for men with erectile dysfunction (Grade of Recommendation = A).

2. VASOACTIVE INTESTINAL POLYPEPTIDE AND PHENTOLAMINE

The first instance of the use of VIP as intracavernosal injection monotherapy for ED was disappointing; Wagner and Gerstenberg reported that VIP did not induce erection when injected [7]. VIP has shown more promise when used for combination therapy with phentolamine. Several observational reports and two randomized clinical trials are available for review.

Dinsmore and Alderdice studied vasoactive intestinal polypeptide (VIP) combined with phentolamine mesylate (PM) in 70 men who had failed previous intracavernosal therapy [8]. Patients were titrated with 25 micrograms of VIP/1 mg PM (VIP1) and if unsuccessful, 25 micrograms VIP/2 mg PM (VIP2). Forty-seven (67%) of patients achieved erections sufficient for sexual intercourse (33 on VIP1 and 14 on VIP2). In a second observational series, 52 men received 30 micrograms vasoactive intestinal polypeptide and 0.5 to 2.0 mg. phentolamine [9]. In this report all patients obtained erection sufficient for penetration with a median duration of treatment was 6 months (range 1 to 22).

Two multi-centered prospective clinical trials using combination VIP/PH therapy have been used to successfully register VIP as an approved pharmacologic agent for the treatment of men with ED in the United Kingdom, Denmark and New Zealand [10,11]. In the first 236 men with primarily non psychogenic were treated with 25 micrograms VIP combined with PM 1.0 mg (VIP/P-1) or 2.0 mg (VIP/P-2) in the office [10]. This was followed with a placebo-controlled phase, during which 171 patients were subsequently treated and self-administered up to 12 injections over a 6-month interval. Erections were graded on a 4 point scale (0-III). The results are shown in Table 10. The second study involved 195 men with organic ED who received 25 micrograms vasoactive intestinal polypeptide (VIP) combined with phentolamine mesylate 1.0 mg (VIP/P-1) or 2.0 mg (VIP/P-2) versus placebo [11].

The combination of vasoactive intestinal polypeptide and phentolamine appears to be safe and well tolerated. Most commonly observed adverse effects were facial flushing and headache, characteristic events noted with vasoactive therapy.

<table>
<thead>
<tr>
<th>Table 10: Numbers of Grade 3 erections achieved [10,11]</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIP/PM 1</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Active drug</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

999
We are able to conclude, on the basis of this evidence that an intracavernosal injection of the combination of vasoactive intestinal polypeptide and phentolamine is an effective treatment for men with erectile dysfunction (Grade of Recommendation = A).

3. PAPAVERINE

Papaverine was the first agent discovered to be effective as intracavernosal pharmacotherapy for erectile dysfunction [2]. It is highly effective but has fallen out of favor as monotherapy because of its high rates of fibrosis. In one series 163,042 papaverine injections were administered to 1,748 patients. The main side effects noted were priapism and fibrosis. Priapism occurred in 106 (6%) of patients after 235 (0.14%) of the injections. Fibrosis or nodule formation occurred in 187 (11%) of patients [12]. In a further study priapism was noted in 92 (7%) of 1300 patients while fibrosis, induration and nodules occurred in 5.7% (60 of 1,056 patients). Other important side effects were injection site pain, which occurred in 4% (18/452 patients), and hematoma, which occurred in 11% (98/858 patients) [13]. Papaverine is currently not licensed for use.

4. TRIMIX (PAPAVERINE, ALPROSTADIL, PHENTOLAMINE)

Combination therapies for intracavernosal injections were conceived both to improve efficacy as a result of the synergistic effects of the drugs, and later, to reduce side effects as a result of using lower dosages of each agent. One difficulty encountered with the use of combination agents is the need for the pharmacy to compound these agents since there are no combination intracavernosal injection drugs currently approved by the FDA. Concentrations of each component vary widely in the literature, but ratios of 12-30mg papaverine: 10-20μg alprostadil:1mg phentolamine appear standard.

Bechara et al reported a crossover study of alprostadil versus trimix in a group of 32 men who had failed high dose bimix therapy [14]. In this study, 50% responded to trimix compared to only 22% responding to alprostadil.

Rates of pain for alprostadil was significantly higher than for trimix (41% vs. 12.5%). Seyam et al. studied multiple combinations of trimix ingredients versus alprostadil in a 180 men with erectile dysfunction [15]. They found that all tested mixtures were highly effective and produce erections that are of equal frequency and quality to those produced by alprostadil. Sixty-eight percent of men using alprostadil and 67% of men using trimix achieved a rigid erection. However, duration of erections was longer than alprostadil and a larger number of episodes of priapism (5% vs. 0.6%) were produced. Interestingly, rates of pain were similar between the combined trimix group and the alprostadil group (14.5% vs. 17.9%, respectively).

5. TOLERABILITY AND SAFETY OF INTRACAVERNOSAL AGENTS

Patients must be made aware of the risk of priapism that occurs with ICI use and educated about the proper course of action to take should they experience a prolonged erection. Some evidence exists to support the use of sympathomimetic drugs, such as pseudoephedrine and terbutaline [16]. Both terbutaline and pseudoephedrine performed better than placebo, with detumescence resulting in 36%, 28% and 12% respectively. The other patients required irrigation and/or phenylephrine injections. None required surgical intervention. A study by Priyadarshi (1994) showing detumescence in 42% of patients with ICI induced priapism compared with 15% detumescence with placebo in 68 men supported the claimed efficacy of terbutaline [17].

Cavernosal fibrosis is another serious side effect of intracavernosal injections. It occurs most commonly with injectables containing papaverine. Rates are less than one percent with alprostadil, approximately 6% with papaverine and around 12% with bimix. Rates with trimix were 4% in a small study. These are likely dependant on dose and frequency of use. There is no treatment to reverse penile fibrosis, though it sometimes regresses on its own. Tsao and Nehra recommend temporary discontinuation of ICI for 3-4 months to allow [18] (Grade of Recommendation = D). Persistence of fibrosis should prompt a change to more invasive methods of improving erectile function, i.e. placing a penile prosthesis.

Reported rates of pain with injection are 7% for alprostadil, 4% with papaverine, 12% with bimix [13] and 12-15% with trimix [14, 15]. Significantly it has been observed that pain decreases substantially during the course of treatment so it is likely that the psychological component plays a large role.

6. CONTRAINDICATIONS TO INTRACAVERNOSAL THERAPY

Intracavernosal injections should not be used in men with conditions which predispose them to priapism. These notably include men with sickle cell disease, multiple myeloma and leukemia. Anticoagulation however is not a contraindication to ICI. In a series of 605 injections in 33 men using warfarin for anticoagulation, Limoge et al recorded only three ecchymoses [19]. This rate of 9% of patients is comparable to the 14% (434/3143) of patients on PGE1, papaverine, or bimix who developed hematoma in Porst’s 1996 literature review [13]. Despite this, it is advisable that the physician stress the need, in anticoagulated patients, to place pressure on the injection site for five full, uninterrupted minutes of pressure to prevent hematoma.
II. INTRAURETHRAL

MUSE (Medicated Urethral System for Erection) is a licensed alternative way to deliver alprostadil to the corporal bodies. MUSE involves the insertion of the delivery catheter into the meatus and depositing an alprostadil pellet in the urethra and the method is based on the absorption of drug through the urethral mucosa and into the corpora cavernosum.

One of the largest studies to describe the efficacy of MUSE was published by Padma-Nathan et al [20]. Notable in this study, 995/1511 patients had in-office responses to MUSE. Of those patients with in-clinic response to MUSE, only 299 of the 461 patients assigned to the MUSE arm of the trial achieved intercourse at home. Thus, the true success rate of MUSE in this large study was only 42.44%. Furthermore, of the patients who did achieve intercourse at home, only 73% of doses (2634/3593) were successful in achieving intercourse, orgasm or a 10 minute erection sufficient for intercourse. MUSE has been used successfully in men who have undergone radical prostatectomy. Costabile et al. reported a 40% rate of home success for MUSE in a group of 384 men greater than three months post-prostatectomy [21].

A systematic review of MUSE therapy (3 RCTs, 1828 men) reported that compared to placebo, alprostadil increased the proportion of men achieving ≥1 successful intercourse (average response: 65.3% with alprostadil vs. 17.6% with placebo; OR 7.22, 95% CI 5.68 – 9.18; p< 0.00001) [6]. In sildenafil failures, this treatment is shown to be effective in up to 43% of men with ED [22]. Direct comparison trials between MUSE alprostadil and ICI alprostadil are summarized in Table 11.

MUSE alprostadil had similar rates of pain to ICI alprostadil, but priapism and fibrosis were rare. Side effect rates are noted in Table 12. Other side effects unique to MUSE compared to ICI were dizziness, hypotension, and sweating. These occurred at a frequency of 1-6%. Syncope occurred at a rate of <1% and urethral bleeding also occurred at a rate of 1-5%.

Overall, we are able to conclude that there is evidence of efficacy and good tolerability for the use of intraurethral alprostadil as a treatment for men with erectile dysfunction (Grade A recommendation). The evidence also suggests that intracavernosal injection therapy is a more effective treatment than intraurethral alprostadil (Grade A).

Table 11: Comparison of MUSE and Intracavernosal Injection Therapy.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number pts</th>
<th>MUSE</th>
<th>ICI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rigid erections</td>
<td>All erections sufficient for intercourse</td>
</tr>
<tr>
<td>Porst 1997 [23]</td>
<td>103</td>
<td>10%</td>
<td>43%</td>
</tr>
<tr>
<td>Werthman and Rajfer 1997 [24]</td>
<td>100</td>
<td>7%</td>
<td>37%</td>
</tr>
<tr>
<td>Shabsigh et al 2000 [25]</td>
<td>68</td>
<td>NA</td>
<td>62% (with penile ring)</td>
</tr>
</tbody>
</table>

Table 12. Complications of intraurethral alprostadil

<table>
<thead>
<tr>
<th>Trial</th>
<th># pts</th>
<th>pain</th>
<th>priapism</th>
<th>Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hellstrom 1996 [26]</td>
<td>68</td>
<td>9-18%</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Porst 1997 [23]</td>
<td>103</td>
<td>31%</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Werthman and Rajfer 1997 [24]</td>
<td>100</td>
<td>24%</td>
<td>1%</td>
<td>----</td>
</tr>
<tr>
<td>Padma-Nathan et al 1997 [20]</td>
<td>486</td>
<td>33%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
III. TOPICAL AGENTS

There have been several advances in the understanding of the pharmacokinetics of topical therapy. The transdermal route has a well established technology to provide durable and constant plasma levels of drugs such as hormonal replacements, narcotics and vasodilators. When it comes to local penile therapy using direct smooth muscle relaxants, the durability and onset of action of such methods may not be useful attributes. In this regard there are several issues worth mentioning: 1) High systemic levels are undesirable as they may result in an unacceptable level of adverse events., 2) Agents may be largely metabolized in the first pass through the lungs or liver., and 3). The vasoactive agent(s) need to reach the corpora cavernosa in a timely fashion with the effective (highest) concentration.

Topical penile therapy has a unique set of anatomic and physiologic issues that are important to consider. There are several anatomic/fascial layers between the penile skin and the corpus cavernosa. The tunica albuginea is presumed to be difficult to penetrate due to its thick layers of collagen. Therefore, topical treatment trials have emphasized exposure to the glans penis as it has direct venous communication to the corpora cavernosa [27,28]. The skin itself is a relatively impermeable tissue due to the stratum corneum. The horny cells at the stratum corneum are bonded with a very tight intercellular lipid matrix bilayer that makes the passage of drugs challenging [29]. To overcome this barrier investigators have used penetration enhancers which permeate this layer and reach the subdermis. Fortunately, the penis and scrotum are unique in that their stratum corneum is the most permeable of all anatomic locations tested.

With the assortment of confounding factors as mentioned above one wonders exactly how gel applied to the penis could ever induce an erection. One attractive possibility is gel applied to the glans is rapidly absorbed through the porous skin of the glans into the venous vasculature of the corpora spongiosum. From that location it could travel into the corpora cavernosa akin to the intrarethral delivery of drug [30].

Several transdermal enhancers incorporated as one of the excipients in topical formulations have been reported [27,28,31,32]. The task of these enhancers is to: 1) Disrupt the stratum corneum lipid bilayer, 2) Interact with the membrane keratin, 3) Produce a weak interaction with the drug molecule, and 4) Reverse all actions in a short time. The available evidence indicates that this agent enhances skin penetration by altering the fluidity of lipids in the stratum corneum, without any interaction with the chemical whose skin permeability is enhanced.

1. TOPICAL ALPROSTADIL

Evidence providing comparative efficacy remains lacking thus this therapy remains investigational. To date no sufficiently effective product exists.. In trials of alprostadil with SEPA, doses of 2500 μg alprostadil were used with a resulting 39% of patients achieving erection sufficient for penetration versus 7% of the placebo group [33]. Unfortunately, baseline characteristics were not provided in this study. Ultimately, alprostadil/SEPA trials were discontinued because of their apparent lack of efficacy at safe doses.

A large trial of topical alprostadil without a skin penetration enhancer was also published by Padma-Nathan et al. which showed a statistically significant but very slight improvement in sexual function with topical alprostadil [34]. This study used 100, 200 and 300μg doses of alprostadil and achieved successful penetration rates of 57.5%, up from a baseline of 50% at the highest dose. A criticism of this study is that its high initial function rates do not adequately represent population seeking treatment for erectile dysfunction.

2. TOPICAL PAPAVERINE

Since the introduction by Virag in the early 1980s of injection of papaverine into the corporal bodies for the treatment of sexual dysfunction has become a widespread and well accepted method. It use as a topical therapy has a much shorter experience and one that has not moved beyond preliminary clinical trials. Serum papaverine levels after topical administration have been measured in a single study with a high performance liquid chromatography assay [35]. At 60 minutes mean serum levels increased 50% suggesting that absorption did occur, but not significantly over baseline values. The papaverine levels in this study indicated that topical absorption is less than 1% of a comparable intravenous dose indicating minimal systemic uptake after topical administration to the genitalia.

3. TOPICAL NITROGLYCERIN

The use of topical nitroglycerin is a standard treatment for unstable angina pectoris because predictable blood levels can be achieved. The use of nitroglycerin ointments, pastes, plasters or patches for the treatment of erectile dysfunction has been tried in several studies. Relaxation of vascular smooth muscle is the principle pharmacologic action of nitroglycerin. Nitroglycerin produces, in a dose dependent manner, dilation of both arterial and venous beds, dilatation of the post-capillary vessels including large veins and decreases in venous return. Contraindications to the use of topical nitroglycerin include those who have allergic reactions to organic nitrates. These are extremely rare, but they do occur. Allergies to the adhesives used within the nitroglycerin patches have also been reported.
REFERENCES FOR LOCAL THERAPIES


Committee 20

Erectile Function Rehabilitation In The Radical Prostatectomy Patient

Chairperson:

JOHN P. MULHALL,

Members:

ANTHONY J. BELLA,

ALBERTO BRIGANTI,

ANDREW MCCULLOUGH,

GERALD BROCK.
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Erectile Function Rehabilitation In The Radical Prostatectomy Patient

JOHN P. MULHALL, ANTHONY J. BELLA, ALBERTO BRIGANTI, ANDREW MCCULLOUGH, GERARD BROCK.

I. INTRODUCTION

Prostate cancer represents the second most common solid malignancy diagnosed in adult men in many Western societies. The American Cancer Society estimates that 9% of all cancer deaths in the US in 2009 will be a direct result of prostate cancer[1]. In spite of advances in diagnosis and early case finding through the widespread adoption of prostate specific antigen (PSA), coupled with advances in surgical technique, significant morbidity is still reported in most contemporary surgical series[2-5]. Our understanding of the pathophysiological basis of post-prostatectomy erectile dysfunction (ED) has evolved over the past decade, with recognition of the anatomical location of the cavernous nerves, their essential role in erection and the impact nerve injury has on cavernous smooth muscle content and function as well as potentially the tunica albuginea[6-8]. Enhanced knowledge of the consequences of cavernous nerve percussion, traction, cautery and transection, accessory pudendal arteries and ultimately their impact downstream on cavernous smooth muscle, has sparked important basic and clinical research evaluating various strategies aimed at minimizing the likelihood of post-prostatectomy ED [9-17].

The concept of penile rehabilitation, the use of any intervention or combination of interventions (medications, devices or actions) whose goal is broadly thought of as being aimed at restoring erectile function to pre-treatment levels, is believed to be based on three inter-related concepts: (i) improving cavernosal oxygenation, (ii) promoting endothelial protection and (iii) preventing cavernosal nerve injury-induced structural changes of the penis [18].

In this chapter, we have undertaken a comprehensive review of the peer-reviewed scientific literature, with the goal of providing an unbiased integrated analysis of the existing knowledge related to preservation of erectile function following radical prostate surgery. As with all areas of sexual medicine, the literature has areas of great strength and significant weaknesses, where further work is needed. In our report, areas of clear consensus are highlighted, controversial questions are discussed and clinical problems in need of further research are identified, with the goal of providing clinically relevant information on erectile function rehabilitative approaches following radical prostatectomy (RP).

1. NON-ED SEXUAL DYSFUNCTIONS

While, the focus of this treatise is erectile function recovery and its optimization, it is becoming increasingly recognized that a number of sexual dysfunctions may occur after RP. These dysfunctions include reduction in libido, anejaculation, alterations in orgasm, penile size alterations and possibly Peyronie’s disease

a) Anejaculation

RP involving the surgical removal of the prostate, seminal vesicles and transection of the vasa, essentially disrupts the ejaculatory mechanism. Data regarding the impact of ejaculation loss following prostate cancer treatments are scarce. Anejaculation has several implications: firstly, it may interfere with subject’s self perception of his manhood and body image. Then as ejaculation and orgasmic sensations are closely related at least in some men, anejaculation may be associated with reduced orgasmic quality, and finally, it renders men infertile. Prostate cancer is perceived as a disease of old men, to whom infertility is no longer an issue. However, in the era of early prostate cancer detection, men are diagnosed at a younger age and generally have excellent long term recurrence-free survival rates[19]. At the same
time, the age of paternity in the general population is increasing and it has been suggested that a cancer diagnosis may actually increase the motivation for parenting[20]. Though advanced sperm extraction and fertilization techniques are available, the issue of anejaculation and its implication on future fertility should be discussed and the clinician should not assume this to be non-relevant and semen should be cryopreserved for men who may potentially bmay desire future fatherhood[21]. The advent of intracytoplasmic sperm injection (ICSI) has allowed the application of assisted reproductive technologies to couples whose male partner cannot deliver sperm in an antegrade fashion. This has particular relevance to the patient who has undergone RP.

b) Orgasm Alterations

Despite major advances in our understanding of the erectile mechanism in the last decade, the process of orgasm remains poorly understood. Both physiological and psychogenic elements contribute to the genesis of orgasm. Ejaculatory events that include smooth muscle contraction of the accessory sex organs, buildup and release of pressure in the posterior urethra, sensation of the ejaculatory inevitability, rhythmic contractions of the pelvic floor muscles and semen emission contribute to the sensation of orgasm. Sensory cortical neurons perceive these events as pleasurable[22]. Normally, orgasm is closely coupled with ejaculation, however, after RP orgasm occurs without semen ejection perse, yet ejaculatory muscular activity does persist.

Though orgasmic changes have received much less attention than ED, such alterations are not uncommon and can be categorized into three areas (i) changes in orgasm presence and quality (ii) orgasmic pain (dysorgasmia) and (iii) orgasm associated incontinence. Schover et al, in a study of 1236 men treated for localized prostate cancer (52% RP, 48% radiation therapy), found that 65% of the sample reported a problem with their orgasms including 31% who no longer tried to reach orgasm, 17% who tried but were unable to reach orgasm and 28% with orgasms that were disappointingly weak[23]. To define the type of orgasmic dysfunction in men after RP, Barnas et al used a validated questionnaire, including questions addressing the presence or absence of orgasm, orgasm quality before and after surgery, the presence of orgasmic pain, the location of orgasmic pain and consistency and duration of orgasmic pain. Of the subjects, 22% of patients reported no change in orgasm intensity but 37% reported a complete absence of orgasm, 37% had decreased orgasm intensity and 4% reported a more intense orgasm after RP than before. Pain during orgasm occurred in 14% of the patients, located in the penis (63%), abdomen (9%), rectum (24%) and other areas (4%). In those respondents who had dysorgasmia, pain was reported to occur always (with every orgasm) in 33%, frequently in 13%, occasionally in 35%, and rarely in 19%. Most patients (55%) had orgasm-associated pain for less than a minute, a third reported pain for 1–5 minutes and pain lasting more than 5 minutes was reported by 12%; only 2.5% of patients complained of pain lasting more than an hour[24]. No consensus exists as to the etiology of orgasmic pain, however it is postulated that bladder neck/pelvic floor spasm plays some role, akin to the condition of chronic pelvic pain disorder. Based on this assumption, a prospective, non-placebo controlled study was conducted to assess the use of tamsulosin, an alpha-adrenergic blocking agent in patients with orgasmic pain. In this study, 77% patients reported significant improvement in pain and 12% noted complete resolution of their pain with significant increase in IIEF libido score, supporting the hypothesis that orgasmic pain is related to bladder neck and/or pelvic floor muscle spasm [25]. Alternatively use of an analgesic taken prior to sexual activity has been described may be a pragmatic approach.

Urinary incontinence during orgasm (climacturia) is another phenomenon that may adversely affect the satisfaction with sexual activity for men following RP and their partner. Choi et al reported that climacturia occurred in 20% of patients following RP (only 4% with radical cystectomy), which they showed was unrelated to the type of prostatectomy performed (open vs laparoscopic). These authors reported that climacturia is more likely to be reported within year 1 following surgery and in men who complain of orgasmic pain and/or penile shortening[26]. Lee et al reported a prevalence of climacturia after RP of 45%. In 68% of the cases reported, it happened rarely or only occasionally, while in 21% it occurred most of the time or always. Urine leakage quantity was only a few drops in 58% of the subjects but 16% reported a loss of more than 1 ounce. Bother was none or minimal in 52% and significant in 48%. Treatment was bladder emptying in 84% and condoms use in 11% [27].

The take-home message for the clinician is that alterations in orgasmic function following RP is common and frequently impactful to the patient and partner. At present, there is no effective treatment to restore the nature of preoperative orgasm. Interestingly, some men report an enhanced orgasmic experience following RP, but this represents a less common scenario. Dysorgasmia can be managed symptomatically using alpha-blockers and climacturia may be managed behaviorally (fluid intake restriction and bladder emptying prior to sexual activity) or mechanically (using a rubber constriction ring or condoms, if the leakage amount is small). The mainstay of treatment is patient and partner education before surgery and supportive care afterwards.
c) Peyronie's Disease (PD)

The prevalence of PD following RP has been addressed by a single paper in the literature and in this analysis of 110 men who presented with ED after RP, 45 (41%) had penile fibrotic changes, representing 11% of all men who had RP in their institute at the specified period. This incidence of PD is higher than that of the general population. The clinical presentation was penile curvature in 93% and 'waistband' deformity in 24%; palpable plaques were present in 31 (69%)[28]. The actual prevalence of PD after RP may be even higher, as this condition, manifested as penile curvature during erection, is evident only in men who achieve some degree of penile rigidity. Originally ascribed to undiagnosed preoperative PD or spongiosis due to urethral catheterization, we routinely see men who had normal genital exams preoperatively who develop PD after surgery. Furthermore, most of these patients have PD plaques dorsally nowhere near their corpus spongiosum. Thus, catheter-related spongiosis is not likely to be a significant factor.

Another explanation that patients are given is that the intracavernosal injections they are using after surgery has caused the tunical fibrosis, despite the fact that there is no data to support this whatsoever[29]. Indeed, it is not uncommon for us to see men three months after RP who are present in clinic for their first penile injection training session, who had no documented PD prior to RP and who on their first injection demonstrate penile curvature never having received an injection prior to that. A review of a prospectively built sexual medicine database at Memorial Sloan Kettering Cancer Center including 1161 RP patients from 2002-2008, the PD incidence was 16.7% at a mean ± SD follow-up of 24±25 months. At multivariate analysis, older age (OR=1.25, for 5 year increase in age) and white race (OR=3.6, vs non-white) were independent significant predictors of post-RP plaque development.

While the precise process of plaque formation leading to eventual clinically evident PD following RP is still ill-defined, it is not unlikely that it may be related to other post RP penile fibrotic changes, secondary to denervation and/or local ischemia [10]. Thus, patients after RP should be routinely evaluated for the existence of penile plaques, as a part of their post-operative follow-up. This condition may also be considered part of the informed consent of the surgical procedure but certainly as a component of the erectile function recovery discussion for men interested in treatment.

d) Penile Volume Alterations

Penile length changes after RP have been described. Penile shortening, even if sexual intercourse is still feasible, once it is identified by the patient or his partner may adversely affect body image, self-esteem, sense of manhood and self confidence. In 1999 Fraiman et al found significant decrease in all penile dimensions after RP: decreased penile length of 9% and decreased volume of 22% in the erect state. The most substantial change occurred between the first 4 and 8 months postoperatively [30]. Munding et al found a measured decrement in penile length in 71% of men after RP, which was greater than 1 cm in 48% of the cases, 3 months postoperatively [31]. Similar findings were obtained in a study by Savoie et al with a decrease in the stretched penile length in 68% of the cases and greater than 15% length loss in 19% [32]. Gontero et al have suggested that penile shortening has been shown to be independently associated with nerve preservation status and postoperative erectile function outcome [33].

The reasons for penile volume changes can be explained by struratical and functional alterations in the penis. Fibrotic changes have been demonstrated in penile biopsies taken in early and late stages after RP (2 and 12 month postoperatively), showing significantly decreased elastic fiber and smooth muscle content as well as increased collagen content [10]. It is postulated that the chronic absence of erectile activity leads to absence of cavernosal oxygenation (see later) [34].

In addition to anatomical changes, there are also functional alterations. It is well recognized that even in the hands of an experienced surgeon using nerve-sparing techniques, some degree of nerve injury, commonly neuropraxia, is likely to occur. Penile smooth muscle and vascular relaxation is accomplished through the release of nitric oxide (NO) from cavernosal nerve endings and the generation of the second-messenger cyclic nucleotides, cGMP and cAMP and is likely to be compromised after surgery. Contractility of the smooth muscle is generally tonic and under the control of erectolytic neurotransmitters such as adrenaline. Sympathetic hyper-innervation (also termed competitive sprouting) refers to the concept that when autonomic nerves are injured, sympathetic fibres are biologically primed to recuperate from injury and regenerate more quickly, resulting in unantagonized sympathetic tone in the end organ [35]. After cavernosal nerve injury, this phenomenon results in a penile hypertonic state. Any factors that result in reduced NO production or increased sympathetic tone, such as nerve injury after RP, may lead to decreased relaxation or diastemibility of corporal smooth muscle and may lead to loss of length. Regardless of the exact mechanism of penile length alteration, most concerning are structural changes that probably result from a combination of neural injury-mediated denervation apoptosis and collagenization of smooth muscle.

It is the recommendation of the ICSM that clinicians discuss with the patient that radical


prostatectomy is associated with a number of sexual dysfunctions, some of which may be permanent. The sexual dysfunctions that should be discussed include, erectile dysfunction, libido reduction, changes in orgasm, anejaculation, penile size changes and possibly Peyronie's disease. Discussion should be held prior to surgery and at regular intervals after surgery. Furthermore, clinicians following patients after RP should examine patients' penis serially to determine if Peyronie's disease has occurred. This was a unanimous committee recommendation.

**RECOMMENDATION 1**

Grade A

The clinician should discuss with the patient that radical prostatectomy is associated with a number of sexual dysfunctions, some of which may be permanent.

**II. PREVALENCE OF ED FOLLOWING RADICAL PROSTATECTOMY**

This field of research began in earnest in the early 1980’s, with the landmark report from Walsh and Donker describing the potential and demonstrating the importance of nerve sparing in radical prostate cancer surgery [36]. The challenges faced by the clinician researcher in achieving the goal of preserving erectile function are significant. The proximity of the cavernous nerves to the prostatic capsule, anatomically arranged as a diffuse poorly visualized nerve plexus adherent to the lateral aspect of the prostate, represents a considerable surgical obstacle. Additionally, the cavernous nerves’ small size, delicate nature and dependent location deep within the male pelvis make visualization and therefore preservation difficult, even in the current era with improved lighting, optics, laparoscopic and robotic instrumentation even among men with low volume disease [8, 37].

Even to the casual observer, it is apparent that success in achieving the goal of preserving and restoring erectile function in all men following RP has not yet been achieved [4]. Prevalence can be defined as the number of all new and old cases of a disease or occurrences of an event in a particular period of time. Prevalence is typically expressed as a ratio in which the number of events is the numerator and the population at risk is the denominator [38]. This contrasts with incidence that defines the rate of increase or decrease of a condition over a specific interval of time.

For the purpose of this section of the chapter, defining the actual prevalence of ED among men following RP is essential in deciding whether there is a clinical need and therefore merit, in pursuing a rehabilitative strategy. The determination of true prevalence of any condition is dependent on knowing both the true number of cases and the number of men at risk. In the case of ED following RP, we generally lack accurate numbers defining the total number of men with ED, but have reliable statistics on the total number of cancers diagnosed (192,000 in the US in 2009) and numbers of procedures [1]. The confounding issues related to the number of men with ED are numerous and include all of the following: inadequate assessments of pre-operative erectile function, poor data collection related to post-operative recovery of erectile function, lack of consensus related to optimal timing for reporting recovery of function, non-uniform agreement of what constitutes ED post RP [4, 5]. The exact scale of the problem is thus inadequately defined owing to significant limitations of data accrual, reporting and perhaps most importantly a lack of consensus of defining what constitutes success from an erectile function recovery standpoint.

Given these limitations, a review of the existing medical literature demonstrates a large variance in reported rates of ED following RP (20-90%) [4, 39-43]. There are many reasons why these differences in reported outcomes exist, and as depicted in Table 1, can best be thought of as: intrinsic patient factors, surgical factors, and reporting biases. In contrast to many of the other post-operative complications such as incontinence, erectile function is more difficult to define and represents a moving target, as recovery from surgery generally shows improving function but with advancing age, a decrease in function would normally be expected. ED is known to increase with advancing age among all men, including those who have undergone definitive management of their prostate cancer. As such measuring erectile function prospectively has a moving baseline [44, 45]. There is an important psychologic component for these men, as well as a subjective degree of assessment and it is further complicated by the necessary partner involvement [46].

At present, no precise and generally agreed upon time-points post-treatment have been defined as the optimal interval post treatment to determine erectile function outcomes. Basic animal and human volunteer data suggest that following an initial period of 3 months may peak and a nadir level of response can be experienced by many men who early in the post-operative course experienced some degree of responsiveness [47, 48]. As one follows men out beyond 2 years, some modest degree of ongoing improvement in erectile function has been reported. It remains unclear whether this represents progressive neural and vascular recovery, an adaptive response of the host and partner to their erectile deficiency and accommodation to use of phosphodiesterase type 5
inhibitors (PDE5i) or other erectogenic agents or the process of confidence restoration, whereby there is significant recovery of the "erectile machinery" by 2 years after RP, but confidence has been eroded and with time (2-4 years), confidence is restored and reported erectile function improves [49]. Additionally, no clear consensus exists defining what an acceptable level of erectile function is, for men and their partners post RP. While some investigators use the IIEF erectile function domain score of 26 points or greater (or 21 on the Sexual Health Inventory for Men also known as the SHIM), others utilize IIEF EF domain scores of 21 or even 17 on a scale of 30. Furthermore, some reports define erectile function with or without the use of PDE5i and only rarely are the response rates segregated based on the use of erectogenic agents [4].

In the current era of early prostate cancer detection, many young and sexually active men are undergoing radical surgery and express concern about preservation of erectile function following the procedure, a fact that is true for older men as well. Since Walsh and Donker published their landmark article describing the etiology and prevention of impotence following retropubic RP in 1982, the nerve sparing technique they described is widely employed and believed to improve postoperative erectile function [50]. Furthermore, there continue to be modifications to the nerve sparing technique in an attempt to minimize nerve compromise and improve post operative erectile function as reported by Chuang et al. and Masterson et al [8, 37]. However, optimal sexual functioning often requires 18-36 months to return, even among men in whom bilateral nerve sparing was performed with reported recovery rates varying from 16% to 86% [51]. Sexual dysfunction has been reported to be an independent determinant of a poorer general health-related quality of life at 2 years after primary treatment for prostate cancer [52].

Recent advances in the understanding of the pathophysiology of post-prostatectomy erectile dysfunction have resulted in great attention being directed towards the concept of penile rehabilitation, in which prophylactic measures are instituted to promote early recovery of sexual and erectile function as well as to modify post-prostatectomy pathophysiologic changes [18].

In this portion of our report, we have reviewed the current English language medical literature in an attempt to provide accurate estimates of the prevalence of ED following RP using contemporary surgical approaches. Ideal prevalence data should be obtained through large, multicenter, multinational prospective studies among large cohorts of men with variable but clearly established erectile function pre-operatively. The ability to define the effect of various surgical approaches, such as laparoscopic/robotic and open RP on recovery of erectile function would be useful (Table 2). Additionally, the ability to determine the optimal time for measurement of erectile function, and the most clinically relevant minimum erectile function score, which would result in sexual satisfaction of the patient and partner would be ideal. Finally, such a study may allow for the identification of an optimally effective post-operative protocol consisting of oral, injectable, intraurethral, externally applied devices or other modalities facilitating recovery of EF. The ability to identify intra-operative techniques to localize the cavernous nerves or in some other manner minimize the negative impact of prostatectomy on erectile function would also be ideal (Table 3) [13].

### Table 1: Predictive Factors For Erectile Function Recovery Following Radical Prostatectomy

<table>
<thead>
<tr>
<th>Factors</th>
<th>Parameters</th>
<th>Positive Effect</th>
<th>Negative Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>≤65 years</td>
<td>&gt;65 years</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td>≤1comorbidity</td>
<td>≥2 comorbidities</td>
<td></td>
</tr>
<tr>
<td>Income</td>
<td>High</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Penile rehabilitation</td>
<td>Unknown</td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>Preoperative erectile function</td>
<td>SHIM ≥15</td>
<td>SHIM &lt;15</td>
<td></td>
</tr>
<tr>
<td>Partner age</td>
<td>Young</td>
<td>Older</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nerve sparing</td>
<td>Bilateral</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Interval from surgery</td>
<td>≥12 months</td>
<td>&lt;12 months</td>
<td></td>
</tr>
<tr>
<td>Surgical Approach</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td>-</td>
<td>≥250 RP lifetime</td>
<td>&lt;250 lifetime</td>
</tr>
<tr>
<td>Surgeon experience</td>
<td>≥50 per year</td>
<td>&lt;50 per year</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Predictive Factors For Erectile Function Recovery Following Radical Prostatectomy
Sadly, the reality of the current literature is a dire lack of well-powered, well-designed prospective clinical studies defining the true prevalence of ED, following contemporary RP. While there exists a plethora of small, poorly powered studies, they all suffer from one or many deficiencies, which limit their validity and make the task of providing accurate information to the individual patient a clinical challenge. The ability to create a nomogram predicting erectile function preservation for an individual patient would, in our opinion, have great utility. The components of such a prediction model would certainly include the key variables previously defined in the literature, predictive of success. These include surgical experience, surgeon volume, extent of nerve sparing, age of the patient, co-morbid conditions, pre-operative erectile function, requirement for adjuvant therapy post-surgery. To the best of our knowledge there are at least two groups (Memorial Sloan Kettering Cancer Center, New York and Vita Salute San Raffaele, Milan) that have nomograms in development. Other factors which should be investigated are: the impact of the partner, the extent of continence, occupation, cultural background, surgical approach (laparoscopic, robotic, open), surgical technique (use of cautery; veil of Aphrodite

Table 2: Confounding Factors Limiting Accurate Assessment of Post-RP ED Prevalence

<table>
<thead>
<tr>
<th>Factors</th>
<th>Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment Tool of Erectile Function (EF)</td>
<td>Interviews, Questionnaires (validated, nonvalidated)</td>
</tr>
<tr>
<td>Definition of Potency</td>
<td>Ability to report sexual activity</td>
</tr>
<tr>
<td></td>
<td>IIEF EF domain scores ranging from &gt;17, 21, ≥26</td>
</tr>
<tr>
<td></td>
<td>SHIM scores ≥21</td>
</tr>
<tr>
<td></td>
<td>Arbitrary 5 point scales</td>
</tr>
<tr>
<td>Assessment of baseline function</td>
<td>variable reporting, investigator, independent research personnel, self</td>
</tr>
<tr>
<td>Determination of nerve sparing status</td>
<td>Intra-operative assessment</td>
</tr>
<tr>
<td></td>
<td>Variable reporting</td>
</tr>
<tr>
<td>Assessment of postoperative erectile function</td>
<td>Variable reporting, use of erectogenic medications variably reported</td>
</tr>
<tr>
<td>Proportion retraining to baseline EF</td>
<td>Rarely reported</td>
</tr>
<tr>
<td>Proportion retraining to normal</td>
<td>Rarely reported</td>
</tr>
<tr>
<td>Proportion satisfied with EF</td>
<td>Rarely reported</td>
</tr>
<tr>
<td>Timing of postoperative assessment</td>
<td>3-60 months</td>
</tr>
<tr>
<td>Rehabilitative strategy</td>
<td>Oral agents, Injectables, Vacuum Devices, Combination</td>
</tr>
<tr>
<td>Patient compliance to protocol</td>
<td>Rarely reported, precise post-operative approach to restore EF rarely reported</td>
</tr>
<tr>
<td>Comorbidity factors</td>
<td>Rarely reported</td>
</tr>
</tbody>
</table>

Table 3: Components of Ideal Study to Define True Prevalence of ED after RP

1. Establish true baseline erectile status prior to diagnosis of prostate cancer.
2. Seek partner confirmation in initial EF assessments.
3. Define comorbidity status of patients.
4. Full intra-operative description of extent of dissection, tumor location, amount of bleeding, duration of surgery, approach (open/laparoscopic/robotic, open) and confidence in nerve preservation (preferably graded).
5. Description of post-operative rehabilitation strategy and level of compliance by patient.
6. Assessment of EF post-op using validated questionnaires at frequent time points (Q 3-6 months) from surgery to at least 36 months.
7. Quality of life assessments for patient and partner at time points listed above.
It is the recommendation of the ICSM that clinicians should discuss ED prevalence rates and the limitations and implications of the currently available literature. Furthermore, patients should be given individualized outcomes based on patient and surgeon factors. On discussion, it was accepted that many urologists do not have accurate data on erectile function recovery from their own patient population. This recommendation was to circumvent the frequent occurrence of surgeons citing the best erectile function recovery figures in the literature, thus giving patients unrealistic expectations. In the absence of an available nomogram, surgeons should make an attempt to categorize the patients’ risk for postoperative erectile function recovery into good, fair or poor. This was a unanimous committee recommendation.

However, even among the very best reports the reliability of their estimated prevalence rates are suspect owing to extensive methodological shortcomings in reporting, patient bias, limited numbers and incomplete data collection related to sexual functioning. In some reports, recovery was defined as an IIEF EF domain score of 17 or greater [54] whereas most men who score in that range would certainly be unhappy with their sexual experience and would likely deem themselves as having ED. While achieving a IIEF EF domain score of 26 points or greater is generally accepted as normal erectile function, only 3 studies using this criterion, involving a total of roughly 300 men, exist in the current medical literature [55-57].

While the IIEF EF domain score of 26 is unequivocally normal, and perhaps should be the gold standard recovery definition, in a study by Teloken et al, approximately 70% of men with EF domain scores of 22-25 agreed completely or somewhat with the statement that “they could have sexual intercourse whenever they wished”[58]. It is likely that somewhere between 22 and 26 on the EF domain score represents functional erectile ability. However, even in reports where an appropriate threshold has been reported, other limitations were significant, including use of non-validated endpoints, with only two reports involving just over 100 men where information on the use of erectogenic agents was provided. In fact, we believe that men who score 26 points or greater on the IIEF EF domain while using a PDE5i or other erectogenic agent are not truly normal.

It is the recommendation of the ICSM that clinicians should use a validated instrument with recognized cut-offs for normalcy and severity in their preoperative and postoperative evaluation of their patients. It is recommended to use either the IIEF erectile function domain or SHIM with score cut-offs of 26 and 21 respectively to define normal erectile function. This was a majority recommendation of the committee. It is appreciated that many men with IIEF EFD scores of <26 and SHIM scores <21 are satisfied with their erectile function and there was significant discussion as to whether an EFD score of 21-24 was adequate. In the final analysis, the committee believed that there were published validated cut-offs for the scores recommended and that the concept of adequate erectile function should be a decision left to the patient/couple. The concept of post-surgical patients regaining erectile function ‘back to baseline’ was also discussed by the committee. We suggest that future research focus on capturing these data so that large data sets can be used to aid patients in defining the probability of returning to their baseline level of erectile function. The committee also appreciates that baseline erectile function assessment is problematic and that the ideal timing of this assessment is poorly defined. The committee understands that many men have a significant negative effect on their erectile function after the diagnosis of prostate cancer and that assessment of EF immediately prior to RP may not be fully representative of the patient’s true EF, however, asking about function prior to diagnosis of cancer is fraught with problems also not the least of which is recall bias.

Furthermore the ICSM recommends that clinicians should discuss the recognized predictors of erectile function recovery. These factors include patient age, baseline erectile function, and nerve sparing status. It should be pointed out to patients also that other factors such as comorbidity status and surgeon experience have been shown to be significant contributors to recovery. This was a unanimous recommendation of the committee. The committee also suggests that surgeons should discuss with patients the definition of nerve sparing and its implications. It is the clinical experience of the expert panel that patients do not have an adequate understanding of the concept of nerve sparing, thinking that nerve
sparing always means complete preservation and that complete preservation means there will be absence of any transient postoperative ED.

The ICSM also recommends that clinicians should provide patients with a realistic time frame for EF recovery. Patients should be informed that the period of potential recovery is 6-36 months, but that the majority of patients have functional recovery within 12-24 months after RP. It is the clinical experience of the expert panel that many patients are given recovery timeframes that are too short and generally unrealistic. This is furthermore reflected in the timing of data reporting in the published prevalence series.

Finally, the committee recommends efforts should be made by interested medical organizations including ISSM to standardize erectile function end-points.

Thus, the prevalence of ED following contemporary RP is poorly defined by the current peer reviewed literature. The existing patient database is limited by numerous methodological flaws, such as: small population reports, incomplete data acquisition, absence of consensus on a definition of success or failure to recover erections, limited data concerning quality of life and satisfaction with sexual life, of the patient and partner, variable questionnaires or in-person interviews and inadequate patient follow up.

The true impact of rehabilitative strategies on rates of erectile recovery in this population is not yet fully defined[59]. Perhaps the most prudent and reasonable conclusion one could arrive at following a careful review of the current literature related to prevalence of ED following RP is that it is common, independent of surgical approach or other patient baseline characteristics. At a minimum half of the men, independent of age, co-morbid status or exposure to adjuvant therapy instituted to improve recovery, will experience significant degrees of erectile function loss. As outlined in this section, large prospective multi-center trials evaluating the many innovative pharmacological and external devices targeting penile rehabilitation strategies are needed, to provide our patients with the essential information optimizing their erectile recovery post-RP.

RECOMMENDATION 2

Grade B
Clinicians should discuss ED prevalence rates and the limitations and implications of the currently available literature. Patients should be given individualized outcomes based on patient and surgeon factors.

III. PATHOPHYSIOLOGY

The pathophysiology of ED after radical prostatectomy involves the interplay of three factors (Figure 1): namely, neural injury, vascular injury, and corporal smooth muscle damage. Additionally, the extent and reversibility of these injuries ultimately will define the degree of recoverable erectile function.

1. NEURAL TRAUMA

It is well appreciated that transection of, or extensive thermal injury to the cavernous nerves will result in permanent loss of erectile function after surgery. However, traction and/or percussive injury to the nerves may be just as deleterious. In a recent study, Masterson et al. demonstrated that alteration in technique whereby the urethral catheter is no longer used as a traction tool to apply tension to the lateral pedicles, resulted in a significant improvement in EF recovery post-prostatectomy [37]. Three hundred seventy-two patients were evaluated: 275 patients (74%) underwent a standard technique while 97 (26%) underwent the no-traction technique. Sixty-five of the 97 patients (67%) who were exposed to the no-traction technique had recovery of functional erections at 6 months. The expected probability of 6-month EF recovery in these patients, had they been exposed to the standard technique, was 45%. Thus, the absolute improvement in EF recovery apparently attributable to the new technique was 22% (95% CI 5-40%; p = 0.013), suggesting that a no-traction approach may maximize EF recovery.
Since the initial description of the anatomic radical retropubic prostatectomy and the elucidation of the course of the cavernous nerves, many urologists have been trained to perform nerve-sparing surgery [60]. The variability in the anatomic location and distribution of these nerves, combined with variations in nerve-sparing technique and nerve handling, has resulted in variable erectile function outcomes after this refined approach. It is irrefutable that the nerve-sparing status of a RP is predictive of recovery of erectile function. Bilateral nerve sparing is associated with superior spontaneous and oral therapy–assisted recovery of erectile function compared to unilateral nerve sparing, which in turn is more likely to lead to functional erections than non-nerve sparing surgery [61-63]. However, the definition of nerve sparing is somewhat arbitrary. The term generally refers to the macroscopic preservation of the cavernous nerves, as defined by the surgeon at the time of the procedure. While rarely reported in a quantitative fashion, the degree to which nerves are spared depends on the amount of nerve handling and stretching as well as the use of electrocautery during RP as outlined above.

It is also becoming increasingly appreciated that postoperative factors, such as edema and inflammation around the bladder neck and the cavernous nerves, may in fact have a significant impact upon erectile function. Clinical experience has shown us that some men respond to PDE5 inhibitors within 4 weeks after surgery but by 12 weeks no longer respond, possibly due to ongoing postoperative Wallerian degeneration, in part perhaps, due to perineural inflammation. Data has shown that 25% of men who were functional with or without PDE5 inhibitors within the first 3 months were non-functional by the sixth month (Katz et al: manuscript under review). Recovery of functional erections was defined as a score of either 4 or 5 on question 3 of the IIEF, “Over the course of the past 4 weeks, how often were able to penetrate your partner?” Of note, in this analysis, only 14% of men were PDE5 inhibitor responders within 3 months of surgery.

Several animal models have recently focused on the pathophysiology of erectile dysfunction (ED) after radical prostatectomy (RP) [11, 64-67]. The elucidation of the key mechanisms involved in the development of ED after cavernous injury has paved the way for the potential application of penile rehabilitation protocols, aimed at reversing the complex cavernosal consequences of nerve injury during RP. Histologically, neuroapraxia/neurotomy leads to cavernosal biochemical, morphological, and functional changes at the level of both smooth muscle and endothelial cells. The first consequence of the transient or prolonged neural injury is the absence of erection and cavernosal oxygenation [11]. When penile smooth muscle cells are exposed to a prolonged hypoxic environment, there is a significant over-expression of hypoxia-related profibrotic substances, like transforming growth factor-$\beta$1 (TGF-$\beta$1) and TGF-$\beta$1 dependent endothelin-1 (ET-1), which promote the deposition of collagen I and III within the corpus cavernosum [11, 68, 69]. The increased level of TGF-$\beta$1 demonstrated in cavernosal tissue exposed to low oxygen tension seems to be mediated by the inhibition of prostaglandin-E1 (PGE1).

2. CORPORA SMOOTH MUSCLE ALTERATIONS

In normal conditions, PGE1 indeed inhibits collagen formation by inhibiting TGF-$\beta$1 that induces collagen synthesis. With the inhibition of PGE1, TGF-$\beta$1 is allowed to induce connective tissue synthesis [70]. The trabecular smooth muscle is then replaced with

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**Figure 1:** Schematic representing the pathophysiology of ED after radical prostatectomy.
collagen, which alters the mechanical properties as well as the integrity of the corpora cavernosa [11, 66]. Several studies have shown a significant increase in collagen content and a decrease in the smooth muscle-collagen ratio in the penile tissue of denervated animals compared to controls [11, 66, 71-75]. However, one of the key processes associated with neural injury and exacerbated by absence of cavernosal oxygenation is represented by apoptosis [66, 72, 75]. Apoptosis, or programmed cell death, is essential for the normal development of multi-cellular organisms as well as for physiological cell turnover. In the penis, denervation has been shown to stimulate apoptosis: it is likely that cellular apoptosis leads to increased deposition of connective tissue that may finally lead to a decrease in penile distensibility, and in turn, veno-occlusive dysfunction [66, 71, 72]. The role of apoptosis in the pathophysiology of post-RP ED has been elucidated in animal models. Klein et al [64] developed the first animal model of cavernous nerve damage aimed at addressing the extent of apoptosis in rat models after specific time intervals following nerve damage. DNA fragmentation and condensed cell nuclei characteristic of apoptotic cells were seen in the glans penis and the corporal bodies of denervated rats. Conversely, this was not seen in the sham-operated controls. Interestingly, the rise in TRPM-2, a gene product that has been postulated to play a role in programmed cell death, had a peak at day 2 after cavernous neurectomy, suggesting an early occurrence of apoptosis after nerve damage. However, the authors were unable to identify the specific cell subtypes undergoing apoptosis.

This issue was later addressed by User et al [66], who randomized post-pubertal rats to bilateral or unilateral cavernous nerve transection or a sham operation. At different time intervals following the procedure, penile wet weight, DNA content and protein content were measured. Wet weight of the denervated penes was significantly decreased after bilateral cavernous neurotomy while unilateral cavernous neurotomy allowed much greater preservation of penile weight. DNA content was also significantly reduced in bilaterally denervated penes. Confirming the findings of Klein et al, bilateral cavernous neurotomy induced significant apoptosis, which peaked on postoperative day 2. In addition, the authors found that the most apoptotic cells were located just beneath the tunica albuginea of the corpus cavernosum, in the area where the subtunical venular plexus is located. Interestingly, these investigators suggested that the apoptotic process involves smooth muscle cells but not endothelial cells. The subsequent hypothesis suggested by the authors was that the bilateral injury to the cavernous nerves may induce significant increased apoptosis of smooth muscle cells, particularly in the sub-tunical area, thus causing an abnormality of the veno-occlusive mechanism of the corpus cavernosum [66].

However, other investigators have found that the apoptotic process involves not only smooth muscle cells but also endothelial cells [76, 77]. Mulhall et have shown in a cavernous nerve crush injury model that neural injury can cause apoptosis in both smooth muscle and endothelium in a more delayed fashion compared to the neurectomy model[65]. Moreover, the exact sequence of the molecular and cellular changes involved in the development of tissue atrophy subsequent to cavernous nerve damage remains to be elucidated. The most plausible theory in explaining why the corporal smooth muscle deteriorates together with an increase in collagen content following RP is that neural injury itself might induce pro-apoptotic (loss of smooth muscle) and pro-fibrotic (increase in collagen) factors within the corpora cavernosa. The ablation by neuropraxia of certain growth factors produced by the cavernosal nerves may be responsible for inducing smooth muscle fibrosis and atrophy observed in corporal tissue [78]. However, the production of cytokines and noxious agents by the damaged nerve axons may also be the causal factor of the increased early smooth muscle apoptosis [71, 74], which in turn, may trigger collagen deposition to replace the lost cells.

3. ARTERIAL INJURY

Vascular injury involves damage to accessory pudendal arteries (APA). These arteries are variable in their incidence in the literature depending on what kind of series is assessed (Table 4): operative series, angiographic series, or cadaveric series [79-87]. APA are supra-diaphragmatic arteries (lying above the levator ani) and are predisposed to injury at the time of RP. Their origin is variable coming from femoral, obturator, vesicle or iliac arteries. These arteries can be visualized on endorectal MRI or CT scan. Cadaveric studies have the highest incidence of APA. Probably the most important study is that of Breza et al[80]. In this study, 10 cadavers underwent extensive pelvic dissection and the arterial anatomy was defined in detail. In this analysis, seven of the 10 cadavers had APA found. In seven cadavers the APA were the major source of arterial inflow into the penis and one cadaver had APA as the sole source of inflow into the corpora cavernosa. Droupy et al have shown in a small study using transrectal and transperineal ultrasound that these arteries are functional [81]. Nine of 12 patients studied had peri-prostatic arteries coursing forward towards the penis. Upon intracavernosal injection, the hemodynamic changes that were seen in the cavernosal arteries were mirrored in the peri-prostatic arteries suggesting that the APA were functional. Rogers et al have shown that APA preservation at the time of open RP translates into an improvement in erectile function recovery and possibly even shortening of the time to recovery of erections [83].
4. CAVERNOUS OXYGENATION

The concept that neuropraxia results in smooth muscle alterations has already been discussed. It is possible that this is amplified by the absence of erections. One of the purported mechanisms by which this happens is the absence of cavernosal oxygenation. This is the concept that the penis is a large vein in the flaccid state and a large artery in the erect state (Figure 2). In the flaccid state, the $pO_2$ is approximately 35-40 mm Hg. It has been postulated that this results in up-regulation of profibrotic cytokines including TGF-beta. TGF-beta up-regulates collagen production, which may eventually lead to smooth muscle fibrosis and venous leak. During erection, the penis is oxygenated with $pO_2$ rising to 75-100 mm of mercury. In vitro evidence demonstrates that oxygenation up-regulates production of endogenous prostanoids as well cAMP [88].

Moreland et al have shown in a series of in vitro experiments that exposure of cultured corporal cavernosal smooth muscle cells to a low oxygen environment suppresses PGE1 and cAMP production. Upon restoring the environment to normoxia, levels of both PGE1 and cAMP are normalized. In a further series of experiments the same authors showed that in the in vitro setting, prostanoids inhibit TGF-beta activity and thus reduce collagen production[89]. Therefore, in a healthy male there is a balance between the flaccid and erect states and as long as men obtain erections with some degree of regularity, erectile tissue health is preserved. However, after RP in a state of unantagonized flaccidity, the normal balance of factors is shifted in favor of fibrogenic cytokine production leading to structural changes and venous leak development. It is important to appreciate that as biologically plausible this mechanism is, the data are purely in vitro in nature.

Table 4: Prevalence of Accessory Pudendal Arteries (APA)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># of Patients</th>
<th>Incidence of APA (%)</th>
<th>APA preserved (%)</th>
<th>Type of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matin</td>
<td>2006</td>
<td>70</td>
<td>26</td>
<td>78</td>
<td>Laparoscopic radical prostatectomy</td>
</tr>
<tr>
<td>Secin</td>
<td>2005</td>
<td>325</td>
<td>30</td>
<td>83</td>
<td>Laparoscopic radical prostatectomy</td>
</tr>
<tr>
<td>Rogers</td>
<td>2004</td>
<td>2399</td>
<td>4</td>
<td>100</td>
<td>Radical retropubic prostatectomy</td>
</tr>
<tr>
<td>Polascik</td>
<td>1995</td>
<td>835</td>
<td>4</td>
<td>79</td>
<td>Radical retropubic prostatectomy</td>
</tr>
<tr>
<td>Droupy</td>
<td>1999</td>
<td>12</td>
<td>75</td>
<td>-</td>
<td>Transrectal color Doppler ultrasound</td>
</tr>
<tr>
<td>Rosen</td>
<td>1990</td>
<td>195</td>
<td>7</td>
<td>-</td>
<td>Angiography</td>
</tr>
<tr>
<td>Gray</td>
<td>1982</td>
<td>73</td>
<td>21</td>
<td>-</td>
<td>Angiography</td>
</tr>
<tr>
<td>Benoit</td>
<td>1999</td>
<td>85</td>
<td>70</td>
<td>-</td>
<td>Cadaveric Dissection</td>
</tr>
<tr>
<td>Breza</td>
<td>1989</td>
<td>10</td>
<td>70</td>
<td>-</td>
<td>Cadaveric Dissection</td>
</tr>
</tbody>
</table>

Figure 2: Schematic representing the concept of cavernosal oxygenation.
In a recent study Mueller et al demonstrated the potential benefit of hyperbaric oxygen therapy (HBOT) in the cavernous nerve injury model [90]. Animals with bilateral nerve crush injury were divided into treatment with room air within a hyperbaric chamber versus hyperbaric O2 (3atm) for 90 minutes. Animals were treated for a period of 10 days consecutively and at 28 days after bilateral nerve crush, animals underwent functional assessment. Using intracavernosal pressure/mean arterial pressure (ICP/MAP) ratios the animals treated with room air had an ICP/MAP ratio of 31%. This compared with ICP/MAP ratio of 55% in animals exposed to 10 days of HBOT (p <0.005).

These data support the concept that cavernosal oxygenation is important to recovery of erectile function. In data, unpublished other than in abstract form, emanating from Pfizer Central labs in the UK, a canine model was used to explore the impact of hypoxic conditions on erectile function (Wayman et al, unpublished data). In the anesthetized, ventilated dog with the cavernous nerve exposed, cavernous nerve stimulation resulted in progressively poorer ICP/MAP ratios as the FiO2 was dropped from 21% to 18%. In a second series of experiments, the pre-treatment of the animals with sildenafil citrate resulted in preservation of erectile response following cavernous nerve stimulation even under profoundly hypoxic conditions. This suggests that sildenafil at least and perhaps PDE5 inhibitors in general are capable of preserving erectile tissue relaxation profiles even under hypoxic conditions.

One of the issues that remains unresolved is what level of erectile rigidity is optimal for cavernosal oxygenation. Based on data from Kim et al and Tal et al [91, 92] it appears that minimal rigidity is required to achieve complete oxygenation of the corpora cavernosa. In 1983, Lue et al published their pioneering study describing penile hemodynamics and oxygenation during erection in a monkey model (3 monkeys) [93]. They induced erections by cavernous nerve electro-stimulation and measured arterial blood flow, corporal pressure and pO2, in the proximal and distal corpora, before and 1, 5, 20 and 30 minutes after the monkeys achieved a sustained erection. They showed that during erection, corporal blood had a higher pO2 than in the flaccid state and it remained oxygenated for the whole erection duration, even after 30 minutes of full erection. These findings were later corroborated in human subjects.

During a fully rigid erection, cavernosal pO2 is close to arterial partial oxygen pressure. Knispel et al reported that after penile injection of an erectogenic agent (papaverine/phentolamine), cavernosal pO2 rose continuously and gradually, starting after 30-60 seconds and continued up to 8.5 minutes after injecting[94]. This is in contradistinction to the steep increase in cavernosal pO2, immediately after injections, followed by a plateau, reported by Kim et al [91]. While Knispel et al did not measure ICP simultaneously with cavernosal pO2, Kim et al showed that an increase in oxygenation occurs before ICP elevation and development of rigidity. Knispel et al assessed duplex Doppler ultrasound peak arterial flow with maximal cavernosal pO2 and found good correlation in 71% of the cases. They hypothesized that in the remaining cases, lack of correlation was due to isolated cavernous perfusion defects, a hypothesis that has never been confirmed or refuted.

While oxygenation is maximal just prior to the development of a full erection, where maximum arterial inflow exists at low corporal pressure, it remains of interest if partial erections are sufficient for adequate oxygenation. In clinical practice, the association of erection rigidity and cavernosal oxygenation state is important in men who wish to regain or preserve erectile function. Commonly, an inability to fully oxygenate their corporal tissue is experienced in the early post-operative period after radical pelvic surgery when many men struggle to achieve spontaneous or medication-induced fully rigid erections. Tal et al studied 13 patients and analyzed 21 corporal blood samples aspirated at the time of cavernosometry [92]. Blood specimens were collected at an ICP range of 6-90mmHg. Mean±SD pO2 was 39±6mmHg at ICP<10mmHg, 87±2 at ICP 11-20mmHg, 89±3 at ICP 21-40mmHg, 93±5 at ICP 41-60mmHg and 103±11 at ICP>60 mmHg (Figure 3), suggesting that low cavernosal arterial inflow and pressure development permits complete oxygenation of the corpora.

![Figure 3: Correlation between intracavernosal pressure and intracavernosal pO2](image-url)
In the urogenital tract, the effect of hypoxia on smooth cell proliferation was studied in an obstructed urinary bladder model. In the initial stages, the compensatory response to bladder outflow obstruction is smooth muscle hyperplasia and hypertrophy. With increased bladder wall thickness and mural pressure, bladder wall perfusion decreases with resultant hypoxia and eventual decompensation. Galvin et al showed in a cell culture study that hypoxia did not induce apoptosis, however it significantly reduced smooth muscle cells proliferation [95]. Unfortunately, for clinical use, frequent cavernosal blood analyses or Doppler ultrasound flow measurements are not practical in monitoring such patients and a more applicable tool is needed to assure adequate cavernosal oxygenation. Thus, cavernosal blood oxygenation occurs at low ICPs, during the initial stages of erection. Additional increases in ICP and consequently, in rigidity, leads only to minimal further increases in cavernosal blood partial oxygen pressure.

5. VENOUS LEAK

Positioned between the tunica albuginea externally and the corporal smooth muscle internally are a series of sub-tunical venules. As the smooth muscle expands in a three-dimensional fashion under nitric oxide control, the sub-tunical venules are compressed against the tunica. This is the veno-occlusive mechanism. In conditions where the muscle fails to expand adequately some or all of the sub-tunical venules are left in a non-compressed state and this results in the concept we know as venous leak (synonyms: corporovenocclusive dysfunction, venogenic ED). The two things that lead to failure of the corporal smooth muscle to expand are adrenaline, the world’s most potent anti-erection chemical, and structural changes such as fibrosis.

Nehra et al. have shown in human corporeal tissue biopsy taken at the time of cavernosometry, once smooth muscle content in the penis drops below 40% venous leak occurs[96] (Figure 4). Indeed, the further this figure dropped below 40%, the greater is the magnitude of leak. Iacono et al have shown that as early as two months after radical prostatectomy in an untreated man there is a marked increase in collagen deposition and a marked decrease in elastic fiber content in erectile tissue[10]. This is in keeping with the animal data outlined above that suggest even in the earliest stages after cavernous nerve injury, structural changes occur.

Mulhall et al have shown in a series of 16 patients who had preoperative and postoperative hemodynamic assessment that more than half of the men had venous leak after surgery[97]. In a more recent analysis by Mulhall et al[98], in men who had partner-corroborated excellent erectile function prior to surgery, who underwent duplex Doppler penile ultrasound after surgery, there was an increase in the incidence of venous leak (based on elevated end diastolic velocities) as time progressed after surgery (Figure 5). The incidence of venous leak less than four months after surgery was approximately 10% and rose to 35% between 8-12 months after surgery and 50% after 12 months. The importance of this information is that in the same series, men with normal erectile hemodynamics were more likely to have recovery of natural erectile function. However, only 8% of men who had venous leak had recovery of natural functional erections after surgery. We also know from other data that men with venous leak are far less likely to respond to PDE5 inhibitors than men with arterial insufficiency [99].

It is the recommendation of the ICSM that in an effort to facilitate the discussion on erectile function rehabilitation, clinicians should discuss the pathophysiology of erectile dysfunction after radical prostatectomy. Factors that clinicians should discuss include including the concepts of accessory pudendal artery injury, cavernosal oxygenation, erectile tissue structural alterations and venous leak. While the committee does not expect all clinicians to be experts in the pathophysiology of post-RP ED, it is suggested that all develop a simple script for patients to communicate not just what the rehabilitation strategy involves but also the rationale behind it, which is based on the pathophysiology of post-RP ED.

*Figure 4: Correlation between cavernosal smooth muscle content and flow-to-maintain values (venous leak) during cavernosometry.*
RECOMMENDATION 6

Grade C

To facilitate the discussion on erectile function rehabilitation, clinicians should discuss the essential elements of the pathophysiology of erectile dysfunction after radical prostatectomy.

IV. BASIC SCIENCE EVIDENCE REGARDING REHABILITATION

1. NEUROMODULATORY AGENTS

As is clearly evident by the limited approaches available for optimization of erectile function post-radical prostatectomy[12], significant therapeutic and knowledge gaps remain between the primary pathophysiologic mechanism responsible (nerve injury) and treatment. Contemporary options available to the clinician are ‘reactive’ responses to the damage initiated at surgery and subsequent downstream changes that result from compromise of cavernous nerve (CN) signaling due to intraoperative injury (for nerve-sparing procedures) or non-reversible nerve damage/nerve excision. Despite a rapid growth in basic science understanding of tissue and cell-level response to injury, the treatment goals of neuromodulation of the cavernous nerve response to injury at surgery (with potential of pre and post-operative optimization) to promote nerve regeneration and neuroprotection remains elusive. Neither PDE-5 inhibitors nor vasoactive injection therapy has been definitively shown to directly influence CN pathobiology. It is likely that future penile rehabilitation treatments will require combination strategies to counter primary and secondary injury, including nerve-centered foci enhancing axonal regrowth, inhibiting apoptosis, and promotion of synaptic plasticity via neurotrophic factors, stem cell therapies, or neural and smooth muscle protectants [100]. For non-nerve sparing procedures, neuromodulatory interventions are more limited, but may include seeded nerve “bridges” or “scaffolds” to counter the significant physical gaps following cavernous nerve excision at radical prostatectomy; penile rehabilitation in these groups will remain a challenge, and likely focus on end-organ preservation (endothelium and smooth muscle) while the nerve signaling continuum is re-established.

At the core, the concept of neuromodulatory therapy post-RP encompasses the basic science of neurotrophic growth factors, neuroprotection, nerve regeneration and establishment of signaling continuity, neuronal stem cells, and the prevention of neuronal cell death as it applies to the nerve supply of the penis [100]. For example, approaches conceivably range from the exogenous supply or endogenous optimization of nerve growth factors that improve axonal regeneration or accelerate target re-innervation, to introduction of progenitor cells allowing for replacement of non-viable tissue. The translational potential of neuromodulatory therapy is based upon the fact that although the peripheral nervous system demonstrates an intrinsic ability to recover after injury, this endogenous response is somewhat limited and does not usually allow for a full recovery of function as axonal degeneration and loss of neurogenic function occur [101-103].

Various types of CN injury have been studied in an attempt to model RP-associated CN injury using primarily rodent models, including crush, freezing, transection, and excision of the CN either unilaterally or bilaterally depending on the underlying aims each particular experiment[104]. Detailed anatomic studies in animal models have demonstrated that CN crush does not disrupt the nerve sheath and may provide a nerve conduit or ‘guide’ for regenerating axons[105]; although it is a less severe injury model (attempting to approximate nerve-sparing procedures), cavernous nerve electro-stimulation proximal to the injury consistently results in decreased intracavernous pressure readings compared to intact animals and allows for testing of hypotheses for new treatment approaches via measurement of physiologic function [13, 65, 106, 107]. More severe types of injury include transection (where the outer neurolemma sheath is disrupted) and excision, the latter excluding the possibility of erectile tissue responsiveness [9, 66]. Burnett and colleagues demonstrated that nitric oxide (NO) is a neuronal transmitter-like messenger and physiologic mediator of erection via CN neuronal fibers innervating the corpora cavernosa [108]. One week after performing...
bilateral CN transection, NOS immunoreactivity was absent in penile neurons, compared to sham. Downstream changes secondary to nerve injury include smooth muscle and endothelial apoptosis, reduced nitric oxide synthase (NOS) nerve density, upregulation of fibrogenic cytokines, pathological signaling responses, and corporal veno-occlusive dysfunction [72, 101, 104].

a) Neurotrophic Factors

Evidence suggests that a return to functional erection status following injury to the CNs is dependent in part, upon axonal regeneration in the remaining neural tissues and upon successful functional re-innervation of the end-organ (intact synapses and neuronal NO reactivation) [109]. Endogenous neurotrophins (NTs) play key roles in the survival, development, and differentiation of neurons in the peripheral nervous system. There is great interest in the potential therapeutic stimulation of endogenous NT response or exogenous application of this family of molecules which include the classical NTs: brain-derived nerve growth factor (BDNF), nerve growth factor (NGF), and NTs 3-5, (binding to two distinct classes of glycosylated receptor: the p75 NT receptor and tyrosine kinase receptors) as well as atypical agents such as erythropoietin (EPO), morphogenetic factor Sonic hedgehog (SHH) protein, glial cell line derived NTs such as neuritun, and bone-morphogenetic proteins (BMP) [100, 101, 109].

The Lue group at the University of California San Francisco, has demonstrated BDNF enhanced recovery of erectile function and regenerated NOS-containing nerve fibers using established in vivo rat models of neurogenic impotence, as well as subsequently showing that CN axotomy upregulates in vivo expression of penile BDNF and leads to endogenous activation of the JAK/STAT pathway in the MPG [110-112]. BDNF has also been shown to exert its effects on several classes of neurons, acting in an autocrine or paracrine fashion early after nerve injury and distally to the site of trauma (end-organ response) [100]. Vascular endothelial growth factor (VEGF) treatment in a rat model of traumatic arteriogenic erectile dysfunction is also associated with intrapenile nerve fiber growth, demonstrating a secondary neuromodulatory role in addition its better known angiogenic effects [112, 113]. Application of IGF-1 and IGF binding protein-3 complex also leads to the regeneration of penile nerve fibers and enhanced erectile function recovery in a rat model of cavernous nerve ablation [114]. Post-bilateral crush injury recovery of erectile function in the rat model has also shown improvement with treatment using growth-differentiation factor-5 (a BMP), whose effector pathways include intermediary serine/threonine kinase receptors [115] and neuritun (a target-derived survival and/or neuritogenic factor for penile erection-inducing postganglionic neurons) [116, 117]; a key point is that the external location of the penis allows for intracavernous introduction and retrograde transport of potential therapeutic agents to the site of injury [116]. However, there have been no translational trials to date for the classical neurotrophins, as potential limitations include whether the administration of neurotrophic compounds to the site of injury or penis itself (which may be feasibly performed before, at, or after surgery) could exert adverse mitogenic effects upon remaining loco-regional cancer cells, and difficulties for in vivo human dosing as positive treatment effects tend to occur within defined neurotrophin concentrations.

The Burnett group at Johns Hopkins has recently explored the use the atypical neurotrophic cytokine/hormone erythropoietin (EPO) as a neutrotrophic factor in the cavernous nerve injury model [118]. Initially, male rats underwent unilateral CN transection and excision of a 5 mm segment of the contralateral CN, with daily rhEPO effectively recovered erections after CN injury compared with saline treatment. Maximal intracavernous pressure area under the curve normalized to mean arterial pressure was significantly greater in EPO treated versus saline treated animals (p <0.05) [119]. EPO receptor expression was localized to neuronal cell bodies of the major pelvic ganglion, penile nerves and endothelial cells in the penis, and electron microscopy revealed significant improvement in axonal regeneration [119].

Podlasek and colleagues have identified substantial potential for sonic hedgehog protein (SHH) for penile delivery in prostatectomy patients at the time of surgery in order to prevent apoptosis induction and long-term ED development [109]. Although SHH is a secreted protein regulating cellular proliferation, apoptosis, differentiation, and cell survival, and is expressed at sites of mesenchymal–epithelial interaction, recent studies have identified the presence of SHH in Schwann cells, suggesting a role for the SHH pathway in maintaining CN integrity [120]. Previously, SHH inhibition in the pelvic ganglia resulted in increased apoptosis in the penis, in addition to SHH’s role in smooth muscle preservation [121]. Cumulatively, these results suggest that SHH may be a Schwann cell factor and that SHH is an important neuromodulatory target for neural regeneration after CN injury.

b) Immunophilin Ligands

Immunophilins are a large group of cellular proteins that were initially identified as targets for drugs like FK506 (FK), cyclosporine, and rapamycin (Rapa) and have undergone extensive preclinical CN injury studies demonstrating CN neuroprotective effects [103, 107, 122-125]. The term immunophilin refers
to two families of soluble, intracellular proteins that act as receptors for the aforementioned immunosuppressant agents. The group identified as FK binding proteins (FKBPs) binds to tacrolimus and rapamycin while cyclophilin binds with cyclosporine A [126]. It is known that the tacrolimus/FKBP-12 complex acts as an immunosuppressant by inhibiting activation of calcineurin, an enzyme required for cytokine transcription and ultimately activation of antigen-reactive T cells. The discovery of increased concentrations of immunophilins in the central nervous system and specifically FKBP-12 in the peripheral nerves has lead to further investigation of a potential therapeutic role for immunophilins [127]. Tacrolimus, a macroline immunosuppressant which is FDA-approved for the prevention of allograft rejection in liver and kidney transplantation. Tacrolimus is an immunosuppressant with proven anti-inflammatory, neuroprotective, and neurotrophic effects. It is currently under development in the United States for asthma, acute stroke, psoriasis, and rheumatoid arthritis. The neuroprotective properties of tacrolimus have been demonstrated using various animal models of focal cerebral ischemia that mimic human ischemic brain damage caused by stroke. Sharkey and Butcher compared tacrolimus to saline in rats that were subjected to middle cerebral artery occlusion [128]. Tacrolimus was found to be neuroprotective at doses of 0.1–1.0 mg/kg body weight; cortical damage was reduced in tacrolimus-treated animals by 58%–65%. This study also examined the timing of drug administration to determine if there was an optimal therapeutic window. Animals that received tacrolimus 60 minutes post-occlusion had significantly less reduction in cortical damage than those who received the drug after 1 minute (p<0.05). Tacrolimus was the only immunophilin ligand that was found to be effective in these experiments.

The process by which tacrolimus exerts its neuroprotective effects is unknown. It is thought that the inhibition of calcineurin may play an important role in the neuroprotective process either by regulating calcium channel activity or by reducing free radicals through the inhibition of the calcineurin-mediated dephosphorylation of an enzyme required for nitric oxide production [128]. Gold et al. first reported on the axonal regenerative properties of tacrolimus following a study of sciatic nerve crush in rats [129]. The animals that received tacrolimus had function return in their hind feet more quickly following injury. In additional studies by the same investigators, animals received two 30-second crushes to the sciatic nerve and were administered daily subcutaneous injections of either tacrolimus or saline. Electron microscopy was used to evaluate axon regeneration after 18 days of treatment. Rats that received tacrolimus demonstrated larger, more myelinated axons distal to the crush site than those treated with saline [129, 130].

Previous studies utilized tacrolimus doses that were considered therapeutic for immunosuppressive properties. An efficacy study was completed using low-dose tacrolimus to potentially reduce associated side effects of the drug [131]. Animals were randomized to receive either no treatment or a 0.5 mg/kg dose for 2 or 3 months after a sciatic nerve transaction and suture. This dose was chosen by the investigator as it had been determined to be sub-therapeutic in previous allograft transplantation studies. Both groups of tacrolimus-treated animals had a faster functional recovery and demonstrated no drug-related side effects. At the 3-month postsurgical assessment, both the tacrolimus-treated groups had significantly greater muscle mass ratios than the untreated group (p<0.05). Both treatment groups had greater fiber density and more neural tissue at the 2 and 3 month assessments despite discontinuing study drug at 2 months in half the animals. There was a significant increase in muscle weight in the treated animals between the 2 and 3 month assessments compared to the untreated animals (36% vs. 7%, p<0.05). This study demonstrated that an immunosuppressive dose of tacrolimus was not required to obtain significant neuroregenerative effects. Several possible pathways have been postulated to explain the regenerative effect of tacrolimus, including increasing growth proteins and stimulating nerve growth factor [131].

Animal studies also provide support for a potential role for tacrolimus as neuroprotective for penile innervation. Sezen, Burnett, and colleagues performed partial penile nerve crush injuries using multiple 15- or 60-second forceps applications to rats in an attempt to mimic the nerve injury associated with nerve-sparing RP [122, 123]. These rats were treated simultaneously with daily injections of tacrolimus (1 mg/kg) or saline solution. Erectile response was measured by changes in the intracavernosal pressure induced by electrical stimulation. Rats that received tacrolimus had a 90% intracavernous pressure response following stimulation of the cavernous nerve compared to the sham operated side. Saline-treated animals response was 50% of the sham-operated side. Tacrolimus-treated animals had a significantly greater erectile response on the uncrushed side, 54% compared to controls, 24% (p<0.05).

Surviving unmyelinated axons in the cavernous nerve distal to the crush site were quantified using electron microscopy for each rat. Saline-treated rats had 30%–40% axonal survival compared to 65%–80% in drug-treated animals. In those that received saline, the degenerated axons manifested swelling of the axon profile and clearing of the axoplasm. These results were found at 1, 3, and 7 days after injury [123].
Burnett et al. demonstrated long-term recovery of erectile function with tacrolimus treatment. A limited pelvic dissection and focal transection of the right cavernous nerve was performed on a rat model. Postoperatively the animals received either tacrolimus or saline solution subcutaneously for a period of 5 days. After 4 weeks, rats treated with tacrolimus showed improved penile erection following neurostimulation of both the non-transected left and transected right cavernous nerves, as measured by intracavernosal pressure (ICP). The percent recovery of ICP in the right cavernous nerve was found to be 77% in the animals treated with study drug versus 43% in the saline-treated animals (p=0.019) [122].

Although the neuroprotective and neuroregenerative mechanism of action of the immunophilin ligands has not been fully elucidated, it may be through calcineurin inhibition that the FKBP12-tacrolimus complex exerts its effect. In a recent study in rats, tacrolimus was associated with better erectile response after cavernous nerve injury than a non-immunosuppressant immunophilin ligand (GP1-1460), as measured by stimulated intracavernous pressure [132].

The immunophilin ligand tacrolimus has been shown to be both neuroprotective and neurotrophic in numerous animal studies using a variety of models. This effect has significantly improved the erectile function in animals receiving injuries similar to those from nerve-sparing retropubic RP. Most recently, Mulhall et al. demonstrated in the rat model of cavernous nerve crush injury that short-term tacrolimus results in significant preservation of cavernous nerve architecture, confirming the findings of Burnett et al. in a slightly different model with a different dosing strategy [103].

The major concern about agents like tacrolimus is their immunosuppressant properties (although no signs of such were seen at the doses used in the aforementioned clinical trial). Thus, great interest in the development of non-immunosuppressant, immunophilin ligands was generated, and Guildford Pharmaceuticals (now defunct) developed a series of compounds. GPI-1046 was shown in vitro to stimulate neurite growth in co-culture models [133]. A recent study examined the effect of FK506 and GPI-1046 on rats who had undergone cavernous nerve injury [132]. This study found that animals treated with either FK506 or GPI-1046 had significantly greater recovery of erectile function compared to animals treated with saline. Electrically stimulated maximal intra-cavernous pressure and rate of tumescence were better in the treated animals compared to controls. Based on these preliminary animal data, a multi-center, randomized, placebo-controlled trial was conducted assessing two doses of GPI-1485 against placebo in patients treated with RP. Six-month data presented at the 2007 annual meeting of the AUA failed to demonstrate any significant differences in IIEF scores between placebo and treatment groups. As the company has since dissolved, it is unclear whether any later data will ever be seen. Most recently, laboratory data has been presented on FK1706 a non-immunosuppressant derivative of FK506 [134].

c) Erythropoetin

Erythropoietin stimulates erythropoiesis under hypoxic conditions. Recently, it has been shown that erythropoietin protein and its receptor are expressed within the central and peripheral nervous systems [135]. Administration of erythropoietin in animal models of neurodegenerative diseases and toxic insults of the brain, spinal cord, and sciatic nerve results in reduced neuronal damage and improved nerve recovery [136]. A recent clinical trial confirmed the therapeutic efficacy and safety of recombinant human erythropoietin administration to recover function in patients suffering from acute ischemic stroke [137].

The recently established role of erythropoietin as a neurotrophic agent has stimulated interest in its use in men after RP. In a rat model of cavernous nerve injury, Burnett and colleagues at Johns Hopkins have shown that erythropoietin promotes the recovery of erectile function [138]. They also confirmed localization of the erythropoietin receptor to the major pelvic ganglia and cavernous nerves [139].

d) PDE5 Inhibitors

Recent evidence has shown a potential neuroprotective effect of chronic PDE5i treatment. In a cavernous nerve injury model, chronic sildenafil treatment (20 mg/kg) was associated with an improvement in neural organization and greater density of myelin sheaths compared with the control group [75]. These descriptive findings of the improved cavernous nerve preservation with daily sildenafil administration were consistent with the functional data reporting increased maximal intracavernosal pressure (ICP)/mean arterial pressure (MAP) ratio during electrical cavernous nerve stimulation [75]. These results are also supported by emerging evidence of enhanced angiogenesis, axonal remodelling and synaptogenesis as well as neurological recovery in a rat model of stroke treated with sildenafil or tadalafil [140, 141].

e) Stem Cells

The neuromodulatory action of stem (progenitor) cells as part of penile rehabilitation may eventually involve their application and subsequent differentiation into elements that function as cellular substrates for axonal growth, release neurotrophic growth factors and cytokines, inhibit demyelination or replace non-viable or non-functional neuronal elements[100]. Embryonic and autologous adult adipose-derived
stem cells have shown improved preservation of cavernous nerve fibers and improved erectile function in rats exposed to CN crush injury [142-144]. Early results for these, and other erectile dysfunction stem cell therapies are promising; however stem cell neuromodulation is in its early phase and clinical application in the post-RP setting is likely years away [145, 146].

2. ERECTILE TISSUE PRESERVATION
   a) PDE5 inhibitors

Recently, emerging experimental data have demonstrated a benefit to penile rehabilitation after cavernous nerve injury in animal models. Recent studies focusing on the molecular mechanisms of apoptosis and fibrosis have elucidated the potential mechanisms involved in the beneficial effect of chronic use of pro-erectile drugs such as PDE5i in this animal model. Emerging scientific evidence suggests that persistently elevated levels of nitric oxide (NO) and cGMP may have an anti-fibrotic effect on a variety of tissues, including tunica albuginea and corporal tissue [147, 148]. Since PDE5i work by inhibiting the enzyme that degrades cGMP, this may be a key means of anti-fibrotic action of PDE5i. In this context, several studies have demonstrated a reduced amount of collagen deposition and fibrosis in penile tissues of animals chronically treated with PDE5i [71-75, 149].

Ferrini et al [71] found that chronic vardenafil was effective in preventing both the fibrosis and loss of smooth muscle seen following bilateral cavernous nerve resection. Compared with the sham group, rats exposed to nerve injury demonstrated a three-fold increase in corporal smooth muscle apoptosis, a 60% reduction in the smooth muscle:collagen ratio, a two-fold increase in inducible NO synthase (iNOS) expression and development of venocclusive dysfunction (CVOD). When vardenafil was given daily for 45 days to the animals that underwent bilateral nerve resection, the corporal smooth muscle:collagen ratio was normalized and the subsequent CVOD was prevented. The authors suggested that the effect of vardenafil in preventing corporal fibrosis might be mediated by an increased iNOS expression and activity. Prolonged endogenous induction of iNOS seems to produce sufficient NO to reduce collagen synthesis, inhibit TGF-β1 expression and myofibroblast differentiation, and activate metalloproteinases that break down collagen [150].

Similar results have been reported in other animal models of post-RP ED using continuous long-term administration of sildenafil as well as tadalafil [14-16,24-26]. Mulhall et al[75] demonstrated that chronic administration of sildenafil given subcutaneously daily for three different durations (3, 10, 28 days) resulted in preservation of the smooth muscle-collagen ratio. In this series of experiments, the investigators also showed increased expression of the endothelial factor CD31 and increased phosphorylation of Akt and eNOS, which may account for the endothelial protection mediated by these agents. Similarly, Vignozzi et al[149] found that chronic tadalafil administration (120 days) to rats reversed the decline in the cavernosal smooth muscle:collagen ratio that occurred after bilateral cavernous neurotomy.

Interestingly, the efficacy of Sildenafil after neural injury seems to be directly related to the timing of its administration. Indeed, the effect of this drug on all post-neural injury alterations (such as penile hypoxia and over-expression of the pro-fibrotic ET-1 type B receptor) was more evident the earlier it was administered [151]. Therefore, at least at the animal level, the effect of sildenafil in reversing the alterations induced by penile denervation and hypoxia was higher in the early stage of the disease. Furthermore, the effect of chronic sildenafil in improving erectile function after cavernous nerve injury has been shown to be time and dose-dependent[75]. The highest rate of erectile function recovery indeed occurred with higher doses and longer time of sildenafil administration. Preliminary work presented by the Mulhall group at Memorial Sloan Kettering Cancer Center, but yet published, suggested that administration of sildenafil 3 days prior to cavernous nerve crush injury resulted in even further improvements in erectile function and tissue preservation.

However, chronic treatment with PDE5i might exert at least some of its beneficial effects through much more complex mechanisms than a simple sustained increase in intra-cellular cGMP. We have previously briefly reviewed the potential for neuromodulatory effects of PDE5i. The effect of chronic administration of PDE5i might also be associated with structural and functional changes, which may involve not only smooth muscle cells but also endothelial function. The first proof of such association was given by Behr Russel et al [152] who showed that a daily, eight-week treatment with sildenafil (60 mg/kg) administered subcutaneously to neurally intact rats was associated with enhanced endothelium-dependent relaxations of cavernosal strips to acetylcholine after chronic treatment with sildenafil. Conversely, relaxations in response to sodium nitroprusside were unchanged after sildenafil treatment. Moreover, the erectile responses to acute sildenafil were greater in chronically sildenafil treated rats. The findings suggested that the endothelium-dependent response is promoted by long-term PDE5i treatment and that the therapy does not confer an adverse effect on cavernosal tissue responsiveness involved in physiological erection. The investigators concluded that long-term sildenafil treatment may have long-lasting, physiologically significant erectile tissue benefits. The effect of chronic treatment with PDE5i seems to be mediated by increased Akt-dependent endothelial NOS (eNOS) activation[153]. This is key,
since the predominant proportion of data suggest that endothelial eNOS plays a major role as homeostatic regulator of penile vascular function and health[154]. Similar results reporting improved eNOS activity and endothelial relaxations after chronic treatment with sildenafil have also been obtained in animal models of diabetes as well as of age-associated ED[152, 155, 156].

The effect of chronic PDE5i on endothelial function might not be only mediated through increased eNOS activation. Indeed, recent studies have suggested a restoration of endothelial progenitor cells (EPCs) to normal levels in patients with ED treated chronically with PDE5-I (either sildenafil, tadalafl or vardenafl) [157-160]. The role of NO in EPC mobilization as well as activation has been recently demonstrated. Moreover, it has been demonstrated that a lack of eNOS induces defective haematopoietic recovery and PC mobilization[161]. The effect of chronic PDE5i in increasing the number of circulating EPCs might be the effect of the inhibition of PDE5 in the bone marrow. Of note, reverse transcriptase-polymerase chain reaction analysis showed that human bone marrow expresses PDE5 messenger RNA [162].

Finally, chronic administration of PDE5i has also been shown to reduce the cavernosal apoptotic process after cavernous nerve injury[75, 76]. The effect of PDE5i in decreasing the number of penile apoptotic cells in cavernous injured models appears to be mediated by the phosphorylation of the survival associated kinases Akt and extracellular signal-regulated kinase (ERK) 1/2 [76]. The effect of chronic PDE5i in reducing apoptosis has also been studied in clinical scenarios other than post-RP models. Salloum et al. demonstrated that both sildenafil and vardenafil reduced the area of cardiac necrosis in a rabbit model of cardiac ischaemia-reperfusion[163, 164]. Das et al. using mouse cardiac myocyte cells exposed to hypoxia and reoxygenation showed that sildenafil-treated cells demonstrated less necrosis and apoptosis than control cells[165, 166]. Interestingly, sildenafil-treated myocytes demonstrated an early increase in the ratio of the antiapoptotic protein Bcl-2 compared with the pro-apoptotic protein Bax, which may have been responsible for the anti-apoptotic effect of sildenafil. The increase of Bcl-2/Bax ratio, as well as the anti-apoptotic effects of sildenafil, were inhibited by treatment with the NOS inhibitor l-nitro-amo-methyl-ester, suggesting the role of NO signalling in the protective effect of the drug against apoptosis[165].

V. CLINICAL EVIDENCE REGARDING REHABILITATION

Regardless of the technique, the removal of the prostate appears to result in an obligate period of neuropraxia with secondary end-organ damage and resulting ED of varying degrees [10]. In a longitudinal penile biopsy study after RP, profound histologic changes were observed in human erectile tissue microstructure in men not enrolled in any penile rehabilitation program [10]. These changes were observed as early as two months after surgery. The erectile tissue became progressively disorganized with a decrease in the number of elastic and smooth muscle fibers, and an increased accumulation of collagen. This was accompanied by a complete lack of response to three challenges of 100 mgs of sildenafil at 2 months. Disappointment with surgical results has led to attempts at improving outcomes. While the aforementioned animal experiments have demonstrated clear benefit to pharmacologic manipulation, few good human rehabilitation trials exist. Rehabilitation strategies have grown over the past decade and include (i) neurmodulatory agents (ii) intracavernosal injections (iii) PDE5i (iv) intraurethral alprostadil and (v) vacuum therapy.

Most studies assessing penile rehabilitation are small, single center, non-randomized and suffer major methodological flaws [4]. Differing outcome measures and non-uniformity of data presentation and inclusion criteria, have made comparison between trials difficult. Despite a lack of robust human data, in a survey conducted by Teloken et al, among 301 physicians from 41 countries, almost 84 % performed some form of sexual or penile rehabilitation, including post operative PDE5i (95%), ICI (75%), vacuum erection device (30%), and intraurethral alprostadil (10)(Teloken, 2009 #4336). Slightly less than half of the respondents (48%) started penile rehabilitation at the time of catheter removal and 37% initiate their rehabilitative strategy within the first 4 months. Though rehabilitation is widely practiced, there exists no consensus on what represents the optimal program.

1. NEURMODULATORY AGENTS

Despite robust data on a variety of neurmodulatory agents in animal models, no such data exists in the RP population. Although a recent clinical trial (phase II, multicenter, randomized, double-blind, placebo-controlled, three-arm, 12-month study) conducted in men undergoing nerve-sparing RP and treated with GPI-1485 did not reveal significant agent efficacy, it is possible that drug formulation or scheduling was suboptimal and further investigation in this area remains warranted (Burnett, A.L. personal communication). Based on the aforementioned animal data, a multi-center, randomized, placebo-controlled trial has recently been conducted assessing the impact of tacrolimus in men undergoing RP. Patients were randomized to placebo versus tacrolimus (2–3 mg) beginning 7 days before RP and continuing for 6 months after surgery. Data should be available in the first half of 2010.
The Johns Hopkins group has recently presented data on the potential clinical use of erythropoietin as a neuromodulatory agent to preserve erectile function in men undergoing RP [167]. In this clinical study, those patients opting for erythropoietin treatment (in a non-randomized fashion) received a single dose (40,000 IU administered subcutaneously) of recombinant human erythropoietin in the form of Epoetin-alpha on the day before surgery. This dosing was consistent with dosing used in the clinical trial for acute stroke. The final analysis consisted of 15 erythropoietin-treated patients (treatment group) and 21 patients who did not receive erythropoietin treatment (control group). The mean preoperative IIEF-5 score for both the treatment and control groups was 24. At 12 months, 87% of the erythropoietin-treated and 68% of the untreated patients reported performing sexual activity, although these rates were not significantly different (p=0.213). However, a significantly greater proportion of erythropoietin-treated patients reported erections that could be maintained to complete sexual intercourse (47%) compared with that of untreated patients (16%; p<0.05). A larger randomized, placebo controlled trial is planned.

It is likely that future patients undergoing radical pelvic surgery will receive multimodal therapy to promote erectile function recovery including agents that are neuromodulatory (Table 5). Future neuromodulatory directions may include (i) oral systemic agents that have proven efficacy in humans, (ii) the perineural application of neuromodulatory molecules to the cavernous nerves at the time of radical prostatectomy, (iii) the use of implantable neurostimulators proximal to the site cavernous dissection in an effort to promote neuroregeneration[168], and (iv) novel means of cavernous nerve visualization. A number of laboratories are exploring proprietary agents that can be applied to the cavernous nerve intraoperatively, but no data has yet been presented or published. Burnett et al have reported on a feasibility study assessing an implantable electrode around the cavernous nerve[168]. Prior work has demonstrated that cavernous nerve stimulation can lead to an intraoperative erection in animal and human models. Electrical stimulation of the cavernous nerve has resulted in increased arterial flow, relaxation of cavernous muscles, and venous outflow restriction in monkeys [169], dogs [169] and rats [170]. Intraoperative stimulation of the cavernous nerves to induce penile erection in humans has previously been performed [171].

2. INTRACavernosal INjections

The first prospective randomized post-RP rehabilitation study involved penile injection therapy. In the late 90’s most urologists believed that long term ED after NSRRP was due to poor surgical technique and men were generally counseled to wait one year before addressing their post operative ED. Montorsi demonstrated a benefit to using intracavernosal injections using alprostadil (PGE1) monotherapy on the return of “spontaneous erections satisfactory for sexual intercourse” [172]. All men “reported normal preoperative erections allowing for satisfactory sexual intercourse at all times”. This study predated validated erectile function questionnaires hence no baseline or postoperative questionnaires were used. One month after surgery, subjects were randomized to intracavernosal injections of alprostadil three times per week versus no therapy. It was not declared whether patients were enrolled into the trial after or before surgery or what the randomization process involved.

This study was conducted in the pre-sildenafil era, so that PDE5i use was not an issue. Injections were started one month after surgery and continued for

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3 months, after which the patients were evaluated. The outcomes were patient reported successful intercourse, nocturnal penile tumescence (NPT), and penile duplex Doppler studies. No preoperative NPT studies or Doppler studies were performed. 8/12 (67%) completers in the treatment group recovered erections vs. 3/15 (20%) in the observation group. The group that recovered erectile function used ICI before sexual activity no more than 1/3 times. For such a short term follow up of 4 months, these results are unparalleled in contemporary studies. Interpretation of the objective results is difficult as authors only provided summary data and did not indicate what NPT or Doppler parameters they considered “normal”. (Figure 6). This study provided the first signal that intervening pharmacologically in the early post operative period might beneficially impact recovery of erectile function after nerve sparing surgery but the study suffered from low numbers and has never been duplicated or carried out on a larger scale. The authors hypothesized that the absence of cavernosal oxygenation occurring during the early postoperative period reduced “the percentage of functional smooth muscle cells with a concomitant increase of cavernous fibrosis and deterioration of erectile function”.

In 2005, Mulhall et al in a non-randomized study of 132 patients compared patients who opted for penile rehabilitation versus those who did not pursue rehabilitation [57]. All patients had partner-corroborated functional erections preoperatively. Patients studied were seen by a sexual medicine physician only after surgery but within the first 6 months. At that time, they opted for either the rehabilitation program or no intervention. The protocol consisted of an initial challenge with sildenafil (on four occasions at 100 mg). If an erection of “≥60% rigidity” (penetration hardness) was obtained, patients were encouraged to use this medication to obtain three erections per week. If sildenafil failed to induce such an erection, patients were encouraged to consider penile injection therapy, depending on tolerability. Three injection-induced erections per week were encouraged. All patients were followed every 4 months until they were 18 months postoperatively. Sildenafil failures were instructed to re-challenge themselves every 4 months after surgery to determine if they had become responders. Once this occurred, they were permitted to cease injections if they wished and to use sildenafil three times a week to achieve erections. All patients were followed every 4 months until they were 18 months postoperatively.

The average time from surgery was over 4 months, missing the benefit of early intervention. The rehabilitation group agreed to participate in the program and comply with the protocol for at least 12 months (58 men). “Patients who decided not to pursue the program of treatment but who presented for follow-up for periodic evaluation of their erectile function constituted the no rehabilitation group” (74 men). Overall, 67% of the group had bilateral nerve

![End-Points in Montors Post-RP Rehabilitation Trial (1997)](image)

*Figure 6: End-points in the Montorsi rehabilitation study using intracavernosal injections as a strategy.*
sparing surgery, 11% unilateral nerve sparing, and 22% non-nerve sparing. No attempt was made to stratify results by nerve sparing as the nerve sparing status was roughly equal between groups.

Those in the rehabilitation group averaged 1.9 erections/week. The patients opting for rehabilitation had significant improvement in natural response (52% vs 19%), sildenafil response (64% vs 24%) and intracavernosal injection response (95% vs 76%). Though the results are supportive of penile rehabilitation the strength of the conclusions are severely weakened by its non-randomized nature, introducing significant potential for investigator bias and patient motivation issues.

3. PDE5 INHIBITORS

There exist two large prospective, randomized, multi-centered controlled studies after BNSRP; one assessing sildenafil and the other vardenafil. The sildenafil trial was designed shortly after the drug’s approval[14]. It was designed when the existing radical prostatectomy literature quoted “potency preservation” rates of greater than 80% after BNSRP at centers of excellence and rehabilitation was not the standard of care. The study designers set out to “evaluate the efficacy of prophylactic, nightly use of sildenafil in preventing long-term ED”. The second objective was to investigate the effects of sildenafil on nocturnal penile erections after BNSRP. It was not designed to evaluate the efficacy of sildenafil after BNSRP. Montorsi et al had previously shown that the use of sildenafil at night enhanced nocturnal penile tumescence [173]. Improving nocturnal erections was thought to improve penile oxygenation and minimize the theoretical hypoxic damage to the cavernous tissue during the period of neuropraxia after RP.

The a priori determined primary outcome in this trial was preservation of natural erectile function, defined as a combined score of at least 8/10 on questions 3 and 4 of the International Index of Erectile Function (Q3 "Over the past 4 weeks when you attempted intercourse, how often were you able to had penetrate your partner?"; Q4 Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?) and a “yes” answer to the question, “Over the past 4 weeks, have your erections been good enough for sexual activity?”. The secondary endpoints were mean IIEF-EF scores and NPT. A subset of men underwent longitudinal NPT testing to assess objective changes in NPT on and off treatment.

The trial design was a three arm parallel design (placebo, sildenafil 50mg, sildenafil 100mg) with treatment starting one month after surgery and lasting for 9 months. The commencement of treatment at one month was an arbitrary choice based on the unknown safety profile of starting men on nightly sildenafil immediately after radical pelvic surgery. Though starting sildenafil immediately after surgery was contemplated, there was concern about postoperative sildenafil induced erections with an indwelling catheter. In retrospect, in light of data demonstrating histologic damage as early as two months, the one-month delay may have resulted in a compromise of therapeutic efficacy. After 9 months, treatment (at 40 weeks after RP) was withheld for 2 months. At 48 weeks after surgery men were then queried with the IIEF and the efficacy question. Though a longer period of observation to allow more complete return of function would have been preferable, it was felt that a longer placebo period might be detrimental to eventual return of function. A mid-study blinded review of data was planned. Active recruitment ceased after 125 men, when a blinded review revealed a 25% response rate, far lower than that reported in contemporary surgical series from centers of excellence.

The two US centers carrying out NPT testing remained open, from which a sub-analysis was possible. At 48 weeks, 27% (14/51) of men on sildenafil vs 4% (1/25) in the placebo arm were considered responders (p<0.01). Mean IIEF-EF domain scores in responders vs non-responders off sildenafil were 26.8 vs 11.5 (sildenafil 100mg), 26.3 vs. 8 (sildenafil 50mg), 23 vs. 7.6 (placebo) (Figure 7). Overall IIEF by treatment was 13.7 (sildenafil 100mg), 12.4 (sildenafil 50mg) and 8.8 (placebo).

The results of the sub-analysis mirrored the larger study[174]. In 54 men, NPT testing was done preoperatively and at 5 postoperative time points (4, 12, 24, 36, 48 weeks). In order to enter the study, men had to demonstrate basal penile rigidity of greater than 55% rigidity for 10 minutes on at least 1 of two nights and have normal preoperative function. The primary penile NPT outcome was the duration at which penile rigidity (base and tip) was ≥55% of maximum rigidity (R ≥ 55%). The clinical outcome measures were the same as those stated for the larger study. Forty-eight weeks after surgery, 6/18 (33%) men who received sildenafil 100mg, 4/17 (24%) men who received sildenafil 50mg, and 1/19 (5%) men who received placebo were categorized as study responders. These response rates in the NPTR subset are similar to those in the overall study (29%, 26%, and 4% respectively). Because only one man in the placebo group was a responder, comparisons between the placebo responder and non-responder groups should be undertaken with caution.

Across the three groups at baseline (preoperative), the mean R ≥55% ranged from 64-81 minutes at the base and from 48-56 minutes at the tip (Figure 8). R ≥55% was decreased profoundly at 4 weeks after surgery. No treatment group returned to baseline values during the trial, but R ≥55% in the
Figure 7: End-points in the Pfizer sponsored nightly sildenafil post-RP study.

Figure 8: Results of serial nocturnal penile tumescence and rigidity analysis in the Pfizer sponsored nightly sildenafil post-RP study.
sildenafil groups increased several-fold from the nadir compared with little change in the placebo group. The sildenafil 100mg group had the greatest improvement from the nadir in R ≥55%, achieving 36% (base) and 65% (tip) of baseline values by the end of the trial. This is the only rehabilitation study clearly documenting longitudinal objective and clinical data showing benefit to pharmacologic intervention in the postoperative period. It underscored the early and profound loss of nocturnal erections after surgery.

Though this abbreviated study met its endpoints and had highly statistically significant p values, it suffered from low numbers, thus weakening the strength of the conclusions. Its strength lies in the congruence between the NPT data and the clinical outcome and provides clinical data to support animal data. Mechanistically, it was suggested originally that men were obtaining nocturnal erections and oxygenating their corporal bodies. However, the NPT data demonstrate what little nocturnal erectile activity was occurring early after RP.

Another less rigorous and smaller observational sildenafil rehabilitation study was conducted by Bannowsky et al.[175] From an unknown denominator of patients, 43 men after nerve sparing surgery by a single surgeon (11 UNS,22 BNS) had NPT testing. The NPT testing was not done preoperatively and only once postoperatively, the night after catheter removal. NPT testing immediately the night after catheter removal is particularly problematic, as many of the men are incontinent during that first week and the penes contract making the ring application for the apparatus a challenge. Patients were distributed roughly 1:3:1 to sildenafil 25 mgs nightly vs. no treatment. Sildenafil was started the day after NPT testing and continued for an unspecified period of time, presumably the entire 52 week observation period. Patients were “randomized” roughly equally between treatment group based on preoperative SHIM, NPT findings and nerve sparing status. The study was observational and not powered for a particular endpoint.

Bannowsky had shown in a previous NPT study, that nocturnal tumescence was preserved at one week in 95% of men after NSRP[176]. As in the current study, only one NPT observation was made, on the day of catheter removal. The results are in stark contrast to the observation of the profound loss of NPT at one month in the longitudinal study in men after strict bilateral nerve sparing surgery by McCullough et al [174]. Men were seen at weeks 6,12,24,36 and 52. The outcomes reported were SHIM score and "the ability to achieve and maintain an erection satisfactory for intercourse", on and off sildenafil. At 36 and 52 weeks a statistically significant difference in SHIM score was seen between the two groups and at 52 weeks a qualitative difference between intercourse success rates was observed. Though the IIEF scores seemed to trend with intercourse success, neither a definition of intercourse success nor any details of a sildenafil challenge at 52 weeks were given. While statistically significant, the 3.2 and 4.8 point difference in SHIM scores between treatment and control patients at 36 and 52 weeks is likely minimally clinically significant. However, this study lends support to the larger prospective study and also demonstrates the profound early loss of clinical erectile function after NSRP. Combining the NPT data from the McCullough with the Bannowsky study, one sees how quickly penile innervation deteriorates, as well as the sensitivity of NPT testing for nerve integrity and recovery.

These analyses have forced us to analyze how a PDE5i may facilitate erectile function preservation. Given what we now know from animal studies, attention has been focused on endothelial protection, smooth muscle protection and neromodulation. All three PDE5 inhibitors in phase II-IV trials have demonstrated a lower incidence of myocardial infarction compared to those patients in the placebo groups of the trials (data on file). We know that PDE5 inhibitors are potent endothelial protectants in the diabetic patient population as well as in patients with increased cardiovascular risk[177, 178]. All three PDE5 inhibitors have been shown to improve flow-mediated dilation at low doses and for a significant period of time after the cessation of the medication. Thus, it would appear that PDE5 Inhibitors result in cellular events that protect endothelium beyond the presence of drug within the blood. Furthermore, as previously mentioned, there is elegant evidence in humans and animals that PDE5 inhibitors generate the production of endothelial progenitor cells from the bone marrow [157-159]. Circulating EPCs originate from hematopoietic stem cells in bone marrow, migrate into the peripheral circulation, and differentiate into mature endothelial cells. In this way, EPCs are able to provide a circulating pool of cells that may contribute not only to endothelial repair, but also to neovascularization[179, 180].

Schwartz et al. conducted a randomized, (non-placebo) controlled trial evaluating the impact of sildenafil on corporal smooth muscle integrity in men after radical prostatectomy [181]. Twenty-one patients used sildenafil every other day at 50mg or 100mg. They had corporal biopsy performed prior to radical prostatectomy and six months postoperatively. Histopathological analysis showed significant preservation of smooth muscle content with sildenafil use at both the 50 and 100 mg level. In this study, each patient served as his own control as they all had preoperative corporal biopsies. Though supportive of the concept of penile rehabilitation the interpretation of the biopsy material is extremely subjective and subject to observer bias and sampling error. No attempt was made to “blind” the person evaluating the tissue. Nevertheless, the rapidity of
the acute histologic findings correlate with a study demonstrating a virtual complete loss of nocturnal penile tumescence activity within one month of nerve sparing prostatectomy.

The third mechanism that has been explored, albeit to a lesser extent, is the concept of PDE5 inhibitors may in fact be neuromodulatory. Zhang et al. have shown with both sildenafil and tadalafil in a rat middle cerebral artery occlusion model of stroke that dosing with medication compared to saline results in significant functional recovery [141, 182]. No human studies have been conducted to date, to demonstrate improved cavernous nerve function in response to PDE5i.

More recently, the vardenafil (REINVENT) trial was published [12]. This study was designed to investigate the effect of early postoperative dosing with vardenafil in three different fashions: nightly (N), vardenafil on-demand (OD), or placebo (P) on the recovery of erectile function in men with ED following BNSRP. As in the sildenafil study its planning and design predated much of the strong supportive animal data for penile rehabilitation after cavernous nerve injury. The design of the study was complex (Figure 9). Each arm had a different titration schedule. The P arm consisted of placebo nightly with placebo on demand with no dose titration. The N arm consisted of 10 mgs of vardenafil nightly with the ability to titrate the nightly dose downward but not upward and then this group used placebo for on-demand sexual relations. The on-demand placebo was not titrated. The OD arm received nightly placebo with no titration, and for on-demand sexual relations, a titratable vardenafil dose (5, 10 or 20mgs). Without considering variability in on-demand dosing in the OD arm there were 6 different possible permutations of drug administration. Thus, the different dosing permutations with 87 sites raises concerns regarding dose accountability. Protocol violations were almost three times more common in this study than the Brock et al. study after BNSRP, Brock et al had reported that in 302 men, 1.7 years after surgery, the per patient success rates using sexual encounter profile questions 2 and 3 (SEP 2 and 3) were 22% and 12% with placebo compared to 52% and 40% with 10 mgs and 20 mgs of vardenafil respectively. The corresponding IIEF scores were less than 10 for placebo and 16 for the treatment group [183]. Based on the Brock study one would expect placebo and vardenafil group response rates less than 30% and 50% respectively with much lower IIEF-EF scores. The authors did not explain how they dealt with men who were not sexually active. A significant difference in sexually active men between treatment arms might blunt a therapeutic effect. A man may not attempt sexual intercourse because of incontinence or partner issues yet still have functional erections.

The use of LOCF in this study, though standard in pharmaceutical trials, could introduce a bias if the dropouts in one arm occur earlier than in another arm. As erectile function is known to improve with time, independent of treatment, if more men drop out early from one arm, their low IIEF EF domain score will be carried to the end of observation and hence lower the end-of-treatment IIEF score, even though they are likely to have improved. The dropout rates were similar between treatment arms: P (31%), N (35%), OD (32%). The dropout rates were largely driven by adverse events, protocol violation and consent withdrawal. Of note, in those categories alone there was a 20% difference between placebo and treatment arms (54%, 74%, 76% respectively). With such large dropout rates, it is important to understand when the dropouts occurred in each treatment arm, as they may have impacted the LOCF.

The primary efficacy variable was not met in the study. There was no difference between the P group and the vardenafil (N or OD) groups at the end of the single blind placebo washout phase. The proportions of patients with IIEF scores ≥22 were 28.9%, 24.1% and 29.1% for the P, N, and OD respectively (Figure 10). Almost 30% of the P group had an IIEF-EF domain score ≥22 and it is unclear why this is so. Data was collected at 3, 6 and 9 months but was not reported. It would have been useful for the authors to include the mean total IIEF-EF domain score in order to able to make comparisons with other studies.
Figure 9: study design for the REINVENT (Bayer sponsored vardenafil) post-RP study.

Figure 10: Primary end-point analysis in the REINVENT study.
Secondary outcomes included percentage of subjects with an IIEF EF domain score $\geq 22$ at LOCF at the end of the double blind treatment period (9 months) and at the end of the open label period (13 months) (Figure 11). Data were further analyzed for the percentage of patients with IIEF-EF score $>17$ and $>22$ at LOCF for each period of the study and per patient success using SEP 2 and SEP 3 were assessed for each period of the study. Authors did not include the data on the proportion of subjects with IIEF-EF scores $>17$ or $>26$ for all of the time points measured. This data is likely important to better understand the outcomes and for the design of future meaningful rehabilitation trials, thus it is hoped that the data will be made available at some point in the future.

The secondary endpoints demonstrated superiority of OD over P at all data points during the double blind period. The OD arm was superior to the N arm at “several visits and at double blind LOCF (9 months)” though no data was presented to accompany the p value of 0.0065. The superiority of on-demand therapy in the placebo-controlled trial is not surprising. Simply put, the OD arm used vardenafil for sexual relations while the N arm used a placebo for sexual relations. It would be expected that the OD group would record higher IIEF EF domain scores and SEP 2 and 3 rates at the end of the intervention phase.

All superiority of the vardenafil arms was lost during the two month open label period with IIEF-EF scores $\geq 22$ of 47.8%, 52% and 54.2% for the P, N, OD arms respectively. The accompanying SEP 3 scores were 57.1%, 59.8% and 62.6%. This is a remarkable study yet the results are in stark contrast to robust data from preclinical animal trials and the sildenafil trial. There was no benefit to rehabilitation with vardenafil at 11 and 13 months. The authors, in their conclusions, state that these data support a shift in the paradigm towards on-demand dosing of PDE5i post-RP, yet other than at the end of the intervention phase, the OD use was no more effective than the nightly dosing not the placebo.

Possible explanations for the lack of difference in response between the placebo and vardenafil arms after drug washout and at the end the open label period (13 months) include: (i) PDE5i play no role in penile rehabilitation and the animal model is not relevant to humans. The number of confounding factors in the NSRP patient is staggering and include patient age at time of surgery, surgeon experience, surgeon expertise, preoperative sexual function, nerve sparing status, partner/relationship issues and status, confounding medications, medical comorbidities, hormonal status, and endothelial function among others. Future studies should be designed and powered to control these confounding variables to obtain clearer answers; (ii) There are differences in the molecular action of sildenafil compared to vardenafil. In the absence of a head-to-head trial between different PDE5i in this population, this will be impossible to answer. However, all three PDE5i have been shown in animal studies...
at least to have a positive effect on erectile tissue and function preservation. On the other hand, there exists a randomized, controlled trial comparing all three PDE5i in the pulmonary hypertension literature demonstrating superiority of sildenafil over vardenafil in a number of end-points (primarily pulmonary artery oxygenation)[184]; (iii) The vardenafil was not dosed correctly for rehabilitation. Of note, doses of vardenafil used in pulmonary hypertension are 10-15mgs 2-3 times per day [185, 186]; (iv) Confounders existed unrelated to lack of efficacy of vardenafil including surgeon and nerve sparing quality variability related to the large number of centers and surgeons included in the trial; (v) It is also possible that the complexity of the trial design obscured any therapeutic effect.

4. INTRA-URETHRAL ALPROSTADIL SUPPOSITORY

The intra-urethral alprostadil suppository (IUA) was approved in 1997 and continues to play a small but definite role in ED management. Given its erectogenic capabilities, interest has existed in assessing its role in penile rehabilitation after RP. Interestingly, Moreland et al suggested that endogenous PGE1 (at least in an in vitro model) suppressed fibrogenic cytokine activity (in the form of TGF-β)[89]. Thus, it has been suggested that exogenous PGE1 may have some protective effects even aside from the production of erection.

Since the intracavernous injection study by Montorsi there have been no large prospective studies incorporating alprostadil in penile rehabilitation. Costabile and Raina have demonstrated the efficacy of IUA to treat ED after RP regardless of nerve sparing status[187, 188]. In a non-randomized, prospective observational study, Raina demonstrated the tolerability of a nine month regimen of three times weekly IUA after RP with a benefit over no treatment in “successful vaginal intercourse with or without erectile aids” (40% vs 11%) [188]. The non-randomized nature of the study limits the validity of the data.

McCullough et al conducted a randomized trial, the purpose of which was to determine if early nightly treatment with IUA after nerve sparing RP hastened return of erectile function (McCullough et al; manuscript under review). This study was conducted in the United States at three high volume prostatectomy centers. Approximately half of the patients had robotically assisted laparoscopic surgery and the other half standard open radical prostatectomy. All surgeries were bilateral nerve sparing. The study consisted of two-arms comparing nightly IUA administration to nightly sildenafil 50 mgs. Inclusion criteria were similar to the other prospective penile rehabilitation studies. Subjects were 69 years of age or less, sexually active in a stable relationship, had an erectile function domain score of at least 26, did not use PDE-5 inhibitors, had a Gleason score less than 8, a PSA level less than 20, and were scheduled to undergo a BNSRP. Post-surgical radiation therapy and androgen deprivation were exclusion criteria. At each visit, mean IIEF scores were calculated for study participants.

Subjects were consented one month prior to surgery, completed the IIEF questionnaire and had a stretched penile length (SPL) measured from the pubic bone to the coronal sulcus with a rigid ruler (V1). Patients were seen at the time of catheter removal (V2), and postoperative months 1 (V3), 3 (V4), 6 (V5), 9 (V6), 10 (V7), and 11 (V8). At V2, within one month after surgery, at the catheter removal visit, all men were randomized to either IUA (125 mcg) or Viagra (50 mg), in a 2:1 ratio and had measurement of SPL. IUA 125mcg was chosen as an initial dose to allow subjects to become familiar with the IUA technique and to minimize the discomfort of IUA administration. The first IUA administration was conducted at the clinical site for safety and tolerability assessment. Subjects were instructed to self-administer IUA or Viagra nightly during the study and were supplied with a one month supply of either drug. Subjects had to complete the sexual encounter profile (SEP) with each attempt at sexual intercourse throughout the trial.

At V3 (1 month), IUA subjects were up-titrated to 250 mcg. All subjects were provided with a two-month supply of IUA or Viagra for nightly administration and remained on that dose for the remaining 8 months. The IIEF, SPL, adverse events (AE), SEP, and medication compliance data was collected at V3-V6 and V8. At V6 (month 9) all nightly medication was discontinued and subjects were given no medication for one month. They attempted sexual activity during this time without using any erectogenic aids. At V7 (10 months), subjects were provided with six Viagra (100 mg) tablets and instructed to use each tablet on an empty stomach one hour before initiation of sexual activity over the ensuing month. At V8, eleven months after surgery, all subjects completed the Erectile Dysfunction Inventory of Treatment Satisfaction (EDIT) in addition to the IIEF, GAQ, SEP and had SPL measured.

The study was powered based on the 27% normalization of erectile function from the sildenafil rehabilitation trial and the 67% intercourse success rates published by Montorsi. The primary outcome was mean IIEF score at each visit and the secondary outcomes were SEP, SPL and EDIT.

A total of 227 men gave consent to enter the trial, 212 subjects started the study, while 156 subjects (97 IUA, 59 Viagra) completed the trial. Average age was 56.8±6.4 years for IUA and 55.6±5.9 years for Viagra. Dropout rates were 19% for Viagra and 30% for IUA. Most of the dropouts for IUA occurred between V3 and V4, when men were dose escalated to IUA 250. After visit 4, dropout rates were identical for both groups. Dropout rates in the IUA arm
were no greater than the REINVENT vardenafil rehabilitation trial despite the more invasive route of administration. As erectile function improves in time after RP, results are based on men available at each visit. LOCF was not used. The primary reason for dropout was the pain associated with the nightly administration of IUA 250.

Overall drug compliance as determined by ratio of dispensed to returned medication was 98% for Viagra and 79% for IUA. For each treatment arm, compliance did not change significantly from V3 through visit V6. At V8, compliance was virtually identical (94% for both IUA and Viagra). The percent of men attempting sexual intercourse and the mean number of attempts at each visit was not significantly different at V3-V6 and V8 between the treatment arms. Men who indicated that they were not sexually active were excluded.

As in the REINVENT trial, the primary outcome was not met. Though IUA trended towards favoring an earlier return of function by all the metrics used, by 11 months, differences in outcomes were not statistically significant. The mean IIEF scores by visit are shown in Figure 12. The IIEF scores increased in both groups respectively from a mean of 9.9/10.4 at the 1-month visit to 15.3/17.7 at the end of the study. At the month 3 and 6 visits there was a slight difference in IIEF EF domain scores in favor of IUA; these differences were not significant (p=0.58 and p=0.27 for months 3 and 6). The mean IIEF EF domain score differences were not clinically significant for the 2 groups at the end of treatment period or at the end of the study. At month 1, 3 and 6 visits the percentage of subjects responding yes to the GAQ was higher in the IUA group compared to the Viagra group; these differences were 17%, 8%, and 27%, respectively. The response at month 6 was statistically significant in favor of IUA. Intercourse success rates for IUA group were 16% higher at 3 months and 41% higher at 6 months when compared to Viagra; these differences did not reach statistical significance (Figure 12). Intercourse success rates correlated strongly with the IIEF EF domain score (r=0.80, p<0.0001). Men with intercourse success rates less than 50% averaged an IIEF score of 7.9 whereas those with success rate greater than 50% of attempts, averaged an IIEF EF domain score of greater than 20 throughout 3-11 months (p <0.0001) for both medications. These differences are not unexpected, as IUA does not require intact cavernous nerve to function while PDE5i response does, thus, at these early time-points when cavernous nerve neuropraxia is at play, PDE5i response is poor.

Stretched penile length generally decreased in length for both treatment arms. Though both treatment arms began and ended at virtually identical SPL, the IUA arm showed less loss of length at V5. Statistical significance was achieved at V5 (p=0.047). Figure 14. Total EDITS score after Viagra challenge was

![Figure 12](image)

**Figure 12:** Primary end-point analysis (IIEF erectile function domain score) in the randomized study of intra-urethral alprostadil suppository versus sildenafil in men after radical prostatectomy.
Figure 13: Secondary end-point analysis (rate of successful intercourse attempts) in the randomized study of intra-urethral alprostadil suppository versus sildenafil in men after radical prostatectomy.

Figure 14: Secondary end-point analysis (penile length) in the randomized study of intra-urethral alprostadil suppository versus sildenafil in men after radical prostatectomy.
not significantly different between arms. Over 75% of patients in both groups felt that their erections were not as hard as before surgery. The end-of-trial IIEF EF domain scores were similar to those in the sildenafil rehabilitation study and the percent of intercourse success were not dramatically different than the REINVENT trial. Despite aggressive rehabilitation, a loss of penile length was seen in both arms, occurring almost immediately. Previous longitudinal studies have demonstrated the frequently observed phenomenon [30-33, 189]. This is the first prospective longitudinal penile length study after RP in men undergoing penile rehabilitation and including only bilateral nerve sparing surgery. Absent of course was a control (no treatment) arm. The etiology of the loss of length remains uncertain but rates of length loss were not affected by the rehabilitation strategies.

5. STEROIDS

In an attempt to improve ED outcomes by modifying the acute post-operative inflammatory response, a 6-day course of methylprednisolone was used in a randomized, placebo-controlled study of 70 men undergoing bilateral nerve sparing RP [15]. The medication was started 16-22 hours after surgery. There was a statistically significant advantage to the placebo group at 3 months that disappeared by 6 months. At 12 months no differences were seen in SHIM scores or in positive responses to the question “Over the past 4 weeks, when you attempted sexual intercourse, how often was it satisfactory for you?” Post-operative complication and continence rates were not affected by the steroid administration. According to the authors, it is possible that the timing, short course of administration and low dose may have resulted in the absence of benefits in this study. A similar study was done with the intra-operative local administration of bethamethasone around the area of the NVB in 60 men [190]. Using similar outcome instruments, no difference in postoperative sexual function was seen and there was no increase in postoperative complications. There appears to be no benefit to short term systemic or topical applications of steroids in penile rehabilitation.

6. VACUUM THERAPY

The vacuum device is one of the oldest effective erectogenic aids. Though the effectiveness of vacuum devices is unquestionable in men with ED, its role in penile rehabilitation is unclear. It has been established that the use of the VED with a proximal constriction band results in penile hypoxia while it is being used [191]. The inflow of blood is predominantly non-arterial and is a result of decreased atmospheric pressure (vacuum) and not smooth muscle relaxation.. In a non-randomized prospective study of 109 patients both nerve sparing and non-nerve sparing, 74 patients were instructed to apply the vacuum device daily for 9 months compared to 35 men with no treatment[192]. Patients self-selected their treatment arm. The duration of the vacuum device application was not specified though the constriction band was used only for intercourse. 60/74 completed the vacuum device arm.

Men and their partners were mailed questionnaires. The results were inconclusive as 19/60 (32%) of the vacuum device group reported spontaneous erections and 10/60 (17%) reported vaginal penetration. In the “no treatment” group 13/35 (37%) reported spontaneous erections and 4/35 (11%) reported erections satisfactory for vaginal penetration. Follow up was done through mailed questionnaires. The vacuum device group reported subjectively that they had less penile shrinkage but no objective measurements were made. 76-86% of men were able to have sexual intercourse with the vacuum device regardless of the nature of the nerve sparing surgery. No long term follow up or PDE5i responsiveness was reported.

Kohler et al reported a randomized study of early intervention with vacuum device compared to no treatment after RP [193]. Thirty-three men undergoing RP were randomized to early intervention (6 months of treatment, starting 1 month after RP, group 1) or no early treatment control group (group 2). Men in the group 1 were instructed to use the vacuum device daily starting 1 month after RP; all used the Osbon ErecAid (Timm Medical, Eden Prairie, MN). The men were instructed to inflate the device for two consecutive 5-min periods after a brief release of suction in between inflations. The use of a tension band for intercourse was forbidden for the first study month (second month after RP). Thereafter, Group 1 was allowed to use the constriction band for intercourse if desired. By contrast, group 2 were not allowed erectogenic aides for 6 months then were given instructions to use the vacuum device after 6 months and to do so whenever they wished to attempt intercourse with the constriction rings. The use of PDE5i was not allowed in the first 6 months in either group, but after the sixth month both groups were allowed to use PDE5i if they desired.

The men were evaluated with the IIEF-5 (SHIM) questionnaire, and with questions on spontaneous erections and adequacy of erections for intercourse. Stretched penile lengths were also measured. Data were acquired preoperatively and at 1, 3, 6, 9 and 12 months after RP. The primary endpoint of the study was the proportion of patients with moderate to severe ED (SHIM score ≤11) after randomizing to groups 1 and 2. Secondary endpoints included penile size, including significant penile shortening, for which 2-cm was used as the threshold, progression of SHIM scores over time, and occurrence of spontaneous erections in the early period after RP. As this was a pilot study, no rationale for the endpoints, study
size or the randomization schedule was given. Four patients withdrew from group 1 and one withdrew from group 2. One patient in each group had a unilateral nerve sparing while the rest had bilateral nerve sparing.

The results were inconclusive. At last follow up (mean of 9.5 months) there was no significant difference between the groups in SHIM score or in the percentage of men with moderate to severe ED. Disappointingly, no spontaneous erections adequate for intercourse were reported in either group. The penile size changes that were reported underscore the vagaries of this endpoint. The vacuum device group actually gained length whereas the no treatment group lost length.

IN SUMMARY

In summary, the committee believes that the term ‘penile rehabilitation’ is easy to understand by patients and should be retained, although some clinicians may prefer to use the term ‘erectile tissue preservation’. The committee defines rehabilitation as the use of a medication, combination of medications, devices (alone or in combination with medication) in the early stages after RP. The goal of rehabilitation is to maximize preservation of all components of the local erectile mechanism and optimize recovery of erectile function.

The ICSM recommends that based on the strong animal and basic science evidence, understanding the strengths and weaknesses of the existing human studies and the negative consequences of long-term ED after RP, clinicians should discuss with the patient that penile rehabilitation has significant potential benefits for the patient/partner and should be considered after RP. This was a unanimous recommendation of the committee and is based on expert opinion thus receiving a grade C because of supportive animal data, combined with conflicting and generally weak human data. The committee appreciates that the animal model may not be fully representative of the human model, or may be representative of only certain forms of nerve sparing surgery. The committee believes taking all of the human data into account, including the two RCTs, two non-randomized studies and also the data evaluating the positive impact of PDE5i on endothelial function and possibly corporal smooth muscle integrity health, that despite the data from the REINVENT study that there remained a signal that PDE5i use after RP had some potential benefit. While the data supporting ICI after RP is weak, the committee believes that the erection induced by ICI may be of benefit possibly mediated through cavernosal oxygination and likely other hitherto unknown factors and pathways.

The ICSM further recommends that key patient factors be taken into consideration when deciding on penile rehabilitation for an individual patient. These factors include but are not limited to: cost to the patient and the health care system, time commitment for patient and clinician, exposure to medications and their adverse effects, the potential benefits of sequential follow-up, early return to sexual intercourse, and potentially maintenance of penile length. The committee appreciates that many patients have no health insurance coverage for medication utilization after RP. However, ICSM feel strongly that this decision should be made by the patient/couple and that the cost be placed in perspective of the long-term sequelae of permanent ED. The ICSM also appreciates that rehabilitation is labor and time consuming for both the patient and clinical staff and that patients be given realistic expectations regarding this prior to commencing rehabilitation. The ICSM suggests that a comprehensive discussion be held with patients regarding the adverse effects of all therapies employed in the rehabilitation program. It is also appreciated that consistent and regular follow-up with patients has potentially significant psychological benefits including dissemination of realistic expectations, offering perspective and psychosocial support. Furthermore, the early institution of erectogenic therapy permits the early resumption of sexual intercourse with a decrease in confidence erosion so often seen in patients who have delayed recovery of EF after RP. The ICSM understands the concept of penile length loss prevention through rehabilitation is highly controversial and based solely on anecdotal information, however, the majority of the committee felt it was reasonable leaving this statement within the recommendation.

The ICSM can give no specific recommendations regarding the structure of the optimal rehabilitation regimen. Numerous confounding variables that at present remain undefined of the ideal rehabilitative approach were discussed including: defining the best time to start rehabilitation after RP, frequency of medication utilization, specifically, daily versus on-demand exposure, the best dosing schedule (low-dose versus maximum dose), duration of rehabilitation after its commencement and strategies used (PDE5i, ICI, transurethral prostaglandin suppository, vacuum therapy), but no definitive evidence exists favoring one rehabilitation strategy over another. This is a unanimous committee recommendation. It was clear that this was disappointing to many clinicians in the audience based on feedback during the presentation of the recommendations by the committee. Unfortunately, no trial has
been conducted and likely will never be that will address all of the significant potential confounders.

RECOMMENDATION 7

Grade C

It is recommended that clinicians discuss with the patient that penile rehabilitation has significant potential benefits for the patient/partner and should be considered after RP.

RECOMMENDATION 8

Grade C

It is recommended that key patient factors be taken into consideration when deciding on penile rehabilitation for an individual patient.

RECOMMENDATION 9

Grade D

No specific recommendation can be given regarding the structure of the optimal rehabilitation regimen.
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Standards for Clinical Trials in Sexual Dysfunction in Women: Research Design and Outcomes Assessment

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INTRODUCTION

Only one pharmacological product has been approved for Female Sexual Dysfunctions (FSD) in the European Union and none in the United States since the last International Consultation (2004). This appears to be related more to the standards for clinical trials in women than to the efficacy of the drugs themselves. The focus of this chapter is on essentials of research design and measurement in female sexual dysfunctions. Accordingly, our recommendations rest upon classical procedures in experimental design and classical measurement theory. Therefore, consideration of rating the quality of level of evidence is not germane for this chapter.

As part of that process, we will review current recommendations, evaluate their appropriateness for regulatory approval, and discuss discrepancies and potential changes that may improve ability to demonstrate efficacy for a specific construct.

I. REGULATORY CONSIDERATIONS

1. REGULATORY GUIDELINES: FOOD & DRUG ADMINISTRATION (FDA)

Introduction of a new device or drug requires regulatory approval by a designated government entity. Unfortunately, as of 2009 only one regulatory body, the FDA, has issued any guidance on standards for clinical trials in women with sexual dysfunction. The FDA’s Draft Guidance of May 2000 (FDA-DG or DG, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071655.pdf) outlines Female Sexual Dysfunctions as “currently” consisting of the same four recognized components as in DSM-IV, decreased sexual desire, decreased sexual arousal, persistent difficulty in achieving or inability to achieve orgasm, and dyspareunia (no broader or more detailed definition for sexual pain syndromes). The FDA-DG states that “the definition of FSD continues to evolve” while not recognizing the Diagnostic and Statistical Manual (DSM-IV) criteria for these disorders. Similar to DSM-IV, however, it specifies that, for a diagnosis of FSD, “these components must be associated with personal distress, as determined by the affected woman.” Unlike DSM-IV, it does not recognize interpersonal difficulties as an alternative requirement, to personal distress.

The FDA-DG allows sponsors to target for treatment development any one of, or combination of, the four named components. It suggests some exclusion criteria “to increase the likelihood of demonstrating a treatment effect in clinical trials of FSD:”

- Relationship difficulties with a sexual partner
- Use of concomitant medications that could affect sexual function (e.g., certain antidepressant medications)
• The presence of medical conditions that could affect sexual function (e.g., depression, anxiety, the first few weeks of the postpartum period)
• Sexual dysfunction on the part of the woman’s partner

2. EMEA

The European Medical Authority (EMEA), while not issuing any guidance on FSD, has in the documentation of its approval of a testosterone transdermal system (TTS) (European Public Assessment Report (EPAR), 2006, effectively established precedents for standards of treatment development in hypoactive sexual desire disorder (HSDD). (www.emea.europa.eu/humandocs/PDFs/EPAR/intrinsa/063406en1.pdf) The EPAR details the discriminant validity of the sponsor’s proprietary patient-based measures of sexual desire (desire subscale of the Profile of Female Sexual Function© [PFSF©] and distress related to a deficiency of desire on the Personal Distress Scale© [PDS©]), in comparisons of post-menopausal women with HSDD to those without FSD, and then focuses on three measures of HSDD as leading to its acceptance of the TTS: satisfying sexual events, sexual desire as measured in the PFSF, and distress related to sexual desire as measured on the PDS. These measures remain proprietary and unavailable in sufficient detail for use except by the sponsor of the TTS, Procter and Gamble.

3. MEASURES

Satisfying Sexual Events (SSE): The DG recommends recording the number of sexual events/encounters daily “using diaries” for 4 to 8 weeks before treatment is initiated, and collecting such information weekly for the duration of the intervention. A count of satisfying sexual events is to be the primary endpoint. Satisfaction is to be determined by the patient herself. Partner diaries are allowed but not recommended as primary endpoints.

Sexual Distress: The Draft Guidance recommends measuring personal distress to ensure appropriate patient selection for trial participation but states that this dimension of FSD “should not serve as the primary endpoint for establishing effectiveness.”

Other Measures: Changes in vaginal/genital physiology are not accepted as main endpoints and must be linked to satisfying sexual events to be accepted. Neither is Health Related Quality of Life to be used as a primary endpoint.

Patient Reported Outcomes (PRO) Measures: The DG recommends that any new measures developed be thoroughly validated prior to use in definitive clinical trials. The USA Food and Drug Administration (FDA) issued its draft guidance in 2006 on PRO measures used as effectiveness endpoints in clinical trials (http://www.fda.gov/CDER/GUIDANCE/5460dft.pdf). [1] A PRO is a measurement of any aspect of a patient’s health status that comes directly from the patient. Thus data generated by a PRO measure can provide evidence of a treatment benefit from the patient perspective. PRO instruments need to demonstrate ability to measure the claimed treatment benefit and to be specific to the intended population and the characteristics of the condition or disease treated. The advent of this guidance had specific benefit to the field of female sexual dysfunction. Previously the FDA had relied on observable outcomes, such as daily calendar reports of intercourse frequency. It can be argued that intercourse frequency, relying on the relationship with a partner, may not directly reflect the domain of female sexual function that a clinical intervention seeks to change. The FDA guidance document notes that PRO-based evidence of improvement in symptoms may not be sufficient to substantiate a claim which may also need to demonstrate how any change in (for example sexual desire) translates into other specific endpoints (such as intercourse frequency).

The guidance recognized that for some treatment effects the patient is the only source of data. This, for example, applies to sexual desire where there are no observable physical measures of this concept. Self-completed questionnaires by patients directly capture the patient’s baseline and perceived response to treatment and are not affected by inter-observer variability. However, the PRO may be affected by inter-patient variability if the instrument is not easily understood and completed by patients. PROs may also be developed to define entry criteria to study populations, and evaluate adverse events.

The adequacy of the PRO instrument as a measure to support efficacy claims depends on the development of the PRO and demonstrated measurement properties. The FDA encourages sponsors to determine whether an adequate PRO exists to assess and measure concepts. If it doesn’t then a new PRO can be developed. A single item PRO can on occasion provide a reliable and valid measure (e.g. pain severity). Multiple domains are usually necessary for general concepts. Documentation is needed of the instrument development process, revealing the means by which domains were identified and named, how individual items are associated with each other, associated with each domain, and how domains associate with each other and the general concept of interest. In some measures domains can be aggregated into an overall score. The FDA will compare the patient population used in the instrument development process to the study populations enrolled in clinical trials to determine whether the instrument is appropriate to that population with regard to patient age, sex, ethnic identity and cognitive ability.
The guidance specifically states that the PRO instrument item generation process is incomplete without patient involvement. Item generation generally incorporates the input of a wide range of patients with the condition of interest to represent appropriate variations in severity and patient characteristics such as age or sex. Adequate numbers of patients are needed to support the opinion that the specific items and instrument are adequate and appropriate to measure the concept. Detail is needed regarding item generation techniques used, including theoretical approach used, population study, pools of items, selection and reduction of items, cognitive debriefing interviews, pilot testing, importance ratings and quantitative techniques for item evaluation such as factor analysis and item-response analysis. The method of data collection and all procedures and instructions and modes of administration must also be detailed. The rationale and appropriateness of the recall period must be established and measures taken to ensure that entries are made into patient diaries according to the study design. Response options need to be adequate, appropriate, associated with clear instructions and avoid potential ceiling or floor effects as well as not biasing the direction of response.

The FDA will review PRO instruments for reliability, validity, ability to detect change and interpretability. The socio-demographic and medical characteristics of any sample used to develop PRO instruments should be appropriate for future clinical study settings.

Measurement properties to be reviewed in clinical trials include:

- **reliability** (test - retest; internal consistency; inter-interviewer reproducibility for interviewer administered PROs only)
- **validity** (content - related; construct - related; predictive validity; discriminant validity)
- **ability to detect change** (calculation of effect size and standard error of measurement)
- **interpretability** (smallest difference that is considered clinically important such as minimum important difference; responder definition).

Modification of an existing instrument requires additional validation studies to confirm the adequacy of the modified instrument’s measurement properties. When an instrument developed in one language or culture is adapted or translated for use in another language and culture, then evidence is needed that the translation processes were adequate to ensure the validity of responses.

In summary, the FDA guidance on PROs represents an advance for the field of clinical trials for sexual dysfunction. The guidance clearly states that the PRO may be used as an endpoint, elevating the patient’s perception to that of an observable outcome. The FDA guidance has also spurred further development of instruments. The method outlined by the FDA does help ensure that instruments will adequately reflect the concepts being measured in any given population. However, the necessity for an integration of that guidance, which also incorporates important recommendations/corrections from sexual medicine professionals, is still awaited. [2,3]

4. PROBLEMS WITH CURRENT GUIDELINES

This Draft Guidance remains unaltered despite much criticism from many academic experts in the field of FSD. These objections are of four main types.

One criticism is to the primacy of SSE despite its absence from the criteria for the various forms of FSD recognized in practice and by DSM-IV. While a decrease in SSE is considerably "downstream" in consequences of the DSM-IV-recognized symptoms defining FSD, in fact, the rate of SSE is markedly decreased in the various types of FSD [4,5,6]. The mean decrease is about 70 to 80% in the various Boehringer-Ingelheim (BI) samples compared, with wide variation from patient to patient but with approximately 70-75% sensitivity and specificity vs women with no FSD. D. Shames, Director of the involved FDA division has stated that the primacy of SSE was established so that improvement could not be claimed based solely on subjective feelings of the subject/patient. It also serves to "level the playing field" between the various types of FSD in terms of the main standard set for proof of efficacy.

A second objection is to the absence of the DSM-IV recognized symptoms of FSD as primary outcome variables, e.g., improvement of sexual desire for women with HSDD. The FDA took the latter particularly into account in its presentation in response to the International Society for the Study of Women’s Sexual Health (ISSWSH) in 2006 and published the next year. [7]. Measuring sexual desire is explicitly recommended as a main endpoint for clinical trials of HSDD, but not to the exclusion of SSE as another primary measure.

Thus, it would not be unreasonable for sponsors to seek claims in terms of the main symptom that defines each of the other types of FSD, e.g., a measure of sexual arousal for women with sexual arousal disorder. However, such measures will apparently not be recognized by the FDA unless they meet the validation criteria recommended by the FDA in its Draft Guidance on Patient Reported Outcomes (PRO) of February 2006. Some measures meet these criteria, but not all are available for use in clinical trials. A path to validate currently available measures is also given which has been followed for at least one measure of a primary symptom of FSD, i.e., the desire domain of the Female Sexual Function Index [8,9,10,11].
A third objection is to the exclusion of distress as a main endpoint, but the FDA has not in practice excluded a well-validated measure of personal distress related to FSD as either a co-primary or a secondary endpoint.

A fourth objection is to the FDA emphasis on daily recording of symptoms of FSD, e.g., of sexual desire in women with HSDD. Recent evidence shows that women with HSDD do not recognize a 24-hour retrospective period as valid for assessing their desire, and that instead they find one to four weeks as a meaningful period for retrospective assessment. The finding was the same for pre- and post-menopausal samples. [12,13]

Given these criticisms, there could be value in an iterative process involving coordination between the two regulatory agencies, FDA and EMEA, and including external input.

5. STUDY DURATION

The FDA's draft guidance requires a six-month treatment period to establish efficacy; the two TTS studies that led to EMEA approval were of this duration, so a six-month treatment period is now the recognized transatlantic standard.

Objections can be raised to this, too. Surely it would be a rarely persistent patient who would comply with a new treatment, its inconvenience and side effects if she felt no improvement until six months had passed, leading to considerable likelihood of selective attrition of placebo-arm patients from clinical trials. Thus, a practical standard for onset of action should be recognized as closer to 1-2 months than 6 months. A practical standard for proof of efficacy would inform a similarly short duration of no longer than 12 weeks, as in typical clinical psychopharmacology indications (depression, anxiety, etc.). This would help not only to conform to practical considerations in routine clinical practice but also to separate the issues related to treatment response from those related to maintenance of efficacy and to long-term remission and recurrence. Three-month extension trials (following a 12-week acute efficacy trial), relapse prevention trials, long-term safety studies (when indicated, such as for hormonal therapies), and trials involving a comparator agent (when available) would add to drug information, but do not appear necessary for regulatory approval.

This recommendation is not for a relaxation of regulatory standards, but to establish standards for the separate goals of demonstration of induction of effect and for proof of maintenance of efficacy.

6. SAFETY OF LONG-TERM TREATMENT AND WITHDRAWAL

Data are accumulating that FSD are highly chronic. The mean duration of HSDD was over 5 years at entry into the fibanserin phase III trials of premenopausal women with HSDD. [4] Thus, determination of long-term efficacy and safety, including the safety of treatment withdrawal, should also be assumed to be regulatory concerns.

With the announcement of two one-year studies and a large two-year controlled study of 549 women, (some on placebo) of TTS for postmenopausal women with HSDD, http://clinicaltrials.gov/ct2/results?term=Intrinsa+female, it might be assumed that concerns for the safety of long-term hormonal therapy in postmenopausal women expressed by the FDA in 2004 (http://www.fda.gov/OHRMS/DOCKETS/ac/04/briefing/2004-4082B1_02_A-FDA-Intrinsa-Overview.htm) have led to a recommendation for studies of this size and duration.

Similarly, with publications arising from the fibanserin ROSE study at the European Society for Sexual Medicine – International Society for Sexual Medicine (ESSM-ISSM) meeting in Brussels in December 2008 and the International Society for the Study of Women's Sexual Health in February 2009, it is reasonable to assume that one or more regulatory agencies have recommended that sponsors perform a clinical study sufficient to determine the effects of drug withdrawal after six months of treatment for FSD (at least in HSDD and based on CNS activity) http://www.em-consulte.com/article/175759, http://www.docguide.com/news/content.nsf/news/852571020057CCF68525751A005D6357.

Finally, additional guidance from other government regulatory agencies was not available at the time this chapter was written in 2009.

II. CHOICE OF STUDY MEASURES AND ENDPOINTS

1. PROBLEMS WITH CURRENT ENDPOINTS: SEXUAL PSYCHOPHYSIOLOGY

Sexual psychophysiology is an emerging field of investigation with the number of publications increasing 10-fold over the last 30 years.[14] Sexual psychophysiology can be defined as the application of psychophysiological methods to the study of sexual arousal, with special emphasis on the interplay between subjective (cognitive and affective) and physiological determinants of sexual arousal.[15] A common finding in psychophysiological research is that correlations between subjective and genital responses are lower in women than in men.[16] The discordant pattern most frequently found in women is that genital responses occur while subjective sexual arousal is low or absent.

As well, there has been comparatively little research on the effects of the experimenter on results. A number of studies have explored differences
between volunteers and non-volunteers for sexuality studies and found differences in sexual experience, frequencies of sexual activity, sexual guilt, exposure to erotic materials, and sexual attitude. [17] These findings suggest that psychophysiological studies are particularly susceptible to volunteer bias. Thus, psychophysiological measures cannot currently be recommended as suitable endpoints for clinical trials, consistent with the FDA guidance.

Rellini and Meston found that only the self-report questionnaire, the FSFI, significantly predicted which women with female sexual arousal disorder improved at post treatment.[18] Event logs, vaginal photoplethysmography, and continuous subjective sexual arousal measured during exposure to erotic videos did not demonstrate or predict women’s improvement at post-treatment. Nevertheless, these results provide strong evidence that validated self report questionnaires such as the FSFI are the most sensitive endpoints to detect treatment-induced changes in women’s sexual dysfunction.

There is little correlation between other biologic measures such as sex steroids, specifically androgens, and self-report measures of sexual functioning. Low levels of androgens, specifically DHEA-S, have been linked to low sexual desire in only one study [19]; however, treatment of distressing low desire with testosterone in women without demonstrated low androgen levels did increase desire over placebo. [20,21,22,23] Elevated levels of sex hormone binding globulin (SHBG) appear to mitigate the increase in desire associated with testosterone treatment, and may be used as an exclusion criteria in studies involving sex steroids. [24] In addition, peripheral measures of neurotransmitters have not been shown to accurately reflect central levels, nor to be correlated with sexual dysfunctions or response to non-hormonal, centrally-mediated treatments.

2. SEXUAL DISTRESS

Current definitions of sexual dysfunction include criteria that there is deficiency in a parameter of sexual function and that this causes personal distress or interpersonal difficulty (DSM-IV). Objective and subjective measures of domains of sexual function have been the focus of study for some decades. A number of instruments which measure the low sexual function component have been validated and have been translated into different languages. [25,26,27,28,29] However these measures did not include items about personal distress. Consensus in definitions has led, in the last decade, to the development of measures of distress.[30,31] When both components (low sexual function and sexual distress) are measured in epidemiological studies, prevalence of sexual dysfunction is greatly reduced. [32,33] However, there is a differential effect of age on aspects of sexual function and sexual distress. For example with increasing age (and reproductive aging) the proportion of women who experience low desire increases, but the proportion of women distressed by low desire declines.[34] Thus, if low desire and sexual distress are combined into the aggregate definition of hypoactive sexual desire disorder, no association with age is detected. [34] Recent Australian epidemiological studies have investigated the relationship of psychological, socioeconomic, physiological and relationship factors to low sexual function and sexual distress components of FSD. [35,36] In a cross-sectional population based study of 1002 women aged 20 to 70, utilizing the Sexual Function Questionnaire (SFQ) and the Female Sexual Distress Scale (FSDS), relationship factors were found to be more important to low desire than age or menopause, whereas physiological and psychological factors were more important to low genital arousal and low orgasmic function. [32] Sexual distress was associated with both psychological and relationship factors. Sexual distress was positively associated with depression and inversely associated with better communication of sexual needs when results were adjusted for age, and other factors. In an 11 year, longitudinal study of mid-aged women using the Short Personal Experiences Questionnaire, a decline in all aspects of sexual function was reported over the duration of the study.[36] Sexual distress (measured by FSDS only once, postmenopausally) was associated with higher depression scores and negative feelings for the partner. Sexual distress was predicted by prior negative feelings for the partner and a greater decline in total scores of sexual function.

Sexually-related distress can be assessed by clinician interview and by patient self-report. Reliability and validity have been consistently demonstrated with the FSDS and PDS as a measure of the central nervous system construct of distress. Measurement of distress as an efficacy measure has been demonstrated.[37]

III. OTHER ISSUES IN FSD ASSESSMENT

The primary focus by regulatory agencies on event measures rather than on whether the construct is comprehensively conceptually appropriate to the specific sexual disorder is based on a desire for quantitative behavioral outcome measures. For example, questions about maximum intensity of sexual desire and frequency of sexual desire collected on a daily basis may not be conceptually relevant to HSSD; neither the daily time frame nor the measurement of intensity are closely linked with the construct of HSSD. Similarly, definition of successful and satisfactory sexual events or encounters over time requires a subjective interpretation of sexual experiences by the woman potentially including sexual intercourse, oral sex, and partner- or self-stimulation, and other associated outcomes such as orgasm and
emotional intimacy. Data clearly show other contextual factors influence reporting such as relationship status in sexual desire, and physiological and psychological factors in genital arousal and orgasmic function, that might need to be controlled-for in criteria for exclusion and inclusion in clinical trials, ultimately affecting generalizability. Such data seem to be even more difficult to interpret than numerical scores on self-report questionnaires, which have been established in control subjects and in target populations. Particularly in women with HSDD, the construct of low desire is only indirectly related to the number of sexual events, satisfying or not, as most if not all sexual events in women with HSDD are partner-initiated. Counting of satisfying sexual events reflects a behavioral outcome, rather than a biological or cognitive event (sexual desire), and may not correspond to the sexual problem about which the woman is distressed. [38] Attempts to quantify the minimum important difference (MID) for an SSE diary in 788 women with HSDD using anchor- and distribution-based estimates suggest a range of mean MID estimates between 0.04 and 0.46 SSEs per week. [39] Measurement of SSEs also fails to count other conceptually appropriate events such as receptivity to partner approach and subject initiation of sexual activity.

In addition, the FDA draft guidance for clinical development of drug products for treatment of FSD (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071655.pdf) requires recording of these events in daily diaries which do not have either face validity (daily measures in women of sexual desire or activity) nor have they been developed using the FDA's own guidance regarding PROs (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071975.pdf). Unfortunately, diaries are often inaccurate; this is particularly true of paper diaries that record behavioral events, which may be completed retrospectively without investigator knowledge, and thus, are subjected to recall bias which daily diaries are intended to avoid. [40] However, even when completed on time, for example, with electronic diaries, repeated daily measurement of the distressing sexual problem (e.g. low desire) may increase distress or may not accurately reflect the experience of the women (e.g. she may not have previously experienced an awareness of sexual desire daily). Also, daily measures may themselves act as an intervention, potentially inflating treatment and placebo effects or magnifying distress.

Validated self-report questionnaires have been standardized in target populations, and permit privacy that may lead to more accurate reporting. (See report of Committee 6; Clinical evaluation and symptom scales: sexual dysfunction assessment) Structured interviews allow for follow-up questions that may better define the problem, but require training and monitoring to establish inter-rater reliability, and avoid clinician bias. Currently, standardized expert interviews have been developed by industry, but have not been psychometrically validated. Concomitant use of self-report measures and clinician evaluation may provide the most accurate assessment. Such an approach has been successful in demonstrating differences between study drug and placebo in other central nervous system-mediated disorders, such as major depression and pain disorders.

Partner assessments have been utilized in post-marketing erectile dysfunction (ED) and premature ejaculation (PE) studies, particularly analyzing the burden of disease, medication adherence, and response to treatment. A woman's sexual difficulties can be contingent on ED in her male partner, and PE in male partners has also demonstrated co-morbid sexual difficulties in the woman, and was associated with greater dissatisfaction and emotional distress. [41,42,43,44] No such studies have been published in women, but FSD would likely also be associated with dissatisfaction and distress in the partner. In addition, FSD trials usually exclude women whose partner has any reported sexual dysfunction. In planning studies to include partners of women with sexual disorders, care would need to be taken to avoid making desire discrepancy between partners into a sexual disorder, and to avoid using partner assessments as a study endpoint.

**IV. RECOMMENDATIONS FOR STUDY MEASURES AND ENDPOINTS**

1. Primary endpoints should directly measure the construct of interest sampled over an interval of time appropriate to the construct, through measures such as:
   a. A validated, self-report measure of sexual functioning to include domains/subscales related to phases of the sexual response cycle (specifically sexual desire, arousal, orgasm and sexual pain – all processes mediated via the nervous system), and/or questionnaires or structured interviews assessing specific phases, and able to measure change over time with an intervention
   b. A validated measure of sexual distress
2. Recall period should be 1 – 4 weeks; daily diaries are not recommended
3. Translations of self-report questionnaires must be linguistically/culturally validated with cross-cultural construct validation established.
4. Hormonal status should be considered to include separate evaluations/stratification of premenopausal vs. post-menopausal women, monitoring of menstrual cycle in premenopausal women, analysis of effect of hormonal therapies.
5. Secondary endpoints may include physiologic measures, satisfying sexual events (this may be least important for HSDD), partner assessments, relationship satisfaction, etc.

V. DEFINITIONS OF THE SPECIFIC DISORDERS WITH APPLICABILITY TO THE RESEARCH QUESTIONS

All research designs in sexual dysfunction clinical trials must have participant inclusion and clinical trial outcome measures that reflect DSM IV-TR sexual dysfunctions. These have been outlined by Committee 2.

With regard to the DSM-IV-TR and its relevance to clinical trials, one of the major goals of the DSM-IV-TR is to allow for the differentiation between sexual complaints (short-lived, transient disruptions) from sexual dysfunctions (persistent problems that are distressing) and warrant treatment. The challenge remains to make more objective the essentially subjective line in the sand of what constitutes a complaint versus a dysfunction. Although Diagnostic and Statistical Manual for Diagnosis (DSM-IV-TR) [44] diagnoses and/or criteria are now often used uncritically by researchers and the legal profession, the DSM-IV-TR does not provide any indication of the huge variability in the level of empirical support for the reliability and validity of different diagnoses.

Similarly, the validity of the classification system is questionable given marked variations occurring across time (e.g., age, stage of life, etc.) and across cultures. Further, DSM-IV does not reflect differences in cultures when establishing norms of behavior and this remains a clinical judgment and may also be reflected in difficulties in validating clinical research across cultures.

There is a great deal of overlap or comorbidity of sexual disorders in women. The Female Sexual Function Index (FSFI), despite not initially meeting development criteria for a Patient Related Outcomes (PRO) measure [1,45], but often used as an outcome measure in clinical trials, shows high correlations between sexual constructs. For example, there was a surprisingly higher correlation between the FSFI arousal (psychological) and desire constructs than FSFI arousal and lubrication which are supposed to be measuring the same construct. (1,45) This also points to the notion that desire and arousal (psychological) may be the same construct in women or too interrelated to effectively tease out and measure independently. Clinical trials of sildenafil to treat Female Sexual Arousal Disorder (FSAD) are clear examples of the problem of overlap of disorders. These trials attempted to include postmenopausal women with only FSAD, but had a significant number of subjects who also met the criteria for HSDD or Female Orgasmic Disorder (FOD) (> 50% overlap) [46,47,48,49]. Some clinical trials of testosterone to treat HSDD in postmenopausal women also showed overlap between HSDD and FSAD or FOD with inclusion criteria that HSDD preceded the onset of other disorders. [20,21,22 23] Often in clinical and research settings, women are unable to differentiate the two constructs of desire and arousal, which begs the question—is it really the same construct we are measuring? More data are needed regarding the separation or overlap of sexual desire, sustained desire, receptive desire, and cognitive/psychological arousal.

VI. OBTAINING A REPRESENTATIVE STUDY POPULATION – ISSUES IN GENERALIZABILITY

1. SAMPLING A REPRESENTATIVE STUDY POPULATION

General Principles. Sample selection for clinical trials of candidate treatments for sexual dysfunction in women is driven by the specific objectives of the clinical trial in question, the degree of sample representativeness required to achieve these objectives, and the requirement for experimental integrity that permits unambiguous attribution of study effects to study treatments. Inclusion criteria for research participants must ensure (a) representation of the clinical phenomenon of interest at levels appropriate to the objectives of the study (e.g., study of safety, tolerability, or efficacy), and (b) representation of participant sample characteristics matched to the target population to which it is wished to generalize clinical trial results, which defines the external validity of the study. [50,51,52]

Exclusion criteria are determined by the requirement to ensure safety of study participants and by the need to avoid clinical trial sampling procedures from introducing confounding factors (e.g., recruiting women who are involved in concurrent treatment efforts that may be productive or interfering, or who are experiencing intractable relationship difficulties rendering their sexual dysfunction refractory to pharmacologic intervention) that would impair ability to attribute treatment effects or lack of effects to the treatment under study. The presence or absence of such confounding factors in the sample population, together with trial design and measurement parameters, help define the internal validity of the clinical trial, or the degree to which it is possibly to unambiguously attribute clinical trial treatment effects to the treatment per se. [50,51,52] There is often a need to balance requirements for internal validity (achieving a pristine experimental design and sample recruitment strategy that permits unambiguous attribution of treatment effects to the intervention of interest) and external validity (ability to generalize from the
Sample Selection in the Context of Clinical Trials. Sample selection in the context of clinical trials is driven by the specific objectives of the Phase I, Phase II, or Phase III clinical trial. Phase I trials focus on assessing safety and tolerability of a study compound beyond data obtained in animal studies. While sampling for Phase I trials of candidate compounds in women may seem merely to require passive participation of physiologically normal women subjects, sampling for such trials may prove to be more complex than first apparent. Examination of safety and tolerability in clinical trials of treatments of sexual dysfunction in women will require healthy female participants, whose hormonal status (e.g., oral contraceptive use, menopausal status, hormone replacement therapy use), pregnancy status or pregnancy intentions, comorbid conditions and concurrent medication use permits generalization of Phase I safety and tolerability results to the intended treatment populations. Moreover, sample selection representativeness requires recruitment of participants who are likely to complete the study across the Phase I time interval and multiple potentially invasive procedures involved in single dose, multiple dose, and pharmacology studies, as systematic attrition of intolerant subjects or those who suffer adverse effects can introduce interval validity violations that will render safety and tolerability findings of limited or no value.

Phase II clinical trials focus on identification of an effective dose range for a candidate treatment of a female sexual dysfunction, and early in the Phase II trial a wide array of inclusion and exclusion decisions must be considered in the selection of an appropriate research sample. Following the general principle that sample selection is driven by the specific objectives of the research in question, it will prove critical to sample women who experience a moderate level of the clinical condition in question, as women with an insignificant or an overwhelming level of the condition will be unlikely to show any effective dose treatment response vs. placebo. Similarly, with respect to exclusion criteria, women experiencing lifelong sexual dysfunction, women whose partner relationships appear overwhelmingly to be a cause of their sexual dysfunction, and women for whom a specific medical or pharmacological issue appears to contribute significantly to sexual dysfunction, would not be appropriate candidates for a Phase II study of a candidate treatment. Selection of participants unlikely to attrit during the course of the trial remains a concern. Phase II sample selection should be guided by the need to create “greenhouse conditions,” in part via selection of a sample with appropriate levels of the dysfunction at focus and lacking characteristics that would render the dysfunction refractory to treatment, for identification of an efficacious dose of a pharmacologic treatment for a female sexual dysfunction. In seeking to do so, the tension of balancing internal validity with external validity is evident. In seeking this balance, many of the sampling issues of core concern in Phase III research, including sampling the diagnostic entity at focus at appropriate levels and exclusion of appropriate potential confounders without unduly restricting generalizability of results, come clearly into focus early in the Phase II trial process.

Phase III clinical trials aim to demonstrate the efficacy of a candidate compound for the treatment of a female sexual dysfunction within a representative sample of those experiencing such dysfunction and who might reasonably constitute a treatment target population. Accordingly, sample representativeness in relation to the population of women suffering from the dysfunction, balanced by the need for exclusion criteria sufficient to ensure experimental precision, are paramount concerns in Phase III research. Inclusion criteria for Phase III research are guided by the need to capture participants who represent the diagnostic entity under study, with representative severity of dysfunction (neither too little nor too much), duration of dysfunction, and distress attendant upon the dysfunction. At the same time, it is necessary to exclude those for whom the trial might prove unsafe and, to ensure internal validity, exclusion of those whose hormonal, comorbid illness or medication, and partner relationships might prove confounding factors that obscure ability to attribute research results to the study compound. Again, a careful balance between representativeness and precision is thus required. In Phase III trials, involving the active treatment of a woman’s sexual dysfunction that may be situated in and affect her partnered relationship, partner willingness and potentially partner consent must be considered. Enrollment of partners as clinical study participants may also be a wise choice to permit detection of positive or negative effects of treatment of the index patient on her partner [53].

2. ADDITIONAL CONSIDERATIONS IN SAMPLE SELECTION

Contextual and Interpersonal Factors. Within the general need to select samples that are appropriate for study of the research question at hand, and to balance sample representativeness with exclusion criteria sufficient to ensure internal validity, it is necessary to consider contextual and interpersonal factors that are relevant to both concerns. External validity may require representation of contextual and interpersonal characteristics in research sample participants (e.g., participants drawn from ethno-cultural groups that tend to inhibit female sexual expression; women with childbearing responsibilities; women with a burden of comorbid illness, or other stressors; women with sexual dysfunction whose partners
Symptom Duration, sexual dysfunction. Research that seeks to identify boundary conditions concurrent relevant conditions may be sampled in protocols, participants with a representative range of treatment efficacy within internally valid research use to smoking to concurrent psychotherapy to these or other characteristics ranging from alcohol to which it is wished to generalize may well have sexual dysfunction in the treatment target population of candidate compounds should exclude women sampling for research seeking to demonstrate efficacy and is a potential treatment-sensitive endpoint. Accordingly, avoidance of exceedingly high or low levels of distress may be advisable in sampling for clinical trials in sexual dysfunction.

Hormonal Status. In all research on female sexual dysfunctions, it is critical to systematically incorporate women’s hormonal status into sampling strategies on the basis of anticipated hormonal status moderation of effects of a candidate compound. At a minimum, it would be anticipated that pre, peri, and postmenopausal status women may differ on the basis of hormonal milieu and anatomic and physiologic aging in response to candidate treatments; as such, sampling and research designs must reflect this reality. In addition, it is likely that hormonal contraception (oral, transdermal or injection routes of delivery), and potentially ovarian cycle phase, may moderate treatment effects and sampling; research design, and assessment of covariate assessment and control must be integrated into research strategies in this area to address related external and internal validity concerns.

Overlap and Comorbid Conditions. A number of overlapping and comorbid conditions may be both representative of women with a particular sexual dysfunction and confounding factors that could serve to obscure clinical trial results. It is likely that women with sexual dysfunction may experience medical illnesses, psychiatric conditions, and medication regimens that may contribute to their dysfunction, and sampling for research seeking to demonstrate efficacy of candidate compounds should exclude women with such cofactors. At the same time, women with sexual dysfunction in the treatment target population to which it is wished to generalize may well have these or other characteristics ranging from alcohol use to smoking to concurrent psychotherapy to relationship distress. Within a progressive approach to increasing external validity after establishing treatment efficacy within internally valid research protocols, participants with a representative range of concurrent relevant conditions may be sampled in research that seeks to identify boundary conditions of efficacy of a pharmacologic treatment of a female sexual dysfunction.

Symptom Duration, Symptom Severity, and Symptom Distress. For a variety of clinical, scientific, and regulatory reasons, it is clear that symptom duration, and as alluded to earlier, symptom severity, and symptom distress need to be considered in sampling strategies. Symptoms that are life long may be refractory to treatment, and symptoms that are highly intermittent are unlikely to show treatment effects within time-limited clinical trials. Similarly, symptoms that are exceedingly severe, or exceedingly minor, as measured via screening or interview metrics are unlikely to be sufficiently responsive to treatment in the context of a clinical trial. Finally, opinion generally holds that distress attendant to symptoms of sexual dysfunction is both necessary for diagnosis of such dysfunction and is a potential treatment-sensitive endpoint. Accordingly, avoidance of exceedingly high or low levels of distress may be advisable in sampling for clinical trials in sexual dysfunction.

The Partner as a Subject. It is well recognized that sexual dysfunction is very often embedded in the context of a couple relationship. Not only may it be advisable for partner willingness and partner consent to be assessed, but it may also prove valuable in exploring treatment effects to examine treatment impact on the female participant as well as on her partner. Placebo-controlled clinical trials in sexual dysfunction have indicated that female partners of treated male patients may experience substantial positive benefits of partner treatment and exploration of the reverberating effects of treatment of women with sexual dysfunction on the index patient and her partner is certainly warranted [54,55] 3. NATURE OF CONTROL GROUP

Selection of a control group for clinical trials in female sexual dysfunction should be guided by the same imperatives as sample selection for those randomized to treatment conditions: representativeness of the clinical parameters under study as appropriate to a Phase I, Phase II, or Phase III study, balanced by the need for internal validity and experimental clarity. Research of this nature may involve crossover or repeated measures designs in which an individual woman participant serves as her own control, with consequently increased statistical power and appropriate consideration of drug washout periods; it may involve a placebo-control group in which a single sample of appropriate representativeness is randomized to treatment or control condition, or it may involve a randomized controlled trial involving randomization of appropriately representative participants to a placebo group, an investigative compound, and a comparator (when available) to determine the efficacy, equality, or superiority of a candidate treatment of a female sexual dysfunction.
Special sensitivity and effort to avoid systematic attrition of control arm participants who may not experience symptom relief and who may bear the burden of side effects is needed to avoid compromising the internal validity of the clinical trial.

### VII. ISSUES IN STATISTICAL ANALYSIS

#### 1. PLACEBO-CONTROLLED TRIALS

Large placebo-response in FSD trials makes it difficult to demonstrate significant drug-placebo differences. Large placebo responses (>50%) are likely to lead to failed trials.

Some concern may be raised for measures with placebo response over 40%, too, but a 42% placebo response on the primary endpoint for a trial of sildenafil for FSAD did not prevent significant statistical separation from placebo. A subgroup of patients with FSAD + HSDD showed poor drug-placebo separation but the placebo response was only 2% higher (44%). [47] Thus, subpopulation assessment may provide direction for future trials, particularly in terms of inclusion and exclusion criteria.

Low placebo response may obviate such problems; e.g., in the primary endpoint of a trial of a melanocortin receptor agonist in FSAD, the published main endpoint, a sexual satisfaction scale from 0 (extremely dissatisfied) to 5 (extremely satisfied), showed 82% of patients satisfied with bremelanotide vs 10% with placebo after twenty attempts at sexual intercourse. Earlier timepoints, after four and twelve attempts, were similar for placebo (12 and 15% satisfied, respectively) but showed increasing rates over time with bremelanotide (52 and 78%, respectively), p=0.01 for all of these comparisons. [56]

Placebo response in excess of 50%, however, can severely limit the assay sensitivity of a clinical trial. The ultimate example would be 100% placebo response, of course, which would allow no differentiation from active treatment. As an illustration of this problem, a daily diary measure of maximum intensity of sexual desire in premenopausal women with HSDD was used as a co-primary endpoint in the libanserin phase III project. Although percent change from baseline was not a pre-specified endpoint and individual percent patient changes were not evaluated, the crude group placebo response on this measure exceeded 50% in all trials, at approximately 60-70% per trial, and the diary desire measure was the least robust endpoint in the series of trials. [57]

**Relationship to measure, recall period, etc.** A given measure tends to have a specific recall period, of one, seven, thirty days, etc. Controversy exists on what is an adequate period for a patient to make sense of her pattern of sexual symptoms, but women with HSDD have newly been debriefed to indicate unequivocally that they do not accept a one-day recall period, but do endorse a one to four week recall period related to sexual desire. [12]

In the same libanserin studies as described just above, with a crude overall 60-70% response to placebo on the daily desire measure, the FSFI desire self-ratings, with a 4-week recall, showed 33% or less mean crude overall effect in the placebo groups. On other endpoints, e.g., changes in sexual distress (seven-day recall period) and proportion of patients rating themselves as improved on a global impression question (recall period: 4 to 24 weeks), placebo response was similarly low. The credibility of the e-Diary’s one-day recall results is thus questionable, as it is such an outlier in terms of placebo response. (Figure 1)

**Relationship to Number of Treatment Arms.** A supposition sometimes made is that the lower the proportion on placebo (the higher number of active arms; the higher the proportion on putatively “active” drug), the higher the placebo response. Too few large-scale trials in FSD have been done to establish this effect in FSD. The BI development program used 2-arm, 3-arm, and 4-arm trials (50, 33, and 25% on placebo, respectively). Of well-powered phase III trials, one out of two 4-arm trials had high placebo response; neither of two 3-arm trials had an excessive placebo response, and neither of the two-arm trials had a high placebo response. The two TTS Phase III and three Phase IIIb/IV trials in surgically or naturally menopausal women were all done with a two-arm design (50% on a single level of TTS, 50% on placebo) and were uniformly positive with moderate placebo response.

#### 2. DOSE-FINDING

**Duration.** Duration of treatment in dose-finding studies must be consistent with onset expected and with practical clinical realities: if an agent shows no obvious onset of efficacy within one, or at most two, months of use, poor (or no) compliance thereafter, and thus poor efficacy should be expected. The maintenance dose should be achieved reasonably early, at least within the first month; consuming more time for titration of dose may be impractical.

**Sample Size.** In general, sample size should be large enough for adequate power of the trial to confirm whether further development of a treatment is worthwhile or not. Trials based on main endpoint separations and variance values consistent with less than 75% power cannot inform such decisions with much accuracy. Dose-finding done early in development with small numbers of subjects (n/treatment of 20-75) may help guide future development in dosage but can mislead by Type I and II errors as to whether the treatment actually works. An alternative
is to perform several trials each with moderate statistical power and look for patterns of confluence.

If done late in development, dose-comparisons multiply costs and patient burden in seeking the minimum effective dose because a large number of patients may be given inactive doses. This is likely to impact compliance and subject retention negatively.

**Controls.** Dose-finding not controlled with parallel double-blind placebo may mislead by overly positive results due to a high “placebo” effect. A positive control, if any were available, is not an adequate substitute for placebo because superiority over a positive standard is highly unlikely, and similarity to a positive standard may mislead because both agents may not have exceeded a placebo if one had been included. However, using a dose of the agent at what is demonstrably a no-effect level in Phase I studies may help surmount the difficulties of using a placebo. These include rejection by some ethics review boards, and poor enrollment due to low expectations of obtaining personal benefit.

**Fixed vs Flexible Dosing.** Fixed dose design can create a barrier to efficacy if side effects arise early and the onset of efficacy comes late, factors often leading to excessive subject dropout, especially in non-progressive conditions such as FSD. Yet, flex-dosing mixes in time effects, potentially obscuring dose effects. A forced up-titration to a fixed dose may be the best compromise to determine the minimum effective dose. Yet flex-dosing is the only way to optimize the dose for all patients in a treatment group, thus maximizing opportunity for drug-placebo separation and to best simulate effects to be expected in clinical practice.

Rescue down-titration may add value to salvage fixed-dose trials by helping lower dropout rates.

**Maximum Dose.** In early dosing studies of patients with FSD, it may be more germane to be guided in the maximum dose not only by toxicology results or side effects in an indication with high patient symptomatology (depression, etc), but more so by the side effect profile in normal female subjects, who tend to approximate closely the tolerability profile of women with FSD.

**Timing of dosing.** Sedative agents should be given at bedtime; activating agents should be given in the morning. Doses of agents which cause nausea, etc should be administered with meals if that does not impair absorption. In general, dosing instructions should seek to minimize side effects in a practical way.

The number of doses per day is another practical issue. Trials should keep the regimen practical for patient compliance, not exceeding twice daily dosing unless strongly informed by short half-life issues.

**Intermittent Dosing.** Trialists and sponsors should consider intermittent dosing if the indication amounts to an episodic disorder; e.g., in arousal, orgasmic,
sexual pain disorders; that is, if symptoms relate chronologically to sexual activity or if the agent works upon first dose. This schedule appears to have less potential for treatment of desire disorders.

**Pharmacokinetics (PK).** A short half-life may dictate dosing before sexual activity, or at the time of day just before sexual activity is most likely. If the half-life is much less than 8 hours, it may still be effective for FSAD if taken just before sex at bedtime but may require exclusion of, or special dosing alarm/reminder system for, women whose pattern is for sexual activity in the morning. The possibility of cumulative effects must also be considered, even for short half-life agents. For agents with long half-lives, cumulative effects (positive and negative) may overshadow first-dose effects, so trial designs must take this into account with slow increases in doses and emphasis on chronic rather than acute efficacy and safety.

Drug interactions must be considered for agents that are CYP-450 metabolized, especially for those with active metabolites.

**Pharmacodynamics (PD).** Pharmacodynamic studies early in drug development can obtain useful preliminary answers to several vital questions:

- Which come first, side effects or efficacy?
- How long must the patient be treated before a dose is found to be effective, or can be assured to be ineffective?
- Can an expected (early-onset) side effect be used to guide dosage for a late-onset drug?

Side effects and their severity may depend on the rapidity of upswing in plasma concentration, not just on the absolute Cmax; slowing absorption (even if only with food) may make a medication more tolerable and allow the patient to persist in compliance until she obtains efficacy.

Carefully chosen surrogate endpoints potentially can guide dose-finding in later studies, e.g., if an agent is sedating, prospective measures of sedation, attention, and/or cognition are likely to give stronger dose differentiation than simply a general inquiry about how the subject feels. Similarly, self-rating scales can be modified to a shorter recall period to fit the restrictions of early (phase I trials), e.g., a 4-week recall can be shortened to 1 week. [31]

3. **DURATION OF TREATMENT**

Three months may be adequate to test for induction of effects on feeling states (sexual desire, sexual distress) but may not be long enough to alter a couple’s dysfunctional pattern of sexual inactivity and/or dissatisfaction, whether it was a consequence of the FSD or not. Thus, this duration may be suitable for Phase II trials, but not for Phase III studies, in which sexual activity, and in particular the frequency of satisfying sexual events, is likely to be required as a primary endpoint. Several trials have shown concordance of improvement in feeling states and satisfying sexual activity over this period [20,21,22,23,58,59,60,61].

Female Sexual Disorders are rarely of short duration. Thus, controlled testing of maintenance for six months or longer may be useful to confirm maintenance of effect. A parallel trial with placebo for over a year is in process for the TTS (www.clinicaltrials.gov) but it may be more practical, particularly for retention of subjects on placebo, to use a randomized crossover from open-label “active” treatment to drug vs placebo after several months to obtain plateau maintenance effects. This has been used successfully in a 48-week design in premenopausal women with HSDD. [37] When considerations of withdrawal are relevant, this design may be particularly useful.

4. **EFFICACY MEASURES AND THE CURRENT PROCESS AND PROBLEMS**

All measures of a particular construct associated with the sexual disorder should have convergent validity. When well-validated measures fail to converge statistically with novel measures, concerns about the suitability of the novel measure arise.

Excessively high placebo response may be measure-specific, as explained above. Excessively low placebo response may also occur, even for measures that discriminate FSD patients well from normal women. Poor response on such a measure can suggest lack of efficacy if the active treatment does not separate from placebo on the measure. However, if it is an outlier among measures, the presumption instead should be that the measure is insensitive to change with treatment, as no history of ability to detect treatment responsiveness is currently available, because all the treatments are novel. This currently appears to be a particular problem for measures in FSD trials as data on treatment responsiveness of validated instruments is not published (e.g. proprietary tools used in TTS trials). This can occur because of irrelevance to patients or because of design flaws in the measure, if other measures in the same trial do show separation between active treatment and placebo, e.g., crude overall group placebo response was about 5% on a daily e-Diary question on intensity of sexual distress (not a thoroughly validated measure) in a set of Phase III trials of premenopausal women with HSDD, whereas crude overall group placebo response on the well-validated FSFI-R (measuring frequency but not intensity of sexual distress) was about 15-20% in the same women at the same time, and crude overall group desire improved 26-33% on the well-validated FSFI desire domain. Thus, the credibility of the e-Diary distress item results is questionable. (Figure 1)
This points to a major potential problem of daily measurement: that the measurement itself influences ratings. Whether the level of placebo response varied so greatly between measures (daily desire, 60% response or more; daily distress, 5% response, both in the same placebo group) because of the frequency of measurement, and/or because of the power of suggestion invoked by the measure, the large disparity between measures suggests a serious problem with daily measurements of feelings related to HSDD. Self-ratings with a 7 to 30 day recall period, the FSFI and FSDS-R, generally showed less than 40% crude overall group placebo response in the same program. This demonstrates the importance of less frequent measurement, which has been argued on theoretical and practical grounds. [62]

5. SAFETY MEASURES AND ADVERSE EVENT MONITORING

Spontaneous reporting of adverse events is the standard method, but it is known in general to give lower incidence rates than prospective, elicited reporting. The prime example in this field is that the first selective serotonin reuptake inhibitor (SSRI) antidepressant, fluoxetine, was originally described in the package insert as associated with a 1.9% rate of sexual dysfunction. Prospective, elicited reporting of sexual dysfunction with now-standard rating scales such as the Changes in Sexual Functioning Questionnaire (CSFQ) have shown rates of FSD more than 15-fold higher. [63]

The FDA's new standards require prospective, elicited reporting of suicidality. The FDA has also mandated prospective, laboratory-based determination of whether an agent causes infertility. As appropriate, determination of relevant endogenous sex hormone levels should be used to inform long-term safety, e.g., carcinogenesis and cardiovascular disease. Thus, certain classes of compounds may require a longer treatment period to determine safety.

VIII. ADDITIONAL ISSUES IN FSD TRIALS

**Comparator trials.** No gold standard treatment for comparison exists, although tibolone, the Eros device, the testosterone transdermal system for postmenopausal HSDD, or behavioral treatments may serve as models to inform calculation of a sufficiently powered trial (not over-powered or under-powered).

**Statistically significant change vs. clinically meaningful effect.** Standards for statistical differences and clinically important differences must be determined a priori or anchored by a global measure of change: efficacy and effectiveness. Achieving a statistically significant difference between a new treatment and placebo is insufficient to define the value, or effectiveness, of the new treatment. The latter can be done only by finding a clinically meaningful difference between the two treatments. This can best be done by comparing the proportion of responders between the treatments.

**Confluence of arbitrary responder values and clinical data to determine responders.** Few normative population data are available to help establish responder criteria for adequate sexual function in pre- and post-menopausal women, but a value of 25, 30, or 50% of normal functioning might be chosen arbitrarily as a responder value for various endpoints. Data from comparisons of women volunteers with a given FSD diagnosis vs volunteers without sexual complaints suggest that such values would be clinically meaningful.

For the FSFI desire domain, the minimum score is 1.2 and the maximum is 6.0. A 20% improvement based on the maximum score would be 1.2. A 50% improvement based on the baseline score would be 0.9, but patients can improve by increments no smaller than 0.6, so 0.9 would amount to 1.2 anyway. The value of +1.2 to define a responder on this measure corresponds with the value determined by anchoring methods (see below).

For the FSDS-R, an improvement of 6 points has been recommended by the author of the scale, L. Derogatis, as a responder value, which corresponds for this 13-item, 52-point scale to approximately a one-half point change per item. It corresponded, in the fibanserin Phase III program, to a 20% improvement toward the scale maximum for functionality, i.e., zero. [4]

**Confluence of anchoring methods to determine responders.** Alternatively, anchoring a responder value in terms of a patient global impression question can be used.

For the TTS Phase III project in surgically menopausal women with HSDD, to define responders on the desire measure, the desire domain of the Profile of Female Sexual Function (PFSF), a value was chosen by anchoring for optimal sensitivity and specificity on the Patient Benefit Evaluation (PBE), i.e., 9.0. Comparing to the baseline mean on the PFSF, 21.3, a responder would be one with a 42% increase in desire.

In the TTS project, responders on the sexual distress measure, the Personal Distress Scale (PDS), were defined the same way, resulting in a responder value of -20 versus the baseline mean score of 65.05; this represents an improvement of 31%.

In the fibanserin Phase III project in premenopausal women with HSDD, responders on the FSFI desire domain or on the FSDS-R distress measure were defined similarly, but the anchoring used the mean difference (on the desire measure or distress
measure) between those self-rated on the PGI-IMPROVEMENT as unchanged vs those minimally improved. The logic here is that a responder is one who achieves the minimum clinically important difference (improvement) between no treatment and treatment. The responder value was the same when calculated as the difference between those self-rated as minimally improved vs those much improved. This method of analysis seeks to determine the minimum clinically important difference between optimal and suboptimal improvement with treatment.

By either the PGI-anchored method of defining a responder, or by anchoring for optimal sensitivity and specificity on the PBE, the responder value was 1.2 for the FSFI-desire domain, and -6 (+1, depending on trial and method) for the FSDS-R. Use of independent data sets on women with HSDD not in a clinical trial, or in different clinical trials derived the same responder value.[11] Seeking and finding such a confluence of values helps assure the clinical meaningfulness of the definition of a responder.

On the 2-to-10 FSFI desire domain score (of two items, each rated 1-5), which in its standard analysis is multiplied by a factor of 0.6, an improvement of 1.2 represents a change of 2.0 in the raw score, i.e., exactly two scale points. The baseline mean in the filbanserin program was 1.8 for the FSFI desire domain. Thus, the PGI-anchored responder value represents a 67% improvement.

FSDS-R mean values of about 30 have been found for untreated premenopausal and postmenopausal women with HSDD or FSAD (vs scores of 3-4 in women with no sexual complaints) [4]. Thus, a decrease of 6.0 points would represent a 20% improvement for patients on the mean.

In any case, a reasonably large ratio of efficacy with active treatment over placebo is required not only for statistical significance but also for clinical relevance. This may alternatively be registered on effect size (mean difference divided by the common standard deviation at baseline) of at least 0.2 (small) to 0.5 (moderate), a statistically significant difference in the proportion of responders (usually >10%; e.g., anchored on the difference between no change and minimal improvement or between minimal improvement and much improvement on the patient’s global impression of change), or an (adjusted) odds ratio close to or exceeding 1.5. In the FSAD trial of Berman et al. [47] for instance, a subgroup with both FSAD and HSDD was included. Their adjusted odds ratio (OR) was 1.09 or 1.14 (primary endpoints question 2, and question 4), which demonstrated that inclusion of such dually–diagnosed patients formed the efficacy issue within the overall analysis, not a high placebo rate. The ORs for FSAD-only patients were impressive, with values of 7.98 and 10.95 on the two respective questions (p<0.001).

An example that involves comparing the proportion of responders is use of the testosterone transdermal system for HSDD in post-surgically menopausal patients. In the two trials of TTS in such patients, the % responders on PFSF desire, defined by anchoring (at a cut point of 8.9) to optimize sensitivity and specificity using a patient benefit evaluation question (yes or no meaningful benefit from the treatment) to define responders vs nonresponders, was reported in the SM1 and SM2 trials as favoring TTS over placebo significantly at 45.7/34.8% and 42.2/25.1%, respectively. For PDS distress, similarly defined, responders were also significant in both trials: 51.3/34.6% and 49.2/33.9% respectively.

The level of improvement required to define a responder on PSFS desire and PDS distress based on the TTS FDA advisory committee slide set of December 2004 was 42% for PFSF Desire (>8.99/mean baseline of 21.3), -31% for PDS distress (<-20/mean baseline of 65.05).

**Remitters.** A higher standard, but the one with the utmost clinical meaning, would be for a new treatment for FSD to produce a meaningfully higher rate of remission than placebo. Treatments for FSD cannot be expected to produce a high rate of remission, given that FSD may often, or perhaps even usually, be not only biologically mediated in part but also mediated and/or perpetuated by psychosocial factors. However, all new treatments should be evaluated not only for ability to induce response but also for ability to induce remission. Clinically meaningful superiority to placebo on the rate of remission should be an achievable goal.

On the FSFI desire domain, for instance, the cutoff between women with HSDD and normal women has been found to be >3.0 on the derived version of the domain. That is, achieving a score of 3.6 would be required for remission. The baseline means in the filbanserin program were 1.8, so an improvement of 1.8 would represent a 100% (mean) improvement. The PFSF-DsR, the baseline value in the filbanserin program was about 30, and the established cutoff between HSDD and no FSD is 15. [4,30] This cutoff, representing a 50% group mean improvement, could be used to designate remitters.

**Ethical Issues.** Ultimately, somatic treatments will be prescribed mostly by clinicians not expert in FSD. Thus, an ethical issue arises as to how well they can screen/diagnose patients as candidates for such somatic treatments. To fill this need, acceptably simple (and brief) screening/diagnostic tools for non-expert clinicians must be well validated before approval of such agents. [64] A method for such validation is a one-way crossover study in which results of two diagnostic interviews are compared after a substantial sample of patients are screened using the new screening/diagnostic tool by a non-
trained, non-expert clinician, followed by diagnosis by an clinician expert/experienced in diagnosing FSD who is not permitted access to the non-expert’s diagnostic decision.

**FSD impairs quality of life.** However, it is, of course, non-life-threatening. Thus, the burden of proving a very high level of safety must be assumed by sponsors of treatments for FSD. No treatment for FSD should be recommended that has not stood the test of a large (multi-thousand-patient), long-term (at least 1-2 year) prospective evaluation of safety in the target population, using appropriate safety measures and appropriate controls, without causing life-threatening side effects or being associated with a rate in excess of placebo of laboratory abnormalities known or expected to be associated with long-term health risks, be they as specific to FSD as prolactin levels or as nonspecific to FSD as cholesterol levels. Thorough, perspicacious, scientifically valid risk management practices and studies must be assumed by sponsors after marketing, also, because of the significant multiple-effect to be expected for patient exposure compared to even large programs of clinical trials.

**Disclosure of results.** For the advancement of the field of treatment of FSD, it is incumbent on sponsors to disclose trial results. Proprietary concerns must be acknowledged and accepted. However, ordinarily in the past an ineffective treatment was seldom acknowledged in public. This can easily prevent or retard research funds from flowing from continuing fruitless mechanisms of action into useful directions.

Trial results (at least in the US) have become subject to disclosure in www.clinicaltrials.gov to be considered for publication in peer-review journals. This new standard has opened doors to disclosure. However, this remains to be seen, as the policy has been in effect only since 2007.

**Post-conduct issues.** Selective publication of positive results obscures difficulties to be expected in replication of trial results, and in effect, magnifies the efficacy of an agent. Thus, this is strongly discouraged in favor of full disclosure of all results in each phase of investigation of a new agent.

Post-hoc analysis of “evaluable patients” rather than intent-to-treat (ITT), and publication of the latter without the former, or failure to provide fair balance between conflicting analyses in publications, are also strongly discouraged. Like selective publication of positive results, these practices unfairly magnify efficacy expectations.

Issuing press releases before submitting results to peer-review publications, while a temptation for sponsors, serves only to negatively affect the view of the FSD scientific community and regulatory bodies alike about the utility of a new agent, and is to be discouraged.

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**VIII. CONCLUSIONS**

Fine-tuning outcome measures to directly assess the specific FSD construct under evaluation should lead to improved ability to demonstrate efficacy when such an effect exists. Future clinical trials should include clear population definitions, direct and indirect measures of the specific FSD construct, and procedures to allow generalizability of diagnosis and treatment to the general/target population.


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Committee 22

Physiology of Women’s Sexual Function

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Understanding the anatomical, physiological, neurobiological and endocrine mechanisms behind sexual function, dysfunction and responses are of paramount importance. The interaction of these with psychological mechanisms is crucial in the field of sexual medicine. In this context, it is important to highlight that in women changes in physiology do not necessarily induce sexual dysfunction, while sexual problems may occur despite a normal sexual physiology.

The sexual response cycle has traditionally been described by the stages of sexual desire, arousal and orgasm. Since the early descriptions of these stages by Masters & Johnson [1] and later, Kaplan [2], the stages have been challenged [3]. Substantial advances have also occurred in the understanding of physiological aspects of sexual function and dysfunction, driven by more and more sophisticated methods of their measurement. Particularly, the application of neuro-imaging methods during the last years has significantly improved our knowledge of central mechanisms related to women’s sexual function and dysfunction. In this context, research on peripheral mechanisms and the interaction between central and peripheral mechanisms have given us a better understanding of feminine desire, arousal and orgasm. There is also an increased awareness of the interaction between physiological responses and psychological/behavioural factors and their influence on sexual function.

Due to ethical constraints and experimental limitations much of our knowledge has been obtained from animal studies, but an increasing amount of evidence is arising from human investigations.

In this context, the aims of this chapter are to describe:

1. Central and peripheral anatomical and physiological aspects of female sexual function and the influence of hormonal milieu, neurobiological factors and interaction with psychological factors;

2. Pathophysiological processes impacting on women’s sexual health. Since the 3rd International Consultation on Sexual Medicine has a number of chapters devoted to comprehensively describing the role of both animal models for studying women’s sexuality and (committee 7) the importance of the hormonal milieu on women’s sexual health (committee 23), the current chapter will not include any large debate about those items. Furthermore the pathophysiological processes are only described briefly as other chapters cover pathophysiological aspects of FSD more extensively (committee 9 and 25).

The chapter reviews existing literature with a focus on the most recent data and includes earlier studies if they are relevant for dealing with the concept of women’s sexual arousal and orgasm. The chapter includes animal studies when no human studies exist.

In accordance with the consultation criteria, wherever possible the basic principles of evidence-based medicine have been used in the evaluations on the included studies. We have primarily included papers which have been through a peer review process. However, the current guideline (ICUD guidelines) for grading level of evidence is often difficult to apply on animal and laboratory studies investigating basic anatomy and physiology.

When describing the physiological fundament of arousal and orgasm it is noteworthy that it is difficult to find out a comprehensive definition for female sexual arousal [4]. It has to be subdivided into an objective
and a subjective part, and is in the literature often based on what is considered dysfunctional. Thus, sexual arousal could be described as “a combination of objective and subjective signs; the bodily reactions as vulvar swelling, vaginal lubrication, heavy breathing and increased sensitivity of the genitalia combined with the subjective experience of feeling pleasure and excitement”. Orgasm, in contrast, may be defined as “a variable, transient peak sensation of intense pleasure, creating an altered state of consciousness, usually accompanied by involuntary, rhythmic contractions of the pelvic striated circumvaginal musculature, of the with concomitant uterine and anal contractions and myotonia that resolves the sexually induced vasocongestion (sometimes only partially), usually with an induction of well-being and contentment” [5].

B. DEVELOPMENT AND DETERMINATION OF SEXUAL PHYSIOLOGY AND ANATOMY

Understanding the physiology of adult female sexual behavior requires knowledge of events that occur early in development and the understanding of the neural control of female sexual behavior includes consideration of those brain regions essential to motivation, consummation and reward. The basic principles of the neural control of sexual behavior apply to an impressively broad range of species, from fish, lizards and birds to rodents, guinea pigs, dogs, rabbits, sheep and non-human primates. The importance of the biological mechanisms regulating reproduction in animals is much greater than that in humans. Stereotyped sexual behavior and coitus occurs normally only in estrous, whilst human copulation can occur during the entire ovarian cycle, and even during pregnancy and in the postmenopausal condition, demonstrating relative freedom from hormonal control [6] and is influenced by cognitive, cultural, and social factors as. Nevertheless, there is still value in understanding the basic cellular mechanisms establishing the physiological and neuronal parameters upon which other variables act to influence human female sexuality. Often only studies in animals can provide this insight by allowing observation, experimentation and hypothesis testing to occur. Reviewed here is the current understanding of the biological principles of sexual behavior at the most fundamental level.

I. SEX DETERMINATION AND DIFFERENTIATION

In mammals, sex is determined by a single gene on the Y chromosome, the Sry, for sex determining region of the Y chromosome, with codes for the protein tdf, for testis determining factor. The tdf is a transcription factor which initiates a cascade of gene expression and protein products that will direct the development of the bipotential gonadal anlage towards a testis [7]. In the absence of the Sry gene, this same gonadal anlage will become an ovary. The brain is also sexually differentiated in males and females by gonadal steroid hormones and this process occurs during a restricted developmental window termed the sensitive period. In rodents the sensitive period is during the last few days of gestation and first week of life and the critical hormone for masculinization is estradiol derived from testicular androgens. In primates, including humans, the sensitive period is largely prenatal, beginning in the 2nd trimester, and the critical hormone for masculinization is testosterone. At first consideration these differences might make it seem that rodents and humans are so different they are not worth comparing, but what really matters is the cellular mechanisms by which the steroids are acting to differentiate the brain. Estrogens and androgens often converge on the same cellular mechanisms and only by identifying those mechanisms can we determine whether there is a commonality is steroid hormone action in the brains of humans and animal models.

II. FEMALE SEX BEHAVIOR IS CONTROLLED BY A HORMONALLY RESPONSIVE NEURONAL NETWORK

Sexual behavior is a simple phrase for a complex set of actions that includes motivation to seek partners, evaluation of critical stimuli, motor execution of the behavior and rewarding physiological processes that reinforce the behavior so it will be repeated again. Each component of the behavior involves multiple brain regions but we can identify specific critical nodes that are essential for gating information in order to produce a functional behavioral output. Not surprisingly, neurons in each of the critical brain regions express high levels of steroid receptors, thereby creating a hormonally sensitive neuronal network (Figure 1). The fundamental core of the network is those regions that control motor execution of the behavior. In rodents, the female adopts a sexually receptive posture, referred to as lordosis, which allows the male to mount and intromit. We know that the ventromedial nucleus (VMN) of the hypothalamus is an essential brain region for the executing of this process; if it is damaged or destroyed the female will not exhibit sexual receptivity. The estrogen receptor expressing neurons of the VMN then project to the estrogen sensitive neurons of the midbrain central grey and those neurons project on down to the spinal cord and activate the motor neurons innervating the critical muscle groups on the back. The sensory information associated with mating is then received at the spinal cord and passed on back up the line to activate the same regions as well as those associated with reward, such as the...
ventral tegmental area and the nucleus accumbens. The VMN receives critical input from the amygdala, which has in turn received olfactory information, an important evaluative signal in the rodent world. The preoptic area (POA) is an additional critical hormonally sensitive region that shares reciprocal connections with the VMN and other brain regions relevant to mating. The POA is considered the critical area for male sexual behavior, but influences female behavior as well, in part by exerting an inhibitory influence over its expression (see for review [8]).

Because the motor patterns involved in male versus female sexual behavior are so notably different, particularly in our animal models, there is a tacit assumption that separate neuronal networks exist within the brain to specifically regulate the expression of each. However there has been no male versus female circuit identified to-date, and it maybe that the reality is the neuronal underpinnings of male versus female sex behavior are largely the same but critical nodes are weighted differently. The weight of a particular node is a function of the number of neurons, the phenotype of the neurons and the synaptic connections of the neurons. In other words, the sex differences we observe in the brain are the weighting that pushes the network towards one or the other behavioral output.

III. THE ORGANIZATIONAL / ACTIVATIONAL HYPOTHESIS OF SEXUAL DIFFERENTIATION OF THE BRAIN.

It was 50 years ago this year that an iconic paper was published by Phoenix, et al. [9] which provided a framework upon which all subsequent research into sexual differentiation of the brain has been hung. Referred to as the Organizational / Activational Hypothesis, this simple postulate states that early actions of gonadal steroids act to organize the neural architecture regulating sexual behavior and that secretion of gonadal steroids in adulthood will activate this previously organized substrate to permit sex-specific sexual behavior in response to appropriate stimuli (Figure 2). The difference between males and females is achieved by differences in the hormonal profile early in development and this is achieved by copious production of testicular androgens in the late gestation fetal male contrasted with the quiescent ovary in the female. The onset of testicular steroidogenesis in the fetus marks the beginning of the sensitive period for sexual differentiation of the brain. Shortly after birth the testis ceases androgen production and both males and females are devoid of circulating gonadal steroids until the onset of puberty weeks (rodents) or years (primates) later. Two critical predictions of this postulate are that reversing the hormonal milieu of adult males and females neonatally will permanently alter their behavior in adulthood and that reversing the hormonal milieu of adult males and females will not reverse adult behavior.

The role of estradiol in the masculinization of sexual behavior in the rodent is undisputed but has recently been challenged as being the sole mediator of the differentiation process [10,11]. Converging evidence suggests that androgens are also a key mediator under normal circumstances, and although the entire process of differentiation can be completed with exogenous estradiol treatment, the natural course of events involves androgens as well. This highlights the complexity of hormonal modulation of the differentiation process and emphasizes the need to understand the mechanisms of hormone action as opposed to just what the hormones are. This is particularly important when we consider the hormonal modulation of sexual differentiation in primates, where the evidence for a critical masculinizing effect of androgens is undisputed, and a role for estrogens considerably more controversial (see for review [12]). Consistent with the importance
of androgens and a lesser role of estrogens, human males with a mutated gene for the estrogen receptor or the aromatase enzyme are phenotypically and psychologically male whereas genetic males with a mutated androgen receptor that renders them completely androgen insensitive, are psychologically female. This does not negate the value of animal models to understand sexual behavior in humans, as the cellular mechanisms initiated by estradiol versus testosterone frequently converge. Whether this is the case for sexual differentiation of the primate brain is currently unknown. So, what are the cellular mechanisms by which steroids induce permanent changes in the developing brain?

IV. MECHANISMS ESTABLISHING SEX DIFFERENCES IN THE BRAIN RELEVANT TO SEXUAL BEHAVIOR

As discussed above, sex differences in the brain occur at the critical nodes regulating sexual behavior and are considered the neuronal underpinnings of male versus female sexual behavior. The cellular mechanisms by which steroids act on the developing brain to induce sex differences can be categorized into four key processes:

1. cell birth
2. cell migration
3. cell death
4. cell differentiation.

The latter process includes the neurochemical phenotype and synaptic patterning of the cell, both of which are essential to its role in the integrated neuronal network and are a major component of the weighting towards male versus female sexual behavior. The second major component is cell death. Some nodal points in the network are larger in the male versus female brain or vice versa. In each instance where this occurs, it has been determined that males and females begin with the same number of neurons, but they then selectively die in one sex of the other. For critical nodes in the control of sex behavior, the most celebrated sex difference is the size of a subnucleus in the preoptic area called the sexually dimorphic nucleus, or SDN. The number of neurons in this region is 5-7 times greater in males.

Figure 2: Sexual Differentiation of the Brain: Organizational and Activational Effects.

The brain is a bipotential organ that adapts a masculine or feminine phenotype as a function of developmental exposure to gonadal steroid hormones. In males, the embryonic testis produces high levels of testosterone which acts on the brain to organize it as male, which then determines the brains responsiveness to steroid post-puberty to direct sex specific behavior. The organizational effects occur during a developmental sensitive period that is operationally defined in rodents as the onset of testicular androgen secretion and the offset as the loss of sensitivity to exogenous testosterone in females. In humans, the sensitive period begins in the second trimester and appears to be largely completed by birth (E = embryonic, PN = postnatal day, T = testosterone, E2 = estradiol). Courtesy of McCarty M.
Similar sex differences are found in other nodes in the sex behavior network but none are as dramatic as that of the SDN. The cellular mechanisms of the differential cell death are only just beginning to be understood but involve the steroid hormone estradiol inducing or repressing the process of apoptosis, also called naturally occurring cell death (see for review [13]). An analogous nucleus has also been found in the sheep and human brain and associated with sexual preference in both cases [14], but there is little evidence for a roll for this subnucleus in sexual behavior per se.

Returning to the issue of synaptic patterning of the cell, here the evidence is far greater that the number of inputs to a particular region exerts an important effect on the execution of sexual behavior. Quantifying synaptic patterning is a difficult and tedious process and to be done correctly requires the use of electron microscopy. A series of detailed and elegant studies in the 1980’s by a group of Japanese neuroendocrinologists established a firm foundation from which others have built (see for review [15]). The process is now considerably simplified by focusing on one particular type of synapse, the dendritic spine synapse. Dendritic spines are small protrusions off of neuronal dendrites and are the principle site of excitatory (glutamatergic) input. The beauty of dendritic spines is that they can be quantified at the light microscope level or indirectly by measuring an essential protein for spines, called spineophilin. In the preoptic area of rodents, males have two to three times more dendritic spine synapses per unit of dendrite than females and this sex difference is established during the first few days of life by the higher gonadal steroids produced in males. The cellular mechanism underlying the increase in dendritic spines synapses in males is a surprising one, the increased production of a prostaglandin called PGE, which initiates a cascade of signal transduction that promotes the formation and maintenance of spines [16]. Prostaglandins are well known for their role in inflammatory processes and induction of fever. Whether prostaglandins mediate masculinization of sex behavior in primates is currently unknown, but if they do, it has important implications for the potential effects of medications designed to inhibit prostaglandin production, which includes multiple over-the-counter analgesics such as aspirin.

There is an equally profound sex difference in the VMN, the major brain region controlling female sexual behavior. Here too, males have two to three more dendritic spine synapses, and the dendrites themselves are longer and branch more frequently than in the female brain. This sex difference is also a function of gonadal steroids that are higher in males during the first few days of life, the critical period. However the mechanism establishing the sex difference is distinctly different in this brain region, involving a rapid non-genomic activation of a membrane kinase that promotes the release of glutamate from nerve terminals which then induces the formation and maintenance of dendritic spine synapses [17]. Key proteins that suppress the outgrowth and branching of neurites are also suppressed in the male brain, allowing for more exuberant growth [18]. Both these cellular processes coordinate to influence the weighting of excitatory input to this key brain region for female sexual behavior.

### IV. SUMMARY

The cellular processes establishing the dynamics of the neuronal networks controlling sexual behavior are still being established but some generalized principles are becoming clear. One fundamental principle is that there are indeed multiple processes. By having multiple mechanisms involved in differentiating the male from the female brain at distinct nodes throughout a neuronal network, there are many more potential points of variation. Genetic differences in specific kinases, enzymes and/or receptors can all be important contributors to the manner in which hormones exert organizational influences. As a result, the phenotypic variability is far greater than that that would be achieved by a single unifying mechanism of hormone action. There is no male brain versus female brain, instead we have a mosaic of overlapping and varying degrees of masculinization and feminization within one brain and the potential that any individual male or female are highly similar in some nodes on the network but highly divergent at others, and which nodes those are will vary from one person to the next. Ultimately, the variety of cellular mechanisms of steroid hormone action in the developing brain contributes to individual variability in adult sexual behavior.

**Box 1**

- Majority of knowledge on sex differentiation of the brain is obtained from animal studies
- The brain is sexually differentiated early in development in response to gonadal steroid hormones
- Masculinization and feminization are regulated by separate cellular mechanisms in different brain regions
- Adult sexual behavior is controlled by a hormonally response neural network
- Variability in the mechanisms of hormone action on the developing brain contribute to variability in adult sexual behavior.
C. CENTRALLY-BASED PHYSIOLOGY OF WOMEN'S SEXUAL FUNCTION

The central nervous system mechanisms that govern female sexual behavior are largely unexplored in humans. Most descriptions are based on neurophysiological investigations in rodents. In particular, lordosis, has served as an important animal model for neural control of female sexual behavior [8,19-23]. As for sexual development, mating habits of many mammalian species, human copulation is characterized by relative emancipation from hormonal control [24] and a highly flexible and resourceful sexual behavioral repertoire [25]. There is strong evidence, especially from neurological patients, that human sexual behavior is guided by the cerebral cortex [26-28]. Given the vast differences in cerebral development between humans and virtually any other animal species, it is questionable if rodents should serve as a model for all aspects of female sexual behavior. Indeed, taxonomic differences between primates and non-primates in mating-related functional neuroanatomy have been shown [29].

Human brain function can be assessed relatively easily using neuroimaging techniques like positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). These research methods, which have become widely available over the last decade, are potentially powerful tools for exploring the woman's brain with regard to sexual function [30].

I. NEUROIMAGING METHODS

1. NEUROVASCULAR COUPLING

PET and fMRI are functional neuroimaging methods that measure metabolic or vascular parameters. The physiological basis of these methods is postulated to reflect the fact that local changes in metabolic demand are coupled with local blood flow and blood oxygenation changes [31].

a) Positron Emission Tomography

The principle behind PET is the use of radioactive positron-emitting isotopes. These isotopes are tagged to molecules of a biological compound of interest, which are introduced into the human body by intravenous injection. The most widely applied radioactive "tracer" for neuroimaging purposes is \(^{15}\)O-H\(_2\)O (oxygen-15 labeled water) and its distribution is a measure of regional cerebral blood flow (rCBF) [32].

b) Functional Magnetic Resonance Imaging

By far the most popular neuroimaging technique is BOLD (blood oxygenation level-dependent) fMRI, which uses a rapid dynamic series of MR images to assess changes in MR signal intensity over time caused by changes in brain activity. Changes in MR signal occur because blood flow responses to neural activity exceed metabolic demands [31]. This leads to an increase in the local concentration of oxygenated hemoglobin compared to deoxygenated hemoglobin, which, because of their different magnetic properties, increases the local MR signal [33].

2. VISUAL SEXUAL STIMULATION (VSS) AND NEUROIMAGING

The stimulus most used to elicit sexual arousal in PET and fMRI studies is VSS, using erotic or sexually explicit photos or film excerpts. A few factors have to be taken into account when interpreting brain responses related to the processing of VSS in general and sexual arousal in particular:

a) Although experimental studies support that men generally respond more to VSS than do women, there is substantial variability in this effect; A potential source of variability is the type of stimuli used which may not be of equal interest to both men and women whose preferences can depend upon the activities and situations depicted [34,35];

b) The activities and situations depicted. VSS type and length varies substantially between studies, ranging from 3-second photos of nude people presented to 3-minute XXX-rated film excerpts;

c) Considerable variation is seen with respect to the "control stimuli", which should match the VSS for elements like luminance, number of subjects depicted in the excerpt, and emotionality. It has been shown that sound is not critical to a VSS to elicit a sexual arousal response in women. Thus, many studies have used silent VSS and control video to avoid the variable of having different types of audio stimuli [36].

d) Correlations between measures of sexual arousal and brain activity are not always performed.

II. VSS-INDUCED BRAIN RESPONSES. WOMEN'S AROUSAL PHASE.

Initial studies of sexual arousal were first undertaken in men [37,38]. Subsequently, similar fMRI studies have also been conducted in healthy women by several different research groups and these studies document activation in multiple cortical and subcortical areas of the brain during VVS.

Park et al performed a study dedicated solely to sexual arousal in healthy female volunteers [39]. This fMRI study, which included only 6 subjects,
found involvement of extrastriate visual areas in the occipito-temporal cortex, the lateral prefrontal cortex, the insula, the cingulate cortex, the inferior temporal lobe, the thalamus, and the basal ganglia. This activation pattern was based on the comparison of brain responses to “erotic video” versus “documentary video”. All subjects perceived significantly more sexual arousal during the erotic video, but no correlations were computed between perceived sexual arousal (PSA) and brain activity. They pointed out that many of the sites of activation were the same as previously demonstrated in male subjects during sexual arousal [38]. Recently, a very similar result was reported in a cohort of 9 healthy women that served as healthy controls for women suffering from major depression [40]. Unfortunately, the experimental paradigm, data analysis, and data reporting employed in both studies were clearly suboptimal.

Maravilla and Yang [30] also studied a group of healthy heterosexual women without sexual difficulties and found activation in many of the same areas described by Park and colleagues [39] (figure 3A). In addition, there was activation in the amygdala and hypothalamus, areas not described by Park et al [39] but subsequently shown to occur by other fMRI investigators (though more prominently in men than in women, see section C.II.3) [41,42]. Importantly, the study by Maravilla and Yang [30] demonstrated decreased activation in bilateral temporal lobe with the VSS arousal stimulus, at sites that have been associated with moral judgement or embarrassment (figure 3B). This group hypothesized that this decreased activity was due to lowering of activity in sites that normally exhibit active inhibition to a sexual stimulus. Such inhibitions may keep us from acting out in response to sexual stimuli at inappropriate times or in inappropriate situations. However, with sexual arousal during appropriate situations, these inhibition areas may have decreased activity, thus allowing one “permission” to act on sexual urges. A possible inhibitory influence of the temporal cortex over sexual arousal has been shown in men [38,43], and was recently confirmed in women [44]. They demonstrated that the entorhinal cortex (part of the temporal cortex) was more activated in women with hyposexual desire than in healthy heterosexual women, when watching VSS stimuli. See Table 1 and figure 4 for summary of brain areas activated during sexual arousal.

1. EFFECT OF STIMULI-MODE ON MEASURED BRAIN RESPONSES

VSS duration and mode (pictures vs. video) is likely to influence brain responses. Maravilla and Yang [30] and Arnow et al. [44] used long periods of VSS (>1 minute film excerpts). Karama et al. [42] did the same using a mixed male-female subject cohort
where female subjects were analyzed separately. In all three studies the erotic video induced increased BOLD signal in the extrastriate visual cortex, the inferior parietal lobule, the orbitofrontal cortex, the anterior cingulate cortex, the ventral striatum, and the amygdala, compared to a control video. In men, largely the same pattern of activation is found with similar VSS periods [37,45]. Differences between studies (like the midbrain activation in Arnow et al. [44] (which was not found in the other two studies) may have been due the fact that the control stimuli were quite dissimilar (“neutral” vs. “sports”). Moreover, the menstrual phase, which is very likely to affect cerebral function (see later section), was not taken into account by Arnow et al [44] and Maravilla and Yang [30], whereas Karama et al. [42] only included women outside their ovulatory period. PSA was assessed in two studies [42,44], and vaginal photoplethysmography (VPP), an objective measure of sexual arousal, in one [44]. only Arnow et al. did a whole-brain correlational analysis between BOLD signal and PSA, which confirmed the activation pattern found with the VSS-sports contrast [44]. Karama et al. restricted their search volume to the hypothalamus [42]. Nevertheless, no significant correlation between PSA and hypothalamic activity was found in either study. The VPP measurements had rather distinct temporal dynamics in Arnow’s healthy control group, showing increased vaginal blood flow towards the end of the experiment.

Table 1: Comparison of major brain activation sites in women during arousal.

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Figure 4: Surface rendered brain from same study as in 3 showing areas of activation mapped onto representative brain for better spatial appreciation showing same areas of activation as viewed from surface of brain. Courtesy of Maravilla K & Yang C
However, this objective measure did not explain much of the variance in BOLD signal [44].

Hamann and colleagues [41] exposed their (male and female) heterosexual subjects to relatively brief 4s-presentations of erotic (nude individuals or couples) and neutral photos. They focused their analyses on the hypothalamus and both amygdalae. PSA ratings were highest for the couples stimuli, but no correlations with BOLD signal were computed. In none of the apriori defined regions did women have a stronger BOLD signal during the erotic stimuli over the neutral stimuli. However, as described before, longer VSS periods with videos consistently activated the female amygdala [30,42,44], and in one instance also the hypothalamus [30]. This suggests that in heterosexual women the amygdala, and probably also the hypothalamus, are not sensitive to brief periods of still VSS. Outside these regions of interest, women had increased BOLD signal in the extrastriate visual areas, the inferior parietal lobule, the anterior cingulate cortex, and the ventral striatum, which they shared with men [41]. This pattern showed substantial overlap with that found using longer periods of VSS using film excerpts [30,42,44].

2. SPECIFICITY OF VSS-INDUCED BRAIN RESPONSES

Sexual arousal has a distinct quality, which should be reflected somehow in terms of brain function. However, many, if not most, of the VSS-induced brain responses are readily found in any given “emotional” neuroimaging experiment. Consider, for example, the most consistent and robust VSS-induced brain activation in the extrastriate visual areas of the occipito-temporal cortex [30,42,44]. This is a well-known (epi)phenomenon in visual paradigms that reflects visual attention processes [46] and that occurs most readily when emotionally laden stimuli are used [47,48]. Likewise, a wide range of tasks activate the anterior cingulate cortex, especially those that require enhanced attention and/or response selection [49,50]. These activations are hallmarks of visually-induced emotional states, but not of sexual arousal per se.

Two interesting mixed male-female cohort studies have attempted to control for the “contaminating effects” of general emotional arousal and attention [51,52]. These studies did not consider the female subjects separately, but their results are relevant to this discussion. Stark et al. designed an experiment with erotic, neutral, and disgusting pictures. The contrast between erotic and neutral pictures resulted in a large cluster of activation in the extrastriate visual areas and the inferior parietal lobule, as well as smaller effects in the hypothalamus, ventral striatum, midbrain, and amygdala. However, when compared to disgusting pictures, which also possess high emotionality, erotic pictures only rendered activations in the ventral striatum, hypothalamus, and midbrain significant [51]. Moreover, the ventral striatum was found to be the main region related to sexual pleasure across groups and stimuli [51]. Walter et al. followed a similar line of thinking, including non-erotic bodily and non-bodily emotionally-laden stimuli. In addition, their rating scales discriminated between sexual intensity, general emotional arousal, and valence. They showed that when VSS was controlled for general emotional arousal and bodily content, only the ventral striatum, caudal anterior cingulate cortex, and superior parietal lobule were significantly correlated with sexual intensity [52]. Figure 5. These studies underscore the importance of sophisticated experimental designs to get closer to the heart of sexual arousal.

3. GENDER DIFFERENCES IN VSS BRAIN RESPONSES

Clearly one of the most exciting discoveries about human sexual brain function obtained with neuroimaging is that VSS (brief, photos) produced greater neural activations in men than in women in the hypothalamus and both amygdalae, even when women reported greater arousal [41]. Male-biased VSS-induced activation in the hypothalamus [42] and amygdala [53] have been reported by other studies. It is fascinating that similar sexual behavioral output, i.e. similar levels of sexual arousal reported by male and female subjects, is associated with fundamental neurobiological differences. Figure 6 & 7. One explanation is that in men visual stimuli have fast access to primordial systems underlying the sexual response, and that this reflects men’s higher propensity to identify cues for sexual opportunity [41], especially in the visual domain. In both the amygdala [30,42,44] and the hypothalamus [30] women showed significant activation only with longer VSS samples, providing further support for the idea that in men this ancient system is more tuned towards sexual cues. A recent fMRI demonstrated that very brief (33ms) VSS, which can not be processed consciously, reliably activated the male amygdala [54]. This would support the theories that women in general take a more thoughtful approach with regard to sexual encounters, as opposed to the more instinctive nature of the male sexual response.

4. SOME CONCLUSIONS FROM FEMALE VSS STUDIES

Consistent effects across studies were found in the extrastriate visual areas, the inferior parietal lobule, the anterior cingulate cortex, and the ventral striatum. However, only the ventral striatum can be convincingly linked to female sexual arousal [51,52]. An important key to female sexual arousal may be buried deep inside the primordial brain in areas like
Figure 5: Common and interacting regions in sexual and emotional processing.

(a) Red voxels indicate regions with a significant interaction in processing of sexual arousal and valence, as revealed by the contrast [positive > negative bodily-emotional pictures] > [positive > negative non-bodily-emotional pictures] at p < 0.05, corrected, k>10. Significantly stronger effects in the first contrast were found in the perigenual anterior cingulate (pgACC) and bilateral occipital cortex (LOC). Blue voxels indicate significant regions for the conjunction of the contrasts [bodily > non-bodily-emotional pictures] and [non-bodily-emotional > non-bodily neutral pictures] at p<0.05, corrected, k>10. In resulting regions, including amygdala, dorsal medial prefrontal cortex DMPFC, LOC, tectum and thalamus, activity during non-bodily emotion processing was found to be lower than during processing of bodily stimuli but higher than during neutral picture presentation, reflecting rather general effects of emotional intensity.

(b) Bar diagrams plot mean percentage signal changes for bodily, non-bodily-emotional and neutral conditions in these common regions. With permission from [52]
Figure 6: Regional activation maps. Activation contrast for the couples stimuli versus fixation (a–c) and the couples stimuli versus neutral contrast (d–f) (P < 0.005, minimum five contiguous voxels). White circles indicate the approximate location of the a priori regions of interest (ROIs); the left and right circles and upper and lower circles show the left and right amygdala ROIs on the coronal and axial views, respectively. The medial circles show the hypothalamic ROI, which is not visible on the axial views at z = −20. Color bar indicates maximal Z values. Note that color scale bars vary from image to image. The right hemisphere is on the right of the coronal images and bottom of the axial images.

(a) Left, coronal image (y = 0) showing greater bilateral amygdala and hypothalamic activations for males versus females for the couples versus fixation contrast. Right, axial view (z = −16) of the same contrast, showing additional right cerebellar activation.

(b) Couples versus fixation contrast for males, at the same coronal and axial views. (c) The same contrast and views for females. (d) Left, coronal image (y = 0) showing greater bilateral amygdala activations for males versus females for the couples versus neutral stimuli contrast, within those regions showing greater activity for males versus females for the couples versus fixation contrast (at P < 0.10). The region of greater hypothalamic activation for males is not visible at this coronal level. Right, axial view (z = −20) of the same contrast, showing primarily left-sided amygdala activation.

(e) Couples versus neutral stimuli contrast for males, at the same coronal and axial views. (f) The same contrast and views for females, showing an absence of differential activity in the ROIs. With permission from [41]
the hypothalamus and the amygdala, which seem to be less sensitive to VSS in women than in men.

A major issue is that seemingly opposite emotional states, such as pleasure and pain [55], or sexual pleasure and disgust [51], show remarkable neurobiological overlap. For VSS-based neuroimaging experiments, which often make use of rather rigid paradigms this may be particularly relevant: under those circumstances sexual arousal does not necessarily imply sexual pleasure per se, but could just as easily cause feelings of guilt, shame or frustration. Technical limitations of neuroimaging in terms of temporal and spatial resolution, suboptimal experimental paradigms and/or analyses further complicate matters.

IV. CLITORIS STIMULATION, CLITORALLY-INDUCED ORGASM AND BRAIN ACTIVATION

1. EXPERIMENTAL DESIGN

Georgiadis et al. [56] reported the results of a series of [15O]-H2O PET experiments in women experiencing sexual clitoral stimulation and clitorally-induced orgasm. They included 12 healthy heterosexual volunteers whose male partners manually performed clitoral stimulation during the experiments. During the PET experiments, rectal pressure (RP) was measured and subjective ratings of sexual arousal (PSA) were obtained to verify women’s reported orgasms. An overview of the experimental tasks that were performed is given in figure 8. The temporal resolution of this PET experiment was roughly one minute, which means that the acquired activity reflected all peri-orgasmic events.

2. SOMATOSENSORY PROCESSING OF CLITORIS STIMULATION

Compared to a passive non-sexual resting state, increased rCBF during sexual stimulation of the clitoris was found in bilateral primary somatosensory cortex (SI), the left secondary somatosensory cortex (SII), and the left supplementary motor area [56].

SI is somatotopically organized, and Penfield in his classical experiments found the genitals to be represented in the paracentral lobule on the interhemispheric surface, ventral to the “foot-region” [56]. Recent neuroimaging studies in men indicate that this location may not be correct, and that the genital portion of SI is on the dorsal convexity of the postcentral gyrus [57-59]. Georgiadis et al. [56] showed that this is also the case for the clitoris. SII, located in the inferior parietal lobule, serves a variety of higher level sensory modalities [60,61]. Sensory stimulation in the pelvic region readily activates SII, for instance during distension of the anal canal.

Figure 7: Average fMRI signal change for males and females for couples, opposite-sex and neutral stimuli (vs. fixation baseline), for ROIs in the left amygdala, right amygdala and hypothalamus. Couples = couples stimuli; O.S. = opposite-sex stimuli; Neutral = neutral stimuli. Error bars indicate s.e.m. With permission from [41]
Figure 8: (A) Scan order and time span of the experiment. Scans (black lines) lasted 2 min. Consecutive scans were made with an 8 min interval (grey line). (B) Main effects of the present study. The glass brain shows an F-map (P < 0.05, corrected), giving an overview of the brain regions involved in any of the experimental conditions. This F-map is also depicted in colour scale, superimposed on sagittal sections of a standard single-subject T1-weighted MR image (SPM99). The location of the section relative to the midline is indicated in the bottom right corner of each section (negative value for x, left hemisphere). Bar graphs in the top right corner of each section indicate how the response in the centre of significant brain clusters varied during the four conditions. This average signal change for each parameter relative to the mean normalised activation over all scans is expressed as a percentage.

Abbreviations: F, F-value; Im, imitation of orgasm; LH, left hemisphere; Or, orgasm; Re, nonsexual passive rest; RH, right hemisphere; St, clitoral stimulation.

With permission from [56]
[62,63], or non-erotic stimulation of the penis [59,64]. In addition, VSS activates the inferior parietal lobule, which contains SII, in both men [43,45], and women [41,42,44], possibly as a result of the sensory input caused by genital arousal [45]. Interestingly, women with vulvar vestibulitis syndrome had more SII activation in response to pressure on the posterior vaginal vestibulum than did healthy controls. This is suggestive of augmented central processing of sensory afferent information in these patients who experience vaginal pain [65]. Thus, it seems that SII activation reflects the context of the sensory stimulus, "weighting" the salience of somatosensory stimuli before they enter the realm of consciousness.

3. CLITORIS STIMULATION AND ORGASM DECREASE BLOOD FLOW IN AMYGDALA AND TEMPORAL CORTEX

Relative to the non-sexual resting state, there were rCBF decreases in the inferomedial temporal lobe including the amygdala during clitoral stimulation and during orgasm (Figure 9). Activity levels in the left parahippocampal gyrus and anterior temporal pole decreased even further from clitoral stimulation to orgasm [56]. In the section on VSS it was stated that the temporal lobe probably exerts a tonic inhibition on sexual arousal [30,66], and that successful release of this inhibition may be imperative in the event of sexual opportunity. This was confirmed by a highly significant inverse relationship between PSA ratings and temporal lobe blood flow [56]. Clinical findings of temporal lobe lesions causing hypersexuality [67], and temporal lobe epilepsy-associated sexual (or even orgasmic) auras [68,69] provide further support.

The female amygdala readily responded to VSS, though only to long periods of VSS [30,42,44,68]. However, Georgiadi et al. found clear deactivation in the amygdala in response to sexual genital stimulation in men and women alike [56,58,70]. Euphoric mental states such as cocaine rush [71], but also romantic love [72] are also characterized by attenuated amygdala (and ventromedial temporal lobe) activity. These 'rush' states share characteristics with the rush experienced during sexual genital stimulation. This switch in amygdala activity may be crucial for sexual encounters to take place. This is also supported by the findings that patients with chronically enhanced amygdala activity, for instance as a result of war- and combat-related Post Traumatic Stress Disorder [73], experience more sexual difficulties than healthy controls [74].

4. ORGASM DECREASES PREFRONTAL BLOOD FLOW

Orgasm induced strong rCBF decreases in the left orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC), in both men and women [56,58,70]. The prefrontal cortex is called OFC where it overlies the orbita, and vmPFC where it borders the midsagittal plane. In women, the largest blood flow decrease in the vmPFC was measured between the non-sexual resting state and orgasm. For the OFC, however, the most prominent blood flow decline was between clitoral stimulation and orgasm (Figure 10) [56].

The PFC in general is instrumental in social behavior and executive function. The vmPFC constitutes a crucial part of a neural network underlying self-monitoring and self-referential thought [75]. Deactivation in a network of midline cortical structures, including the vmPFC, is a rather common phenomenon in neuroimaging studies, and is most prominent when scans during passive, low arousal states are compared with scans during goal-directed behavior that usually entail higher arousal levels [76]. Thus, the vmPFC deactivation is unlikely to represent orgasm-specific neurobiology.

The OFC deactivation certainly connects to sexual consummation in a much more specific way. Subjects recorded the highest OFC blood flow levels not during the non-sexual resting state, but during clitoral stimulation and failed orgasm attempts, during which they perceived high sexual arousal (Figure 10) [56]. The OFC consists of functionally distinct lateral, middle, and medial parts [77]. The peak of the orgasm-related OFC deactivation was located on the border of lateral and middle OFC. The middle OFC is believed to specifically encode hedonic experience, as it becomes activated with increasing satiation and subjective pleasantness, and deactivated with feelings of satiety [78,79]. The lateral OFC is strongly linked to urge suppression, shown both by functional neuroimaging studies [80,81], and by studies evaluating the effects of OFC damage [82,83]. Georgiadis et al. suggested that the activity level of the OFC reflects conscious control over the sexual urge: high control during clitoral stimulation (because orgasm was not allowed) resulted in increased rCBF, whereas decreased rCBF during orgasm could indicate the release of that conscious control. The failed orgasm attempts, too, were associated with increased rCBF in the OFC [56], providing strong evidence that OFC activity levels significantly determine sexual behavioral outcome. Possibly, the loss of conscious control and the release of tension that people report when they describe an orgasmic experience [84] relates to this decreased OFC activity.

A major limitation of the PET technique is the restricted temporal resolution, which prohibits parceling out the blood flow responses related to different peri-erotic events is not possible. Therefore, exploring the precise function of the OFC in female sexual behavior, and how it relates to psychosexual disorders, will be an important research direction in the near future.
Figure 9: t-Contrasts: clitoral stimulation and orgasm vs. rest. The significance threshold in this figure is $P < 0.001$, uncorrected. For each comparison, a t-map of rCBF changes is depicted (glass brain: left side of the figure). These rCBF increases (red scaling) and decreases (blue scaling) are also superimposed on horizontal sections of a standard single-subject T1-weighted MR-image (SPM99). The top row shows the result for stimulation vs. rest, the bottom row for orgasm vs. rest. The location of each section relative to the anterior commissure (AC) is indicated in the bottom right corner of each section (negative value for $z$, ventral to AC).

Abbreviations: MI, primary motor cortex; OFC, orbitofrontal cortex; PFC, prefrontal cortex; rCBF, regional cerebral blood flow; SI, primary somatosensory cortex; SII, secondary somatosensory cortex.

With permission from [56]
Figure 10: t-Contrasts: orgasm control comparisons. The significance threshold in this figure is \( P < 0.001 \), uncorrected. For each comparison, a t-map of rCBF changes is depicted (glass brain: left side of the figure). These rCBF increases (red scaling) and decreases (blue scaling) are also superimposed on horizontal sections of a standard single-subject T1-weighted MR image provided by SPM99. The top row shows the result for orgasm vs. stimulation (sexual arousal control comparison), the bottom row for orgasm vs. imitation (motor output control comparison). The location of the section relative to the anterior commissure (AC) is indicated in the bottom right corner of each section (negative value for \( z \), ventral to AC).

Abbreviations: MI, primary motor cortex; OFC, orbitofrontal cortex; PFC, prefrontal cortex; rCBF, regional cerebral blood flow; SI, primary somatosensory cortex. With permission from [56].
5. ORGASM-RELATED ACTIVITY OF THE CEREBELLMUM

The left anterior lobe of the cerebellar vermis and adjacent deep cerebellar nuclei activate during orgasm, in men and women alike [56,58,70]. Women showed a strong positive association between blood low in the left anterior vermis and rectal pressure luctuations [56], a measure of pelvic and abdomi- nal muscular contractions. Other investigators have demonstrated similar cerebellar activation in women performing voluntary pelvic motor contractions in a non-sexual context [85,86].

The vermis takes part in axial motor control, but also in autonomic regulation and affect [87]. Indeed, orgasms are characterized by substantial cardio-vascular and respiratory arousal [84], and vast emo- tional changes [88]. Yet, the precise nature of the cerebellar contribution to orgasm remains unclear. Table 2 shows different brain areas which are acti- vated/deactivated during rest, clitoral stimulation or orgasm.

Table 2: Comparison of major brain deactivation (↓) and activation (↑) sites in women during orgasm and clitoral stimulation. Courtesy of Georgiadis JR

<table>
<thead>
<tr>
<th></th>
<th>Orgasm vs rest</th>
<th>Orgasm vs clitoris stimulation</th>
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<tbody>
<tr>
<td>parietal lobe</td>
<td></td>
<td></td>
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<tr>
<td>↑ primary somatosensory cortex, genital</td>
<td>↓ secondary somatosensory cortex (SII)</td>
<td></td>
</tr>
<tr>
<td>↓ superior parietal lobule</td>
<td>↓ precuneus</td>
<td></td>
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<tr>
<td>frontal lobe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ primary motor cortex, pelvic (floor)</td>
<td>↑ primary motor cortex, pelvic (floor)</td>
<td>↓ lateral orbitofrontal cortex</td>
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<td>↓ ventromedial prefrontal cortex</td>
<td>↓ ventromedial prefrontal cortex</td>
<td>↓ dorsomedial prefrontal cortex</td>
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<tr>
<td>temporal lobe</td>
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<tr>
<td>↓ inferior temporal gyrus</td>
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<td>↓ middle temporal gyrus</td>
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<td>↓ temporal pole</td>
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<tr>
<td>occipital lobe</td>
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<tr>
<td>↓ lingual gyrus</td>
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<tr>
<td>limbic system</td>
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<tr>
<td>↑ posterior insula</td>
<td>↑ posterior insula</td>
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<tr>
<td>↓ amygdala</td>
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<tr>
<td>cerebellum</td>
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<td>↑ deep cerebellar nuclei</td>
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<td>↑ anterior vermis</td>
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<td>↑ cerebellar hemisphere</td>
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6. PAUCITY OF SUBCORTICAL EFFECTS

VSS often induced significant activity in subcortical parts of the brain. Georgiadis et al. [70] found significant subcortical effects only through correlational analysis with the PSA ratings. A positive correlation between the subjects’ PSA and rCBF was found in the ventral rostral midbrain and the right head of the caudate nucleus. It is quite possible that this correlation represents increased activation of
dopaminergic cell groups in the midbrain and their striatal target cells.

Despite this nice correlation, it is quite striking that no other subcortical effects were found. In particular, the hypothalamus plays a major part in the sexual response of female rodents [8], while in women hypothalamic function predicts sexual orientation [89,90] and indicates visual sexual stimulation [30]. Moreover, elevated levels of the pituitary hormones oxytocin and prolactin have been associated with orgasm [91,92]. Perhaps, the neuronal events that might occur in the hypothalamus during sexual consummation did not require a metabolic increase that sufficiently increased rCBF, or maybe the temporal resolution of the PET experiment was too limited to detect short-lasting events occurring in the hypothalamus. The same explanation could hold true for the absence of activation in the ventral striatum, a region that has been specifically linked to sexual arousal [51,52]. Improvements in terms of subcortical activations are to be expected with the use of neuroimaging techniques with better sensitivity for detecting short-lasting events, like fMRI.

7. GENDER DIFFERENCES IN BRAIN RESPONSES DURING SEXUAL CONSUMMATION

When directly compared to activation patterns for penile stimulation, women showed significantly more activation in left fronto-parietal regions, most notably in the posterior parietal cortex and the supplementary motor area [70]. Given that these regions are important for making a mental representation of another person’s actions [93], differential activity in these regions as a function of gender may reflect behavioral gender differences related to perspective taking and empathy [94]. By contrast, women’s brain responses during orgasm did not differ significantly from the male counterpart [70]. This suggests that men and women use different cerebral strategies to reach orgasm. Future research may elucidate how these difference can best be understood, and if this intriguing theory is tangible.

V. SEXUAL AROUSAL AND ORGASM FUNCTION IN SPINAL CORD INJURED WOMEN - BRAIN ACTIVATION PATTERNS

Although spinal cord injury (SCI) is a common cause of anorgasmia, irrespective of the level of the lesion, some 50% of women with lesions above the tenth thoracic level report that they still achieve orgasm [95]. This is truly astonishing, because clitoral sensation is lost in these patients. One way for women with complete transection of the spinal cord to reach orgasm is via vaginocervical stimulation [96]. The vaginocervix receives innervation from the parasympathetic vagal nerve (cranial nerve X), which enters the central nervous system in the caudal brainstem (in the nucleus of the solitary tract), therefore bypassing any SCI. Thus, salient genital information may still reach the brain. Similarly, sensory information from the internal genitalia may be conveyed by the sympathetic nerves [95].

Komisaruk et al. [97,98] performed neuroimaging studies of women with SCI at or above the T10 level who were able to achieve arousal and even orgasm with cervical self stimulation. Using a custom-made self-stimulation device, subjects were able to stimulate their vaginocervix to eventually induce orgasm. In a first (PET) study, the authors reported rCBF increases in the lower brainstem during vaginocervical stimulation, possibly representing the nucleus of the solitary tract [98].

However, this result was based on only three subjects (one without SCI), and the authors did not explain how brain responses were modeled and statistically analyzed. In a subsequent fMRI study, the same authors included five women with complete SCI [97]. It confirmed the conclusion from their earlier PET findings, in that the lower brainstem was consistently activated across subjects in response to vaginocervical stimulation. Orgasm-related activity was reported to be consistent in the middle cingulate cortex, the insula, the hypothalamus, and the amygdala. Orgasm, however, was achieved by only three volunteers. The authors concluded that cerebral sexual activation response in these SCI women was mediated through an alternative paraspinal pathway via the vagus nerve.

Unfortunately, these studies suffered from suboptimal experimental design, analysis, and execution. No information about the data analysis procedure or the significance of the effects was disclosed.

Therefore, it was not obvious why certain “activations” were labeled as consistent effects, and others were not. Surely, the number of subjects (five for stimulation; three for orgasm) was too small to identify any meaningful group effects.

Another potential problem is MR scanner instability and subject motion, especially when data are collected over longer periods of time as was the case in Komisaruk et al. [97]. These slow signal drifts are usually removed during data analysis, but this also erases any real biological effects that develop slowly (like sexual arousal). Alternatively, these drifts may induce random artifactual activity if not corrected for [99]. Obviously, other factors like the type of genital stimulation (clitoral vs. vaginocervical) and the subject cohorts (healthy vs. SCI) may also explain the different findings compared to the studies of Georgiadis et al. [70].
D. FACTORS INFLUENCING BRAIN PATTERNS DURING SEXUAL STIMULI IN WOMEN

I. SEXUAL ORIENTATION

1. HYPOTHALAMIC FUNCTION DEPENDS ON SEXUAL ORIENTATION

The putative role of the hypothalamus in sexual orientation [100-102] has been confirmed at a functional level in humans. Using neuroimaging ([(15)O]-H2O PET) and volatile sex-specific odors; pheromones, it was found that sexual orientation predicted hypothalamic responses. More specifically, heterosexual women activated the ventromedial hypothalamus and preoptic area when smelling an androgen-like substance, whereas heterosexual men smelling an estrogen-like odor activated the (more posteriorly located) dorsomedial and paraventricular nucleus [90]. Lesbian women, interestingly, showed partial congruence with heterosexual men in the dorsomedial and paraventricular hypothalamus [89]. Similar congruent activity has been found between homosexual men and heterosexual women in the preoptic area and ventromedial hypothalamus [103], suggesting a coupling between hypothalamic function and sexual preference, irrespective of gender. Even when anatomical distinction between adjacent hypothalamic areas is quite challenging given the relatively limited spatial resolution of the PET technique (ca. 10mm), it seems safe to conclude that sexual orientation and sex-specific behaviors depend heavily on hypothalamic structure and function.

2. SEXUAL ORIENTATION BIASES BRAIN ANATOMY AND CONNECTIVITY

Neuroanatomical gender differences have been found in large parts of the brain [104], but most notably in the amygdala, hippocampus and prefrontal cortex [105-107]. These regions are important for memory and learning, executive function, and emotion, and, together with sexual dimorphism of basic structures like the hypothalamus, might explain why women behave differently from men.

In a very interesting recent paper [108] it was demonstrated that individuals who prefer male sexual partners have symmetrical cerebral volumes, whereas those who prefer female sexual partners possess a rightward cerebral asymmetry. Moreover, sexual preference determined the functional connectivity patterns of the amygdala, a putative part of the emotional and memory system. Heterosexual women (and homosexual men) showed more widespread connections from the left than from the right amygdala, whereas the opposite was the case for homosexual women (and heterosexual men). More specifically, in heterosexual women the connections were primarily with the contralateral amygdala and anterior cingulate cortex, in homosexual women with the prefrontal cortex, caudate and putamen [108].

II. HORMONAL MILIEU

Hormonal fluctuations during the menstrual cycle not only influence mood, cognition, memory, and arousal [109,110] but also sexual interest [111]. Heterosexual women in their follicular phase showed less metabolic effort in the right lateral orbitofrontal cortex and the caudal anterior cingulate cortex when performing a cognitive task involving male faces than when they were in their luteal phase. Because task performance remained unchanged, the authors proposed that most efficient neural processing of sexually salient stimuli occurs when pregnancy is possible [112]. Likewise, testosterone administration during the early follicular phase shifted memory processes in the hippocampus and inferior temporal gyrus towards the encoding and retrieval of male faces [113], indicating relatively automatic processing of sexually salient stimuli under the influence of testosterone. Prefrontal activation dominates the response to female faces in this group, suggesting less automatic processing of sexually irrelevant stimuli [113].

Hormonal influences have been studied using fMRI and have been shown to correlate with measurable changes of brain activation responses with general (non-sexual) arousal. Gizewski et al. demonstrated that VSS induced more brain responses in women during their midluteal phase than during their menses. The increase in activation was most apparent in the anterior cingulate, left insula and orbitofrontal cortices [114]. Similarly, Goldstein et al. [109] performed fMRI during the early follicular phase and again during the late follicular phase (midcycle or ovulatory phase) and documented significant differences in activation of hypothalamic–pituitary–adrenal (HPA) circuitry. Pictures consisted of negative valence/high arousal images versus neutral/low arousal visual stimuli. The fMRI results were validated by concomitant electrodermal activity (EDA) measurements. Significantly greater magnitude of BOLD signal changes were found during the early follicular phase, most notably in the amygdala, hypothalamus, hippocampus, orbitofrontal cortex (OFC), anterior cingulate gyrus (ACG), and brainstem - a network of regions implicated in the stress response. Arousal (EDA) correlated positively with brain activity in amygdala, OFC, and ACG during late follicular but not in early follicular phase, suggesting less cortical control of amygdala during early follicular phase, when arousal was increased. This is the first evidence suggesting that estrogen, which is elevated in early follicular phase, may attenuate arousal in women via cortical–subcortical control within HPA circuitry.
Premenopausal women had greater global brain signal than menopausal women in response to VSS [115]. (Figure 11). Archer et al. [116] studied a group of surgical menopausal women compared to a control group of age-matched premenopausal women. Brain activation was studied by fMRI during erotic and neutral videos. The menopausal women were studied at three time points; while not on hormone therapy, while on estrogen (E_2) therapy, and while on E_2 plus testosterone (T) therapy. Compared with premenopausal women, untreated postmenopausal women had significantly decreased areas of brain activation during both erotic and neutral video stimulations. Administration of E_2 increased global brain-activation patterns during both neutral and erotic visual stimulations, with erotic video viewing causing a limited increase in limbic system activation. Combined E_2 and T therapy was associated with a greater activation of the central nervous system (CNS), with more limbic system activated during the erotic video. Brain-activation patterns of the postmenopausal women were similar to the premenopausal group only during the E_2 and T treatment phase. These studies suggest that both E_2 and T act independently and in a complimentary fashion to increase the central arousal response in women. They also illustrate the potential of fMRI to document response to treatment.

Together with similar central effects of T observed in men [66] this underscores the importance of gonadal hormones in mediating the sexual response. It also illustrates that in female neuroimaging studies of any kind the menstrual phase has to be considered if there is any possibility to do so.

### III. HYPOACTIVE SEXUAL DESIRE DISORDER

Arnow et al. [44] conducted fMRI studies in a group of women with hypoactive sexual desire disorder (HSDD) compared with a control group of women with no history of sexual dysfunction. This study was notably not only in the unique study population, but also in the study design since fMRI measures were correlated with simultaneous vaginal photoplethysmography recordings and subjects were studied at three different time points for validation of reproducibility. The study used a standard VVS block design previously described comparing control video of sporting activity versus sexually stimulating couples activity. Results showed significantly greater subjectively reported arousal response in the group without a history of sexual dysfunction. They observed many similar areas of brain activation correlated with sexual arousal in both groups but only a limited number of brain regions showed significant differences of activation between the groups, when comparing erotic versus neutral videos.
control video stimulus. Notably there was increased activation in the HSDD group compared with control subjects with normal desire in 3 areas;

1) medial frontal gyrus [Brodmann area (BA) 10];
2) the right inferior frontal gyrus (BA 47);
3) the putamen on both sides.

The entorhinal cortex on both sides was the only area that displayed reduced activation. The authors concluded that the increase in activation in the medial frontal and the right inferior frontal gyri suggested that the HSDD group was directing more of their attention to self evaluation of their responses which may have been distracting and interfered with the normal sexual arousal response [44]. Interestingly, this study also compared simultaneous vaginal photoplethysmography (VPP) with the fMRI and found no between group differences in VPP-fMRI correlated activation, nor was VPP correlated with subjective arousal response [117]. Also of note is the fact that these investigators performed the fMRI study 3 times in each subject and a repeated measures ANOVA analysis on the activation sites detected in the erotic–sports paradigm across the three sessions did not reveal any significant activation differences across sessions [44].

This validated the reproducibility of the fMRI techniques and the paradigm used for this study as well as having major implications for fMRI as a research methodology, in general.

**E. SUMMARY**

The last years introduction and increased use of neuroimaging methods have enabled us to explore cerebral activation and deactivation during sexual stimulation and to hypothesize on the importance of different brain areas for functional and dysfunctional sexual function. The cerebral sexual response has been shown to be modulated by hormones, age and sexual orientation. Furthermore the research shows that it is crucial that the neuroimaging methods as well as sexual stimulation are standardized in order to obtain better and clearer results and be able to compare studies. In Appendix 1 a suggestion for a guideline for female sexological brain activation studies is given.

**BOX 2**

- The hypothalamus and amygdala are crucial for sexual orientation and early pre-consummatory stages of the female sexual response, albeit to a lesser extent than in men.
- Amygdala and parts of the temporal lobe deactivate once sexual consummation commences, and this may be part of a brain mechanism that enables sexual interaction.

- The ventral striatum is specifically related to sexual arousal.
- The left orbitofrontal cortex is the seat of sexual self-control. It is deactivated during orgasm, but activated when orgasm fails.
- Clitoral sensory information is predominantly processed in neocortical somatosensory and motor areas. This type of genital central processing is much more prominent in women than in men.
- Menstrual cycle phase, age, and sexual orientation clearly influence brain activity patterns, and should be taken into account if possible.
- Vaginocervical stimulation may induce orgasm in spinal cord injured women, because this information is conveyed by the vagal nerve, which enters the central nervous system in the lower brainstem. fMRI data provide some support for this concept.
- Aging does not change the brain activation pattern in terms of anatomic sites activated with arousal but may affect the magnitude of activation in selected areas especially the paralimbic system, temporal and parietal regions.
- Lack of arousal in HSDD may in part be related to subject self reflection on performance causing distraction from “letting go” and responding to the moment.

**F. GENITAL ANATOMY AND PHYSIOLOGY OF WOMEN’S SEXUAL FUNCTION**

**I. FUNCTIONAL ANATOMY**

The female genitalia can be subdivided into the internal genitalia (vagina, cervix, uterus, fallopian tubes and the ovaries and external genitalia (vulva) including mons pubis, clitoris, the labia majora and minora which are the structures surrounding the urogenital cleft [118] (Figure 12). This chapter describes the structures involved directly in the physiological sexual response.

1. **MONS PUBIS**

is the hair-covered area over the pubic bone and forms the anterosuperior limit of the urogenital cleft and ends posteriorly at the anterior margin of the perineal body [119].
2. LABIA MAJORA

are the two prominent, fatty lateral boundaries of the urogenital cleft. Anteriorly they meet creating the anterior commisur in front of the glans of the clitoris, posteriorly forming the posterior commissure. Each labium has external pigmented hairy, slightly wrinkled skin and internally a smooth surface lined with multiple sebaceous glands. The labia majora often meet and close the vaginal introitus.

3. LABIA MINORA

are smaller and may vary in size (length 61 ± 17 mm, Mean ± SD, range 28-100 mm; width 22 ± 9 mm, range 7-50 mm.). Anteriorly they split into two layers forming the clitoral prepuce and the clitoral frenulum. They consist of no subcutaneous fat, elastic skin and contain erectile tissue and appear from smooth surfaced to extensively corrugated [119,120].

Little attention has been paid to the neural innervation of the labia minora. Malinovsky et al. [121] reported that the types of sensory nerve endings could be divided into 4 main groups namely:

i) free nerve endings and arborizations;

ii) spray-like nerve endings;

iii) 7 types of ‘claw’ like endings;

iv) Pacinian corpuscles (only a few).

The exact functions of this innervation are still under study but the free nerve endings subserve pain while the Pacinian corpuscles subserve pressure and vibration, whilst the possible roles of the different types of ‘spray and claw nerve endings’ are unknown but they are unlikely to be only for pain.

4. THE CLITORIS

is unique in that the only known function is the generation of sexual pleasure when stimulated by touch or vibration.

Its gross structure is like an iceberg in that only a fifth is visible on the surface while the rest is hidden beneath the skin and deeper. According to O’Connell et al. [122] internally, it is a triplanar complex of erectile tissue comprising a midline shaft of some 20 cm long and 1-2 cm wide dividing internally into a pair of crura some 5-9 cm in length (Figure 13A & B). The erectile tissue consists of trabecular smooth muscle and collagen connective tissue encircled by a thin fibrous capsule surrounded by large nerve trunks [119,123]. Externally, the shaft is covered by the prepuce and is capped by a glans some 20 mm in length and 30 mm wide [124,125]. Linked into the structure are two vestibular (clitoral) bulbs on either side of the vaginal introitus closely applied the urethra. The erectile compartments consist of the clitoris and the clitoral bulbs. The functional and histological distinction of the trabecular vascular tissue of the clitoris and the bulbs are alike indicating this type of tissue to be erectile vascular tissue [122,126,127], very similar to the erectile tissue found in the penis. It has been further demonstrated [128] that autonomic innervation of the clitoris and the clitoral bulbs show striking similarities further supporting their observation that these are responsive erectile structures. The function of these bulbs is unclear; one speculation is that when filled with blood they support the vaginal wall during the thrusting of coition. Whether they create any erotic pleasure when stimulated by pressure has not been examined.

5. PERIURETHRAL GLANS.

The term ‘periurethral glans’ [129] describes and delineates a triangular part of the vaginal vestibule that surrounds the urinary meatus, extending from below the clitoral glans to the vaginal introitus and laterally to the beginnings of the labia minora. Contrasts exist, since the same area has been described in one study as part of the corpus spongiosum of the female which is far more widespread than in the male [130] and others have described the periurethral glans/corpus spongiosum/pars intermedia/root of the clitoris as the same structure [131].

During coitus, the thrusting of the penis causes the area to be pushed into and then dragged out of the vagina. As the area is an innervated mucous membrane, this induced movement will create pleasurable erotic stimulation. When women are asked to list hierarchically their most pleasurable erotic sites the periurethral glans area of the vaginal vestibule is rated second after the clitoris. The area, its mobility and density of innervation could be the answer as to why a sub-group of women can have orgasms.

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**Figure 12:** A diagrammatic representation of the vulva highlighting many of its named features in relation to the underlying structures it is “covering or wrapping”. With permission from [131] and with the courtesy of Dr. O’Connell HE and Anatomedia.
from simple penile coital thrusting alone (so-called 'vaginal orgasms') [131]. Remarkably, the area has not been the focus of any biothesiometric study and is generally overlooked as a potentially important source of erotic pleasure during coitus for women.

6. THE VULVAR VESTIBULE

includes the vulvar area comprised between the inferior part of the clitoris, the medial part of the labia minora and the fourchette [131,132].

7. VAGINA

In the unaroused condition the vagina is a potential space with its anterior and posterior walls collapsed and resting together but they do not adhere because the walls are covered with a thin film of fluid (see, in this context, the specific section dealing with vaginal lubrication). Its shape is complicated so no single structure can describe it. The cross-section is similar to either a 'H' or 'W' while the longitudinal axis is like a greatly stretched out 'S' (length range 6-12 cm). Its entrance (introitus) is usually gated by the labia minora (see section above ) while its back culminates in a cul-de-sac the anterior wall of which is penetrated by the cervix of the uterus usually at right angles to the vaginal longitudinal axis [119,133].

The layered structure of the vagina consists of the luminal stratified squamous epithelium (a multicellular layer with new cells continually created in the basal layer by oestrogen-stimulated mitosis which then migrate to be shed off (desquamated into the lumen), a lamina propria layer containing connective tissue, blood vessels, nerves and receptors, collagen, elastin fibres and finally a layer of smooth muscle [129,134-136] (Figure 14). The organ is set in the pelvis surrounded by powerful striated pelvic musculature while at the introitus two superficial striated muscles, the ischiocavernosus and bulbocavernosus can contract around the penis during orgasmic arousal [137].

a) Microcirculation in the basal condition.

The vaginal microcirculation is supplied with blood from at least 3 main arteries and drained by numerous veins. Like all microcirculations it consists of a circuit of arteries→arterioles→met-arterioles→capillaries→venules→veins.

The vaginal vessels are richly innervated by adrenergic, cholinergic and vipergic nerves together with neuuropeptides like substance P (a sensory transmitter), neuropeptide Y (a vasonconstrictor) and calcitonin gene related peptide (CGRP), a possible sensory transmitter and a peptide influencing capillary permeability) and Nitric Oxide (NO) [134,138-144]. The exact functions of the various innervations have yet to be ascertained [145].

Like other microcirculations it has a preferred path for most of the blood flow during quiescence (and for the vagina that is quite often) which means that most of the time the capillaries are closed due to
contraction of the pre-capillary sphincters. When the local area around one of these becomes hypoxic the released metabolites (\(pCO_2\), lactic acid, \(K^+\), ATP) cause sphincter relaxation and the supplied capillaries open up washing away the metabolites and refreshing the local area with oxygen and nutrients. This intermittency of the microcirculation is known as 'vasomotion', it is seen in a number of other genital tissues such as the testis [146] but has only recently been observed and quantified in the vagina by photoplethysmography [147]. The degree of vaginal vasomotion is a sensitive and useful index of genital arousal. Thus, during basal conditions, a high vasomotor tone of the arterial supply through central sympathetic activation and a high level of vasomotion keep the blood flow to the vagina at minimal levels. A corollary of this is that the surface \(pO_2\) of the vagina wall is basally at a low, hypoxic level [136].

Recently Allers et al. described slow oscillations in vaginal blood flow in both rats and humans as a marker of sexual arousal [148,149]. They are influenced in rats by the central nervous system namely the PVN (Paraventricular Nucleus) and modulated by the autonomic nervous system [149]. They also demonstrated that in humans and rats the oscillation appear independent of vaginal vasocongestion. VSS induced an increase in the total power of slow oscillatory activity in vaginal blood flow in healthy human volunteers but no increase was observed in women with Female Sexual Arousal Disorder (FSAD). They concluded that slow oscillations in vaginal blood flow are correlated with subjective physiological arousal and display diminished responsiveness in women with FSAD and may be used as a model when studying female sexual arousal [148]. Relations, if any, between vaginal vasomotion (147) and the slow oscillations have not been discussed.

8. THE CERVIX

The cervix pierces the anterior vaginal wall normally at approximately right angles the longitudinal vaginal axis. In the basal non-stimulated state, the cervix can rest on the posterior vaginal wall. Its central canal is some 3 mm in diameter and 2-3 cm in length and is lined with a greatly folded epithelium of columnar cells creating crypts (some 10,000) that look like glands and are often mistaken for them. The cells secrete mucus under the influence of oestrogens (increasing the production) and progesterone (decreasing the production). Around mid-cycle the mucus is viscous like egg white and it provides the optimum environment for sperm movement and survival. At other phases of the cycle the mucus is thick and relatively hostile to sperm movement and survival.

The innervation of the cervix is poor so that some minor surgery can be carried out without anaesthesia but it has the second highest concentration of VIP in the female genital tract. The functions of this VIP have not yet been elucidated but it is unlikely that it is involved in increasing cervical blood flow during arousal because fMRI imaging does not indicate the
organ becoming vasocongested [127]. It is more likely to be involved in the neuroimmunology of the cervix acting as an anti-inflammatory agent [150].

II. ARTERIAL SUPPLY

Women’s genitalia have a rich arterial blood supply [118,132]. The labia are supplied from the inferior perineal and posterior labial branches of the internal pudendal artery as well as from superficial branches of the femoral artery. The clitoris is supplied by the ileohypogastric pudendal arterial bed. After the internal iliac artery has given off its last anterior branch, it traverses Alcock’s canal and terminates as the common clitoral artery, which gives off the clitoral cavernosal arteries and the dorsal clitoral artery (Figure 13B). The proximal (middle) part of the vagina is supplied by the vaginal branches of the uterine artery and the hypogastric artery. The distal part of the vagina is supplied by the middle hemorrhoidal and clitoral arteries.

III. PERIPHERAL NEUROPHYSIOLOGY

The female genitalia are richly innervated [125,134,143,151,152]. Knowledge of the innervation is clinically important. Firstly it is essential for our understanding of the physiology and pathophysiology of arousal and orgasm. Secondly in our understanding of possible disruption of neural pathways during surgery and other iatrogenic procedures [153].

The uterine nerves arise from the inferior hypogastric plexus formed by the union of the hypogastric nerves (sympathetic T10-L1) and the splanchnic fibers (parasympathetic S2-S4). This plexus has three portions: vesical plexus, the rectal plexus and the uterovaginal plexus, which lies at the base of the broad ligament, dorsal to the uterine vessels and lateral to the uterosacral and cardinal ligament. This plexus provides innervation via the cardinal ligament and uterosacral ligaments to the cervix, upper vagina, urethra, vestibular bulbs and clitoris, for review see [145].

At the cervix sympathetic and parasympathetic nerves form the paracervical ganglia. The larger one is called the uterine cervical ganglion. It is at this level that injury to the autonomic fibers of the vagina, labia and cervix may occur during hysterectomy. The pudendal nerve (S2-S4) reaches the perineum through Alcock’s canal and provides sensory and motor innervation to the genitalia.

Consequently the anatomic structures involved in the female genital sexual response are innervated by autonomic and somatic nerves

1) the pelvic nerve issuing from level S2-S4 of the spinal cord (parasympathetic);

2) the hypogastric and lumbosacral chain issuing from level (T12 – L2) of the spinal cord (sympathetic);

3) the pudendal nerve (somatic) with cell bodies of the motoneurons located in the Onuf’s nucleus (S2 – S4);

4) the vagus nerve issuing from the nucleus tractus solitaries.

Sensory stimuli relevant to sexual function are conveyed by afferent pathways consisting of pudendal, pelvic and hypogastric nerves and the lumbosacral sympathetic chain. They relay information to the dorsal horn, medial central and lateral gray matter of the lumbosacral spinal cord, and the vagal afferent fibers convey sensory information from the genital apparatus to the nucleus tractus solitarius (NTS) [154].

A great variety of neurotransmitters/mediators and receptor types have been demonstrated in nerves in the female genitals in both animal and human studies (see [135,139] for references). The functional implications of each transmitter are not fully understood.

IV. PHYSIOLOGY OF AROUSAL

During sexual stimulation the female sexual arousal response is elicited by sensory stimulation as well as central nervous activation resulting in increased blood flow to the genitals. This culminates in a series of vasocongestive as well as neuromuscular events leading to physiological changes.

Berman et al. [155] demonstrated that sexual stimulation resulted in a significant increase in clitoral, labial, urethral and vaginal blood flow. High resolution MRI studies of the female genitalia have detailed the living anatomy of the female genitalia and have demonstrated the changes that occur with arousal and engorgement [126,127]. Studies by Yang et al [128] correlating in vivo MR imaging of genitalia together with gross and histologic examinations of cadaveric specimens have demonstrated five vascular compartments comprising the external female genitalia; the clitoris, clitoral bulbs, labia minora, urethra, and vestibule/vagina. (Figure 15A) These compartments are composed of erectile as well as non-erectile tissues with erectile tissue demonstrating the greatest volume change with engorgement during sexual arousal [127,156] (Figure 15B).

1. EXTERNAL GENITALIA

a) Labia

During sexual arousal the labia become engorged with blood increasing in size by as much as two to threefold [1,157] and their sensitivity to touch is enhanced. Because they are the gateway into the vagina, painless initiation of coitus by penile thrust-
ing requires their lubrication. If their resistance to insertion is greater than the buckling pressure of the penile erection, usually quoted as an axial pressure equal to or greater than 550gm [158], penetration will be difficult and ‘insertional dyspareunia’ may occur making the initiation of coitus uncomfortable for both partners. Masters and Johnson [1] proposed that their lubrication during arousal was due to the ‘spill over’ of excess vaginal lubrication. However, a pilot study [159] that used tampons in the vagina to prevent any fluid leaking out onto the labia found that sexual arousal still caused labial lubrication, strongly indicating that the labia could actually form their own lubricative fluid presumably by plasma transudation similar to that produced by the vagina during arousal (see details in the subsequent section on vaginal lubrication).

As the labia minora become engorged with blood during arousal - unlike the labia majora [157] - they have been experimentally used as an indicator of genital sexual arousal, the increase in engorgement being monitored either by the increase in labial temperature using a thermistor [160] or by thermographic imaging [161]. (Figure 16)

b) Clitoris

As described above the clitoral shaft is composed of two corpora cavernosa surrounded by a capsular fibrous sheath (tunica albuginea). Under basal conditions the blood vessels in the clitoris have a high tone (through sympathetic activity) and are mainly closed [162] but show evidence of vasomotion [163] the random opening and closing depending on local tissue needs (as described previously). The neural innervation is through vipingic nerves releasing Vasoactive Intestinal Peptide (VIP) dilating the arterial supply [129,164] and NO, formed by the enzyme nitric oxide synthase (NOS), found in the nerves (nNOS) and lining endothelium of the corpora cavernosa (eNOS) relaxing the smooth muscle of the cavernous sinuses [165-173]. During sexual arousal the central reduction of sympathetic tone and the release of the two vasodilator neurotransmitters create an increase in the blood flow to the clitoris and relaxes the smooth muscles of the cavities in the clitoris so that they become filled with blood and the organ becomes vasocongested. Unlike the penis, which when it becomes fully erect cannot be bent, the clitoris, because it has no subalbugineal layer between its tunica and the erectile tissue [174], even when fully-filled only becomes swollen or tumescent and not rigid. Genital MRI techniques have been used to dynamically study and quantitatively the clitoral engorgement response in women during VSS [126,127,156,175] Dynamic genital MRI techniques have documented and measured the engorgement response in vivo during arousal and showed increased width of the clitoris during arousal [127]. (Figure 15B).

Surprisingly, the vibration sensitivity of the clitoris is known to decrease during and immediately after arousal [176] a feature similar to the tumescent
penis [177]. No satisfactory explanation for the genital decreases in response to vibration has yet been proposed.

Data regarding the correlation between the measured degree of physiologic engorgement and the subjective level of arousal have been mixed. There has been a non-significant trend suggesting correlation between these two measures but further studies are needed to validate this [156]. A preliminary uncontrolled, randomized, blinded crossover MRI study of the genital response following ingestion of sildenafil vs. placebo in a group of women with (FSAD) demonstrated a non-significant trend toward improved engorgement with sildenafil [175]. MRI studies documented an increase in clitoral volume following sildenafil compared with placebo in 6 of 12 subjects, no significant change in either imaging session in three subjects while in three subjects, there was a robust clitoral response in both MR sessions. This indicates that MR measurements of clitoral volume can provide an objective measure of engorgement change following a vasoactive medication in women with FSAD, but larger scale studies are needed.

2. INTERNAL GENITALIA

a) The urethra

The female urethra is only 4 cm long but in its wall are venous sinuses that are filled with blood. They are part of the closing pressure of the urethra thus aiding in maintaining urinary continence. In the lining of the urethra are found, triangular- shaped paracrine cells that are thought to have mechanoreceptor properties and are rich in serotonin (5-hydroxytryptamine). This neurotransmitter is known to potentiate the sensitivity of nerve endings [178]. Stretching of the urethra occurs during coitus [179] or during digital stimulation of the anterior wall and this may well activate these mechano-receptor cells to release serotonin sensitising the nerve endings in the urethra and thus creating pleasurable sensations [179]. The urethra is thus converted from a urinary tube into a genital sex organ.

b) Vagina: microcirculation in the aroused condition

At the beginning of sexual arousal the blood supply to the vagina is minimal due to the high sympathetic vasomotor tone and vasomotion as detailed in the previous section. Then, usually within seconds of an acceptable or consensual sexual stimulus, the central sympathetic tone is reduced and the arterial supply is enhanced through the action of released neuronal VIP and some NO via the sacral anterior nerve roots [181] and vasomotion decreases as more closed capillaries are recruited [147]. Fairly rapidly the recruitment of the capillaries becomes maximal and the vagina becomes fully vasocongested (along with the labia and clitoris) vasomotion is absent and the woman will subjectively perceive that her pelvis ‘feels full and congested’. While consensual sexual stimulation is obviously the preferred behavior it is known that vaginal vasocongestion, lubrication and even orgasm can be induced in some women even by non-consensual unwanted sexual stimuli [182].

c) The aroused vagina and the formation of vaginal lubrication

As described above, within the sexually aroused vagina, the capillaries of the micro-circulation are filled with blood and the increased hydrostatic pressure inside them forces out a plasma transudate (ultrafiltrate) into the interstitial space around the blood vessels. Continued formation of this neurogenic transudate fills up the interstitial space and then passes through and between the cells of vaginal epithelium to leak onto the surface wall of the vagina as the vaginal lubrication. The final fluid is a modified plasma filtrate because the cells of the vagina can transfer Na⁺ ions vectorially from the lumen back into the blood [183] and add K⁺ ions by secretion and the cell shedding [136,184,185]. Thus the ionic concentrations of these ions are much different to those in the plasma, vaginal basal fluid having a higher K⁺ and a lower Na⁺ than plasma throughout the menstrual cycle [186].
However, during arousal the greatly enhanced transvaginal flow of filtrate from blood vessels to the vaginal lumen has a much reduced contact time with the vaginal cells and their ability to transport Na\(^+\) is of limited capacity so that the transport of Na\(^+\) back into the blood is saturated and much Na\(^+\) escapes into the vaginal transudate. Thus the arousal lubrication fluid has a much higher Na\(^+\) concentration than the basal fluid approaching that of plasma [185]. (Figure 17) The fluid formed on the surface of the vaginal wall is more than just a modified plasma transudate because it feels slippery to the touch and has obvious lubricant properties. Exactly what these substances are is not known but it is thought that they may include glycerol manufactured by the vaginal cells [187] and sialoproteins secreted into the vagina by the cervical epithelium [187]. On cessation of the sexual arousal the vaginal Na\(^+\) together with osmotically drawn fluid is transferred back into the blood [179,187] resetting the vagina to the basal ‘just moist’ condition.

In a number of fluid transporting tissues water channel proteins called ‘aquaporins’ (AQP’s) are found, they facilitate the transport of water and other small molecules like glycerol. There are some 13 members of the AQP family; AQP 1,2,4,5 and 8 are specific for water transport while AQP 3,7,9 and 10 transport are less specific transporting water and small molecules. AQPs have been localized in rat vagina. Park et al [188] found that AQP1 was primarily expressed in capillaries and venules, AQP2 in the cytoplasm of the epithelial cells and AQP3 was associated mainly with the plasma membranes of the epithelial cells. Stimulation of the pelvic nerve, known to induce increased vaginal blood flow, caused the translocation of AQP1 and 2 from their cytosolic site to the membrane compartment but AQP3 was unchanged. The authors interpreted their results to suggest that the AQPs could play a role in the fluid movements of vaginal lubrication. A later study, again in rats, reported that estrogen deprivation decreased the expressions of vaginal AQP2 and NOS but they were restored by 17- beta estradiol treatment. While these animal results are interesting, as yet, there is only a poster study [189] reporting that the distribution of AQP 1, 2 and 3 in premenopausal human vagina has the same distribution as that in the rat. Any possible role of these water channels in human vaginal lubrication has yet to be determined.

d) The uterus

Masters & Johnson [1] reported that the uterus increased its size by 50-100% during sexual arousal and then returned to normal after its cessation when monitored by palpation suggesting vasocongestion. Later studies with MRI imaging did not confirm this swelling [190]. During high levels of sexual excitement and at orgasm the uterus contracts...
PuTATIVE EROTIC STRUCTURES

3. THE ANTERIOR VAGINAL WALL AND ITS PUTATIVE EROTIC STRUCTURES

The anterior vaginal wall, when stimulated by deep pressure, is known to generate a more sexually pleasurable feeling than either of the lateral or posterior vaginal walls. This is not due to it having a greater innervation than the other vaginal areas as it has been reported that vaginal nerve density is relatively homogenous [143,187].

Closely associated with this wall, however, are 3 anatomic components that are reputed to create the sexual feelings when stimulated. These are:

a) the urethra (see description in previous sections);

b) the so-called ‘G-Spot’;

c) Halban’s fascia.

As these structures are all packed into a relatively small space in and along the anterior wall it is obvious that any deep pressure on the anterior wall will likely activate all three, it will be nearly impossible to isolate and stimulate just one. It may thus be more sensible to talk of the ‘antero wall erogenous complex’ [191]. This is also why the claim of Chua Chee Ann [179,192] to have found a new erotic site of the anterior vaginal wall, described by him as the “anterior fornix erogenous zone”, which when stimulated by digital pressure created vaginal lubrication and orgasm must be looked at with a high degree of scepticism especially as it was claimed without any evidence that the stimulus acted locally and did not reach the brain.

a) The ‘G spot’

Ernst Grafenberg in 1950 described a site on the anterior wall of the vagina that when stimulated by deep pressure became swollen and or enlarged protruding into the vaginal lumen and was highly effective in causing orgasm in women when stimulated [193]. Two authors, Whipple and Perry, of a popular, non-peer reviewed book [194] named the site the ‘G spot’ in recognition of Grafenberg and this appellation has stuck although it is more of a zone than a spot [195]. Several papers (actually, more than 250) have been published as to whether the area exists and its possible connection with female ejaculation (see [191] for references). Despite the passage of nearly sixty years controversy still surrounds the ‘G spot’ because

1) of its inexact anatomic placement- in the short female urethra its position is unsettled. Some places it at the junction of the bladder with the urethra [196] while others place it at the middle [193] or possibly even the distal part of the urethra [197].

2) its putative structure – some suggest it to be the ‘female prostate’ paraurethral or periurethral glands/ducts [see 131,198,199] for references).

b) Halban’s fascia

Attention was drawn to this genital structure as a source of sexual pleasure in the report of Minh et al. [200] The fascia is in the space between the bladder and the anterior wall of the vagina and is filled with connective tissue, blood vessels, nerves and neuroreceptors. Strong stroking pressure on the anterior vaginal wall transfers the stimulus to the fascia inducing highly pleasurable sensations that can lead to orgasm. Recently a report suggested that the greater the thickness of the fascial space (called the urethrovaginal space in this report) the greater was the ability of women to have an orgasm from penile thrusting alone [201]. They had no proposal as to why such a relationship should exist. Unfortunately, the authors erroneously confused the anatomical site that they described also as the ‘human clitoris-urethrovaginal complex’ as the ‘G-spot’.

4. NIPPLE/BREAST STIMULATION

While genital stimulation is very effective in creating female sexual arousal the stimulation of the fe-
male nipple/breast can significantly enhance sexual arousal. Levin & Meston [202] noted that the role of nipple stimulation during lovemaking was just the subject of opinion-based comment rather than any evidence-based study. They gave a short questionnaire on nipple stimulation during lovemaking to 153 sexually experienced women undergraduates and 149 males. The major findings were that 81.5% of the women (and even 51.7% of the males) reported that stimulation of their nipples/breasts caused or enhanced their sexual arousal while 78.2% of the women (and 39% of the men) agreed that when sexually aroused stimulation of their nipples further increased their arousal. During lovemaking, 59.1% of the women (and 17.1% of the men) had asked for their nipples to be stimulated. Only 7-8% of the population questioned reported that nipple stimulation decreased their arousal [202].

No evidence exists exploring the role of skin in the arousal response

5. SEXUAL PHYSIOLOGY - THE REFLEXES GENERATED FROM VAGINAL STIMULATION

An overlooked subject is the generation of a number of genital reflexes claimed to be activated by vaginal pressure or stretch stimuli. They have been reviewed previously by Levin [203]. The earliest report of reflexes from the vagina was by Ringrose [204] who mechanically stimulated the vaginal wall with a wooden tongue depressor and observed a number of reflex muscle contractions. Because they did not appear to have any obvious physiological function they were ignored. A subsequent study [205] revealed that the reflexes could not be elicited in women up to 12 hours after they had been raped. No studies have been undertaken since to establish whether this finding could be of significant forensic importance. Lavoisier et al. [206] reported that the vaginal insertion and withdrawal of a balloon induced an increase in the velocity of blood supply to the clitoris and inferred that the same scenario would occur during coitus facilitating clitoral arousal. By far, the most extensive studies of female vaginal reflexes have been those of Shafik and his co-workers [207-210] which are listed in Table 3 together with their proposed function. The reflexes were all elicited by inflating an intravaginal balloon and the authors have assumed that this is equivalent to the mechanical stimulation of the penis in the vagina during coitus thus claiming that the recorded reflexes are physiological and occur during coitus. Such an assumption may be questionable and it still needs to be established whether the reflexes will be useful in the diagnosis of FSD.

VI. SEXUAL PHYSIOLOGY - MRI STUDIES OF INTERCOURSE

Pelvic MRI studies have been done of couples during intercourse [190,211,212]. Studies were done with couples in the missionary position and in posterior position to study the living anatomy of intercourse and to determine if previous theories about anatomic relationships are correct. In the missionary position, the penis is observed by MRI to be boomerang-shaped and reaches the anterior vaginal fornix with preferential contact along the anterior vaginal wall. Prior to penetration the vagina is parallel to the pubococcygeal line and has a normal anterior convexity. After penetration, the anterior vaginal wall is lengthened and the posterior bladder wall is pushed upward and anterior while the uterus is pushed upward and posterior. With a posterior position the penis reaches the posterior fornix and there is preferential contact along the posterior vaginal wall. Both the bladder and the uterus are pushed anterior in this position [212].

VII. THE PERIPHERAL PHYSIOLOGY OF ORGASM

Changes occur in the striated pelvic muscles, the smooth muscle of the uterus and vagina and circulation of the genitalia at orgasm. These have been reviewed extensively by Meston et al. [213] and only a brief account with updating is given below.

<table>
<thead>
<tr>
<th>Reflex name [reference]</th>
<th>Stimulus/ Activation</th>
<th>Putative sexual or reproductive role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vagino-cavernous [210]</td>
<td>Fast vaginal distension Transient contraction of ISC &amp; BC muscles</td>
<td>Enhanced tumescence of clitoris 'milking' penile urethra</td>
</tr>
<tr>
<td>Vagino-levator [209]</td>
<td>Fast vaginal distension Contraction of levator</td>
<td>Facilitates vaginal tenting</td>
</tr>
<tr>
<td>Vagino-puborectalis [207]</td>
<td>Fast vaginal distension Contraction of puborectalis</td>
<td>Prevention faecal leakage</td>
</tr>
<tr>
<td>Vagino-vesicourethral [208]</td>
<td>Vaginal distention Relaxation of bladder Contraction urethral sphincter</td>
<td>Prevention urine leakage Protecting sperm</td>
</tr>
</tbody>
</table>

Table 3: Human female genital reflexes activated by balloon inflation in the vagina.
ISC= ischiocavernosus, BC = bulbocavernosus
Modified with permission from [203]
1. STRIATED PELVIC MUSCLE CHANGES

The striated muscles of the female pelvis are categorized into superficial and deep musculature. Surprisingly, despite extensive studies, a simple, clear and unambiguous description of this musculature is remarkably difficult to make. As van Houton [137] has remarked this is because of ‘unhelpful generalisations, confusing and overlapping terminology and misleading metaphors’.

Classical accounts describe the superficial muscles (urogenital diaphragm) as the ischiocavernosus, the bulbocavernosus and the deep and transverse perinei, while those of the deep pelvic floor, often described as the ‘pelvic diaphragm’, consists of the coccygeus (ischio-coccygeus) and the levator ani which contains the iliococcygeus and pubococcygeus muscles. The pubococcygeus is itself said to be made up of the pubourethralis and puborectalis muscles together with other smaller muscles (puboperinealis and puborectalis) a strange concept where a muscle is said to be constructed from other muscles. However, it is adequate for the present purposes to accept this simplistic picture. According to Graziottin & Giraldi [132, 214], the function and dysfunction of these pelvic muscles have an important impact on female sexuality. Hypoactivity of the muscles (low tone) leads to poor sexual function and lack of pleasure during coitus and orgasm while hyperactivity (high tone) is associated with the pain disorders of dyspareunia (namely, either coital or non-coital pain) and vaginismus (namely, difficulties in allowing entry into the vagina despite wanting it) a leading cause of unconsummated marriages in women [215].

Like all striated or voluntary muscles those of the pelvis have both afferent (sensory) and efferent (motor) innervation. Their innervation is by the pudendal nerve [216] and is the neural path for nerve impulses creating the rhythmic contractions of these muscles that occur in most women at and during orgasm. Masters and Johnson [1] described the pelvic contractions as an intrinsic part of the orgasmic process but Kinsey et al. [217, 218] regarded them as the ‘after-effects of orgasm’. The actual number of the contractions varies with the duration and intensity of the orgasm [1,219] and their frequency, strength and pleasurable power all decrease after the first few. It is thought that neurally-controlled genital muscular events that occur at orgasm are mediated at the spinal cord level which is involved in integrating the afferent impulses from the muscles and the efferent discharge from the supraspinal origins.

It has often been stated that the contraction of the pelvic muscles is mandatory (indispensable) as an indicator for the occurrence of the female orgasm [1,220]. However, claims have been made by women that while they have orgasms they do not have pelvic contractions [219]. Unfortunately, as no laboratory measurements of the pelvic musculature have ever been made in such cases we cannot be sure whether they really don’t possess these contractions rather than they don’t perceive them, perhaps because they are weak or that they have low interoceptive awareness. Attempts to relate aspects of the physical nature of the vaginal contractions to the pleasure felt during their activity have not been successful. Masters and Johnson [1] stated that the stronger the orgasm the greater was the number of contractions experienced, mild orgasms had 3 to 5 contractions, normal orgasms 5 to 8 contractions and the most intense 8 to 10 contractions but there has been no confirmation of this claim. Recordings of the intraluminal vaginal pressure during orgasm have not shown any linkage between the orgasmic contractions and the intensity of pleasure [221].

a) Purpose of the pelvic muscle contractions

In the male the purpose of the involuntary rhythmic contractions of the pelvic muscles at orgasm is clearly to eject forcefully the semen from the urethra, without them only a dribbling emission occurs. The role(s) of the muscular contractions in the female at orgasm is less attributable. Some five possible functions have been suggested namely:

i) to eject glandular secretions from the urethra (viz female ejaculation);

As a significant number of women do not appear to have such urethral ejections it is unlikely to be a significant or major function of the muscles that needs to be preserved.

ii) to create sexual pleasurable feelings;

When the muscles are contracted voluntarily they do not create sexual pleasure (but such voluntary contractions can facilitate the induction of arousal/orgasm in some women).
iii) to restore the vasocongested pelvic tissues to their basal state;

Orgasmic contractions from a single orgasm only partially restore the vasocongested tissues to the pre-aroused basal state of vasomotion [147].

iv) to stimulate the male to ejaculate;

By creating increased pressure on the thrusting penis the sexually-excited male is pushed over his threshold of ejaculatory containment and delivers his semen into the vagina thus the female captures the spermatozoa of her chosen male inseminator. Most women also vocalize nonverbally at each pelvic contraction [222].

v) to end sexual arousal;

As women are multiorgasmic a single orgasm with the concomittant contractions does not necessarily end their sexual arousal.

Thus none of the suggested functions hold up well on examination except perhaps that of stimulating the male to ejaculate. Another explanation is simply that both the female and the male pelvic muscles arise and develop from the same embryonic structure. While they are essential for the forceful ejaculation of male semen they have no apparent functional purpose for the female, but as they do no harm in their occurrence they are of no consequence and take too much energy and trouble to remove so they have been ignored and remain. They are an example of a 'biological spandrel', a structural feature that has a specific function in one sex but of little or no apparent use in another [223].

2. VAGINA

Because the vagina is a compliant organ and is set in a surround of powerful pelvic striated musculature (see previous section) the motility of its coats of smooth muscle per se has been poorly characterized. Its innervation by vipersic nerves suggests that the muscle will become relaxed during arousal and coitus probably to avoid occluding its blood vessels and thus reduce its lubrication and aid in the tenting process. At orgasm, the contractions of the striated muscles will impinge on the vagina causing passive increases in its intraluminal pressure. How much the vaginal smooth muscle contributes to the activity is uncertain as no study has measured the vaginal smooth muscle and the striated at the same time during orgasm. When Gillan and Brindley [224] recorded what was presumably the electrical activity of the vaginal smooth muscle using steel wire electrodes or silver discs sucked onto the vaginal wall an increase in its electrical activity was induced by clitoral vibration but at orgasm the continuous activity was replaced with intermittent activity associated with the orgasmic contractions. Shaflk et al. [225] also studied the electrical activity of the vaginal wall but the slow waves and the intermittent action potentials they recorded were observed in women who were not sexually aroused. The action potentials were concomitant with increased intraluminal vaginal pressure and represent the spontaneous vaginal motility described previously (see [187] for references). The function of these basal contractions were assumed to be for 'housekeeping', clearing the vagina of cellular debris, secretions and blood and possibly as maintenance to activate vaginal blood flow during sexual quiescence.

3. UTERUS

Although orgasmic contractions of the uterus have been described, unlike Kinsey et al. [217] who regarded them as having a sucking effect, Masters and Johnson [1] proposed controversially that they were expulsive and not involved in up-sucking material from the vagina (see section on sexual arousal and reproduction). Their experimental evidence for this conclusion was that blood was ejected forcibly when an orgasm was induced at menstruation and that no fluid was taken up at orgasm when a fluid-filled cap was placed over the cervical os. Others have criticized these experiments and argued that neither of these conclusions rules out uterine up-sucking. Unfortunately, remarkably few measurements of this uterine activity during orgasm have been recorded and published and those that have, electrical measurements by Masters and Johnson [1] and intrauterine pressure measurements by Fox et al. [226], are technically difficult to analyze and interpret and leave much to be desired [163]. Although a number of studies have been made on uterine contractile activity in relation to sperm transport they have all been undertaken in the sexually non-aroused condition (see section on arousal and reproduction).

What actually creates the uterine contractions is still under debate as discussed previously.

Masters and Johnson [1] and Kinsey et al. [217] differ significantly in their descriptions, both in the appearance and in the placement of the uterine contractions. According to Kinsey et al. [217] 'the upper end of the uterus goes into rhythmic contractions of considerable frequency whenever there is sexual arousal' but Masters and Johnson [1] claimed that 'specific uterine patterns do not develop unless the individual subject undergoes an orgasmic experience'. In conclusion, there are simply too few published recordings/data to resolve these unanswered problems [203].

4. CERVIX

The only change that appears to occur in the cervix is a minimal dilatation of the os immediately after orgasm lasting for 20-30 minutes [1]. It was suggested that this could facilitate spermatozoal transport through the endocervical canal. The mechanism for this dilatation has never been investigated but as the
The cervix has the second highest concentration of VIP in the genital tract; it is possible that its relaxant action on the sparse smooth muscle present could be involved.

5. RECTAL SPHINCTER AND PRESSURE

The rectal sphincter contracts at orgasm, especially in younger women [1], mirroring the contractions of the vagina [219, 227]. Older women do not always show such contractions [1]. More recently rectal pressure changes during orgasm have been analysed by calculating the spectral power in various frequency bands [228]. It was found that an objective rule (algorithm) based on the spectral power in the alpha band (8-13 Hz) identified 94% of the orgasms induced in normal women by clitoral masturbation undertaken by their partners. The alpha fluctuations only occurred during orgasm and were not seen in attempts to mimic orgasm or in failed attempts to induce orgasm (Figure 18). The authors proposed that the integrated spectral power in this 8-13 Hz band of rectal pressure was a specific and sensitive marker for attributing that an orgasm had taken place.

VIII. SUMMARY OF PERIPHERAL SIGNS OF ORGASM

While orgasm is a subjective experience it is normally accompanied by a number of physiological body changes. These changes can be classified as [229]:

i) Prospective – those changes that indicate an impending orgasm;

ii) Current – those changes taking place at orgasm;

iii) Retrospective- those changes that indicated that an orgasm had occurred

See Table 4 for more details

G. TRANSLATIONAL SCIENCE: WHAT IS THE ROLE OF SEXUAL AROUSAL AND ORGASM IN FEMALES?

Sexual arousal in women serves both procreation/reproduction and recreation/pleasure. The changes that occur in the female genitals and genital tract can be divided into those that serve procreation, those that serve recreation and those that serve both procreation and recreation. This section will describe briefly those changes induced by sexual arousal that have functional importance for reproduction (for greater details see [163, 230]).

II. DOES ORGASM HAVE ANY ESSENTIAL ROLE TO PLAY IN FEMALE REPRODUCTIVE MECHANISMS?

1. THE UTERINE UPSUCK HYPOTHESIS

The possible role(s) of orgasm and their importance in the female have always been disputed. A recent book by Lloyd [234], a philosopher, examined critically some 26 papers on the topic and she concluded that there was little or no real evidence to show that orgasm was important for reproduction. One school of thought argues that orgasm plays no essential role...
Table 4: Specific objective indicators or markers of the female orgasm with permission from [229]

<table>
<thead>
<tr>
<th>Prospective (changes indicating an impending orgasm)</th>
<th>i) Changes in the colour of the labia minora (from pink to deep red)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current (changes occurring during orgasm)</td>
<td>i) vaginal contractions</td>
</tr>
<tr>
<td></td>
<td>ii) uterine contractions</td>
</tr>
<tr>
<td></td>
<td>iii) anal and rectal contractions</td>
</tr>
<tr>
<td></td>
<td>iv) release of prolactin</td>
</tr>
<tr>
<td>Retrospective (changes occurring after orgasm)</td>
<td>i) areolar decongestion causing corrugation of the areolae</td>
</tr>
<tr>
<td></td>
<td>around the nipple</td>
</tr>
<tr>
<td></td>
<td>ii) raised and maintained plasma prolactin levels (up to 60</td>
</tr>
<tr>
<td></td>
<td>minutes after orgasm)</td>
</tr>
<tr>
<td></td>
<td>iii) increased vaginal pulse amplitude (VPA) measured by pho-</td>
</tr>
<tr>
<td></td>
<td>toplethysmography</td>
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<tr>
<td></td>
<td>iv) rectal pressure fluctuations (specifically 8-13 Hz)</td>
</tr>
</tbody>
</table>

Figure 18: Rectal pressure (left), an index of perineal muscle activity and spectral analysis on the rectal pressure data (Right). The spectral power was calculated in the frequency bands delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), and beta (13-25 Hz). The most significant and most important difference in spectral power between orgasm and both control motor tasks (imitation of orgasm and failed orgasm attempt) was found in the alpha band. With Permission from [228]
in the mechanism of reproduction promoting the facts that numerous women have become pregnant without an orgasm and that artificial insemination creates pregnancies without orgasm. Another arm of their argument is that as female orgasm created by penile thrusting alone is far from a universal feature among women [235] natural selection has clearly not favoured those who could orgasm easily from such stimulation indicating that it could not be an essential for the reproduction of our species. The other school of thought has proposed that the uterine contractions observed at orgasm (thought to be induced by the orgasmic release of oxytocin) create a uterine ‘upsuck’ and hasten the transport of the sperm. The initial basis for this scenario was the very early paper of Beck [236] who described a case of a patient with a pronounced vaginal prolapse of her uterus making the cervical os easily observed. She was also extremely sensitive to clitoral stimulation. Beck aroused her sexually by stimulating her clitoris digitally and observed that at orgasm the os made 5 or 6 ‘gasps’. He suggested that such activity would suck sperm up into the uterus when immersed in the vaginal seminal pool. Dickinson [237], in fact, using a glass test tube as a surrogate penis and arousing women by clitoral vibration did not find any evidence of such cervical ‘gasping’.

The proposed second supporting study was that of Fox et al [226] who used radio-telemetric pressure pills to measured the intrauterine and intravaginal pressures in a couple during coitus in the face-to-face position. They interpreted their recordings to indicate that the intrauterine pressure fell below that of the vagina during intromission and male ejaculation and after female orgasm suggesting that uterine upsuck of semen could occur. The size of the pressure pill placed inside the uterus, however, was such that it would have expanded the intrauterine virtual cavity abnormally introducing the influence of an unphysiological intrauterine stimulus. As has been pointed out, single-based case studies can be illustrative of a mechanism but they do not necessarily verify it [238]. Thus, the foundations of the upsuck hypothesis appear to rest on results from a 134 year old ‘single patho-physiological uterus and measurements in an over-distended normal one, hardly the firmest of experimental foundations for the putative importance to reproduction of this mechanism’ [163].

Since these early reports other studies [239] on enhanced genital particle transport in women (patients suffering from primary or secondary infertility) injected i.v. with oxytocin have been interpreted to indicate that the oxytocin released at orgasm by, enhancing uterine contractions, will cause the ‘upsuck’ of sperm and facilitate their rapid transport into the uterus and then fallopian tube (see section below for details).

III. SPERM TRANSPORT IN THE UNARoused AND AROUSed FEMALE GENITAL TRACT

Most, if not all, authors describing the influence of sexual arousal and orgasmic uterine contractions on sperm transport in the female reproductive tract have described it as facilitating and speeding up their movement through the cervix into the uterus and fallopian tube (see [163] for references). All have overlooked the crucial influence of vaginal tenting on this putative facilitation. Moreover, it has been shown that there is indeed a fast transport of spermatozoa in the female tract even in the sexually unstimulated woman. Spermatozoa present in liquified semen, when placed on the cervical os in women who are anaesthetised, are found in the fallopian tubes within 5 minutes of their application [240]. In another study, sperm-sized spheres of albumin labelled with 99mTechnetium (surrogates for spermatozoa) when placed in the posterior vaginal fornix in conscious women are found in the fallopian tube on the side of the ovulating ovary within 1- 2 minute of their application [239]. Note that the cervix in these women would be resting on the vaginal posterior wall unlike that in the aroused woman. The mechanism for this remarkably rapid transfer even in the basal state is surprisingly not contractions of the main uterine myometrium (stratum supravasculare and stratum vasculare) but that of the archimyometrium (stratum subvasculare), a thin layer of mainly circular smooth muscle that lies beneath the endometrial cell lining of the uterus and extends from the lower part of the cervix into the uterus and at its upper part dividing into two and continuing into the muscular layer of the fallopian tubes [241]. These cervico-fundal archimyometrial contractions create the rapid, passive uptake of the spermatozoa and direct them into the fallopian tube on the side of the ovulating ovary rather than into the contralateral tube. They are at a maximum intensity and frequency prior to ovulation, are not blocked by high doses of an oxytocin inhibitor (atosiban) and are not enhanced by injected oxytocin [241]. The authors concluded that the contractions were independent of systemic oxytocin but probably sensitive to local endometrial-synthesized oxytocin [242]. Unfortunately there appears to be a conflict with the possible role of systemic released oxytocin and its effect on sperm transport in the studies. According to the findings of these authors, on the one hand they state systemic oxytocin has no effect on the archimyometrial contractions thought to power the spermatozoal transport yet on the other hand, as they themselves report, ‘Surprisingly, oxytocin stimulated directed sperm transport, although given systemically’ [241]. They conclude that ‘oxytocin may not play a critical role in the control of the continuous wave-like activity.
of the archimyometrium, but appears to be a very potent and fast stimulator of uterine contractions! However, comparing the actions of bolus injections of oxytocin with that released at orgasm may be a flawed procedure because the injections were in women who were not sexually aroused, their genital tracts are in a different receptive state and also may have different responses and the dose of intravenous synthetic oxytocin used appears far greater than that released at orgasm making it pharmacological rather than physiological. The physiological role of oxytocin in spermatozoal transport in natural coitus is thus far from clear.

### IV. THE ‘TENTING’ OF THE CERVICOUTERINE COMPLEX – A MECHANISM TO DELAY SPERM TRANSPORT

As described previously, in the basal unaroused state the vagina is a potential space with the cervix close to or touching its posterior wall. Sexual arousal causes the release of VIP from vipergic nerves innervating the vagina which relaxes its smooth muscle during the initiation of coital thrusting. High sexual arousal then causes the contraction of the pelvic levator ani muscle followed by the smooth muscle in the connective tissue septa attached to the uterus. The former, being a striated muscle, fatigues quickly within seconds [209] but the latter can maintain contraction for long periods without fatigue [230]. The contractions lift the cervicouterine complex away from the posterior wall and up into the false pelvis. The back cul-de-sac of the vagina (fornix) becomes ballooned out creating a receptacle for the ejaculate to come. This lifting of the cervix and ballooning of the vagina was named ‘vaginal tenting’ by Masters & Johnson [1]. It has been confirmed by MRI [190,211] and by direct filming [243]. While Masters & Johnson [1] realised that this tenting would remove the os cervix from the path of the ejaculate thus greatly reducing the possibility of rapid sperm entry into the uterus they did not fully appreciate the importance of the mechanism to the reproductive process. This may be to impart a delay in the transport of spermatozoa into the cervical canal and hence through the uterus to the fallopian tube to fertilise the ovum. To understand why delaying sperm transport is of importance it is first necessary to describe the status of semen and sperm at insemination.

Freshly ejaculated spermatozoa in semen in the vagina are barely motile, are trapped in a gel formed by coagulation of semen protein and are incompetent to fertilise the ovum. They have to be reprogrammed into a fertilising state (called capacitation) and liberated from the trapping gel. According to Eisenbach [244-245], once capacitated they remain in this state for only 4 hours, they then become post-capa-
cicitated and irreversibly nonfunctional. Fortunately, not all the spermatozoa are capacitated at the same time and there is a continuous replacement of capa-
cicitated spermatozoa [245,246] from the semen pool. Sperm guidance in the female oviduct to the ovum is probably by thermotaxis (responding to a thermal gradient) and chemotaxis (responding to a chemo-attractant gradient). Only capacitated sper-
matozoaoa are capable of sensing a temperature dif-
ference of 0.5°C and responding to it by swimming from a cooler to a warmer temperature, possibly that of the oviduct and only a fraction of the sperm that are capacitated are chemotactically responsive, be-
ing attracted by chemo-attractants secreted by the ovum [245]. As the experiments to study these func-
tions are undertaken in vitro we have no knowledge whether, or how, sexual arousal influences such guidance in vivo.

It is now known, however, that the process of activating sperm to become capable of fertilisation is far more complex than previously thought [247,248]. The delay imposed on sperm transport by vaginal tenting is essential to allow a variety of mechanisms to operate that are involved in this activation. These currently include:

i) the activation of sperm motility by the enhanced vaginal oxygen pressure and enzymic breakdown of sperm motility inhibitors in the semen [163],

ii) enzymic decoagulation of the gelated semen [249].

iii) mixing and contact of the spermatozoa with activators and inhibitors present in the various component fluids of semen especially the prostate (prostasomes) and seminal vesicle secretions [163],

iv) activation of capacitation and then its suspen-
sion by first messengers in the semen which prevents spontaneous acrosome exocytosis reaction occurring before fertilisation thus preserving fertilising functionality [247].

All these processes are needed to create sperma-
toza that are competent to fertilise an ovum when they are transported from the vagina to the fallopian tube. Rapid transport without the spermatozoa under-
going these changes would deliver incompetent spermatozoa unable to fertilise.

One possible criticism of the importance of vaginal tenting to reproductive fitness is that it will only be most effective when coitus is performed in the face-
to-face or missionary position. Coitus with ejaculation in the rear entry would allow a greater likelihood of semen falling onto the cervix thus negating the delay. This may well, however, mean that fertilisation
in this position becomes more difficult. However, the missionary position is regarded by many, if not the most, as the basic one for achieving pregnancy. The answer to the critics is that ‘no evolved biological mechanism can be effective and can ensure reproductive fitness in every contingency. Biological adaptation can serve only one particular set of conditions there are always selective compromises’ [163].

Finally, while the elevation of the cervix by vaginal tenting is the major mechanism by which spermatozoal transport is delayed other mechanisms may also be involved. There is evidence, admittedly in a single case, that uterine motility is inhibited after orgasm [250] and that genital muscular reflexes are suppressed [163,205].

V. TIMING OF THE FEMALE ORGASM AND REPRODUCTIVE CONSEQUENCES?

The female orgasm can occur at three particular time points during coitus, these are:

i) before ejaculation occurs,

ii) during ejaculation,

iii) after ejaculation.

Clearly the first scenario will not influence the immediate transport of spermatozoa as there are none to transport. Baker & Bellis [251] proposed, however, without any experimental measurements, that such an orgasm would upsuck the acidic vaginal fluid making the cervical fluid hostile to sperm and could thus influence subsequent sperm uptake. This scenario obviously overlooked the fact that vaginal tenting in the fully sexually aroused state would have removed the cervical os from any contact with the vaginal posterior floor. Sexual arousal per se has no effect on the pH of cervical fluid it being unchanged from the basal values [233].

While orgasm can occur simultaneously with male ejaculation, scenario ii), its likelihood is low as most males ejaculate before women have their coital orgasms. Moreover, as the semen coagulates at ejaculation the relative immobile spermatozoa are trapped and uncapacitated so little effective transport into the cervix/uterus would occur. By far the most prevalent coital scenario will be that of iii), female orgasm after ejaculation. Not surprisingly, a study of women who were desirous of becoming pregnant indicated that they had their coital orgasms after their partner’s ejaculation [252].

A highly contentious proposal was that women could consciously reduce the amount of semen leaking from their vagina (termed ‘flowback’) thus controlling the amount of semen retained which would aid fertilisation from a chosen partner by the timing of their orgasm during coitus [251,253]. Low sperm retention was claimed to be associated with female orgasms earlier than 1 minute before the ejaculation whereas maximum retention was said to occur with orgasms from greater than 0 to 1 minute after ejaculation. The effect only lasted for 1 minute before ejaculation to 45 minutes after. These studies and the statistics used have been heavily criticised by Lloyd [234] who does not think that they can be relied on.

VI. OTHER PROPOSED REPRODUCTIVE FUNCTIONS OF THE FEMALE ORGASM

Various postulated functions for the female orgasm were collected by Levin [178]. Those that could have a bearing on reproduction were a) to create lassitude in order to keep the female horizontal thus delaying the occurrence of gravity-created ‘flowback’ of semen and the subsequent sperm loss, b) to release antidiuretic hormone (ADH or vasopressin) for the possible contraction of uterine and vaginal smooth muscle and to inhibit urination and thus any subsequent sperm loss from a need to urinate shortly after coitus with ejaculation, c) to release oxytocin for a possible bonding effect, d) because of the difficulty in creating orgasm through coitus per se, orgasm, when so induced, acts as a ‘Mr Right’

Box 4

- Sexual arousal increases vaginal lubrication which partially neutralises its basal acidity facilitating sperm survival and increases its oxygenation facilitating their function.

- Vaginal tenting – the elevation of the cervico-uterine complex from the posterior vaginal wall delays sperm transport.

- The delay is essential to allow seminal decoagulation which frees sperm allowing contact with semen pre-capacitation and capacitation factors to make the sperm functional for fertilisation.

- Proposed rapid uptake and transport of sperm by systemic oxytocin-induced uterine contractions at orgasm is unnecessary as sperm is effectively and rapidly transported by spontaneous contractions of the uterine archimyometrial smooth muscle layer.
indicator aiding in creating a strong pair-bond with the male, e) to create the loss of body boundaries and separateness allowing a unique merging or fusion with the chosen coital partner g) to resolve uncomfortable pelvic vasocongestion (fullness). Though these are mostly speculative.

**H. PATHOPHYSIOLOGY OF FEMALE SEXUAL DYSFUNCTION (FSD)**

It is evident from the physiological descriptions above that changes of the the female physiology and/or anatomy may play a role in pathophysiological processes of and in some cases lead to FSD. However, as most research in FSD has focused on psychological and relational aspects of risk factors for FSD there is limited evidence for into what extent pathophysiological changes predispose for and elicit sexual problems in women and often physiological, psychological and relational factors will interact.

As described above possible pathophysiological processes may interact on several levels of the female physiology and have an impact on different phases of the sexual response: desire, arousal, and orgasm. The pathophysiological changes can be at many levels: the central or the peripheral physiology of the female sexual response and may, amongst many factors, include pathophysiological changes in cell-to-cell communication, changes in endocrine milieu, disruption in homeostasis of neurotransmitters and signal molecules, tissue damage, organ damage, vascular changes and neurological changes central and peripheral. However it is important to keep in mind that women with impaired physiology may have no sexual problems as well as women with no physiological changes can experience sexual problems.

Consequently, endocrine, neurological, cardio-vascular, dermatological, neurological and psychiatric conditions as well as cancer, medication and surgical procedures all have the potential to induce pathophysiological processes influencing the sexual function in women.

Most of the pathophysiological aspects of FSD are covered in other chapters and the reader is referred to these chapters for more information.

However, Female genital mutilation/cutting (FGM/C) is not addressed in other chapters and a short section is therefore added to this chapter.

**I. FEMALE GENITAL MUTILATION/CUTTING (FGM/C)**

Female genital mutilation/cutting is an intervention with irreversible change of the female genital physiology. Different types of FGM/C refer to a spectrum of surgical excisions [254,255] of the female genitalia as outlined in table 5.

The complications to FGM/C are at different levels and can be immediate and delayed:

The trauma itself, as it is often done in infancy or just before puberty and often without anaesthesia[255]. The immediate complications at the time of the procedure can be, hemorrhage, infection, shock, septicemia and death. Delayed gynaecological complications as menstrual disorders, hematocolpos, vaginal stenosis, infertility and sterility, incontinence, urethral stenosis, urinary infections, obstetric complications and fistula formations [254,256,257]. Psychological/psychiatric problems may also be a longterm complication, as depression, phobia, anxiety, depression and somatization [258] secondary to the physical and psychological trauma.

All these complications may evidently have a possible affect on womens’s sexuality, though only few studies have addressed this and the reports are conflicting. Besides the sexual problems induced by side effects as mentioned above the damaged or missing structures and tissues can have a impairing effect on sexual desire, arousal, orgasm, satisfaction and pain during intercourse. Depending on which type of circumcision that is performed, genital sensitivity and orgasmic response may be affected. In the study by Thabet & Thabet [259] it was shown that desire, arousal and orgasm were significantly negatively affected in the more mutilated women and women with complications to the intervention. In the study of Elsashar [258] on 200 circumcised women, they showed a significantly lower libido, arousal and satisfaction with husband and higher level of dyspareunia in FGM/C women compared to non-circumcised women. Furthermore the FGM/C women experienced significantly more gynaecological problems. In the study by Catania et al. [260] it is reported that 86% of the FGM women experienced orgasm in almost all cases. They conclude that cultural factors in combination with the changed physiology is determining whether the

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Type I</td>
<td>Known as ‘Sunna’ and involves the excision of the prepuce and/or partial or total clitoridectomy</td>
</tr>
<tr>
<td>Type II</td>
<td>Involves removal of the clitoris and partial or total excision of the labia minora</td>
</tr>
<tr>
<td>Type III</td>
<td>Known as the ‘pharaonic’ and involves clitoridectomy, and excision of the labia minora and majora and reapproximation of the cut ends (infibulation)</td>
</tr>
<tr>
<td>Type IV</td>
<td>Any other form of genital manipulation, e.g burning, pricking, or piercing</td>
</tr>
</tbody>
</table>

**Table 5: Female genital mutilation/cutting. Genital mutilation classifications. Adapted with permission from [255]**
woman can reach an orgasm, but also underlines that one explanation may be that not all erectile tissue necessarily is removed during the FGM/C and that the vestibular bulbs are still preserved and functioning as erectile organs.

In conclusion FGM/C is a devastating intervention with serious risk for the women's general and sexual health and with a direct impact on the genital physiology.

I. INTERACTIONS BETWEEN PHYSIOLOGICAL AND PSYCHOLOGICAL STATES OF WOMEN'S SEXUAL RESPONSE

Until now the chapter has focused on physiology and pathophysiology of women's sexual response, but it is clear there is an interaction between physiology and psychology in the sexual response, and recently growing evidence has shown a gender difference in this interaction.

Among women, there is a lower degree of correspondence between the physiological and psychological states of sexual response, termed concordance, than is typically observed among men. Similarly, low agreement has also been observed between physiological responses and psychological traits, namely sexual orientation, particularly among heterosexual women, a phenomenon termed nonspecificity.

The potential for low concordance and nonspecificity of sexual response are examples of the relative independence between physiological, psychological, and behavioral aspects of women's sexuality. This section of the chapter examines current research on concordance and nonspecificity of women's sexual arousal within the broader context of implications for psychophysiological assessment of women's sexuality and sexual functioning, and for understanding the development and expression of female sexual orientation.

I. CONCORDANCE OF WOMEN'S SEXUAL AROUSAL

Psychological and physiological processes characterize human sexual response. Sexual arousal is an emotional state [261] and, similar to other emotions, sexual arousal possesses distinct antecedents (e.g., sexual stimuli) and patterns of expression (e.g., psychological, physiological, behavioral) serving to regulate behaviors fundamental to sexual reproduction [262].

The degree to which the individual's experience of sexual arousal corresponds with her physiological response (concordance) is a matter of interest to researchers and practitioners in sexual medicine, since subjective (or self-reported) experience and genital measures of sexual arousal do not always agree. Knowing the extent of concordance, and identifying factors that moderate subjective-genital agreement, informs our understanding of the best methods to assess each aspect of sexual response, and models of sexual response and sexual dysfunction.

The most frequently cited moderator of concordance is gender, such that men show significantly greater concordance than women. A recent meta-analysis of the sexual psychophysiological literature concluded that, across 134 studies assessing subjective and genital sexual responses, the gender difference in concordance was a robust phenomenon that was not accounted for by methodological or statistical factors [263].

First, agreement between actual genital arousal and self-reported arousal in women is not zero; the average correlation reported by Chivers and colleagues was +.31 for agreement between subjective state of sexual arousal and actual genital response, and +.20 for agreement between perception of genital arousal and actual genital response. Physiological sexual response is, therefore, positively related to subjective experience of and awareness of genital sexual arousal in women [263].

Second, it is notable that the relationships between subjective experience of sexual arousal and actual physiological response are significantly greater than the relationship between awareness of genital response and actual physiological response [263]. This suggests that women's experience of sexual arousal is not primarily related to experience of physiological responding and is mediated by additional cognitive and emotional mechanisms. It is not clear how much appraisal of subjective sexual arousal is influenced by perception of genital responding, or vice versa, but these measures are highly positively correlated in women [264]. That these two self-report measures differ in their relationship with psychophysiological measured genital sexual arousal suggests there is a difference between experiencing sexual arousal and perceiving physical changes.

Concordance between perception of genital response and actual genital sexual arousal is an index of interoceptive awareness, that is, the psychological capacity to perceive internal physiological changes. The tendency for women to demonstrate low sexual interoceptive awareness may result from the information women use to appraise their emotional state of sexual arousal; women attend more to external, situational cues when appraising their emotional states than men do [265]. The greater reliance on external information suggests that women's experience of sexual arousal is more influenced by their attitudes, beliefs, and values regarding sexuality, as well as immediate contextual factors such as sexual
stimulus properties and their appraisals of these properties [266].

Women’s concordance estimates can vary widely such that some women’s reports of sexual arousal are unrelated or even negatively related to genital responses, whereas other women show large and positive correlations between self-reported sexual arousal and genital vasocongestion [267]. This variability in women’s concordance estimates may reflect the multitude of psychological factors that influence women’s experience of sexual arousal more so than physiological factors, suggesting a role for individual differences in moderating concordance between self-reported and genital sexual arousal. This raises fascinating questions as to the origins of concordance among women and whether concordance is a desired state (see next section).

II. CONCORDANCE AND THE PATHOPHYSIOLOGY OF FEMALE SEXUAL RESPONSE

Cognitive models suggest that concordant sexual response is a desirable, or even necessary, state for satisfactory sexual functioning [268]. The potential for concordance to vary with sexual functioning has been demonstrated in studies of sexually dysfunctional women; women with sexual arousal problems report lower subjective sexual arousal to sexual stimuli in the laboratory, but typically do not show significantly lower genital responses when compared to women without sexual arousal problems [269,270]. Studies comparing the concordance of sexual responses of sexually functional and dysfunctional women have yielded mixed results: some report greater concordance among the functional women [269,271-275], some report negative concordance for the functional women [276-278], and one reported no group differences [279]. The strongest evidence in favor of lower concordance among women with sexual dysfunction comes from Chivers et al.’s [263] meta-analysis, which found lower concordance among women with sexual dysfunctions versus sexually-functional women.

Among sexually functional women, concordance may be related to better sexual functioning, such that women who show greater concordance also report greater frequency of orgasm during penile-vaginal intercourse, but not during other sexual behaviours [280,281]. Similarly, significantly positive concordance estimates have been obtained for frequently orgasmic women [282]. While orgasm frequency, particularly during heterosexual coitus, is an inadequate means of determining women’s sexual function, these studies do indicate an association between concordance and orgasmic frequency that suggests concordance may be a useful index of integration of physiological and psychology sexual information among women, and thus may prove to be a useful predictor of sexual functioning.

III. NONSPECIFICITY OF WOMEN’S SEXUAL AROUSAL

The relationship between the psychological and physiological sexual response, and psychological traits, like sexual orientation, also shows marked discordance in women. Gender differences have been observed in the relationship between self-reported sexual attractions (toward males or females) and patterns of genital and self-reported sexual arousal to female and male sexual stimuli; men’s sexual arousal patterns are very strongly associated with their self-reported sexual orientation, whereas women’s are not (see figure 19) [283-289]. Women’s genital arousal responses are less related to their sexual preferences; although a woman might report psychological (attraction, thoughts, self-reported sexual arousal) and behavioral preferences for women or men, her genital responses are not higher to sexual images of her preferred gender.

Women report increased sexual arousal to both preferred and non-preferred sexual stimuli [288,290-292], which suggests that their cognitive and affective responses to sexual stimuli are not dependent upon their sexual preferences, such as sexual orientation. Sexual desire, as evidenced by masturbation and partnered sexual behaviors, is also kindled by exposure to both preferred and non-preferred sexual stimuli [290] suggesting that, among heterosexual women, motivation for engaging in sexual behavior is also less dependent upon sexual preferences.

The nonspecificity of heterosexual female sexual responses measured using sexual psychophysiological methods is congruent with research in which other psychophysiological methodologies, such as electroencephalograms, fMRI imaging, and viewing time, were used to examine gender differences in the specificity of sexual responding [42,293-297]. For example, Wallen [298] reported that heterosexual women showed similar patterns of activation in brain areas associated with sexual arousal to both preferred and non-preferred sexual stimuli. Using still pictures of female and male nudes, Sylva et al. [42,294] have investigated the brain correlates of the specificity of women’s sexual response using fMRI to examine brain activity while processing still pictures of female and male nudes.

Contrary to data on peripheral genital responding, heterosexual and lesbian women’s brain responses showed specificity in areas associated with processing of visual stimuli and motivation, that is, greater response to stimuli matching a woman’s sexual orientation. Hypothalamic response, however, did not show category-specific response for either group.
Similar to the pattern of genital responses [288], specificity in amygdala function was found for lesbian women only; heterosexual women showed nonspecific amygdalar responses. The general pattern of results from these different lines of research demonstrates that specificity and nonspecificity of peripheral sexual responses are mirrored in central aspects of sexual functioning in women.

IV. NONSPECIFICITY OF SEXUAL AROUSAL AND WOMEN’S SEXUAL ORIENTATION

Research on the specificity of women’s sexual arousal converges with current models of female sexual orientation that emphasize flexibility in women’s sexual attractions and sexual identities. Flexibility refers to a pattern of intraindividual variability in sexual preferences, attitudes, and behaviors [266]. With respect to sexual orientation and identity, women are more likely than men to experience and express same-gender attractions and less likely to engage in exclusively heterosexual or homosexual sexual behaviors [217, 218, 266, 299-301], and women’s sexual identities show less temporal stability than men’s [302-307]. Diamond [308] has suggested that the processes underlying romantic and affectionate bonding are not intrinsically gendered toward females or males, and that romantic and affectionate feelings have the capacity to kindle sexual desire, particularly among women. Therefore, a woman’s sexual desire

Figure 19: Heterosexual women’s and men’s mean genital responses, in standardized z-scores (top panel), and self-reported sexual responses, in percentage increase from baseline (bottom panel), to various categories of stimuli.

Error bars represent the 95% confidence interval for the mean. E=exercise; M=masturbation; I=intercourse; C=control; NH=nonhuman; FM I=female–male intercourse. The stimulus category “Intercourse” in the male and female panels represents responses to depictions of two men and two women, respectively, engaged in intercourse. Figure adapted with permission from [288]
for another woman may emerge from a close emotional relationship instead of from sexual attraction to and arousal by women. Self-report data on the development of female sexual orientation support this proposition; women report that social and emotional factors are more salient than sexual arousal to the development of their sexual interests in either the same gender [305, 306] or opposite gender [309]. Nonspecific sexual responding may increase the potential for flexibility in women’s sexuality because patterns of sexual arousal do not constrain women’s sexual behavior, feelings, or identity.

V. NONSPECIFIC SEXUAL RESPONSE AND INFERENCES ABOUT WOMEN’S SEXUAL INTERESTS AND DESIRES

The potency of stimuli depicting any sexual activity to evoke genital response, regardless of the actors portrayed or context of the sexual activity [288] (Figure 19) is also highlighted in studies where women show physiological sexual responses to other clearly nonpreferred sexual stimuli, such as films of nonhuman sexual activity [287, 288] and sexual threat stimuli [285, 291, 310-312] In these studies, although women demonstrated significant increases in vaginal vasocongestion to nonpreferred sexual stimuli, they did not also report significantly greater self-reported sexual arousal to these stimuli compared to their preferred sexual stimuli.

Overall, current research suggests that little can be inferred about a woman’s sexual orientation or motivation from her genital responses alone. Some have proposed that physiological sexual response in women is an automatic reflex that is elicited by sexual stimuli before conscious appraisal of a sexual stimulus as being sexually arousing or preferred [313-315]. Genital response precedes subjective sexual arousal [316], is evident within seconds of the onset of a sexual stimulus [317], and can occur in the absence of subjective experience of sexual arousal [287].

Primary sexual cues, such as sexual activity [288], may initiate reflexive vasocongestion, leading to vaginal lubrication, and preparing the genitals for possibly sexual activity. Reports of women’s genital response and orgasm during sexual assault [182] and research showing that women experience genital responses to sexual threat stimuli suggests that genital response under conditions of nonpreferred sexual stimuli may be typical in women. For this reason, inferences regarding a woman’s sexual desire and relative sexual attractions based solely on her genital responding would very likely be inaccurate.

VI. CONCLUSION/SUMMARY

Gender differences exist in the relationships among psychological, behavioral, and psychophysiological aspects of sexuality, with greater flexibility observed in women. Low concordance between genital and psychological measures of sexual arousal is typical for women and not necessarily indicative of problematic sexual functioning. Nonetheless, there is some evidence that higher concordance may be associated with better sexual function (in terms of orgasm frequency during sexual intercourse). Concordance may, therefore, be a useful measure of the integration of physiological and psychological sexual response in research on sexual functioning. Women show nonspecific sexual responses, with respect to their sexual orientation; this effect is most pronounced in heterosexual women, and under certain stimulus conditions. The potential for discordance between physiological sexual response, psychological states of sexual arousal, and psychological traits, such as sexual orientation, strongly suggests that objective measures of sexual response should not be used in isolation to draw conclusions about women’s sexuality.

Box 5

- Gender difference in concordance; women show lower agreement between physiological and psychological aspects of sexual response than men.
- Concordance is variable in women, suggesting that individual differences, such as sexual functioning, moderate agreement between physiological and psychological aspects of sexual response.
- Gender difference in specificity of sexual response; men’s responses are category-specific and women’s are nonspecific, with respect to sexual orientation.
- Nonspecific sexual responding may underly flexibility in women’s sexual attractions.
- Female genital response is a reflexive response to exposure to any sexual stimulus depicting sexual activity, whether preferred or not.
- Nonspecific genital vasocongestion suggests that genital response is not a valid indicator of sexual desire or sexual orientation.
Recommendations for future research in physiology and pathophysiology of women's sexual function and dysfunction. It is recommended that future research focus on

- Sexual brain development and how extrinsic factors can alter it
- Neuroimaging of sexual function and dysfunction
- Central and peripheral neuromodulators and their interactions
- Integration of central and peripheral mechanisms
- Interaction between physiological and psychological mechanism

In recent years there is considerable and growing interest in using neuroimaging techniques to explore and understand the cerebral correlates underlying the sexual response. These techniques are powerful tools that are capable of providing a great deal of information on brain activity in response to sexual stimuli as has been summarized in this chapter. However, there are many limitations and potential pitfalls that one should be aware of when planning a study using these tools or even when reading a literature report describing results of a functional brain imaging study.

Use the appropriate technique

- [15O]-H2O PET is less sensitive to head motion than other techniques, but has relatively poor spatial and temporal resolution.
- BOLD fMRI offers good spatial and temporal resolution with exquisite sensitivity for detecting areas of brain activation, but is not sensitive to mental and emotional states that develop over minutes (like sexual arousal?). BOLD scanning loses sensitivity with stimuli > 1 minute.
- PET-signal is not stable over time because of radioactive decay and a single bolus infusion of isotope.
- BOLD signal is unreliable in air-tissue transition zones like the medial temporal lobe and the ventral prefrontal cortex adjacent to air-filled paranasal sinuses, because of magnetic susceptibility effects that cause rapid decay of T2*.

Multi-subject experiments are the rule

- In a single subject the level of activation is small and there are many sites of brain activation. Multi-subject studies will show which sites have high reproducibility and are likely to be connected to the (sexual) task, thus enhancing the power of the study. A typical multi-subject (BOLD) fMRI study comprises 10-20 subjects. For multi-group studies, 15 subjects per group are usually necessary. The number of subjects needed to yield an expected effect size may be calculated using the freely available tool G-power (http://www.psycho.uni-duesseldorf.de/aap/projects/gpower/).

Carefully attention to experiment design is essential

VSS

- Have good arguments for choosing videos versus still pictures. If video is used with BOLD fMRI, the duration of each video block should be as short as possible, ideally < 1 minute. Mode and duration of the stimuli will bias the activation pattern.
- Validate the effectiveness of the chosen stimuli (and the paradigm) outside the scanner in a separate group of subjects.
- Appropriate control stimuli should be chosen for a selected (sexual) activation task. Inappropriate, neutral or mildly pleasant control stimuli may result in considerable non-specific activation due to differences in emotionality produced by disparate stimuli.
- Check to determine whether subjects were attentive to the stimuli, e.g. by instructing them to pay attention to certain features in the stimuli and then to either respond to these during scan or answer a questionnaire at end. Number of correct responses can be used to validate attentiveness.

Sexual consummation

- Decide the type of genital stimulation to
use. The selected stimulus should induce as little head motion as possible.

Sexual arousal assessment

- Many tools are available to assess perceived level of sexual arousal that may be used during scanning or at end of scan (i.e., perceived level of arousal questionnaire). Note that rating process itself if performed during scan may cause distraction. For fMRI and objective sexual arousal (e.g., vaginal photopletysmography), make sure that devices you want to use are MR-compatible (are not paramagnetic).

Subject cohort(s)

- Subjects should be matched as closely as possible on gender, sexual orientation, menstrual cycle phase, age, handedness, etc. to reduce statistical noise in the data. If not possible remember to collect information on heterogeneity.

Limit head motion

- MAJOR LIMITATION of fMRI technique. A priori limits for head motion should be set and images that exceed these limits should be removed from data set. Translational and rotational head motion can be easily measured and can be used to remove motion-related noise in the data. Motion correction software should be used to align remaining images within data set. If task-induced head motion correlates with the model (such as for sexual consummation study), these procedures can become problematic since such correlated motion may remove ‘true’ task-related activity or introduce “false activations”.

Analysis strategies

- Parametric: Most widely used. Assumes brain activity correlates with pre-defined model and/or behavioral parameters.

- Non parametric: may be used to find brain activation patterns uncorrelated with a model or behavioral parameters that were nevertheless important during the experiment. Is particular to find sites where activation sites/patterns are correlated with each other (network) rather than with the model.

Analysis software

- There are many available software packages commonly used to assess functional neuroimaging data sets.

  - SPM: free download at http://www.fil.ion.ucl.ac.uk/spm/. Uses Matlab for calculations (version 6.5 or higher).
  - FSL: free dowload at http://www.fmrib.ox.ac.uk/fsl/. Requires Linux or Linux virtual machine (Vmware).

Non parametric

  - SnPM: free download at http://www.sph.umich.edu/ni-stat/SnPM/. Requires SPM to be installed.
  - GIFT: independent component analysis, plug in for SPM
  - MELODIC: independent component analysis, part of FSL toolbox

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Committee 23

Endocrine Aspects of Women’s Sexual Function

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Endocrine Aspects of Women’s Sexual Function

MARGARET E. WIERMAN, ROSELLA E. NAPPI, NANCY AVIS, SUSAN R DAVIS, FERDINAND LABRIE, WILLAM ROSNER, JAN L. SHIFREN

INTRODUCTION

Although our understanding of the physiology of sexual function in women is limited, there has been a renewed interest in the role of estrogens and testosterone in normal sexual functioning in women. Endocrine changes during aging as well as endocrine disorders may either directly or indirectly modulate sexual function by altering sex hormones, or by impacting on vascular, neurogenic and/or psychologic factors. This review will outline our current state of knowledge concerning the impact of the hormonal changes across the lifespan or those due to endocrine disorders on female sexual function and information on the risks and benefits of hormonal treatment.

I. REVIEW OF THE LIMITATIONS OF PAST AND CURRENT SEX STEROID MEASUREMENTS AND REFERENCE RANGES FOR WOMEN

1. PROBLEMS OF QUALITY CONTROL, ACCURACY, AND SENSITIVITY FOR TESTOSTERONE ASSAYS (LEVEL 1 EVIDENCE)

Like those in the physical sciences, we should insist that there be a fixed traceable standard for all measurements. The International Organization for Standardization (ISO) defines “traceability” as the property of the result of a measurement or the value of a standard whereby it can be related to stated references….through an unbroken chain of comparisons all having stated certainties.” [1] This definition forms the basis for accuracy-based proficiency testing. Although this is easier said than done, it can and has been done for a number of important analytes [1]. For testosterone and estradiol proficiency testing in the United States, however, the principle of traceability is not followed. Rather, analytes embedded in a synthetic matrix are sent to client laboratories for assay; the laboratories’ competences are not evaluated by the accuracy of their results but rather by a comparing their results to others using the same method. If a clinical laboratory changes instruments, new assays on the same patient cannot be compared to previous ones with confidence. Epidemiologic studies dealing with these hormones cannot be compared to another in which a different instrument/method was used. Nor can a new study by the same investigator be compared to a previous one if the original methods have become obsolete.

a) Total Testosterone (T)

In 2005, The College of American Pathology (CAP) sent multiple unknown samples to over 1,000 participating laboratories to measure total testosterone[2]. The mean levels of total T ranged from 33 to 772 ng/dL in the tested specimens and revealed a 2-fold difference in peer group means across all levels of total testosterone. More strikingly, for samples in the mid-normal range for women, the spectrum of results obtained (mean=32.7 ng/dl), was 7-100 ng/dl! Alternatively a single laboratory can compare the accuracy, sensitivity and reproducibility of immunoassays for testosterone with one another, and with a mass spectroscopy-based method. This approach has been the basis of a number of excellent studies [2-9]. The profound lack of accuracy, sensitivity and reproducibility of most immunoassays for testosterone is graphically illustrated by comparing 10 immunoassays [8] to a method based on mass spectroscopy (MS). For the higher values of T, e.g. in the male range, there was at least a relationship between the MS-based method and the immunoassays. However, this was not true for values below about 8 nM, i.e. levels seen in the plasma of women and children. The disagreements are severe enough to render current immunoassay results, in women and children, are virtually useless. Since normal women, both pre- and postmenopausal, have a plasma testoster-
one concentrations less than about 2.5 nM[10], it is clear that methods better than current automated immunoassays are needed to establish normal ranges. Together, these data suggest that prior studies attempting to correlate T levels with sexual function may not have been sensitive or specific enough to detect changes in women across the lifespan.

**b) Free Testosterone (FT)**

Testosterone binds SHBG and albumin. In men, albumin binds 50%, SHBG binds 48% and 2% is free; in women the respective percentages are 66%, 33% and 1%.[10]. The unbound portion, free testosteron (FT) and/or that bound to albumin, is often considered the moiety that gets into the cell and results in androgenic effects. The situation is more complicated than that [11, 12] but, as a practical matter, FT often correlates better with the hyperandrogenic state of the patient than does total testosterone [13]. The optimal method to measure FT is disputed and the advantages and disadvantages of each method have been recently reviewed. Importantly, all measurements of FT depend, among other things, on an accurate determination of total T (see discussion above). The measure of FT using a direct immunoassay has been soundly rejected in the literature [2, 14-17] and ought not to be used.

In the US, the Centers for Disease Control and The Endocrine Society have partnered to develop traceability in the measurement of testosterone and to invite the clinical laboratory community to join in the effort [18].

A number of laboratories are focusing on the use of mass spectroscopy-based methods to assay testosterone in biologic fluids [9, 19]. The various methods differ somewhat, particularly in how the sample is treated before entering the mass spectrometer. Although the agreement among MS-based methods is much better than among immunoassays, compared either to each other or to MS-based methods, there is as yet no universally accepted method. However, compared to immunoassays, the agreement above 5 nM is excellent and below this concentration, is significantly better than any of the immunoassays.

**2. RECOMMENDATIONS ON TESTOSTERONE ASSAYS**

As the methods for the measurement of testosterone gain the accuracy, sensitivity, and reproducibility that are necessary, normal ranges for women will have to be ascertained across the life span, across the menstrual cycle and among various ethnicities. The study of testosterone in women then will be able to proceed on a firm and rational basis. We therefore recommend the use of new assays to reassess changes in testosterone levels across the lifespan and their relation to sexual function and dysfunction (Grade A).

We recommend the use of total T, in an assay of optimum sensitivity and specificity, and SHBG to calculate FT to assess plasma androgens (Grade A).

**3. THE PROBLEMS OF QUALITY CONTROL, ACCURACY, AND SENSITIVITY FOR ESTRADIOL ASSAYS (LEVEL 1 EVIDENCE)**

**a) Total Estradiol (E2)**

The state of affairs with respect to estradiol is similar to that for testosterone. In postmenopausal women, where E2 levels are routinely <15 pg/ml, the risk of breast cancer and vertebral and/or hip fracture, may vary with E2 concentrations that are below the sensitivities of current commercial assays [20]. Other circumstances requiring more sensitive assays include: pubertal disorders; estrogens in men; monitoring of E2 in the context of antiestrogen therapy (e.g. aromatase inhibition), and research in Alzheimer’s disease and cardiovascular disorders [21]. Immunoassays for E2 lack the sensitivity, and hence the accuracy, to quantitate E2 in plasma at the concentrations present in the circumstances described above[22]. The CAP does “peer group” proficiency testing for estradiol[23]. The lowest sample distributed, 70 pg/ml, is substantially greater than the values seen in men and postmenopausal women. Even so, the overall coefficient of variation of 66.4%, and the overall ratio of highest to lowest value of 70 on the same sample suggests the need to improve these assays at low concentrations.

**b) Free estradiol**

Like T, E2 is bound to SHBG and albumin in plasma. A major difference in binding constants results in a quite different distribution of the steroid in its major three physical states. In men, about 78% of E2 is bound to albumin, 20% to SHBG and 2% is free whereas in women the respective percentages are 61%, 37% and 2%[10]. There has been substantially less investigation of physiology/disease with free E2 as an endpoint. Like T, its estimate depends upon an accurate assay for total E2, leading to the same major difficulties seen with FT assays. LCMS based methods for E2 have been cumbersome [22, 23], and until recently were not optimized for routine clinical use or for large epidemiologic studies. Of late there has been a substantial effort to modify the methods to increase both their sensitivity and throughput [19, 24-28]. Little data are available for estrone (E1) or other estrogens.

**4. RECOMMENDATIONS FOR ESTRADIOL ASSAYS**

We recommend that E2 levels across the lifespan be assessed with the newer assays to test whether levels correlate with female sexual function or dysfunction (Grade A).
5. THE POTENTIAL IMPACT OF INTRACRINOLOGY AND FEMALE SEXUAL DYSFUNCTION (LEVEL 1-2 EVIDENCE)

a) Overview

Primates have adrenals that secrete large amounts of the inactive precursor steroid DHEA which is converted into active androgens and/or estrogens in specific peripheral tissues [29, 30]. Since estrogen secretion by the ovaries stops at menopause, a major source of androgen and estrogenic precursors in women after menopause is DHEA of adrenal origin. There is also a significant decrease of androstenedione (a proximate precursor of both estrogens and testosterone) secretion by postmenopausal ovaries. This change, coupled with a marked reduction in the formation of DHEA by the adrenals with age [31], results in a parallel fall in the formation of androgens and estrogens in peripheral target tissues for want of appropriate precursors and/or reduced activity of converting enzymes.

Classically, the effects of sex hormones were assumed to be secondary to the ovarian secretion into the plasma, followed by their uptake by an appropriate target tissue. Thus, one could assess their activity by measurement in peripheral plasma. Local biosynthesis and action of prohormones that can be converted into androgens and estrogens in target tissues termed “intracrinology” may bypass the exposure of other tissues to the hormones [29]. This process may be important in normal physiology, i.e. aromatization of prohormones to estrogens in the brain or androgenic precursors in the vagina. Alternatively, risks may be increased by local biosynthesis of sex hormones, e.g. increased aromatization of androgens to estrogens in breast tissue. Data on the conversion of DHEA to active sex hormones in target tissues have raised the possibility of its use as a prohormone replacement therapy[32].

II. ROLE OF ESTROGENS IN FEMALE SEXUAL FUNCTION AND DYSFUNCTION: EVIDENCE FROM LOW ESTROGEN STATES AND EFFECTS OF ESTROGEN TREATMENT

1. WHAT IS THE EVIDENCE THAT ESTROGENS PLAY AN IMPORTANT ROLE IN FEMALE SEXUAL DYSFUNCTION?

With the menopausal transition, women often experience cognitive changes, mood instability, night sweats and disrupted sleep [33]. Urogenital atrophy results in dyspareunia which may adversely impact on sexual function. Although vasomotor symptoms generally improve with time, in the absence of treatment urogenital atrophy may worsen with time since cessation of menses[34]. Vasomotor symptoms are more severe with surgical than with naturally occurring menopause, likely due to the abrupt decline in estrogens at the time of bilateral oophorectomy (BSO) [35-39]. One difficulty of using menopause as a model for studying the effects of estrogen deficiency and treatment on sexual function is that T levels also change, in some but not all studies [40-42]. Naturally menopausal women have gradual changes in their T levels with aging; surgically menopausal women experience an approximate 50% decrease in circulating concentrations at the time of bilateral salpingo-oophorectomy (BSO)[37, 38, 43-46]. Surgical menopause also is an imperfect model for studying the effects of estrogen on sexuality, as most women undergoing hysterectomy and BSO have underlying uterine pathology, e.g., fibroids, pelvic pain or dysfunctional uterine bleeding; thus, sexual function may improve with treatment of the underlying gynecologic problem, independent of hormonal status [35, 47]. Alternatively, BSO may be unwelcome, imposing premature infertility and negatively affecting sexual self image and function.

Most evidence supports an important role for estrogens in healthy sexual functioning, principally by treating bothersome vasomotor symptoms and maintaining vaginal health. Estrogen deficiency results in sexual dysfunction if vaginal atrophy and dyspareunia occur, often leading secondarily to decreased sexual interest, arousal and response [34, 48, 49]. Sexual sensitivity of genital and non-genital skin is also linked to estrogen status. Vasomotor symptoms with associated sleep disruption, fatigue and impaired quality of life also will have a negative effect on sexual function [34, 50] Estrogen therapy may improve sexual function by treating vaginal atrophy and bothersome hot flashes and night sweats [51-53]. To summarize, a significant direct effect of estrogen on sexual interest, arousal and orgasmic response, independent of its role in treating the foregoing menopausal symptoms, is not supported by current evidence.

2. EVIDENCE FROM OBSERVATIONAL STUDIES IN SURGICALLY MENOPAUSAL WOMEN (LEVEL 2 & 3 EVIDENCE)

Women who undergo BSO prior to natural menopause experience an abrupt decline in plasma estrogens [36-38, 44, 54, 55]. The remaining estrogens present after BSO results from peripheral aromatization of adrenal prohormones. Optimally, oophorectomized women should be compared to hysterectomized women who retain their ovaries. Studies are imperfect, however, as the indications for surgery, the surgical procedures, and the accompanying testosterone deficiency following oophorectomy may impact sexual function post-operatively.
In the Maryland Women's Health Study, over 1,000 women were interviewed before and after hysterectomy. Although 44% of the women had concurrent BSO, improvements in sexual functioning post-operatively were observed. The majority of women (88%), however, were taking hormone therapy (HT) post-operatively. Thus, the independent impact of estrogen deficiency on impaired sexual function could not be assessed. Predictors of post-hysterectomy low libido were pre-hysterectomy low libido and depression [36]. In a retrospective study that controlled for post-operative estrogen therapy, approximately 100 women ages of 47-55 years were evaluated 2-6 years after hysterectomy. Comparisons were made between oophorectomized women not using estrogen therapy (ET), those using ET, and non-oophorectomized women. There were no differences in frequency of intercourse or orgasm, dyspareunia, arousal, or partner satisfaction between groups [44]. Non-estrogen-treated oophorectomized women had significantly worse scores for depression, anxiety, and psychological well-being compared to intact women, but these problems were not apparent in oophorectomized women receiving estrogen. Since this study was not randomized, however, symptoms may have influenced the prescription of ET to the women and thus affected the outcomes. In summary, the ability to draw conclusions about the effects of estrogen on sexuality from studies of oophorectomized women is limited; women with higher sexual function preoperatively are less likely to elect BSO at the time of hysterectomy [54], and women with problems are more likely to elect post-operative ET.

3. EVIDENCE FROM CLINICAL TRIALS OF ESTROGEN THERAPY IN SURGICALLY MENOPAUSAL WOMEN (LEVEL 1 EVIDENCE)

To assess the effects of estrogen and progestin therapy on sexual behavior, 49 women who had undergone hysterectomy with BSO were randomized in a double-blind, placebo (PL)-controlled cross-over study to 3 months each of ethinyl estradiol (EE), levonorgestrel (LNG), EE + LNG or PL [56]. Comparing estrogen-containing regimens to PL, estrogen treatment was associated with significantly greater sexual desire, enjoyment, orgasmic frequency and lubrication. Of note, hot flashes occurred without HT use, and a significant effect of hot flashes on orgasmic frequency was observed. These data support a detrimental effect of menopausal symptoms on sexual function, which may be treated effectively with HT.

4. EVIDENCE FROM OBSERVATIONAL COHORT STUDIES IN NATURALLY MENOPAUSAL WOMEN (LEVEL 2 EVIDENCE)

There are conflicting results on the role of estrogens in sexual functioning as women undergo natural menopause. Most of the studies are cross-sectional, although several cohort studies examine the association between change in E2 levels and change in sexual functioning over the menopausal transition. The Penn Ovarian Aging Study was a longitudinal population-based cohort designed to examine the associations between variability and changes in reproductive hormones and symptoms associated with ovarian aging [57]. Women were aged 35-47 at baseline, had normal menstrual cycles, with yearly hormonal measurements and various measures of sexual functioning assessed. At 4 years in 326 women, there were no significant differences in E2 levels between women with and without self-reported deceased in libido[57]. However, depression, vaginal dryness and children living at home were associated with decreased libido. A major limitation of this study is that only 7.7% were classified as late menopausal and 4.3% as post menopausal.

Followup analysis [58] using the Female Sexual Function Index assessed desire, arousal, lubrication, orgasm, satisfaction, and pain. Sexual dysfunction was defined as a total Index score of 20 or below. Although sexual dysfunction increased over the transition, there was no association between sexual dysfunction and any of the domain scores and estrogen level or variability. Predictors of sexual dysfunction were absence of a sexual partner, high anxiety, and children under the age of 18 living at home. A limitation of this study is the small number of women classified with dysfunction (N=102, 33% of sample). Freeman and coworkers [59] examined the association between hormones and reports of decreased libido or interest in sex over 9 years of follow-up of this cohort. A moderate association between lower mean levels of E2 and reports of decreased libido or interest in sex 9 years of follow-up. Freeman and coworkers also found a significant association between E2 and E2 variability and change in libido.

In the Melbourne Women’s Health Project (MWHP), a population-based longitudinal study of Australian-born white women aged 45-55 at baseline, annual assessments included hormone levels, the Short Personal Experiences Questionnaire and collection of a wide range of covariates. Among 336 women followed for 8 years, there was a significant association between decreasing E2 levels and sexual responsiveness (interest, arousal, enjoyment, orgasm) and dyspareunia, but not frequency of sexual activity [60]. Sexual responsiveness was adversely affected by aging and menopause transition[33]. Those women who had lower baseline scores on the Short Personal Experiences Questionnaire (SPEQ) had lower E2 levels, and lower scores over time.
correlated with lower E2. Further studies examining relationship factors [61], showed that while E2 was related to libido, sexual responsiveness and dyspareunia, prior function and relationship factors were more important than hormones.

More recently, Modelska et al.[62] examined the association between E2 and changes in sexual function over 3 years in postmenopausal women who participated in the raloxifene evaluation trial. All women were sexually active and at least 2 years post menopause with a mean age of 65 years. E2 was assessed at baseline and dichotomized at 20 pmol/l. The sexual history questionnaire was administered at baseline and at 3 years. At baseline, women with E2 levels <20 pmol/l reported significantly greater discomfort during sex and inability to relax, but there was no difference between groups in reported enjoyment, satisfaction, orgasm, interest, arousal, or difficulty during intercourse. After 3 years, women with E2 > 20 pmol/l had significantly less decline in sexual enjoyment, satisfaction and sexual feelings. There was no difference from women with low E2 in orgasm, lack of interest, inability to relax, arousal difficulty, or discomfort during intercourse, while pain was more evident. Limitations of the study included that only 121 women showed a decline in sexual functioning and E2 was measured only at baseline.

Thus, some evidence supports the hypothesis that decreases in estrogens may be associated with changes in sexual functioning after menopause. Relationship factors and physical or mental health contributed to sexual functioning to a greater degree than either menopausal status or hormonal levels. Limitations of sex hormone assay sensitivity at lower levels used in all of these studies may have influenced the lack of clear correlation with hormonal levels (discussed in section I).

5. EVIDENCE FROM OBSERVATIONAL CROSS SECTIONAL STUDIES IN NATURALLY MENOPAUSAL WOMEN (LEVEL 2 EVIDENCE)

A cross-sectional study of 141 women aged 40-60 with natural menopause with a current partner showed that no hormonal measure (including E2 and estrone (E1)) correlated with various measures of sexuality [63]. Predictors of sexual functioning were the quality of the relationship and measures of wellbeing. Similarly, Gallicchio et al.[64] evaluated 265 perimenopausal sexually active women aged 45-54 and found no association between overall sexual satisfaction and plasma E2, E1 or the free estrogen index (FEI). However, depressive symptoms and poor overall health were related to lower satisfaction.

More recently, Avis and coworkers [48] reported cross-sectional analyses from the Massachusetts Women’s Health Study of the association between log E2 and various domains of sexual functioning among 200 women aged 51-61. Log E2 was negatively related to reporting pain during or after sexual intercourse in both univariate and multivariate analyses. Plasma E2 was not significantly related to a decline in sexual interest with age or satisfaction with current sexual relationship, desire, frequency of sex, arousal, or difficulty reaching orgasm. Factors predictive of better sexual functioning were physical and mental health, marital status (or new partner), and not smoking. Similarly, in the Study of Women’s Health Across the Nation (SWAN), no association between sexual desire or arousal and E2 levels was detected among 2981 pre and perimenopausal women [40].

Thus, the literature in natural menopausal women provides conflicting data concerning the correlation of plasma E2 levels and sexual function. Issues related to sensitivity of sex hormone assays in postmenopausal woman must be considered (discussed in section I). Observational studies show that factors relating to mental and physical health and the partner relationship are more consistently related to sexual function than levels of estrogens.

6. EVIDENCE FROM CLINICAL TRIALS OF ESTROGEN THERAPY IN NATURALLY MENOPAUSAL WOMEN (LEVEL 1&2 EVIDENCE)

The effects of a transdermal patch containing 0.014 mg/day of transdermal E2 on sexual function in 417 postmenopausal women was studied in a randomized, double-blind, placebo-controlled 2-year trial [65]. Participants were aged 60-80 (mean age 66.8) with an intact uterus, and not recruited on a basis of sexual dysfunction. Outcome measures included frequency of sexual activity and the Medical Outcomes Study Sexual Problems Index, which includes items on loss of sexual interest, inability to relax and enjoy sex, difficulty becoming aroused, and difficulty in having an orgasm. Women assigned to E2 had significantly greater improvement in vaginal pain/dryness, but did not significantly differ in frequency of sexual activity or other sexual function domains. A study of 223 postmenopausal women aged 45-65 “requiring hormone replacement therapy for climacteric symptoms” randomly assigned to 0.05 mg/day of transdermal estrogen reported greater sexual satisfaction and fewer sexual problems than those in the placebo group[66]. Women in the E2 group reported greater satisfaction with frequency of sexual activity, greater sexual enjoyment and decreased dyspareunia, but no difference in sexual arousal or orgasm [44]. A double-blind, randomized, placebo-controlled study was performed in 285 sexually active postmenopausal women aged 45-65 (mean age 54 years) of daily oral low dose conjugated estrogens (0.45 mg) plus progesterone (1.5 mg) combined with 1g conjugated estrogen vaginal cream (0.625 mg) [67]. Treated women showed a significant decrease
in frequency of dyspareunia and an improvement in sexual interest, frequency and pleasure of orgasm compared both to baseline and placebo group, but no effect on frequency of sexual intercourse. Because this trial used a combination of oral estrogen/progestin therapy and vaginal estrogen cream, it is not possible to determine the relative impact of systemic vs. local estrogen treatment.

Thus, numerous studies of ET, whether oral, transdermal, or vaginal have demonstrated positive effects on vaginal pain and dryness. However, results on other aspects of sexual functioning are more mixed, with stronger results found for younger women. It is not surprising that results are less consistent for other aspects of sexual functioning, as observational studies show that sexuality in women is particularly complex and influenced by multiple hormonal and non-hormonal factors.

7. SUMMARY OF DATA ON NATURAL MENOPAUSE AND ESTROGEN

a) Estradiol levels and Sexual Function (Level 2 evidence)

Limitations of current research include: use of single hormone levels compared to fluctuations, variability in sexual functioning questionnaires with analysis of changes in individual items or a composite index, and also variability in the covariates included in analyses. Despite these differences, several patterns can be discerned. Studies of older women show consistent benefit. This would suggest that postmenopausal E2 levels may be more critical to sexual functioning than those during the transition. Studies including relationship factors and physical or mental health observe that these factors contribute more to sexual functioning than either menopausal status or hormonal levels.

b) Risks of systemic HT and ET (Level 1 and 2 evidence):

Daily estrogen/progestin therapy is associated with an increase in cardiovascular events in older postmenopausal women [68, 69]. Recent guidelines support the limited use of Estrogen alone in hysterectomized women and estrogen-progestin in women with intact uterus for women reporting menopausal symptoms (mainly hot flushes) across menopausal transition and beyond. The benefit-risk ratio for menopausal HT is favorable during the years close to menopause (the so-called "window of opportunity") but decreases with aging and with time since menopause in previously untreated women [68, 70, 71]. Estrogen or estrogen/progestin therapy should be used at the lowest dose for the shortest duration that meets treatment goals. Any woman treated with ET or HT requires ongoing monitoring, which should include annual breast and pelvic examinations, mammography, and evaluation of abnormal bleeding.

c) Benefits and risks of low dose vaginal ET (Level 2 evidence):

Vaginal estrogen preparations are effective and generally safe for treating urogenital atrophy and can improve vaginal lubrication and reduce dyspareunia [72, 73]. Vaginal ET products include Conjugated Estrogens, estriol (E3) (not available in the US market), and E2 at doses to avoid systemic absorption [74]. Vaginal E2 is contraindicated in women with a history of breast cancer because of the risk of increases in circulating estrogens [75, 76]. All of the low-dose vaginal estrogen products are equally effective at the recommended doses. The choice of therapy should be guided by clinical experience and patient preference. Local ET should be continued for women as long as bothersome symptoms remain.

8. EVIDENCE FROM STUDIES OF WOMEN WITH PREMATURE OVARIAN FAILURE (POF) (LEVEL 2 & 3 EVIDENCE)

Evaluating the effects of estrogens on sexual function using models other than natural or surgical menopause is difficult. Premature ovarian failure, menopause prior to the age of 40 years results in estrogen deficiency symptoms, but with the added psychological burden of unanticipated menopause and infertility. Testosterone levels also are lower, further complicating the assessment of the role of estrogens in sexuality in women with POF. In addition, POF may be associated with other autoimmune diseases, or be due to chemotherapy, pelvic surgery or radiation. The associated psychological burden and the underlying disease may independently alter sexual function.

Sexual well-being was compared in 81 women with POF and 68 age-matched control women with regular menstrual cycles [77]. Forty-eight of the women with POF (59%) were using HT. As expected, women with POF not using HT had significantly lower levels of E2 than HT-users, while those using HT had lower bioavailable T levels than HT non-users, likely due to the effects of oral ET on SHBG. Overall, women with POF were less satisfied with their sexual life. They had fewer sexual fantasies, masturbated less frequently, and reported less arousal, lubrication and increased genital pain during sexual activity. Sexual desire and frequency were similar to control women, although sexual satisfaction was lower [77]. Women with POF reported more anxiety, depression, somatization, sensitivity, hostility and psychological distress. HT users had higher scores for anxiety, depression and psychological distress than non-HT users, without differences for sexual activities, problems and satisfaction. A limitation of the study is that women with problems may be more likely to elect HT use.
9. EVIDENCE FROM WOMEN WITH HYPOTHALAMIC AMENORRHEA (LEVEL 4 EVIDENCE)

Women with hypothalamic amenorrhea experience estrogen deficiency due to lack of hypothalamic-pituitary function and anovulation [78-81]. There may be urogenital atrophy, but vasomotor symptoms do not usually occur. Hypothalamic amenorrhea typically is caused by excess stress, intensive exercise, eating disorders, or other physiologic or psychologic conditions. Sexual function has been poorly investigated in these conditions. Since HT typically is given to young women with hypothalamic amenorrhea to preserve bone mineral density, maintenance of vaginal health would be an expected benefit. No intervention studies, however, have been performed on the effects of HT on sexual function in women with hypothalamic amenorrhea.

10. EVIDENCE FROM STUDIES OF WOMEN USING, SELECTIVE ESTROGEN RECEPTOR MODULATOR (SERMS) AND USE OF AROMATASE-INHIBITORS (AIS), ORAL CONTRACEPTIVES AND TIBOLONE

a) SERMs and sexual dysfunction (Level 2 and 3 evidence):

Tamoxifen and raloxifene are selective estrogen receptor modulator with estrogen agonistic activities on bone and antagonistic activities on breast [82]. Tamoxifen is used in the treatment of patients with breast cancer and for chemoprophylaxis in high risk women. Tamoxifen causes estrogenic changes in the vaginal epithelium [83, 84] increased vaginal discharge, [85] but can also cause pain, burning, or discomfort with intercourse [86]. Tamoxifen increases SHBG [87]. In breast cancer survivors older than age 50, tamoxifen did not worsen sexual function [88]. Major confounding influences related to sexual dysfunction in breast cancer survivors include concerns about relationships, depression and increasing age[84].

Raloxifene is a newer SERM currently approved for the prevention and treatment of postmenopausal osteoporosis, and the prevention of breast cancer in high-risk women [82]. Raloxifene also increases SHBG levels. In healthy postmenopausal women, raloxifene lowered neither total nor free T, or DHEAS levels (Shifren et al unpublished observations). Others however found modest changes in prohormones and adrenal steroids after one year of raloxifene 89. The effects on sexual function was assessed in a study of a large, multicenter, RCT of the effects of 3-years of raloxifene on 600 postmenopausal women with osteoporosis compared to 300 receiving placebo [90]. No differences between groups were observed in sexual desire, frequency, enjoyment, satisfaction, orgasm or sexual problems. The effects of local vaginal ET with and without concurrent raloxifene were examined in two RCTs. In women treated with either conjugated estrogen cream [91], or an estradiol vaginal ring [92], raloxifene vs. placebo treatment resulted in similar improvements in signs and symptoms of vaginal atrophy, suggesting raloxifene did not block local E effects.

b) Aromatase-inhibitors (AIs) and sexual dysfunction (Level 4 evidence)

Examining the effects of aromatase inhibitors is an interesting way to try to understand the impact of estrogen deficiency on female sexuality. Inhibiting the conversion of androgens to estrogens in postmenopausal women results in profound hypoestrogenemia by eliminating peripheral estrogen synthesis [93]. Limitations of this model are that these subjects are being treated for breast cancer. This diagnosis and the effects of chemotherapy, radiation and mastectomy also have independent effects on sexual function. Women using AIs commonly experience urogenital atrophy, dyspareunia and bothersome vasomotor symptoms and arthralgias. As estrogen therapy is contraindicated, treatment of hot flashes with non-hormonal alternatives and regular use of non-hormonal vaginal moisturizers and lubricants is advised to improve sexual function in these women. Until such time as additional safety data are available on the effects of vaginal estrogen in women on AI therapy, routine use of local estrogen in women on AIs cannot be recommended.

c) Oral contraceptive use and sexual function (Level 2 evidence)

Oral contraceptives used by premenopausal women comprise supraphysiologic levels of estrogens in combination with supraphysiologic progestins of variable androgenic activity to block ovulation [94]. The estrogenic components increase SHBG. Some have argued that the nonandrogenic progestins increase SHBG further and some suggest that these compounds may in turn decrease free T levels and impact on female sexual function[95]. Comparison studies across OCPs are limited with few prospective randomized controlled studies [96-98] Over the years changes in dose and types of both estrogens and progestins confuse the issue. Clinically, practitioners may choose to change the type of OCP administered in a premenopausal woman with sexual dysfunction.

d) Tibolone as postmenopausal therapy and sexual function (Level 1&2 evidence)

Tibolone is a synthetic steroid not available in the US which is metabolized to two estrogeneric metabolites, 3α and β, which then circulate predominantly in their sulfated inactive forms [99, 100]. These metabolites
become estrogentially active when desulfated by the sulfatase enzyme in target tissues. Tibolone itself and its 3β metabolite is also converted to a Δ4-isomer which can activate both the progesterone and androgen receptor. Tibolone lowers SHBG and increases circulating free testosterone, adding to its androgenicity [101]. Tibolone alleviated postmenopausal vasomotor symptoms and improves urogenital atrophy by increasing the vaginal maturation index [102, 103] and was effective in postmenopausal women with symptoms of sexual dysfunction. [99, 104-106]. In a recent multicenter, double-blind, randomized, clinical trial tibolone improved sexual wellbeing in postmenopausal women with low libido with improvements in desire arousal, satisfaction and receptiveness compared to those receiving transdermal estrogen-progestin therapy [107]. Some concerns have been raised regarding the use of tibolone and risk of ischaemic stroke in women over 60 years [100].

11. RECOMMENDATIONS

a. Based on a systematic review of the clinical trials evidence of estrogen therapies for treating sexual problems in women, we conclude the following:

The decision to institute any hormonal therapy must be individualized and the patient adequately informed about risks and benefits (Grade A).

Estrogen therapy (ET) may improve sexual function in those postmenopausal women with vaginal atrophy (Grade A).

A significant effect of estrogens on sexual interest, arousal and orgasmic response, independent of its role in treating menopausal symptoms, is not supported by the majority of current evidence (Grade B).

Tibolone is effective for the treatment of menopausal symptoms and vaginal atrophy, and in many women results in improved sexual function (Grade A). Potential risks of treatment, including a possible increased risk of ischaemic stroke, must be balanced against potential benefits.

Women with premature menopause should use hormone therapy until the age of natural menopause, unless medically contraindicated (Grade C) [70, 108].

b. Based on expert opinion, findings from various studies and understanding of hormone physiology and pathophysiology, we conclude the following:

Due to the known potential risks, systemic ET may be recommended for the treatment of bothersome vasomotor symptoms in healthy menopausal women, while local vaginal estrogen therapy may be preferred for the treatment of isolated vaginal symptoms (Grade A).

As oral estrogen therapy results in increased levels of SHBG and resulting low free testosterone levels [109], transdermal ET may be considered when ET is elected and sexual function is a concern, although no RCTs to date have compared sexuality with oral vs. transdermal ET (Grade C).

III. ROLE OF TESTOSTERONE IN FEMALE SEXUAL FUNCTION AND DYSFUNCTION: EVIDENCE FROM LOW TESTOSTERONE STATES AND EFFECTS OF TESTOSTERONE TREATMENT

1. EVIDENCE FROM POPULATION-BASED, EPIDEMIOLOGIC STUDIES (LEVEL 3 EVIDENCE)

If androgens serve an important role in female sexual function, then clinical states associated with decreased androgens should be associated with sexual problems including low desire, arousal, and orgasmic response. Low androgen states include aging, surgical menopause, premature ovarian failure, hypopituitarism and adrenal insufficiency. Although natural menopause is not associated with an abrupt decline in androgen concentrations, menopausal women have decreased T levels compared to younger women due to aging [41].

Observational studies assessed the effects of age and menopausal status on sexual function. A population-based study estimated the prevalence of self-reported sexual problems accompanied by personal distress in approximately 31,000 U.S. women aged 18 years and older. Although low desire, arousal and orgasm difficulties increased with age, distressing sexual problems peaked in women aged 45-64 and actually were lowest in the elderly women [50]. A community-based, cross-sectional study of approximately 3,500 European and U. S. women showed that the prevalence of low desire increased with age, while the proportion of women distressed about their low desire decreased with age [110]. A survey of 2207 US women, using the same validated questionnaire confirmed an increased prevalence of low sexual desire with increasing age, and among surgically and naturally menopausal women compared to premenopausal women. Distress about low desire in older and younger women with relatively recent BSO was similar to age matched women with intact ovaries. Women older than 45 years who underwent oophorectomy prior to menopause had fewer complaints of low desire as compared to women of similar age but with intact ovaries [111].

Several population based studies have assessed the direct relationship between T levels and sexual function. In a population-based, longitudinal study, 438 Australian women were studied for eight years across the menopausal transition [60]. Sexual re-
responsiveness was adversely affected by both aging and the menopausal transition, but all other aspects of sexual function, including frequency and libido, were adversely affected by becoming postmenopausal. In a cross-sectional analysis of data from 201 women aged 48-58 years in this same cohort, sexual responsiveness again declined with age, but T levels were not associated with any aspects of female sexual functioning [112]. A limitation of this study is that T was measured by a kit that lacked the sensitivity to measure T levels <20ng/dl, commonly seen in women over the age of 45. A study of androgen concentrations and self-reported sexual function in a community-based, cross-sectional study of 1423 Australian women ages of 18 to 75 years [45] found no clinically significant relationships between a low score on any domain of sexual function and a low total T, FT or androstenedione level. There were associations between a plasma DHEAS level below the 10th percentile and low scores on several sexual function domains; however, the majority of women with low DHEAS levels did not have low sexual function [45].

2. EVIDENCE FROM OBSERVATIONAL STUDIES IN OOPHORECTOMIZED WOMEN (LEVEL 2 & 3 EVIDENCE)

To evaluate the isolated effects of T loss, oophorectomized/hysterectomized women should receive ET and be compared to hysterectomized women who retain their ovaries. However, the indications for surgery, the surgical procedures, the decision to keep or remove the ovaries and the accompanying estrogen deficiency or ET all may impact sexual function post-operatively. In the Maryland Women’s Health Study, over 1,000 women were interviewed before and after hysterectomy [36]. Despite the fact that approximately 44% had concurrent BSO, significant improvements in sexual functioning post-operatively were noted. Oophorectomy, however, was associated with a 2.7-fold increase in the likelihood of not experiencing orgasms 12 months post-operatively [36]. Similar results were found in a retrospective Swedish study of approximately 700 women under age 55 who underwent hysterectomy for benign disease. Although the majority of women reported an improved sexual life following hysterectomy, oophorectomized women receiving ET were significantly less likely to report improvement and more likely to report a worsening than non-oophorectomized women [37].

In a retrospective study that controlled for post-operative estrogen therapy use, approximately 100 women between the ages of 47-55 years were evaluated 2-6 years following hysterectomy [44]. No differences in frequency of intercourse or orgasm, dyspareunia, arousal, or partner satisfaction was observed between groups. The only difference noted was decreased pleasure from intercourse in the oophorectomized women. No correlations were found between sexual function variables and androgens, including total T, free T, A or DHEAS. A prospective, observational study of the effects of oophorectomy on sexual function in 362 perimenopausal women scheduled for elective hysterectomy for benign diseases also identified lower post-operative sexual function scores in women who underwent concurrent BSO compared to women with intact ovaries [54]. Interestingly, sexuality scores were unchanged by surgery in the hysterectomy plus BSO group, so these differences were all due to lower pre-operative sexuality scores in women electing BSO. In addition, there were no correlations between changes in androgen levels post-operatively and changes in sexuality measures. Two further prospective studies failed to show a worsening of sexual function after elective hysterectomy in women followed for 3 years [113, 114].

In a national sample of approximately 952 US women with sexual partners, the prevalence of HSDD was compared between premenopausal, naturally postmenopausal and surgically postmenopausal women [115]. Although the prevalence of HSDD was significantly greater in young surgically postmenopausal women (aged 20-49 years) than in age-matched premenopausal women, there was no significant difference in HSDD prevalence between surgically and naturally postmenopausal women, aged 50-70 years. Observational studies of oophorectomized women, therefore, are not generally consistent with the hypothesis that decreased T levels affect sexual function in women.

3. EVIDENCE FROM CLINICAL TRIALS OF T THERAPY IN POSTMENOPAUSAL WOMEN (LEVEL 1 EVIDENCE)

Two Cochrane reviews have examined the benefits and risks of testosterone plus HT versus HT alone for peri- and postmenopausal women. The most recent analysis included 35 studies with 4768 participants [116, 117]. Most trials included only postmenopausal women, both naturally and surgically menopausal. Many different testosterone regimens were examined, both pharmacologic and physiologic dosing regimens. The median study duration was 6 months (range 1.5-24 months). The major methodological limitations described were differences in diagnostic criteria for study entry, a lack of a washout period in the cross-over studies and attrition bias. The pooled estimate from the clinical trials suggested that the addition of testosterone to HT regimens improved sexual function scores and number of total satisfying sexual episodes in postmenopausal women who were able to have some (2-3 / month) satisfying sexual episodes at baseline [117]. Beneficial effects were seen for the composite sexual function score and domains of sexual activity, coital frequency, responsiveness, and libido. Adverse effects included
decreases in high-density lipoprotein (HDL) cholesterol levels with oral therapy that was not observed with transdermal treatment and increased incidence of excess hair growth and acne. Discontinuation from treatment was similar between groups. There was insufficient evidence of a treatment effect for perimenopausal/premenopausal women or for other outcomes examined, including wellbeing, fatigue, menopausal symptoms, cognition, body composition and bone health. Another large review of safety data also concluded that except for hirsutism and acne, the therapeutic administration of testosterone in physiologic doses was safe for up to several years [118].

Several recent clinical trials add clarification of the role for T therapy in improving female sexual function. A series of double-blind, randomized, placebo-controlled studies examined the efficacy and safety of a transdermal T patch (300 mcg) in postmenopausal women with HSDD [119, 120]. Two multicenter trials evaluated 24 weeks of testosterone patch treatment in over 1,000 surgically menopausal women with HSDD receiving concomitant ET. At baseline, women reported approximately 3 satisfying sexual episodes in 4 weeks, with a mean increase of approximately 2 events in testosterone-treated women, compared with an increase of 1 satisfying event with placebo. A 450 mcg patch, however, did not confer benefit beyond placebo [121] suggesting the lack of a dose response effect of the T patch.

In addition to increased sexual activity, significant improvements were seen in all domains of sexual function in T-treated women compared with placebo, including desire, arousal, orgasm, pleasure, concerns, responsiveness, sexual self-image and distress. More women receiving testosterone reported a "meaningful overall benefit" compared with placebo-treated women. Despite the low absolute change in satisfying sexual events, the degree of benefit seen with T therapy in these studies was "clinically meaningful" to women [122].

Adverse event profiles were similar except for a higher incidence of unwanted hair growth in T-treated women. Other androgenic adverse events such as acne, alopecia or voice deepening were more common in T-treated women, though not statistically significant. The safety and efficacy of transdermal T (300 mcg) for 24 weeks was also studied in a double-blind, placebo-controlled, randomized trial of 549 naturally menopausal women with HSDD on concomitant estrogen therapy. Total satisfying sexual episodes increased significantly from baseline in testosterone-treated women compared with placebo (2.1 episodes vs. 0.5) [123]. Small but statistically significant improvements also were seen in all domains of sexual function assessed, including sexual desire and personal distress.

As almost all studies of T therapy were performed in the setting of concurrent ET, a double-blind, placebo-controlled trial examined the safety and efficacy of testosterone treatment for HSDD in 814 postmenopausal women not receiving ET [124]. Women were randomized to 150 or 300 mcg of transdermal T per day or placebo; efficacy was measured to week 24 and safety to week 52. The increase in the 4-week frequency of satisfying sexual episodes was significantly greater in the women receiving 300 mcg T per day compared with placebo (2.1 episodes vs. 0.7), although not in the group receiving the lower T dose (150 mcg per day) [124]. Both doses resulted in significant increases in desire and decreases in distress compared with placebo. Androgenic adverse events, principally unwanted hair growth, was higher in the women receiving 300 mcg T compared with placebo, although rates of acne, alopecia and voice deepening were similar among the three groups [124]. Vaginal bleeding was more common in the 300 mcg T group, though no cases of endometrial hyperplasia or carcinoma were diagnosed. There were no differences between groups in vital signs or weight, serum lipid or lipoprotein profiles, measures of carbohydrate metabolism, liver function, or other laboratory tests. Breast cancer was diagnosed in four women who received testosterone, as compared with none who received placebo (p=NS).

Transdermal T has been studied in only limited populations of premenopausal women with HSDD [125]. Premenopausal women ages 30-45 with HSDD were randomized to treatment with a testosterone cream (10 mg/d) versus placebo in a double-blind crossover study for 12 weeks with a 4-week washout. Thirty one women completed the study. Testosterone treatment resulted in statistically significant improvements in the composite scores and many subscale scores of both the Psychological General Well-Being Index and the Sabbatsberg Sexual Self-Rating Scale. Resulting T levels were in the high normal to high range. In a larger randomized controlled trial, 261 women age 35 to 46 years were randomized to placebo or 3 different doses of a transdermal T spray [126]. Over the 16 week treatment period, the two higher doses were associated with a significant increase in satisfying sexual events compared with placebo.

Variable recommendations by international medical societies concerning T therapy in women have been published. In 2005, The North American Menopause Society concluded that postmenopausal women with decreased sexual desire associated with distress and with no other identifiable cause may be candidates for T therapy [127]. Transdermal formulations were preferred over oral products due to the absence of first-pass hepatic effects. Treatment was contraindicated in women with breast or uterine cancer, or in those with cardiovascular or liver disease. Women should be informed of all potential risks and that data on long term use were lacking.
Several epidemiologic studies have raised the concern with different conclusions [129-131]. The potential effects of T therapy on breast cancer science research and observational studies address cancer. Several thorough reviews of relevant basic women, including cardiovascular disease and breast are as yet unknown long term risks of T treatment in resolve with cessation of therapy. of greatest concern problems, which are easily recognized, treated, and but unwanted hair growth and acne are cosmetic adverse events appear to be increased with T use, however, showed a relationship with SHBG and cardiovascular event free survival [134]. Bell et al, current biochemical hyperandrogenemia was associated with more angiographic CAD and worsening cardiovascular event free survival [134]. Bell et al, These epidemiologic data may reflect the detection of an aging cohort of women with prior premenopausal hyperandrogenism and its associated insulin resistance. However, further studies are needed to balance the potential benefits and risks of long term T therapy in postmenopausal women.

5. RECOMMENDATIONS

a. Based on a systematic review of the clinical trials evidence of androgen therapies for treating sexual problems in women, we conclude the following:

The decision to institute any T therapy must be individualized and the patient adequately informed about known and potential risks and benefits (Grade A).

Testosterone patch therapy increases satisfying sexual activity, libido, arousal and orgasmic response in postmenopausal women with HSDD (Grade A).

Long term safety data for testosterone therapy are lacking, so additional safety data are required before long term use of T therapy in women can be recommended (Grade A).

Current data are not adequate to support the use of T therapy in premenopausal and perimenopausal women (Grade A).

Achieving physiological free T levels by transdermal delivery appears to be the best approach for minimizing the adverse effects of androgens (Grade C).

Relative contraindications to T therapy include androgenic alopecia, seborrhea or acne, and hirsutism (Grade C).

T therapy is relatively contraindicated in women with hyperlipidemia or liver dysfunction (Grade C).

T therapy is contraindicated in women with, or at high risk for, breast cancer, endometrial cancer or cardiovascular disease, pending additional safety data. The safety of T therapy in women with or at high

5. RECOMMENDATIONS

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The decision to institute any T therapy must be individualized and the patient adequately informed about known and potential risks and benefits (Grade A).

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Current data are not adequate to support the use of T therapy in premenopausal and perimenopausal women (Grade A).

Achieving physiological free T levels by transdermal delivery appears to be the best approach for minimizing the adverse effects of androgens (Grade C).

Relative contraindications to T therapy include androgenic alopecia, seborrhea or acne, and hirsutism (Grade C).

T therapy is relatively contraindicated in women with hyperlipidemia or liver dysfunction (Grade C).

T therapy is contraindicated in women with, or at high risk for, breast cancer, endometrial cancer or cardiovascular disease, pending additional safety data. The safety of T therapy in women with or at high
risk for cardiovascular disease, venous thrombotic event or breast cancer is unknown (Grade C).

b Based on expert opinion, findings from various studies and understanding of hormone physiology and pathophysiology, we conclude the following:

Any woman treated with androgen therapy requires ongoing monitoring, which should include annual breast and pelvic examinations, annual mammography, and evaluation for any abnormal bleeding. When T therapy is given, continuation for longer than 6 months should be contingent on a clear improvement in sexual function and satisfaction and absence of any adverse effects, considering the substantial placebo effects found in all studies to date. Women must be informed that data on long term safety are lacking. Physical examination at follow-up visits should include inspection of skin and hair for seborrhea, acne, hirsutism and androgenic alopecia which may appear very gradually. Laboratory monitoring should include total T and SHBG levels, and a calculated value for FT, with the goal of keeping these values within the normal range for premenopausal women. Whether a lower target level for older women should be advised remains unknown. Although no adverse effects on lipids have been found with androgen therapy, a lipid profile and metabolic screening should be considered.

IV. ENDOCRINE DISORDERS: EFFECTS ON FEMALE SEXUAL FUNCTION

1. HYPOPITUITARISM (LEVEL 2 EVIDENCE)

a) Evidence that supports the influence of pituitary hormone deficiencies on female sexual dysfunction.

Hypopituitarism is defined as multiple pituitary hormone deficiencies, either genetic or commonly after removal of a pituitary and/or hypothalamic tumor or radiation [136]. Combination of sex hormone, thyroid hormone, glucocorticoid and /or growth hormone deficiency may occur and require physiologic replacement. There are limited studies concerning sexual function in these patients. A 12 month randomized study in 51 women with hypopituitarism demonstrated improvements in mood and sexual function in addition to increased bone density, fat-free mass, quality of life but not cognitive function in women randomized to T patch [136]. These women had variable forms of estrogen replacement with either oral contraceptives or low dose ET. Side effects included 1/3 with hirsutism and 65% with skin irritation due to the patch. 38 women with hypopituitarism on standard hormonal replacement were randomized to DHEA (30mg/d if <45 and 20mg/d if >45) or placebo for 6 months [137]. Women on DHEA had improved alertness, stamina and initiative as perceived by their partners and a trend toward improved sexual relations (p=0.06). Increased interest in sex or activity at 6 months was noted in 50% of women receiving DHEA 30mg/d but none receiving 20mg/d. These data support a modest effect of aromatizable androgens or androgen and estrogen precursors (ie DHEA) on sexual function in women with hypopituitarism after optimization of standard hormonal therapies. Whether the effects are due to androgenic, estrogenic actions or both is unknown.

b) Recommendations

Women with hypopituitarism have profound estrogen and androgen deficiency and should be considered for therapy with ET and T therapy at least until the age of natural menopause, unless medically contraindicated (Grade B).

2. HYPERPROLACTINEMIA (LEVEL 2&3 EVIDENCE)

a) Evidence that supports the influence of elevated levels of prolactin on female sexual dysfunction.

Hyperprolactinemia may be due to physiologic, pharmacologic or organic causes [138]. Elevated levels of PRL inhibit gonadotropin releasing hormone (GnRH) pulsatility and thus ultimately decrease ovarian hormone secretion (estrogens, androgens). Hyperprolactinemia is observed in primary hypothyroidism and commonly with medications that inhibit dopamine tone such as the antidepressants and serotonin reuptake inhibitors [138, 139]. Elevated prolactin may alter libido via direct neuroendocrine effects (impaired negative dopaminergic and positive serotoninergic control of PRL release) and indirect endocrine mechanisms (i.e. secondary effects of hypoestrogenism) [140]. Although menstrual disturbances are a more common symptom than sexual dysfunction, hyperprolactinemic women without depression or other hormonal disorders reported lower scores for sexual desire, arousal, lubrication, orgasm and satisfaction in comparison with controls [141]. Hulter et al observed that 79% of 48 women with pituitary disease had a decrease in sexual desire, while problems with lubrication and orgasm were reported in 65% and 69%, respectively [142]. However, neither prolactin or T levels, but instead a normal pattern of menses, young age and intra-sellar tumor correlated with normal sexual desire and sexual function. In 109 women with hypothalamo-pituitary disorders, 63% had decreased sexual desire [142]. Altered sexuality was reported in 84% of the hyperprolactinemic women, but only in 33% of women with normal serum prolactin. Despite these ob-
servations, PRL-normalizing agents (bromocriptine, cabergoline) have not been evaluated as to potential beneficial effect on female sexual dysfunction [143].

Antipsychotic and neuroleptic drugs reduce sexual drive and may cause anorgasmia, in part related to drug-induced hyperprolactinemia, as demonstrated by less sexual dysfunction in patients treated with the so-called PRL-sparing drugs in comparison with those with a higher incidence of PRL elevation [144, 145]. Antidepressant agents such as SSRI>s may induce hyperprolactinemia and therefore impact negatively on sexual function [146, 147]. Decreased sexual drive and orgasmic disorder [148, 149] have been reported. These studies are limited by few containing proper control groups, variable dosages of agents and variability in underlying mood disorder.

b. Recommendations

Women with hyperprolactinemia may develop sexual dysfunction, especially loss of sexual drive and impaired orgasm, but it is unclear if these symptoms are independent of associated estrogen deficiency (Grade B). Studies are lacking to prove that lowering circulating prolactin levels improve sexual function in women.

3. THYROID DYSFUNCTION AND FEMALE SEXUAL DYSFUNCTION

Although the literature is replete on the effects of both hypothyroidism on menstrual cyclicity and fertility [150-152], there are no clinical studies on the effect of thyroid disorders on female sexual function. This is an area for future research.

4. EFFECTS OF ADRENAL DISEASE ON SEXUAL FUNCTION

a) Adrenal prohormones

Dehydroepiandrosterone (DHEA) is produced by the ovaries and adrenal glands whereas its sulphate ester, DHEAS, is produced primarily by the zona reticularis of the adrenal cortex [29, 153]. Together DHEA and DHEAS are the most abundant steroids in plasma, providing a large precursor reservoir for the intracellular production of androgens and estrogens in non-reproductive tissues. Thus DHEA and DHEAS are not androgens (ie bind to the androgen receptor to activate transcription) but are precursor hormones that are metabolized to androgens and estrogens in the brain, bone, breast and adipose tissue [154]. Serum levels of both DHEA and DHEAS decline with age in women independent of menopausal age [55].

b) Adrenal insufficiency and sexual dysfunction (Level 4 evidence)

Primary adrenal insufficiency is characterized by abnormally low, serum concentrations of DHEA and DHEAS. Secondary adrenal insufficiency is due to loss of pituitary ACTH production and may be isolated or with low T levels because hypopituitarism results in combined ovarian and adrenal insufficiency [155]. Adrenal insufficiency, irrespective of cause, has been associated with impaired quality of life, low libido and lack of wellbeing. However, there are no data comparing sexual function in women with adrenal insufficiency with normal age-matched controls using validated questionnaires.

c) Clinical trials of DHEA therapy in adrenal insufficiency (Level 1 evidence)

There are few, small studies of DHEA treatment to improve sexual wellbeing in women with adrenal insufficiency. In Addison’s Disease [156, 157], a randomized controlled trial (RCT) of DHEA 50mg/day versus placebo in 24 women demonstrated no improvement in sexual function [156]. Arlt et al. randomized 24 women with primary (n=14) and secondary (n=10) adrenal insufficiency to treatment with either 50 mg oral DHEA daily for 4 months or placebo in a double-blind, crossover trial [158]. Improvements in sexual function (thoughts, interest and satisfaction measured by a visual analogue scale) and mood were reported. However, more recent randomized studies have not shown benefit.

A randomized controlled trial of DHEA 50mg/day versus placebo for 12 months in 62 women showed no improvement in sexual function measured by a visual analogue scale [157]. Similarly, other groups reported no benefit of DHEA, 25mg/day for 9 months, on sexual function using the Norwegian version of the McCoy’s Sex Scale Questionnaire in a placebo-controlled, parallel group trial involving 39 women with primary and secondary adrenal insufficiency [159]. A placebo controlled trial for 6 months followed by 6-month open label phase of 38 women with hypopituitarism and secondary adrenal insufficiency [159]. A placebo controlled trial for 6 months followed by 6-month open label phase of 38 women with hypopituitarism and secondary adrenal insufficiency suggested that 20-30 mg of DHEA/day increased sexual interest and activity only during the open label phase with no significant change in quality of life in either phase of the trial [137]. No effect of DHEA 50mg/day on sexual function was found in a double blind crossover study of 15 patients with secondary adrenal insufficiency [160].

d) Recommendations

DHEA therapy is not currently recommended for women with primary or secondary adrenal insufficiency: the majority of clinical trials of DHEA replacement in women with primary or secondary adrenal insufficiency do not show any benefits on sexual function (Grade A).
5. EVIDENCE FROM WOMEN WITH ANDROGEN INSENSITIVITY SYNDROME (AIS) (LEVEL 4 EVIDENCE)

There are limited data concerning the sexual function of XY males with androgen insensitivity due to mutations in the androgen receptor [161, 162]. These subjects are phenotypically female with normal breast development, but variable shallow vaginal development which may impair sexual performance. Limited retrospective case series suggest these subjects have a heterosexual orientation and normal libido and orgasmic response under the influence of high estrogens with complete or partial absence of androgen action at all target tissues. This model suggests that androgens are not necessary for normal sexual function.

V. HORMONAL EXCESS STATES

1. POLYCYSTIC OVARIAN SYNDROME (LEVEL 3 EVIDENCE)

a) Current state of the field

Polycystic ovarian syndrome (PCOS) is the most common cause of female hyperandrogenism, occurring in 5-10% of premenopausal women [163]. Clinical manifestations of androgen excess (e.g. hirsutism, acne, seborrhea, alopecia etc) together with obesity and infertility may cause emotional distress, but data are limited concerning psychosocial and sexual functioning in PCOS. [164]. An increased risk for depressive disorders, particularly in women with higher body mass index (BMI) and evidence of insulin resistance, has been recently outlined. Anxiety, vulnerability to distress, abnormal eating attitudes coupled to body dissatisfaction and low self-esteem and quality of life have been also reported. In addition, PCOS women seemed to be less satisfied with their sex life and found themselves less attractive, presumably because of being frequently overweight and suffering from cosmetic androgen-related symptoms [165, 166]. The relationship between androgen excess in PCOS and sexual function has been difficult to study, probably as a consequence of the comorbid conditions which confound outcome measures. Indeed, PCOS women display a similar partner status and frequency of sexual intercourse in comparison with controls [167].

A recent study by Battaglia et al [168] failed to demonstrate any significant difference in clitoral circulation between women with PCOS and controls. Moderate hirsutism and hyperandrogenism in these women did not induce a sense of loss of feminine identity and had no impact on sexual self-worth and sexual satisfaction. Treatment of women with androgen excess using antiandrogens has produced mixed results in a small case series of women presenting with hirsutism (increased desire in 6 women and decreased desire in 13 women) [169], while the use of the insulin-sensitizer, metformin, improved the psychosocial, emotional and psychosexual situation of PCOS women [170], presumably because of the reduction in other clinical symptoms.

b) Recommendations

Overweight women with PCOS may have an increased incidence of sexual dysfunction mainly due to emotional difficulties related to clinical manifestations of androgen excess and obesity. (Grade C/D) These data have not been confirmed in lean PCOS women, suggesting that moderate hyperandrogenism alone may not significantly modulate sexual function. Further research is needed to understand if normalizing androgen excess and/or insulin resistance would improve sexual function in PCOS women.

2. SEX HORMONE PRODUCING TUMORS (LEVEL 3&4 EVIDENCE)

Many kinds of ovarian tumors produce estrogens or androgens. Sertoli-Leydig cell tumors is an example of an androgen-producing tumors that cause virilization [171]. Conversely, granulosa cell tumors and thecomas are well-known estrogen-producing tumors. Pediatric or postmenopausal women with estrogen-producing tumors present with postmenopausal bleeding or isosexual precocity. Other forms of sex hormone producing tumors are extremely rare [172]. Androgen excess from these tumors might be expected to result in a state of hypersexuality in women, but no studies on sexual function are available in women with sex hormone producing tumors [173]. Thus, this is an area for further research.

3. CONGENITAL ADRENAL HYPERPLASIA (LEVEL 2&3 EVIDENCE)

Congenital adrenal hyperplasia (CAH) refers to a family of inherited disorders in which defects occur in one of the enzymatic steps required to synthesize cortisol from cholesterol in the adrenal gland [174]. In 21-hydroxylase deficiency (21OHD), responsible for 90–95% of CAH cases, accumulation of precursors immediately proximal to the 21-hydroxylation step in the pathway of cortisol biosynthesis are shunted into androgen precursor pathway. Three forms of 21OHD CAH can be distinguished by clinical, hormonal, and molecular criteria: the classical salt-wasting, classical simple-virilizing, and nonclassical forms. Postnatal androgen excess leads to various hyperandrogenic signs that manifest from childhood to adulthood, depending on the severity of the 21OH enzyme deficiency [174]. Meyer-Bahlburg and coworkers [175] reviewed the sexual orientation in women with classical or non-classical CAH and reported that most women were heterosexual. The
rates of bisexual and homosexual orientation in their subjects were increased above controls in women with classical and nonclassical CAH, and correlated with the degree of prenatal androgenization. Limitations of this report include that this patient cohort was derived from a specialized referral base and may represent a biased group of subjects and lack appropriate controls. Importantly, the sexual functioning of women with non classical 21OHD did not differ from that of controls, unlike women with classical CAH who showed impaired sexual functioning, presumably as a consequence of disturbed body image, repeated genital examination and surgery [176, 177]. Retrospective qualitative data revealed a history of discomfort and social stress related to their extent of masculinization prior to treatment.

4. Recommendations

Caring for women with CAH requires careful individualized management, including appropriate therapy for their signs and symptoms of androgen excess as well as psychosexual counseling when needed (Grade C).

VI. CHRONIC ENDOCRINE DISORDERS

1. DIABETES (LEVEL 3 EVIDENCE)

a) Current state of the field

Women with diabetes have many factors potentially contributing to their risk of sexual dysfunction, including vascular, neurogenic, metabolic, sex hormone and psychologic abnormalities. Data on the incidence of female sexual dysfunction in diabetic women was recently reviewed by Bhasin and Basson [143]. The literature is limited by few studies with control groups, the poorly validated types of tools used to diagnose female sexual dysfunction, and the changing definitions of female sexual dysfunction from older to newer studies. The authors noted rates of decreased desire ranged from 9-60% in controls to 17-85% in female diabetics, and of decreased arousal from 41% in controls to 76%. Reduced lubrication was about 2-fold more common in diabetic all in but one study; pain and orgasmic difficulties were more prevalent in diabetics than nondiabetics. Overall dissatisfaction with sexual function ranged from 7-37% in controls to 42-52% in diabetics. A careful dissection of any differences in the incidence of or etiologies of sexual dysfunction in Type 1 compared to Type 2 diabetics was not examined in most studies. Importantly most studies did not separate pre- versus postmenopausal women and estrogen status was not controlled. Sexual dysfunction was consistently linked to comorbid depression.[143].

Several other studies have been published showing similar increased risks of sexual dysfunction in various populations [178 179], suggesting the incidence is independent of cultural norms. Studies have postulated altered reactive oxygen species activity in the mechanism underlying both male and female sexual dysfunction in diabetes [180]. A recent review of the literature of 400 citations concluded that research on sexual function in women with diabetes is limited, but multiple reports suggest that abnormalities in sex hormone levels contribute [181]. In contrast to men with diabetes and erectile dysfunction where the diabetic control and length of the disease correlate with incidence of impotence, no such correlation has been observed in women diabetics with sexual dysfunction. No intervention studies are available concerning changes in sexual function with aggressive treatment of vascular or metabolic derangements in women with diabetes. The impact on sexuality of living with a chronic, serious medical illness, and the confounding effects of obesity in many Type 2 diabetics should not be underestimated.

b) Recommendations

Women with Type 1 and Type 2 diabetes have an increased incidence of sexual dysfunction which may be due to metabolic, vascular, neurogenic, hormonal as well as psychological etiologies (Grade C). No studies are available concerning the impact of improved glucose lipid or hypertensive control or hormonal therapies on the sexual dysfunction in these patients. Thus, these women should be screened for sexual dysfunction. Further research is needed.

2. OBESITY AND METABOLIC SYNDROME (LEVEL 2-3 EVIDENCE)

a) Evidence that obesity influences sexual function

The metabolic syndrome (MetS) is a constellation of findings including central adiposity, insulin resistance, hypertension and various other clinical features. The International Diabetes Federation consensus definition for MetS includes a waist circumference >80cm in addition to 2 of the following factors: triglyceride >150mg/dl (1.7mmol/l), decreased high density lipoprotein cholesterol <50mg/dl (0.9mmol/l) or treatment for lipids, elevated blood pressure or treatment for hypertension, and/or elevated fasting serum glucose >=100mg/dl (5.6mmol/l) or known Type 2 diabetes [182]. Esposito initially described an independent effect of the MetS on the incidence of FSD in 100 premenopausal women with MetS compared to controls matched for age and BMI [183]. Sexual function was measured by the Female Sexual Function Index (FSFI). Ponholzer and coworkers recently performed a modified German Female Sexual Dysfunction (FSD) questionnaire

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on 538 women (mean age 44, 61% pre- and 39% postmenopausal women). Of the group, 18% had MetS[184]. FSD prevalence was 4.8% for disorders of low satisfaction and 39% for HSDD. The rate of these disorders increased with transition to menopause. There was no increased risk of disorders of arousal, pain or orgasm in this cohort. Impaired desire was present in 59% in premenopausal women with MetS compared to 32% of controls. In postmenopausal women, however, there was no effect of MetS on the incidence of FSD. Thus, although age increases the risk of FSD overall, the concomitant presence of MetS had a more profound effect on premenopausal women. No data are available concerning interventions to reverse MetS and incidence of FSD.

b) Recommendations:

Women with MetS may have an increased incidence of sexual dysfunction, which may be due to vascular, metabolic, neurogenic, hormonal, or psychosocial causes (Grade C). We recommend screening women with MetS for sexual dysfunction and study of treatment interventions; none are currently available in these patients.

Summary and Conclusions

This review has summarized the scientific evidence supporting the mechanisms by which hormonal changes associated with aging and endocrine disorders contribute to sexual dysfunction in women. Data on the impact of hormonal therapies in female sexual disorders has been discussed. Many studies suggest that plasma T and/or E2 concentrations do not correlate with female sexual function or dysfunction. However, the limitations of past and current sex steroid hormone assays and normal reference ranges for women suggest additional studies are needed. The potential importance of intracrinology, i.e. local production and action of hormones, on sexual function and the well documented age related decline in substrate precursor hormones remains unclear. Natural and surgical menopause and endocrine disorders that alter estrogens and androgen precursors may impact female sexual function. The consequences of hormone therapies in these states including, hypothalamic amenorrhea, premature ovarian failure, surgical and natural menopause and chemically induced estrogen deficiency with selective estrogen receptor modulators (SERMs) and aromatase inhibitors is variable but is indicative of benefits of low dose HT in individuals. Hypopituitarism, hyperprolactinemia, thyroid disorders and adrenal insufficiency alter a variety of hormones, each to a variable extent. Data are limited on the effects of therapies with estrogens, testosterone and DHEA in each of these disorders, but they may provide additional model systems for future interventional trials. Studies on the effects of hormonal excess observed in PCOS, hormonally active ovarian or adrenal tumors, congenital adrenal hyperplasia and obesity induced hyperandrogenism do not suggest that excess androgens and/or estrogens per se promote normal or hypersexuality, suggesting an optimal balance of hormonal milieu is critical to normal sexual functioning. Information on the effects of diabetes and metabolic syndrome on female sexual dysfunction suggest that the disorder is common in these populations, but no interventional trials have been performed show that improved metabolic control alters female sexual function.

Most importantly, the available literature emphasizes that hormones are only one component of the many factors that contribute to normal sexual function in women. It is hoped that this review of the state of the field will spur new research into the impact of hormones and endocrine disorders on female sexual dysfunction and additional research into the benefits and risks of hormonal therapies for these patients.

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Committee 24

Women’s Sexual Desire and Arousal Disorders

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REFERENCES
I. DEFINITIONS, EXPRESSIONS, AND PREVALENCE OF SEXUAL COMPLAINTS

1. DEFINITIONS OF SEXUAL DYSFUNCTION

Women’s sexual desire, arousal, and orgasm disorders have traditionally been conceptualized, studied, assessed, and often treated from a perspective which compartmentalizes them. This is reflected in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition text-revised [1] whereby Hypoactive Sexual Desire Disorder (HSDD), Female Sexual Arousal Disorder (FSAD), and Female Orgasmic Disorder (FOD) are discrete disorders with criteria and descriptions in the text that do not overlap and the explicit statement that diagnosis of another Axis I Sexual Dysfunction is permissible.

However, despite the common finding in recent population-based epidemiological studies in which low sexual desire is the most prevalent of concerns relating to women’s sexual functioning, women’s sexual complaints are rarely experienced as discreet entities and there is often comorbidity with impaired sexual arousal and orgasmic dysfunction. Due to these overlapping symptom criteria, it may be difficult to determine which sexual dysfunction is primary for a woman. The four DSM-IV categories pertaining to lack of desire, arousal, to orgasm problems or to sexual pain, are not independent. In clinical practice, classification is often based on the way in which complaints are presented [2]. For example, a recent study on Malaysian women found a high degree of overlap in the desire and arousal domains of the Female Sexual Function Index (FSFI) with both domains loading significantly onto one factor [3] (Level 3). A number of both qualitative and quantitative studies find comorbidity between desire and arousal [4-6] (Levels 2 and 3). In a qualitative study of women with and without sexual arousal disorder, both groups of women articulated great difficulty in differentiating sexual desire from arousal, and there was increasing confusion about this distinction as the interviews progressed [7] (Level 2). In reality, the distinction between subjective arousal and desire may be unclear at best. In part, this may be because women express difficulties differentiating desire from subjective arousal [7-9]. Also, some women report their experience of desire to precede arousal (mimicking the Human Sexual Response Cycle as conceptualized by Masters and Johnson [10]), whereas for other women, desire appears to follow arousal [8], as women do not seem to follow one universal sexual response cycle [11]. Treatment outcome research also highlights the overlap between phases of the sexual response cycle in that a psychological intervention for low desire also significantly improved subjective sexual arousal [12].

In research, the overlap between sexual desire and arousal is also evident. For example, some conceptualize sexual desire entirely as the cognitive component of sexual arousal [13]. Others prefer the term “arousability” in place of sexual desire as it reflects the notion that sexual desire is considered to be an early arousal process [14].

Over the years, many have criticized the DSM-IV-TR classification of sexual dysfunctions in women. Hartmann and colleagues [9] proposed that a new classification system for women’s sexual function be considered in light of this significant comorbidity. They suggested that sexual problems were not the result of a single phase of a “virtual response cycle,” but, rather, sexual problems may be due to a global lack of interest, arousability, and arousal. Thus, they suggested that sexual desire disorder be classified as (i) in combination with sexual arousal disorder, (ii) in combination with orgasmic disorder, (iii) associated with depressive symptoms, (iv) associated with low self-esteem, and/or (v) associated with partner conflict (Level 4). Although their idea was compelling
and supported by much of the literature and clinical findings, this is not the currently adopted system.

To illustrate the overlap between phases of the sexual response cycle, consider the following case example. Julie is a 44-year-old chartered accountant who was married for the past 15 years. Her children are 12, 10, and 7. She reported a decrease in her sexual desire and arousal shortly after the birth of her first child. Whereas in the past Julie would often initiate sexual contact, she increasingly found herself rejecting her husband’s invitations for sex, and avoiding sexual contact altogether. When she did engage in sexual activity (once/month compared to twice/week previously), she experienced only a minimal increase in subjective excitement, minimal genital sensations, and great difficulty in attaining orgasms. Intercourse was occasionally painful if she was inadequately aroused, though provoked vestibulodynia was ruled out. Her loss of sexual response was highly distressing and negatively impacted her mood and self-esteem.

2. CRITICISMS OF EXISTING DEFINITION OF HSDD

Criticisms of the DSM-IV-TR definitions of women’s sexual dysfunctions are considered here because the definitions of sexual dysfunction which are adopted by this classification system have a direct and profound impact on instrument development, epidemiological studies, treatment protocols, etc. Using DSM-IV-TR criteria (See Table 1), Julie would meet criteria for HSDD, FSAD, FOD, and possibly even Dyspareunia. The DSM-IV-TR [1] diagnosis of HSDD focuses on “persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity” which causes marked distress or interpersonal difficulty. This definition has been criticized as overpathologizing women on the basis that women themselves may not necessarily consider sexual fantasies and desire for sexual activity to be an index of their sexual desire. In a qualitative study of mid-aged women with and without sexual dysfunction, the majority of women did not mention fantasies in their narratives of desire, although, interestingly, the vast majority did endorse having fantasies when asked on a questionnaire [7]. It was suggested that rather than fantasy being an expression of desire, some women may deliberately evoke fantasy as a way to boost their sexual arousal. Another problem relates to the fact that although HSDD is defined as the lack of desire for sexual activity, when 3,262 multi-ethnic perimenopausal women were assessed, 70% reported desiring sex less than once a week; however, the majority (86 - 89%) were at least moderately to extremely emotionally sexually satisfied and reported moderate to intense physical pleasure [15]. Others have also found desynchrony between reported sexual satisfaction and frequency of sexual activity [16] (Level 2). With such a high proportion of sexually satisfied women, it is curious that their low frequency of desiring or engaging in sex would be considered dysfunctional. Similarly, among 5,892 partnered women with low desire, the majority (71.2%) were happy with the relationship [17] (Level 2). Collectively these studies suggest that women may experience a satisfying sexual life with a partner without the outright desire for sexual activity.

Complicating this issue of the validity of fantasy and desire for sex as a hallmark sign of sexual desire is the finding that clinicians and researchers may differ from patients in how they define sexual desire. For example, 401 women attending a British general practice clinic were asked if they thought they had any kind of sexual problem and how distressing it was for them. Based on responses to the Brief Index of Sexual Functioning for Women [18], 38% of women were diagnosed with at least one ICD-10 sexual dysfunction [19]. Among women with an ICD-10 diagnosis who also self-reported having a sexual problem, the prevalence dropped to 18%. The prevalence dropped further to 6% if women received the diagnosis, acknowledged it, and reported distress. There was more agreement between the diagnosis and self-report of problems for dyspareunia (74%) and vaginismus (77%) than for FSAD (38%) and HSDD (39%). A mere 48% of women given an ICD-10 diagnosis agreed that there was a sexual problem but 69% of women with no diagnosis agreed on the absence of a problem. Age, ethnicity, employment, and recent sexual activity were unrelated to these associations [19] (Level 3).

Another criticism of the DSM-IV-TR definition of HSDD relates to the implication that women experience a “spontaneous” sexual desire for sex. A large body of research [20-24] has supported an incentive-motivation model of sexual response which argues that all sexual desire is triggered (Level 2 and 3); therefore the notion of spontaneous sexual desire is nonsensical. Rather, several recent studies have illustrated the large number of cues that provoke sexual desire (125) and sexual activity (237) in women [25-26] (Level 2). Engaging in sexual activity in the absence of an identifiable external trigger (e.g., “because the opportunity presented itself”, “because I was in the mood”) was an unlikely reason women provided for having sex.

These empirical findings combined with the clinical observation that women (at least women in long-term relationships) report sexual desire as emerging during a sexual interaction after sexual arousal, led to the conceptualization of a new sexual response cycle [57-59] (Level 4). This model (Figure 1) proposes that women initiate sexual activity for any number of reasons or incentives, and that “feeling” sexual desire is not a usual trigger. Moreover, this clinical model emphasizes that sexual desire is responsive (i.e., it emerges after sexual arousal).
**Table 1: Diagnostic criteria for women’s sexual dysfunctions according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text-Revised (DSM-IV-TR) [1] and American Urological Association Foundation (AUAF) [41]**

<table>
<thead>
<tr>
<th>DSM-IV-TR</th>
<th>AUAF</th>
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<tbody>
<tr>
<td><strong>Desire</strong></td>
<td><strong>Sexual Interest/Desire Disorder:</strong> Absent or diminished feelings of sexual interest or desire, absent sexual thoughts or fantasies and a lack of responsive desire. Motivations [here defined as reasons/incentives] for attempting to become sexually aroused are scarce or absent. The lack of interest is considered to be beyond a normative lessening with life cycle and relationship duration.</td>
</tr>
<tr>
<td><strong>Arousal</strong></td>
<td><strong>Subjective sexual arousal disorder:</strong></td>
</tr>
<tr>
<td><strong>Female Sexual Arousal Disorder:</strong></td>
<td>Persistent or recurrent inability to attain, or maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement. The disturbance causes marked distress or interpersonal difficulty. The sexual dysfunction in not better accounted for by another Axis I disorder (except another Sexual Dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.</td>
</tr>
<tr>
<td><strong>Orgasm</strong></td>
<td><strong>Female Orgasmic Disorder:</strong> Persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase. Women exhibit wide variability in the type or intensity of stimulation that triggers orgasm. The diagnosis of Female Orgasmic Disorder should be based on the clinician’s judgment that the woman’s orgasmic capacity is less than would be reasonable for her age, sexual experience, and the adequacy of sexual stimulation she receives. The disturbance causes marked distress or interpersonal difficulty. The orgasmic dysfunction in not better accounted for by another Axis I disorder (except another Sexual Dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.</td>
</tr>
<tr>
<td><strong>Women’s Orgasmic Disorder:</strong></td>
<td>Despite the self-report of high sexual arousal/excitement, there is either a lack of orgasm, markedly diminished intensity of orgasmic sensations or marked delay of orgasm from any kind of stimulation.</td>
</tr>
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</table>
In such a model, the woman who lacks feelings of sexual desire at the outset but who is able to become sexually excited during the interaction would not be deemed to have a sexual desire disorder.

When 580 women from “The Nurses Sexuality Study” were presented brief descriptions of different models of sexual function, only a third endorsed the Masters and Johnson linear model of sexual function [11]. The findings from this study suggest that there might be great heterogeneity in women’s perceptions of the source of their sexual responses and the models they can most relate to. Most recently, a large random sample of Australian women responding to an online survey showed that women with and without sexual dysfunction were equally likely to endorse the circular model which emphasizes responsive desire [27].

With the upcoming publication of DSM-V in 2013, there have been proposed criteria for low desire in women which incorporate the overlap between sexual responses, attempt to fit the wide heterogeneity of women’s responses, and depathologize normative declines in “spontaneous” desire [28].

**Recommendation:**

The current accepted definition of HSDD in women is highly problematic and the emphasis on sexual fantasies and desire for sexual activity is not applicable to all women. We recommend that desire be regarded as the result of an incentive (sexually competent stimulus) which activates the sexual system, of which the subjectively perceived desire is one of many components. **GRADE C**

### 3. CRITICISMS OF DSM DEFINITIONS OF FSAD AND FOD

In the most recent edition of the DSM [1], FSAD is defined as the pervasive or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement, coupled with marked distress or interpersonal difficulty. In contrast to the 3rd edition of the DSM, subjective sexual experience is no longer part of the definition of arousal disorder, possibly in an attempt to match norms and criteria for men’s and women’s sexual dysfunctions [29].

There are a number of problems with the current DSM-IV criteria for FSAD, defined according to a deficient “lubrication-swelling response” ([Table 1](#)). Lubrication problems are not necessarily distressing for women. For example, although 11% of women were classified as having “manifest” lubrication problems, none of them reported distress about their symptoms [30]. In another study of 31,581 American women [31] with distress measured by the Female Sexual Distress Scale [32], whereas the age-adjusted prevalence of current “low arousal” was 25.3%, the prevalence of arousal problems with associated distress was far lower (3.3% - 6.0%, depending on age) (Level 2). In a closer exploration of personal versus interpersonal distress associated with lubrication problems, Bancroft and colleagues [33] found that among the women who complained of lubrication difficulties (31.2% of their sample), 7.3% reported “marked distress” about the relationship and 6.5% personal distress (Level 2). In the total sample, lubrication problems was a poor predictor of relationship distress and the best predictors of distress were indicators of emotional and relationship well-being and the quality of the emotional relationship with the partner. Lack of lubrication is often a poor predictor of distress, except among postmenopausal women. In the clinical setting, complaints of “genital deadness” or absent/impaired subjective sexual arousal are far more common.

Secondly, although the DSM-IV explicitly requires the clinician to assess the adequacy of sexual stimulation only when considering the diagnosis of Female Orgasmic Disorder (FOD), adequacy of sexual stimulation is a critical factor in the evaluation of the other female sexual dysfunctions, and FSAD in particular. Exactly what is adequate sexual stimulation? Some sort of physical (genital) stimulation is usually a necessary, but not necessarily sufficient, prerequisite for arousal. For many women, adequate sexual arousal involves physical as well as ‘psychological’ and ‘situational’ stimulation, such as intimacy with a partner, the exchange of confidences, the sharing of hopes and dreams and fears, and not only directly prior to the sexual event [34] (Level 3). What if certain types of sexual stimulation have been adequate in the past, but not anymore? Is it evidence of FSAD, or could it be explained in terms of habituation or an adaptation to changing life circumstances [33] (Level 4)? And what is meant by “completion of the sexual activity”? Is it masturbation to orgasm, sexual contact with a partner, sexual contact including coitus? These are very different activities that are known to differ in their sexually arousing qualities [35] (Level 2).

Thirdly, the description of the first problem demonstrates that clinical judgements are required about sexual stimulation and the severity of the problem, the validity of which is questionable. The clinician has to evaluate what is normal, based on age, life circumstances, and sexual experience. Research, on the basis of which clear criteria can be formulated, is lacking. There is a great variety in the ease with which women can become sexually aroused and which types of stimulation are required [2] (Level 4).

In general, women have difficulty perceiving genital changes associated with sexual arousal [23] (Level 2). However, women who report little or no desire for sexual activity, lack of orgasm, or sexual pain, may in fact be insufficiently sexually aroused during sexual activity. It is particularly difficult to differentiate
between FSAD and FOD. FOD is defined as the persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase [1]. In cases where the clinician does not have access to a psychophysiological test, it cannot be established that her deficient orgasmic response occurs despite a normal sexual excitement phase, unless she reports feelings of sexual arousal. Ironically, this subjective criterion has been removed from the DSM-IV.

Studies investigating the efficacy of psychological treatments for sexual dysfunction have demonstrated that directed masturbation training combined with sensate focus techniques is very effective for women with lifelong anorgasmia to become orgasmic. In fact, this is the only psychological treatment of sexual dysfunctions that deserves the label 'well-established', and is probably efficacious in acquired orgasmic disorder [36] (Level 2). The success of directed masturbation suggests that lack of adequate sexual stimulation is an important etiological factor underlying lifelong, and probably also acquired, FOD. Consequently, if the clinician would strictly adhere to the DSM-IV criteria, neither the diagnosis of FSAD, nor FOD, would be appropriate, because the problem can be reversed by adequate sexual stimulation. Perhaps the diagnosis FOD should be restricted to those women who are strongly sexually aroused, but have difficulty surrendering to orgasm [37] (Level 4).

There are no clinical or epidemiological studies that differentiate between women with lifelong or acquired FOD. Whereas Segraves posited that FSAD hardly exists as a distinct entity [38], it can be argued that in a classification system based on etiology, FSAD (meaning lack of subjective arousal) should be considered to be the most important female sexual dysfunction, with complaints of lack of desire and orgasm, and pain, frequently being consequences of FSAD (Level 4).

Finally, there is a good deal of evidence that, especially for women, genital response does not coincide with subjective experience [23] (Level 2). Instead, women's subjective experience of sexual arousal appears to be based more on their appraisal of the situation [39] (Level 3). This gender difference in concordance between subjective experience of sexual arousal and genital response was confirmed in a large meta-analysis with total sample sizes of 2,505 women and 1,918 men, and therefore not likely to be a methodological artefact [40] (Level 1). Thus, it is highly problematic that the current definition of FSAD neglects the most important aspect; namely that of subjective sexual arousal.

**Recommendations:**

The focus on “lubrication/swelling response” in the DSM-IV-TR definition of FSAD is highly problematic...
given that this is rarely a complaint motivating treatment seeking. Moreover, there is minimal, if any, correlation between subjective and genital sexual arousal. Given the importance of “adequate sexual stimuli” for sexual arousal and desire, this should be assessed clinically when evaluating whether an arousal or orgasm disorder is present.

GRADE C

4. ALTERNATIVE CLASSIFICATIONS FOR SEXUAL DYSFUNCTION IN WOMEN

Because of these criticisms of the DSM, an international classification committee sponsored by the American Urological Association Foundation (AUAF) met to deliberate and propose alternative criteria to sexual dysfunctions experienced by women [41]. The resulting classification system maintained the same four categories of the DSM-IV (i.e., desire, arousal, orgasm and pain disorders), however the definitions characterizing these changed (Table 1). Sexual Interest/Desire Disorder emphasized that lack of sexual desire prior to engaging in sexual activity was not symptomatic of a sexual dysfunction if the woman was able to become sexually excited and experience desire during the sexual encounter. Instead, the diagnosis of Sexual Interest/Desire Disorder was given if there was also a lack of responsive sexual desire during the sexual interaction or following sexual arousal.

Changes in the diagnostic criteria for FSAD were also proposed. Three separate sexual arousal disorders were proposed based upon the self-reported difficulty of subjective versus genital arousal impairment (Table 1). With the evidence to date that genital vasocongestion demonstrated by the majority of women with loss of subjective arousal, is comparable to that of healthy women, and given that women differ in their awareness of these genital changes, recognition of a Subjective arousal disorder was advocated (Table 1).

Women may be subjectively aroused by, for instance, viewing an erotic film, or pleasuring her partner, being kissed or receiving breast stimulation, but complain of a marked loss of intensity of any genital response, including orgasm. Awareness of throbbing/swelling/lubrication is absent or markedly diminished. This clinical picture has been described by the following groups of women: Women with autonomic nerve damage [42], some postmenopausal estrogen replete women with demonstrable lack of vasocongestive response and some for whom there is no evidence of physically impaired vasocongestion but a lack of sexual sensitivity is still present [43]. Therefore, a category of Genital sexual arousal disorder was proposed (Table 1). However, this is a clinical diagnosis based on the woman’s report for which there may or may not be demonstrable physical pathology or evidence of psychophysiological impairment when tested in a laboratory [44]. Despite many women disclaiming genital swelling, pleasurable sensations from direct stimulation of their genitalia or awareness of lubrication, it is highly possible that there may be reflexive genital vasocongestion [14,45].

The most common clinical presentation, however, was thought to be Combined genital and subjective arousal disorder (Table 1). Again, research suggests that many women with this presentation may still be genitally vasocongesting in a healthy manner [14,44] (Level 2). It is the lack of report of subjective excitement from any type of sexual stimulation that distinguishes these women from those with genital arousal disorder.

These definitions (Table 1) were adopted by the last International Consultation on Sexual Medicine: Men and Women’s Sexual Dysfunction, in Paris in July 2003 [46]. Some work was done on the validity of these new definitions. Basson and Brotto aimed to assess genital response using vaginal photoplethysmography in 34 estrogenized, postmenopausal women diagnosed clinically (using a detailed semi-structured interview) with acquired Genital Sexual Arousal Disorder and orgasmic impairment [43] (Level 2). They found this group of women to be heterogeneous, with psychophysiological arousal responses varying from absent to robust. In another study, Brotto and colleagues found that women with Genital Sexual Arousal Disorder exhibited lower levels of sexual psychophysiological arousal than women with Subjective Sexual Arousal Disorder and women with Combined genital and subjective sexual arousal disorder [47] (Level 2). Clearly, validation of this differentiation based on clinical presentation awaits further replication.

Recommendation:

The available evidence suggests that there are problems in existing definitions of sexual desire, arousal, and orgasmic disorders in women. Given the upcoming publication of the DSM-V in 2012, it is likely that the current diagnostic criteria for these disorders may change. The proposed definitions that were sponsored by the AUAF in 2003 present alternative criteria for these disorders that are currently recommended for the clinical setting.

GRADE B

5. PREVALENCE OF SEXUAL DESIRE AND AROUSAL DYSFUNCTION IN WOMEN

There has been a recent surge in epidemiological studies estimating the prevalence of sexual desire, arousal, and orgasm complaints in women. These studies have been conducted on pre and postmenopausal women, naturally and surgically menopausal women, women of varying ages up to 105, and
of sexual arousal beyond lubrication. Bancroft and colleagues [33] looked at a composite measure of arousal labelled “Impaired physical response”, which included feeling arousal during sexual activity, pleasant genital tingling, and enjoying genital touch. The presence of impaired physical response increased the probability of marked relative to no distress about the relationship by 51% but was unrelated to personal distress, and it was overall less problematic for older women (Level 2). A British study by Dunn and colleagues asked more generally about “problems becoming sexually aroused” and found that 17% reported this problem in the previous three months [53]. Similar to the issue with prevalence on low desire, the prevalence of low arousal plus distress drops markedly (Witting and colleagues [56] found the prevalence of impaired lubrication plus distress to be only 7%). When considering the association between duration of complaints and prevalence, lubrication difficulties lasting 6 months or longer were found to be much more common than those lasting one month (2.6% vs 9.2%, respectively) [49].

6. SEXUAL SATISFACTION AND THE ASSOCIATION WITH DESIRE AND AROUSAL

Sexual satisfaction is an important component of contemporary models of women’s sexual response [57-59], but across studies, the precise definition either varies or is not provided. It is recognized, however, to have personal and relational domains [60]. Hartmann and colleagues defined satisfaction with sexual intercourse as being both relational (e.g., feeling safe, not lonely, not distant from partner) as well as individual (e.g., not feeling unsettled inside, feeling content, free of sexual tension, pleasantly indulged, relaxed, happy) [61]. Byers [62] pointed out that one’s level of sexual satisfaction depends on one’s frame of reference (e.g., expectations and past experiences). Therefore, a woman who does not expect to experience orgasm during sexual encounters with her partner may be more sexually satisfied than a woman who occasionally doesn’t experience orgasm. Among several recent population-based studies of sexual difficulties in women, a proportion of women will report being sexually satisfied despite the presence of sexual symptoms. In a study of 290 British women aged 18-75, 79% indicated being very satisfied with their current sex life despite the fact that 24% had not engaged in any sexual activity in the past 3 months [16]. Similarly, in the Study of Women’s Health Across the Nation (SWAN), 70% of women reported thinking about sex less than once/week but 86% remained sexually satisfied [15]. Sexual fantasies and sexual satisfaction are also not correlated in women [15,33]. The interesting counterpart to this finding is that a number of studies have found that a proportion of women without sexual symptoms will report dissatisfaction [19,30,33,50,63]. Moreover, sexual satisfaction is associated with, but is not the

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Across different countries and cultures. Three of the most widely cited epidemiological studies in the sexological literature are discussed and several others are presented in Table 2. The National Health and Social Life Survey (NHSLS) [48] found that between 27-32% of women aged 18-59 who had been sexually active over the past year reported a lack of interest in sex (Level 2). However, the investigators did not stipulate the duration of time the symptom had to be experienced, which likely resulted in an inflation of dysfunction rates. In the National Survey of Sexual Attitudes and Lifestyles (NATSAL) conducted on 11,161 British men and women aged 16-44 who participated in a computer-assisted self-interview, low sexual desire was the most common complaint in women, at 40.6% over the past month and 10.2% for the past 6 months [49] (Level 2). In the Global Study of Sexual Attitudes and Behaviors (GSSAB), 13,882 women across 29 countries took part either in a computer-assisted telephone interview or a face-to-face interview [50] (Level 2). Lack of interest in sex was the most common problem in women, ranging from 26-43%. Of course the very low response rate from this survey (19%) renders the external validity of the findings questionable.

Although different assessment tools have been employed and in differing formats (e.g., face to face interview versus questionnaire versus computer assisted interviewing), in general these studies find convergence on the frequency of reported low desire in women to be approximately 20-30% (Table 2). However, when the complaint of sexual distress is also included, the prevalence of desire difficulties drops usually by half. In addition, the age-associated decline in sexual desire that is found somewhat consistently is not found when low desire plus distress are taken into account. Hayes (2008) found that low desire and age were positively correlated (i.e., complaints of low desire become more prevalent as women age); however, low desire, together with its associated distress, was not significantly associated with age [51]. In analyses of both European and American women participating in the Women’s International Study of Health and Sexuality (WISHeS) study, Hayes et al [52] found low desire to significantly increase with age but the proportion of women with low desire who were distressed by it decreased with age (Level 3) [52]. Table 3 lists the specific predictors of sexual distress across a number of recent epidemiological studies.

Among these epidemiological studies, most have also assessed the prevalence of sexual arousal complaints. However, these studies have tended to use the DSM-IV-TR definition of FSAD with a focus on the “lubrication-swelling response” [1]. The prevalence of FSAD is listed in Table 2, with an overall range between 10.9% and 31.2% [30,33,48,49,53-56]. Few studies have attempted to explore other aspects
Table 2: Prevalence of sexual desire and arousal difficulties in cross-sectional representative studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample characteristics</th>
<th>Age</th>
<th>In a sexual relationship</th>
<th>Distress measured</th>
<th>Prevalence of desire difficulties</th>
<th>Prevalence of arousal difficulties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laumann et al. (1999). JAMA, 281, 537-544. [48]</td>
<td>1,749 American women (NHSLS)</td>
<td>18-59</td>
<td>Had to be sexually active over the past 12 months</td>
<td>No</td>
<td>27-32% Critical symptom for diagnosis had to be present in the past 12 months</td>
<td>20.6% trouble lubricating</td>
</tr>
<tr>
<td>Fugl-Meyer &amp; Fugl-Meyer (1999). Scand J Sexol, 2, 79-105. [381]</td>
<td>1,335 Swedish women</td>
<td>18-74</td>
<td>Not necessary</td>
<td>Indirectly with the question: “Has this been a problem in your sexual life during the last year?”</td>
<td>Sexual disability was defined as having low desire quite often/nearly all the time/all the time = 34%. Among these, 43% viewed it as a problem. Symptom had to have occurred in the past 12 months.</td>
<td>Sexual disability was defined as having insufficient vaginal lubrication during intercourse quite often/nearly all the time/all the time = 12%. Among these, 63% viewed it as a problem.</td>
</tr>
<tr>
<td>Mercer et al. (2003). Br Med J, 327, 426-427. [49]</td>
<td>11,161 British men and women (NATSA)</td>
<td>16-44</td>
<td>Must have had at least one sexual partner in past year</td>
<td>No</td>
<td>Low desire lasting 1 month: 40%; lasting 6 months: 10%</td>
<td>Lubrication problems lasting 1 month: 9.2%; lasting 6 months: 2.6%</td>
</tr>
<tr>
<td>Bancroft, Loftus, &amp; Long (2003). Arch Sex Behav, 32, 193-208. [33]</td>
<td>987 American women; half were African-American</td>
<td>20-65</td>
<td>Not necessary</td>
<td>Assessed distress over the relationship and distress to one’s own sexuality</td>
<td>Low desire: 7.2% Sexual experiences over the preceding month were assessed</td>
<td>Lubrication problems: 31.2%; Impaired arousal: 12.2%</td>
</tr>
<tr>
<td>Oberg, Fugl-Meyer, &amp; Fugl-Meyer (2004). Int J Impot Res, 16, 261-269. [30]</td>
<td>1,056 Swedish women recruited in 1996</td>
<td>19-65</td>
<td>Must have had sexual intercourse once in past year</td>
<td>Manifest distress if experienced quite often/nearly all the time</td>
<td>Low desire: Manifest – 29%; Mild - 60% Symptoms were assessed over the previous 12 months</td>
<td>Insufficient lubrication: Manifest – 12%; Mild – 50%</td>
</tr>
<tr>
<td>Laumann et al. (2005). Int J Impot Res, 17, 39-57. [50]</td>
<td>13,882 women recruited internationally. Analyses based on 9,000 sexually active women (GSSAB)</td>
<td>40-80</td>
<td>Must have had sexual intercourse once in past year</td>
<td>No</td>
<td>26-43% across countries reported a lack of interest in sex lasting for a period of 2 months or more</td>
<td>16.1-37.9% across countries</td>
</tr>
</tbody>
</table>
Table 2: Prevalence of sexual desire and arousal difficulties in cross-sectional representative studies. (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample characteristics</th>
<th>Age</th>
<th>In a sexual relationship</th>
<th>Distress measured</th>
<th>Prevalence of desire difficulties</th>
<th>Prevalence of arousal difficulties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiblum et al. (2006). Menopause, 13, 46-56. [197]</td>
<td>952 American surgically or naturally women (WiSHES)</td>
<td>20-70</td>
<td>Currently sexually active</td>
<td>Personal Distress Scale</td>
<td>24-36% depending on age and menopausal status. Among those who also had distress, rates of HSDD ranged from 9-26%. Symptoms occurring in the past 30 days were assessed</td>
<td>n/a</td>
</tr>
<tr>
<td>Dennerstein, Koochaki, Barton, &amp; Graziottin (2006). JSM, 3, 212-222. [198]</td>
<td>2,467 European women from France, Germany, Italy, UK, and United States (WiSHES)</td>
<td>20-70</td>
<td>Currently sexually active</td>
<td>Personal Distress Scale</td>
<td>16-46% depending on age and menopausal status. Among those who also had distress, rates of HSDD ranged from 7-16%. Symptoms occurring in the past 30 days were assessed</td>
<td>n/a</td>
</tr>
<tr>
<td>West et al. (2008). Arch Intern Med, 168, 1441-1449. [199]</td>
<td>755 American premenopausal, 552 naturally menopausal, and 637 surgically menopausal women</td>
<td>30-70</td>
<td>In stable relationships for at least 3 months</td>
<td>Personal Distress Scale</td>
<td>Overall rate of low desire 36.2%. Overall rate of HSDD 8.3%. Symptoms in the past 30 days were assessed</td>
<td>n/a</td>
</tr>
<tr>
<td>Witting et al. (2008). J Sex Med, 5, 2587-2599. [381]</td>
<td>5,463 Finnish women</td>
<td>18-49</td>
<td>Must have engaged in sexual activity with a partner over the past 4 weeks.</td>
<td>Female Sexual Distress Scale</td>
<td>Using FSFI cut-off score of 3.16, 55% had low desire. Using FSDS cut-off score of 8.75, 23% had low desire and distress. Symptoms were assessed in the past 4 weeks</td>
<td>Using a FSFI cut-off score of 4.31, 10.9% had lubrication difficulties. Using FSDS cut-off score, 7% had lubrication problem plus distress.</td>
</tr>
<tr>
<td>Shifren et al. (2008). [31]</td>
<td>13,581 women</td>
<td>United States</td>
<td>18-102</td>
<td>Not necessary</td>
<td>Questionnaires: Sexual desire assessed with one question: “How often do you desire to engage in sexual activity?” Distress assessed by Female Sexual Distress Scale</td>
<td>34% had low desire, overall 10% had low desire and distress</td>
</tr>
</tbody>
</table>
same as, lack of sexual distress and deserves further study in population-based studies. For women, sexual satisfaction does not equal sexual function. In using the NHSLS data to explore individual, relational, and cultural sexual satisfaction in 1,035 mid-life women in a sexual relationship, women’s health positively influenced her emotional satisfaction [64] (Level 2). Interestingly, relationship duration was not a predictor of sexual satisfaction in this study. Both studies focusing on sexual satisfaction found an important role for orgasm consistency [61, 64].

**Conclusions and Recommendations:**

Overall, the prevalence of desire complaints ranges from 10-40% and for arousal difficulties from 10-30%, depending on the study methodology, participants, and geographic location. Moreover, when the assessment of distress is included, the prevalence of these complaints drops to approximately half. Given these disparate rates, we recommend that distress or some other measure of severity always be included in future epidemiological trials and that clear operational definitions of the sexual domain be given, along with a duration of complaints of at least 3-6 months for denoting difficulty. Sexual satisfaction is rarely correlated with sexual frequency and is not consistently associated with sexual symptoms; thus, sexual satisfaction must be assessed clinically. Future research is needed on the definition of sexual satisfaction, on the correlates of sexual satisfaction in women, and how these correlates may differ for men. *GRADE C*

### II. ASSESSMENT

#### 1. THE BIOPSYCHOSOCIAL INTERVIEW

Assessment of sexual desire/arousal problems is critical in planning meaningful and sensible treatment interventions. Assessment is important not only for diagnosis but for determining the incidence and prevalence of various disorders and for evaluation of treatment outcome [65]. The most common approach to diagnosing sexual difficulties is via a comprehensive clinical interview of both the identified patient and her partner when possible. Such an interview includes discussion of the presenting problem and the predisposing, precipitating and maintaining factors that govern its appearance and

**Table 3: Predictors of sexual distress among epidemiological studies of women’s sexual difficulties and their associated levels of evidence (LOE)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Predictor of Distress</th>
<th>LOE</th>
</tr>
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<tbody>
<tr>
<td>Bancroft, Loftus, Long (2003) [33]</td>
<td>Age: Aged 20-35 more likely to view their lack of sexual thoughts as distressing to the relationship and to their own sexuality compared to &gt; 36yrs</td>
<td>2</td>
</tr>
<tr>
<td>Bancroft, Loftus, Long (2003) [33]</td>
<td>Negative mental state predicted marked distress about the relationship and marked distress about the woman’s own sexuality</td>
<td>2</td>
</tr>
<tr>
<td>Bancroft, Loftus, Long (2003) [33]</td>
<td>Physical health predicted distress about a woman’s own sexuality</td>
<td>2</td>
</tr>
<tr>
<td>Rosen et al. (2009) [17]</td>
<td>Having a sexual partner</td>
<td>2</td>
</tr>
<tr>
<td>Rosen et al. (2009) [17]</td>
<td>Sexual dissatisfaction</td>
<td>2</td>
</tr>
<tr>
<td>Rosen et al. (2009) [17]</td>
<td>Depression</td>
<td>2</td>
</tr>
<tr>
<td>Rosen et al. (2009) [17]</td>
<td>Use of hormonal therapy</td>
<td>2</td>
</tr>
</tbody>
</table>
intensity [66]. Table 4 provides an overview of the contributory factors that may be etiologically relevant in such a biopsychosocial interview (adapted from Table 1 in Graziottin and Leiblum, 2005 [66]).

In addition to the various considerations described in Table 4, there are a wide array of precipitating factors that may “tip the balance” from satisfactory sexual function to dysfunction. Among these factors are life stage stressors such as childbirth, infertility, divorce or partner loss, unemployment, extra-relationship affairs, humiliating or traumatic sexual experiences, partner sexual inadequacy or clumsiness, and most significantly, relationship discord.

Often, there is not a clear distinction between either predisposing and precipitating factors or precipitating and maintaining factors. As a predisposing factor, for example, anxiety can increase an individual’s vulnerability to sexual dysfunction. It can also serve as a maintaining factor leading to sexual avoidance or arousal inhibition. Nevertheless, it is helpful to attempt to determine what the immediate triggers or precipitating factors are for the appearance of a recent sexual complaint since these are likely to be important areas to address in the early stages of treatment.

As far as the perpetuating or maintaining factors to consider, the clinician also should assess the current contextual factors that affect sexual expression and interest such as relationship satisfaction, privacy issues, current health of self and partner, medical or psychiatric issues, use of medications or recreational drugs/alcohol that may affect sexual expression and current stressors.

### 2. SELF-REPORT ASSESSMENT TOOLS

Many practitioners find that the use of standardized self-report questionnaires can be helpful in terms of saving time, identifying problems, and providing direction or greater focus for follow-up interview and evaluation. The assessment tools listed in Table 5 have demonstrated good reliability and validity and

<table>
<thead>
<tr>
<th><strong>Table 4: Etiological Factors that should be evaluated when assessing desire and arousal complaints in women</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predisposing Considerations</strong></td>
</tr>
<tr>
<td><strong>Biological</strong></td>
</tr>
<tr>
<td><strong>Psychosexual</strong></td>
</tr>
<tr>
<td><strong>Contextual</strong></td>
</tr>
</tbody>
</table>
can identify problems with the various components of female sexual response, many of which overlap. Often, it is difficult to determine which is the primary and which is the secondary diagnosis. Consequently, the scales listed in Table 5 can provide a helpful overview of problematic areas to be assessed further in a clinical interview, and should not be used to form a diagnosis on their own. Caution in using these self-report questionnaires and the tradition of focusing on (sexual event) quantity as opposed to these self-report questionnaires and the tradition of forming a diagnosis on their own. Caution in using these self-report questionnaires and the tradition of focusing on (sexual event) quantity as opposed to quality are real criticisms of existing measures that must be taken into account [67].

In addition to these more general scales that focus on all or several aspects of female sexual response, there are some scales that focus on a particular population. For example, for the assessment of HSDD in post-menopausal women, there is a brief assessment tool called the HSDD Screener [68] which consists of four self-report questions with an interpretable cut-off score. Depending on the responses the woman provides, the screener is followed by a more detailed face to face interview. The newest self-report assessment instrument for identifying HSDD is the Decreased Sexual Desire Screener (DSHD) [69]. It consists of four yes/no questions concerning both past and present sexual interest, whether or not the woman is bothered by her lack of, or diminished interest in sex, whether she wants her interest to increase, and a fifth seven-part question covering various factors that may be relevant to the differential diagnosis of HSDD such as medical procedures, medications, or partner’s sexual problems.

Finally, there are several instruments that are available which may be used to guide or direct a diagnostic interview in order to obtain a more comprehensive picture of the various contributions to desire or arousal problems. These include the Sexual Interest and Desire Inventory–Female Version [70] and the Women’s Sexual Interest Diagnostic Interview (WSID) [71] for assessment of sexual functioning in postmenopausal women. The latter instrument consists of 39 questions which allow for the identification of HSDD, FSAD, FOD, sexual pain, and personal distress associated with these complaints. In addition, the WSID provides a structured format for the identification of partner relationship problems, partner sexual dysfunction, and symptoms of depression.

**Recommendation:**

Although instruments may be helpful in guiding diagnosis or treatment, none is a substitute for a thoughtful and sympathetic clinical interview that includes the woman and her partner (if possible). **GRADE C**

### 3. THE PHYSICAL EXAMINATION

A physical examination is recommended for reasons of good medical care and for education and reassurance. The examination is also a setting to explore perceptions, beliefs, and attitudes about a woman’s own anatomy and encourage a patient’s positive approach to her genitals and body.

The examination is particularly important for ruling out or identifying medical factors when concomitant complaints such as loss of sensitivity or sexual pain exist. A gynecological examination should include an evaluation of the level of voluntary control of the pelvic floor muscles, pelvic floor muscle tonus, presence of vaginal wall prolapse, signs of vaginal atrophy, size of introitus, presence of discharge, or evidence of infection (acute or chronic), epithelial disorders and/or pain.

In Multiple Sclerosis [72,73] and other neurological diseases there may be sensory loss in the genitalia. In renal disease, there may be anemia, hyperprolactinemia and other disturbances of the hypothalamic-pituitary-gonadal axis (with reduction in androgens and estrogen levels) and subsequent vulvovaginal atrophy [74,75]. Vulvovaginal hypotrophy or atrophy is a common finding after natural or iatrogenic menopause, in hypothalamic or pituitary disease, breast-feeding women, and in women using low-dose estrogen or progesterone only contraceptives.

**Recommendation:**

A gynaecological examination is recommended in the assessment of women with desire and arousal complaints to assess and rule out medical/physical contributors. **GRADE C**

### 4. PSYCHOPHYSIOLOGICAL TOOLS

Over three decades, several techniques have been developed to assess genital physiological changes in response to sexual stimuli. In 1975, Sintchak and Geer introduced a method for the laboratory measurement of vaginal vasocongestion, using vaginal photoplethysmography (Level 3) [76]. The most widely used type of vaginal photoplethysmograph is a menstrual tampon-sized device, easy to insert and sterilize, containing an infrared light-emitting diode as a light source and a photo transistor as a light detector. The light source illuminates the vaginal tissues, and the photo transistor responds to the incident light that is backscattered from the vaginal wall and the blood circulating within it. Because of the opacity of the tissue, the amount of light backscattered is largely dependent upon the volume of blood within it; thus, the vaginal photoplethysmograph provides a measure of vaginal vasocongestion.

Two components are obtained from the same output signal of the photo transistor. When the signal is DC
Table 5: Scales useful for the evaluation of sexual desire and arousal problems in women

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golombok-Rust Inventory of Sexual Satisfaction (GRISS) [382]</td>
<td>A 28-item questionnaire designed to assess the existence and severity of sexual problems across five domains relevant to women: anorgasmia, vaginismus, avoidance, nonsensuality and dissatisfaction. Items are presented with a five point response format ranging from never to always. Interpretation of the data is based on patterns across the different subscales and Rust and Golombok note that “this leads to indications for therapy, rather than to a diagnosis”. The GRISS was standardized on couples receiving sex therapy. Split half reliability is 0.94 and test-retest reliability is 0.65 for women. It was validated in those with a known sexual dysfunction versus a control group and found to have good discriminant validity.</td>
</tr>
<tr>
<td>Brief Index of Sexual Functioning for Women (BISF-W) [18]</td>
<td>A 22-item questionnaire that provides domain and total scores on the following aspects of sexual function: desire, arousal, frequency of sexual activity, receptivity/initiation, pleasure/orgasm, relationship satisfaction and problems affecting sexual function. A principal components analysis resulted in three discrete factors: sexual interest/desire, sexual satisfaction, and sexual activity. BISF-W was also shown to possess a high degree of concurrent validity with the DSFI, displaying a Pearson correlation of 0.69. BISF-W, however, is much easier to administer than the DSFI and results in a more detailed evaluation of current sexual functioning.</td>
</tr>
<tr>
<td>Sexual Desire Inventory (SDI) [383]</td>
<td>A 14-item questionnaire that measures dyadic and solitary sexual desire on the basis of factor analysis. Using Cronbach’s alpha, SDI exhibited high internal consistency estimates with coefficients of 0.86 for dyadic sexual desire and 0.96 for solitary sexual desire, suggesting excellent reliability.</td>
</tr>
<tr>
<td>Derogatis Interview for Sexual Functioning (DISF) [384]</td>
<td>A 25-item questionnaire that includes five domains: cognition, arousal, behavior, orgasm and drive/relationship as well as a total score. The DISF/DISF-SR appears to fulfill fundamental psychometric criteria. High reliability scores and a nearly ideal subtest-total score relationship have been found. The hypothesized internal structure as well as the discriminative capacity of the scale have also been firmly established.</td>
</tr>
<tr>
<td>Female Sexual Function Index (FSFI) [203]</td>
<td>A 19-item questionnaire specific to women that assesses six domains (desire, subjective arousal, lubrication, orgasm, satisfaction and pain). FSFI was shown to possess excellent test-retest reliability for each domain with a range of reliability coefficients from 0.79 to 0.96. High internal consistency was also determined using Cronbach’s alpha which yielded values of 0.82 and higher. More importantly, greatly significant mean difference scores between women with Female Sexual Arousal Disorder and controls attest to the scale’s construct validity (p &lt; 0.001). Suggestions for improved scoring of the FSFI so it does not penalize women who are not currently sexually active have been offered. [385,386]</td>
</tr>
<tr>
<td>Sexual Function Questionnaire (SFQ) [387]</td>
<td>A 31-item relatively new instrument designed to assess eight domains of women’s sexuality: desire, physical arousal/sensation, physical arousal/lubrication, enjoyment, orgasm, pain, partner relationship and cognition. This scale features exceptional internal consistency, respectable reliability, excellent discriminant validity and sensitivity. Specifically, internal consistency of the domains was found to range from 0.65 and 0.91, and test-retest reliability was noted to be between 0.21 and 0.71 for Cohen’s weighted kappa and 0.42 and 0.78 for Pearson’s correlation coefficient. In terms of validity, there was a significant difference between the baseline mean SFQ domain scores of female patients with sexual dysfunctions and scores of controls. Additionally, SFQ scores at the end of the study also significantly diverged between patients who reported improvement in their sexual functioning and those who did not.</td>
</tr>
<tr>
<td>Female Sexual Distress Scale (FSDS) [32]</td>
<td>A 12-item instrument for determining the amount of current distress experienced by a woman who reports sexual difficulties. A cut-off score of 15 or greater is believed to indicate personal distress. Using Cronbach’s alpha, a high level of internal consistency was established for FSDS with a range from 0.86 in an early study to the low 0.90s in later clinical trials. Test-retest reliability has also been found to be respectable. In regards to discriminative ability, FSDS was found to successfully distinguish women with and without sexual dysfunctions.</td>
</tr>
</tbody>
</table>
coupled, slowly developing changes in vaginal blood volume (VBB) are observed, which are thought to reflect pooling of blood in the vaginal tissue [77] (Level 3). With AC coupling, a measure of vaginal pulse amplitude (VPA) is obtained, reflecting short-term changes in vaginal engorgement. Fluctuations in VPA reflect the phasic change in blood content or volume of the illuminated tissue at each heart beat, with larger amplitudes reflecting higher levels of vasoengorgement. Specificity and construct validity of VPA and VBB were investigated during sexual, neutral, as well as nonsexual emotional states, convincingly showing that changes in VPA are specific to sexual stimuli, while VBB appears to increase in response to both sexual and anxiety-inducing stimuli [20,78-80] (Levels 2 and 3). VPA is usually increased by sexual arousal up to, but not including, orgasm due to movement artifacts [81] (Level 3). To reduce interference with signal recording, they can be deleted using modern signal-processing and data reduction software [78,82]. Depth of the probe and orientation of the light source can be controlled by an acrylic plate that is usually attached to the cable within 5 cm of the optical sensor [78].

Although the use of vaginal photoplethysmography has been of great value for indicating the arousal status of the vagina per se, it is still unclear exactly what VPA actually represents [83]. This may, in part, be explained by its lack of an absolute scale. VPA is measured on an ordinal scale rather than an interval or ratio scale, hampering the development of this measure as an individual diagnostic method of genital responsiveness.

Despite this limitation, all studies that have compared genital responsiveness between women with and without sexual problem were done using VPA, and nearly all of these have failed to find group differences in VPA, whether between women with dyspareunia and controls [84-87], women with HSDD, FOD, and controls [88], women with FSAD seeking treatment and controls [89], women who improved on sexual arousal symptoms following sex therapy, placebo, or gingko biloba versus those who did not improve [90], women with broad sexual problems and controls [91], and medically healthy women with FSAD versus controls [44] (Level 2). When using the AUAF definition of genital sexual arousal disorder, one study found that VPA differed significantly from women with subjective sexual arousal disorder [47] (Level 2). These findings suggest that genital responsiveness in somatically healthy women, at least as it is defined by the DSM-IV, may not play an important role in women’s sexual problems. It is unlikely that these findings are the result of VPA not being a sensitive measure; there is abundant evidence that VPA is a sensitive measure, distinguishing baseline levels of premenopausal women from postmenopausal women [44,92-94], discriminating sexual stimuli varying in intensity [24,95], and differentiating responses from heterosexual and homosexual women when stimuli depicting solitary males and females are used [96] (Level 2). In women with medical conditions, VPA proved sensitive as well. In fact, one of the few psychophysiological studies to date that found a significant effect of sildenafil on VPA in women with FSAD was done in women with spinal cord injury [42] (Level 2). A study comparing genital response during visual sexual stimulation of women with diabetes mellitus and healthy women found VPA to be significantly lower in the former [97] (Level 2). A Dutch study measured VPA in medically healthy women who had undergone a simple hysterectomy, and women with a history of radical hysterectomy for cervical cancer [98] (Level 2). Only in the latter group was VPA during visual sexual stimuli impaired, despite the fact that the women with simple hysterectomies reported more sexual problems than the other two groups. Similar findings came from a later study from the same group, with VPA differentiating between women who had undergone nerve sparing radical hysterectomy from women who underwent conventional radical hysterectomy [99] (Level 2). The latter group had lower VPA increases than the former group, whose VPA levels were similar to those of a healthy control group. Summarizing these findings, Laan and colleagues concluded that not presence of sexual arousal problems but presence of a somatic condition that influences genital response may be the most important determinant of impaired genital responsiveness [44].

Several alternative, albeit to date less well researched, methods for measuring genital response in women have been developed. One of the earlier methods was a heated oxygen electrode fitted into a suction cup that could be applied to the vaginal wall and held there by a partial vacuum generated in the rim of the cup [100] (Level 3). The silver disc electrode is heated by an electric current to a set temperature (usually 43°C). The amount of electrical power needed to keep the disc at this temperature can be monitored. Heat is lost from the disc mainly by conduction through the tissue and tissue fluid to the blood. Increased blood perfusion under the electrode will increase its heat loss and thus a greater power output will be needed to maintain the electrode at the set temperature. The changes in power in milliwatts thus become an indirect measure of the changes in blood flow under the electrode, reflecting the pooling of blood in the vascular bed. The electrode also records the amount of oxygen that diffuses across the skin, reflecting transient changes in blood flow. The greater the blood flow beneath the disk the greater will be the apparent oxygenation of the flow as it gradually approaches that of the saturation of the arterial blood. A number of studies have documented that the heat dissipation measure
and the oxygen perfusion measure are sensitive to sexual arousal and orgasm [101-103] (Level 3). In those studies subjects usually applied clitoral self-stimulation as a means to induce sexual arousal. A great advantage of this device is that it combines two measures of blood flow. Also, it is relatively free of movement artifacts because it is attached to the surface of the vagina [104] (Level 3). This makes the device suitable for monitoring changes in blood flow from low levels of sexual arousal up to orgasm. In a similar vein, the reliability of the signal obtained does not seem to be compromised by masturbation and clitoral vibration. Finally, both measures can be calibrated in terms of absolute blood flow. Nevertheless, use of this method has been limited. Disadvantages are its expense, the fact that the electrode should not be applied for very long periods of recording to protect the vaginal mucosa from heat damage, and that the device needs to be attached by the experimenter. A general disadvantage of temperature methods seems to be that subjects require relatively long resting periods to show temperature stability, and after moderate to high sexual arousal the measures do not appear to return to baseline very easily [104,105] (Level 3).

Another commonly used physiological measure of female genital response is the labial thermistor. This device consists of a thermistor placed on a small clip that is attached to the labia minora [106-108] (Level 2-3). Unlike VPA, the units of change are measured on an interval scale (degrees Celsius), allowing direct comparisons across participants. Also, labial temperature is unaffected by orgasm [109] (Level 3). At the same time, menstrual cycle effects have been reported for labial temperature change recorded during the follicular and luteal phases of the menstrual cycle [5,107] (Level 2, 3). Onset of change in labial temperature is typically slower than VPA and temperature takes longer to return to a pretrial level of response. Payne and Binik have argued that labial temperature is a more consistent measure of genital response than VPA and is more strongly correlated with self-reported sexual arousal than VPA [110] (Level 3). Recently, Prause and Heiman directly compared the labial thermistor with VPA [111] (Level 3). Participants wore the labial thermistor simultaneously with the vaginal photoplethysmograph. The labial thermistor discriminated sexual from nonsexual arousing stimuli and was sensitive to different levels of sexual arousal. One woman reported that the labial thermistor was very uncomfortable, while others indicated no or mild discomfort from each instrument. In contrast to earlier findings [23,95] in this study VPA did not discriminate sexual stimuli of different intensity.

A new approach, the labial photoplethysmograph, relies on measurements of genital responses that are similar to the vaginal photoplethysmograph [112] (Level 2). The labial photoplethysmograph is a small plastic clip, which can be attached to the labia majora, originally designed to measure blood flow in the ear lobe. In a small study, the labial photoplethysmograph was compared with VPA while participants viewed neutral, sexual, sexually threatening and threatening film clips. Both instruments were specific to sexual content and correlated strongly with participants’ own ratings of their sexual arousal. Although participants reported that the labial photoplethysmograph was somewhat more difficult to place and less comfortable, the labial device exhibited fewer movement artefacts than the vaginal photoplethysmograph [82].

A very recent development is measurement of clitoral photoplethysmography in conjunction with vaginal photoplethysmography [113] (Level 2). A clitoral photoplethysmograph was attached to the silicon tube of the vaginal plethysmograph, along with a silicon placement device holding the clitoral photoplethysmograph in the correct anatomical position. Subjects are able to insert the probe and attach the clitoral device without supervision. The shape of the clitoral probe follows the anatomical curves of the area surrounding the urethral opening up to the clitoris, between the labia minora and just above the introitus. Thirty-two women, 20 of whom with mixed sexual problems, participated in the study. Clitoral photoplethysmography, but not VPA appeared sensitive to a sudden (planned but unannounced to the subject) interruption of the visual stimulus. No differences between women with and without sexual problems were found for either measure.

Devices have also been designed to measure vagina pH. On average, vaginal pH increases with increasing sexual arousal [114] (Level 3). Measurement of pH, however, requires potentially disruptive experimenter involvement, and pH seems to vary nonsystematically across different areas of the vagina [82] (Level 3).

Clitoral color Doppler assessment of clitoral blood flow was first attempted in 1995 [115] (Level 3). This non-invasive, reproducible, low-cost, and quantitative technique allows for ultrasonographic identification of the clitoris and for color Doppler assessment of clitoral blood flow. More than a decade later, Kukkonen and colleagues examined the convergent and discriminant validity of this measure by assessing its ability to discriminate between sexual and other forms of arousal. Results from 63 healthy premenopausal women indicate that ultrasonography was not successful in differentiating sexual arousal from a humor control condition [116] (Level 2). Caruso and colleagues studied 30 women with type 1 diabetes using clitoral color Doppler ultrasonography and found that they had a lower pulsatility index, peak systolic velocity, and end-diastolic velocity values compared with controls [117] (Level 2). Because the technique requires a
A new method that may prove to have better ecological validity is Laser Doppler perfusion imaging (LDPI). This is a method of measuring superficial skin microcirculatory blood flow (no deeper than 1.5 mm below skin surface) that doesn't require genital contact nor (presumably) the presence of a technician in the subject's room. The Laser Doppler perfusion imager allows measurement of tissue blood flow over a defined area. It is noninvasive, as the laser is placed between 15 and 40 cm from the vulva. It is based on the Doppler principle, i.e. the frequency change that light undergoes when interacting with objects in motion. Styles and colleagues [118] measured LDPI in two separate sessions coinciding with the follicular and luteal phase in 16 sexually functional women before and after sexual stimulation (reading a chapter of erotic fiction). The method requires women to undress from the waist down and to assume a lithotomy position allowing unimpeded access to the vulval area. In this study, the room was temperature controlled and scans were performed in a dark room to ensure consistency in flux (units of blood flow) readings. Styles and colleagues used a piece of black card, with an individualized hole cut out, taped so that it covered the subjects' genital skin apart from her vulva, to ensure that backscattered light was kept to a minimum. Percentage of change in blood flow after sexual stimulation was significantly different in all four areas that were measured: the clitoral area, right and left labium, and the fourchette. Flux change was greatest in the latter area. There were no differences between the first and second visits or follicular and luteal phases. Increases in blood flow did not correspond with subjective sexual arousal reports. In this study, scans could not be made continuously while the subjects were reading, as the scans had to be made in the dark. Other forms of stimulation or technical advances in stimulus delivery can be used to overcome this disadvantage. A second, very recent study [119] measured LDPI in 65 sexually functional women in their luteal phase while they viewed three 15-minute films (two nature films and one of four experimental films: erotic, humor, anxiety or neutral) through i-goggles. During each film, scans were produced every 163 seconds. The region of interest included parts of the labia majora, labia minora, and clitoral hood; one general vulvar blood flow score was generated from these data. Results showed that the erotic condition generated significantly more vulvar blood flow than the nonerotic conditions, which were not significantly different from each other. Genital blood flow during the erotic condition was significantly and positively associated with subjective ratings of sexual arousal. The authors presumed that when female genital response is measured externally, women are better able to accurately describe their level of sexual arousal. This hypothesis presupposes that women can differentiate between sexual feelings in their vagina and other genital areas; this has never been tested empirically. Alternatively, simultaneous measurement of an internal measure such as VPA and an external measure such as LDPI is another possible way to elucidate possible differences in genital-subjective arousal correlations associated with these measures. In all, this (expensive) technique shows promise in that in contrast to the current gold standard, data obtained are on an interval scale and therefore do allow comparison between individuals.

Recently, Kukkonen and colleagues investigated thermal imaging technology as a means to measure genital response. Infrared thermography detects natural thermal radiation from the body and is able to produce an image representing temperature distribution of body areas. During sexual arousal, there is increased blood flow to the genalia, resulting in vasocongestion and a rise in temperature. This measure discriminated between a sexually arousing, humorous, and neutral clip, in a student sample [120] and between a sexually arousing, humor, anxiety and neutral clip in an older sample [121], using between-subject designs (Level 2). In the latter study, within-subjects correlations between temperature change and subjective continuous arousal were variable with significantly positive correlations in 4 of 10 women who were measured in the sexual arousal condition. In principle, thermal imaging is a promising technology for the assessment of genital sexual arousal in both women as well as men, even though its high cost may prevent widespread use of this measure.

Magnetic resonance imaging of the pelvic area is another new method to evaluate genital response in women. Initially, this method required a contrast agent to observe dynamic changes in blood flow and engorgement, which yields the risk, albeit small, of an adverse reaction [122], but more recent techniques without contrast agent proved to be equally sensitive [123] (Level 3). A limitation of the noncontrast magnetic resonance technique is that it is not possible to obtain quantitative regional blood volume measurement, but since this is less robust than three-dimensional, anatomical clitoral volume measurements [124], this is not a significant limitation (Level 3). During sexual arousal, the crura and body of the clitoris as well as the vestibular bulbs, which according to O'Connell and colleagues should be considered part of the clitoris and therefore renamed as clitoral bulbs [125] demonstrate a very prominent increase in size and signal intensity [126] (Level 2). Measurement of other structures, including analysis of vaginal mucosa, vaginal wall thickness, or changes in the labia proved either unsuccessful or less reproducible than the clitoral volume measurement. Thus far, no differences were found between small groups of premenopausal and postmenopausal women when changes during sexual arousal of the vaginal wall, vaginal mucosa, clitoris, femoral vein...
signal intensity, relative regional blood volume, and clitoral volume were measured [127] (Level 2). Moreover, the mean unaroused clitoral volume (not including the vestibular, or clitoral, bulbs) of premenopausal women (2.8 cc) did not differ from that of postmenopausal women (3.1 cc), implying that even absolute changes in clitoral volume do not differ between groups [128] (Level 2). To date, none of the studies using this technique have compared women with and without sexual difficulties.

Most recently, Foldes and colleagues studied the clitoral anatomy in a sexually unstimulated state using functional 3D sonography [129,130] (Level 3). This technique requires a sonography probe placed on top of the vulva with a coronal, transversal, orientation to obtain coronal and transversal planes and the probe placed sagittally on the majora labia to obtain a sagittal scan. An echo-scan provides a fine anatomy of the clitoris and visualizes the displacement of structures during movement or perineal contractions in real-time. These images reveal the clitoris as a three planes (cross-section, sagittal section and coronal section) organ, with the clitoral bulbs reaching as far posteriorly as the perineal body, supporting the anatomical findings by O’Connell and colleagues [125]. The authors suggest that the special sensitivity of the lower anterior vaginal wall called the Grafenberg or G-spot could be explained by pressure and movement of the clitoral’ root during a vaginal penetration and subsequent perineal contraction.

Recommendations:

To date, psychophysiological techniques have been reserved largely for the research setting and are not a standard component of the clinical assessment or treatment in women, due in part to its invasive nature. Although vaginal photoplethysmography, the best researched measure to date, is a sensitive tool, it is not useful diagnostically because it cannot be calibrated. More research is needed using one of the newer psychophysiological techniques to explore whether these methods hold utility in discriminating clinical subgroups. Findings from psychophysiological studies to date suggest that in somatically healthy women, the potential to become genitally aroused is not disrupted. GRADE B

5. LABORATORY INVESTIGATIONS

The possibility that laboratory testing will identify causes of sexual dysfunction is low. Estrogen deficiency is best detected by taking a history and performing a physical examination [131]. Measurements of estradiol and follicle stimulating hormone (FSH) are indicated in amenorrheic young women or in women with irregular menstrual patterns or to evaluate menopausal status in hysterectomized women without a clear symptom history. Although some interpret the “hypo” in HSDD to infer a biological deficiency of testosterone [132], the majority of studies have failed to find a correlation between low sexual desire and serum testosterone levels in women [133-139]. In women with symptoms or signs of thyroid disease or hyperprolactinemia (galactorrhea, irregular menses and/or infertility), diagnostic assays should be taken.

Recommendation:

In women with symptoms or signs of thyroid disease or hyperprolactinemia (galactorrhea, irregular menses and/or infertility), diagnostic assays should be taken. GRADE C

6. HORMONES AND SEXUAL RESPONSE: ESTROGEN

The naturally occurring estrogens 17β-estradiol (17β-E2), estrone (E1), and estriol (E3) are C18 steroids derived from cholesterol. The most abundant and potent estrogen before menopause is 17β-estradiol (or estradiol). Estril and estrone are present at much lower levels and display less activity on estrogen receptors [140]. The primary source of estradiol in premenopausal women is the granulosa cells of the ovaries. After menopause, estrogen is produced in extradragonial intracellular sites from dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulphate (DHEAS), and androstenedione (A4). This peripheral production of estrogens from adrenal and ovarian prohormones and their interconversion depends on several factors, such as local activity of aromatase, 17β-hydroxysteroid dehydrogenases, and estrogen sulfatases [141,142]. The major estrogen in serum of postmenopausal women is E1 which is not measured by clinically available assays.

There are two subtypes of estrogen receptors (ERα and ERβ) and several isoforms and splice variants of each subtype. The overall degree of homology of the receptors is low, causing binding of ligands to the two receptors with different affinities. Estrogens act on estrogen receptors found in the vagina, vulva, urethra, and neck of the bladder [143,144]. Estrogen has been demonstrated to stimulate maturation and proliferation of vaginal and skin epithelia, to enhance vascularity and blood flow and to stimulate glandular secretion. In animal models, estrogens have been found linked to the regulation of vaginal and clitoral nitric oxide synthase expression [145,146], the enzyme responsible for the production of nitric oxide, a primary mediator of the physiological vasocongestive sexual response.

Several clinical studies have shown that an adequate estradiol level is important for maintaining vaginal lubrication and avoiding dyspareunia [147-150]. However, this is not to say that low estrogen levels invariably cause dyspareunia. Several studies showed
that baseline vasocongestion levels are related to estrogen levels in postmenopausal women, but in-
crease in genital arousal during sexual stimulation is not [93,94]. Thinning of the vulvo-vaginal epithelium,
atrophy of vaginal wall smooth muscle, diminished blood flow and reduced activity of specialized glands
are known consequences of the lack of estrogen. Hypoestrogenism has also been found to cause a
decrease in the resistance of the intercellular tight junctions in ectocervical epithelial cells. This has
been suggested as the cellular mechanism responsible for the decreased permeability which leads to
decreased lubrication of the lower genital tract [151].

A weak correlation between lower levels of estradiol and decreased sexual desire has been found by some
[150,152,153], but not by others [154-156]. Of note, studies have significant methodological differences:
assessment of women at different menopausal transition stages, different study designs and the use
of different sexual function questionnaires. Table 6 summarizes recent population-based studies that
have explored the association between estrogens and women’s sexual response.

Vaginal shortening and narrowing and introital stenosis are known complications of severe
vulvovaginal atrophy. Severe pain and/or bleeding from attempted penetration may occur; inability to
penetrate or avoidance may follow. Fear of hurting his partner and/or physical difficulty from introital
or vaginal narrowing might deteriorate the erectile function of the male partner.

Effects of menopause and hypoestrogenism on genital sensitivity are not well known. The sensory
field of the pudendal nerve has been found to be significantly larger in estrogen treated ovariectomized
female rats than in untreated controls [157]. A study measuring vaginal and clitoral warm, cold,
and vibratory thresholds in 89 women aged 18-78 found increasing age to be a positive predictor of
increased thresholds and worsening neurological function, but the study did not control for menopausal
status [158]. Interestingly, they found a smaller age
effect for the clitoral measurement, attributed to the richer innervation of the clitoris. Another study randomized 39 postmenopausal women with mixed lower-genitourinary-tract complaints into four arms: one group received topical estradiol (E2) cream and pelvic muscle biofeedback training, the second received topical E2 cream and sham biofeedback, the third received placebo cream and pelvic muscle biofeedback training, and the fourth received placebo cream and sham biofeedback. They concluded that topical estradiol cream significantly improved mechanical sensitivity of the vulvar vestibule compared with placebo cream [159] (Level 1). Another study compared 17 premenopausal against 15 postmenopausal women for vulvar sensitivity to pressure/touch. A clear association was found between reduced vulvar sensitivity to pressure/touch and estrogen deficiency. Significantly further reduced sensitivity was found in postmenopausal women not using estrogen replacement therapy [160] (Level 2).

Non-genital symptoms characteristic of the menopausal transition are hot flushes, breast
tenderness (at early stages, ceasing at later stages of transition) and insomnia. These could affect
sexuality indirectly. Estrogen modulation of central α2-adrenergic receptors has been linked to an
elevated sympathetic activation with menopausal estrogen withdrawal, which plays a role in the
initiation of hot flushes. Plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), the main metabolite
of norepinephrine, have been found to be significantly higher in symptomatic than in asymptomatic
postmenopausal women and increased significantly more during hot flushes. However, there is no
correlation between hot flush occurrence and plasma, urinary, or vaginal levels of estrogen, nor
are there differences in plasma levels between symptomatic and asymptomatic women [161].

Atrophic changes of the urogenital tract cause urgency, frequency, dysuria and predispose for urinary
tract infections [162,163] which could indirectly affect sexual function, or become consistently precipitated by intercourse.

Recommendations:

Lack of estrogen has been found related to dyspareunia and vaginal dryness. However, many
hypoestrogenic women do not have dyspareunia. When sufficiently sexually stimulated, low estrogen
may be irrelevant. An association between reduced estrogen and decreased sexual desire has been
only described clinically. There is some limited evidence to affirm that there is an association
between reduced vulvar sensitivity to pressure/touch and estrogen deficiency. GRADE B.

7. HORMONES AND SEXUAL RESPONSE:

The term “androgen” is applied to the class of C19 steroids, which are produced by the gonads and the
adrenals in both sexes from circulating low-density lipoprotein (LDL) cholesterol (a C27 molecule), and
include Testosterone (T), dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulphate (DHEAS),
androstenedione (A4), and 5 α-dihydrotestosterone (DHT) [164,165]. Of the androgenic steroids, T and
DHT have the most potent biological activity. DHEA, DHEAS, and A4 are adrenal and ovarian precursor
steroids that can be metabolized into T, DHT, and estrogen in peripheral tissues [166,167].

To date, no nuclear or membrane receptor for DHEA
has been identified. DHEA exerts its effects via the androgen receptor (AR) and/or estrogen receptor
(ER) after its conversion to androgen or estrogen, although direct effects of DHEA on the AR (exerting
both agonistic and antagonistic effects) and ER (as
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Design</th>
<th>Hormonal assessment</th>
<th>Sexual assessment</th>
<th>Significant findings</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dennerstein et al. (1997)</td>
<td>438</td>
<td>Pre-, peri- and postmenopausal Australian cohort. Cross-sectional analysis (year 4) of a longitudinal study. The Melbourne Women's Midlife Health Project (MWMHP)</td>
<td>E₂ was sampled on cycle days 4-8 (premenopausal) or after 3 months of amenorrhea (postmenopausal)</td>
<td>Personal Experiences Questionnaire (PEQ) validated for Australian women</td>
<td>Role for low E2 in vaginal lubrication and dyspareunia, marginal association with sexual desire</td>
<td>2</td>
</tr>
<tr>
<td>Dennerstein et al. (1999)</td>
<td>354</td>
<td>Longitudinal, year 6 follow-up.</td>
<td>As above</td>
<td>As above</td>
<td>Significant effect of menopausal status on vaginal dryness/ dyspareunia</td>
<td>2</td>
</tr>
<tr>
<td>Dennerstein et al. (2002)</td>
<td>226</td>
<td>Year 8 follow-up.</td>
<td>As above</td>
<td>As above</td>
<td>Sexual responsivity and desire were affected by low estradiol</td>
<td>2</td>
</tr>
<tr>
<td>Dennerstein et al (2007)</td>
<td>336</td>
<td>Longitudinal, year 9 follow-up, overall analysis of the influence of hormonal changes during the menopausal transition on a range of health outcomes</td>
<td>As above</td>
<td>As above</td>
<td>Declining levels of E2 during the menopausal transition affected certain health outcomes, vasomotor symptoms, vaginal dryness, and sexual response. Relationship factors and mood also affect sexual response.</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 6: Prevalence studies exploring the association between estrogens and women's sexual response and their levels of evidence (LOE)
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Design</th>
<th>Hormonal assessment</th>
<th>Sexual assessment</th>
<th>Significant findings</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guthrie et al. (2004) [150]</td>
<td>51</td>
<td>Year 9 follow-up. Only women still menstruating and had never taken hormonal therapy were interviewed.</td>
<td>As Above</td>
<td>As above</td>
<td>Estradiol was found to significantly affect sexual response (desire and responsivity) and dyspareunia. Sexual behavior predominately determined by previous behavior, change in partner status and feelings toward partner.</td>
<td>2</td>
</tr>
<tr>
<td>Avis et al. (2000) [155]</td>
<td>200</td>
<td>Cross sectional, pre-, peri-, or postmenopausal women</td>
<td>In subjects with regular cycles, E$_2$ was sampled on cycle days 2-10</td>
<td>Self administered sexual activity questionnaire</td>
<td>Low E$_2$ was related to dyspareunia. Menopause status, but not E2, was related to some, but not all, aspects of sexual function. Other factors such as health, marital status (or new partner), mental health, and smoking had a greater impact on women’s sexual functioning than menopause status.</td>
<td>3</td>
</tr>
<tr>
<td>Freeman et al. (2007) [153]</td>
<td>404</td>
<td>Longitudinal, pre- or peri-menopausal at baseline, 9 years follow up. Every 9-months for 4 years, then 3 annual intervals, and a last visit 2 years later.</td>
<td>Blood drawn in the first 6 days of two consecutive menstrual cycles or twice-1 month apart if noncycling</td>
<td>Questionnaire designed for the study asked about menopausal symptoms, including decreased libido or interest in sex; and vaginal dryness</td>
<td>Lower mean levels of E$_2$ were associated with decreased libido. Estradiol levels were not significantly associated with vaginal dryness in the menopausal transition of this cohort.</td>
<td>2</td>
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</table>
agonist) have also been demonstrated. Moreover, DHEA can act via non-steroid-receptor nongenomic pathways [168,169]. Androgens circulate in the body bound by a variety of proteins, including albumin, cortisol-binding globulin, α2-glycoprotein, and most importantly, sex hormone-binding globulin (SHBG). The affinity of androgens for SHBG is several orders of magnitude higher than that of albumin, and thus SHBG binds the largest portion of circulating testosterone. Androgens bound to SHBG are essentially not bioavailable; in contrast, androgens complexed to albumin are rather available due to their lower affinity. The liver produces SHBG—production which is stimulated by estrogen, particularly oral forms, and inhibited by androgens, and more importantly, insulin.

Androgen levels peak when women are in their 20’s and drop gradually with age, so that women in their 40’s have approximately half the level of circulating total testosterone as women in their 20’s. Testosterone levels do not decline consistently during or after menopause [170,171]. Androgens are known to act on multiple tissue and receptor sites, including the central nervous system pathways in the hypothalamus and limbic system, and peripheral sites such as bone, breast, pilosebaceous unit, skeletal muscle, adipose, and genital tissues [165].

The role of androgens in maintaining overall health, mood and sexual function has been the subject of research for more than 50 years, and its potential use in treating sexual problems of women is still under debate. This is covered in much more detail in Chapter 23. In 2002, a Consensus Conference on androgens agreed that androgen insufficiency in women with adequate estrogen levels could lead to a diminished sense of well-being and energy, fatigue, and decreased sexual desire [165]. The conference noted, however, that these symptoms were non-specific, and that there is lack of epidemiological data as well as limitations in laboratory assays to link these psychological changes to androgens. More recent guidelines from the Endocrine Society recommended against making a diagnosis of "androgen insufficiency", because of the lack of a well-defined clinical syndrome and normative data on testosterone levels across the lifespan that can be used to define such a disorder [172]. However, a panel of sexual medicine clinicians challenged the conclusions from the Endocrine Society Guidelines as ignoring some of the available data in support of androgen therapy [173] (Level 4).

As reviewed in Table 7, population-based studies have shown minimal or no correlation between androgen levels and sexuality in women. In the Melbourne Women’s Midlife Health Project, a representative sample of women from the general population was recruited and followed yearly during the menopausal transition. Fasting morning samples of estradiol, serum testosterone, SHBG, and DHEAS were taken along with a number of physical measurements at 2 year intervals. At their 9 year review, findings showed minimal change in testosterone levels measured in 438 women. Also, androgen levels did not correlate with any aspect of sexual functioning [150]. In the Study of Women’s Health Across the Nation (SWAN) [139], 2,961 pre-menopausal women aged 42-52 were recruited to participate in a longitudinal study that aimed, among other things, to characterize the reproductive hormone patterns of women as they approached and traversed menopause. DHEAS, T, and SHBG concentrations measured at baseline showed T to be minimally associated with increased desire (odds ratio=1.09) and very weak or no correlation between androgens and sexual function or mood. Another Australian study which included 1,021 women aged 18 to 75 found no correlation between T or A4 levels and sexual function but higher odds of low sexual responsiveness if DHEAS was less than the 10th percentile. Nevertheless, most women with low DHEAS levels did not report low sexual function [134].

The lack of accuracy of current assays to measure testosterone is a well known limitation [174]. Most clinically available assays are designed to measure testosterone in the male range or to identify hyperandrogenic states in women [175]. Tandem mass spectrometry methods in combination with gas chromatography or liquid chromatography have been developed for testosterone and are the methods of choice for the precise measurement of the low levels [176]. Unfortunately, these assays are not widely available in clinical settings. Recently, the Centers for Disease Control and Prevention, National Center for Environmental Health, Division of Laboratory Sciences (CDC/NCEH/DLS) have initiated a project to standardize and to improve steroid hormone measurements [177].

An additional aspect to consider here is the intracrinology of sex hormones. Steroidogenic enzymes are widely distributed in peripheral cells to convert adrenal DHEA, DHEAS and A4 (and for pre-menopausal women, also ovarian DHEA and A4) to T, DHT, estrone (E1) and estradiol (E2). This intracellular production is a major source of T and DHT, and is known to reduce by 80% through adult life. Active androgens, whether produced in a peripheral cell or stemming from the ovaries, are inactivated to glucuronide derivatives before their diffusion from the intracellular compartment into the general circulation (plasma), where they can be measured as the androgen metabolites, androstenedione glucuronide (ADT-G), 3α-diol-G and 3β-diol-G [178]. Although glucuronide derivatives, appeared as reliable markers of the total androgen pool, since they are the obligatory route of elimination of all androgen [179], a recent study comparing glucuronide derivatives levels in 121 women with sexual dysfunction vs. 124 controls, did not show a significant difference between the groups [180].
**Table 7: Population based studies relating androgen levels to female sexual function and their levels of evidence (LOE)**

<table>
<thead>
<tr>
<th>Citation</th>
<th>n</th>
<th>Design and inclusion criteria</th>
<th>Hormonal assessment</th>
<th>Sexual assessment</th>
<th>Significant findings</th>
<th>LOE</th>
</tr>
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<tbody>
<tr>
<td>Cawood and Bancroft, 1996 [133]</td>
<td>141</td>
<td>Prospective study over 5 weeks; healthy community volunteers, aged 40–60 years</td>
<td>Four weekly blood samples (midcycle samples excluded), averaged 4 samples; measured T, SHBG, A, DHEA, DHEA-S, E2, E1, P, FSH, LH, FAI.</td>
<td>Five structured interviews over 5 weeks; Frenken Sexual Experience Scale.</td>
<td>Hormones and menopausal status not significantly correlated with sexual function. Sexual function better if adequate vaginal lubrication, good relationship, higher socioeconomic status, lower BMI, and normal mood.</td>
<td>3</td>
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<tr>
<td>Gracia et al., 2004 [137]</td>
<td>326</td>
<td>Prospective study over 4 years; random population women aged 35–47, intact uterus and at least one ovary, premenopausal at baseline.</td>
<td>Blood sample on days 1–6 every 8 months; T, DHEAS, E2, FSH, LH. Used RIA.</td>
<td>One question on “decreased libido” in last month and one on vaginal dryness.</td>
<td>Twenty-seven percent of women had low desire. No difference in their mean hormone levels, but had greater fluctuation of total T over time. Low desire related to depression, vaginal dryness, and having children at home.</td>
<td>3</td>
</tr>
<tr>
<td>Dennerstein et al., 2002, 2005 [135, 136]</td>
<td>336</td>
<td>Prospective study over 8 years; random population sampling of women aged 45–55 years, menstruating at baseline. The Melbourne Women’s Midlife Health Project (MWMHP).</td>
<td>Yearly fasting morning blood sample days 4–8 of menstrual cycle or after 3 months of amenorrhea; FSH, E2, T, SHBG, DHEA-S, inhibin, FAI. Used RIA.</td>
<td>Personal Experiences Questionnaire validated for Australian women; Sexual response score included desire, arousal, pleasure, and orgasm.</td>
<td>Androgens had no impact on sexual function. Most important factors were previous sexual function, losing a partner (negative) or getting a new partner (positive), and satisfaction with current relationship. E2 level impacted sexual desire/arousal and dyspareunia.</td>
<td>2</td>
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</table>
Table 7: Population based studies relating androgen levels to female sexual function and their levels of evidence (LOE) (continued)

<table>
<thead>
<tr>
<th>Citation</th>
<th>n</th>
<th>Design and inclusion criteria</th>
<th>Hormonal assessment</th>
<th>Sexual assessment</th>
<th>Significant findings</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis et al., 2005 [134]</td>
<td>1,021</td>
<td>Cross-sectional study in Australia; random selection from community, aged 18–75 years; 9% response rate.</td>
<td>One fasting morning blood sample; if premenopausal after cycle day 8 and before onset of menses (to avoid the early follicular phase testosterone nadir): T (direct RIA), DHEAS and SHBG (immunometric assays); A1 (direct RAI); FSH, TSH, LH, and prolactin using automated machines.</td>
<td>Profile of Female Sexual Function, validated questionnaire (7 domains of desire, arousal, orgasm, pleasure, sexual concerns, responsiveness, and self image).</td>
<td>No significant relationship between androgen levels and sexual function, most women with low DHEAS did not report sexual problems.</td>
<td>2</td>
</tr>
<tr>
<td>Santoro et al., 2005 [139]</td>
<td>2,961</td>
<td>Longitudinal study, report of cross sectional measurements at baseline. Multi-ethnic community-based sample of women aged 42–52 years, menstruating at baseline. The study of women’s health across the nation (SWAN)</td>
<td>Blood drawn after 10-hour fast on days 2–7 of follicular phase. Serum E2 (automated analyzer immunoassay). T (polyclonal anti-T antibody binding), SHBG and DHEAS (chemiluminescent assays). FAI calculated. Assays were calibrated for low levels of T in women.</td>
<td>Questionnaire designed for the study asked about frequency of desire for sex and about arousal during sex.</td>
<td>Androgen levels weakly associated, if at all, with sexual desire, sexual arousal, or mood but were associated with having the metabolic syndrome.</td>
<td>2</td>
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<tr>
<td>Gracia et al., 2007 [138]</td>
<td>313</td>
<td>Penn Ovarian Aging Study; 3-year prospective data of equal samples of African-American and Caucasian women aged 35–47 years at baseline, menstruating.</td>
<td>Blood sample on days 1–6 of menstrual cycle in two consecutive cycles once a year; E2, FSH, LH, SHBG, DHEAS, total T. Radioimmunoassay commercial kits.</td>
<td>Female Sexual Function Index.</td>
<td>Sexual dysfunction did worsen as menopause progressed. Although low DHEAS was correlated with vaginal dryness, pain, and orgasmic dysfunction, much stronger relationship of sexual dysfunction was found with lack of a partner and with high anxiety.</td>
<td>2</td>
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<tr>
<td>Gerber et al., 2005, [389]</td>
<td>23</td>
<td>5-year longitudinal study, community-based including premenopausal (at baseline) women aged 45–55 years.</td>
<td>Free T measured by enzyme immunoassay. T levels obtained twice, four years apart.</td>
<td>Questionnaire designed for the study asked about desire, sexual initiative, sexual satisfaction.</td>
<td>No significant relationship between androgen levels and sexual function. Exercise improves sexual function.</td>
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Over the last two decades it has become clear that the brain is a steroidogenic organ.

The steroids synthesized de novo by the brain and nervous system, given the name neurosteroids, have a wide variety of diverse functions [181]. In general, they do not mediate their actions through classic steroid hormone nuclear receptors, but through stimulation of rapid changes in excitability and direct activation of membrane receptors in neurons [182]. Current evidence in animals points to important roles for neurosteroids in sexual and gender-typical behaviors, control of ovulation, and behaviors that strongly influence sexual interest and motivation [182]. Sex steroid production and action within the brain may be more relevant to women’s sexual desire and function than peripheral androgens.

The great variability in the responsiveness of women to treatment with androgens is another confounding factor. For example, there are contradictory findings on the effects of the oral contraceptive pill on sexual interest. The former increases the concentration of SHBG thereby lowering the bioavailable testosterone [183-185]. A possible explanation could be the polymorphic variations of the androgen receptor (AR) gene. The AR gene is located on chromosome Xq11–12. A polymorphic polyglutamine stretch in the amino-terminal domain of the AR, encoded by the nucleotides cysteine, adenine, and guanine (CAG), appears to influence the function of the receptor. Long CAG repeat fragments have been associated with a low level of receptor function [186]. The polyglutamine region is assumed to be involved in interactions between the AR and different coactivators; recent data suggest that long repeat regions are inhibitory to these interactions, which could explain the lower activity of the receptor [187]. Although androgen receptor CAG repeat length has not been studied in regard to sexual function, its relation to dermatological, oncological, fertility and behavioral conditions has been established. Further elucidation of the genetic determinants for serum androgen activity could explain why some women are more sensitive to androgens than others [188].

** Recommendations: **

Although controversial, the majority of evidence fails to find a significant correlation between sexual desire and response and testosterone levels in women. There are significant limitations in this research: (i) the lack of standardized assays which are suitable for detecting androgens in the female range; (ii) the inability to quantify neurosteroid production and action, (iii) the current lack of understanding of the role of the androgen receptor gene polymorphism in the extent of serum androgen activity and (iv) the current lack of a clear definition of sexual desire and consensus about what constitutes sexual desire problems, Testosterone level measurements in women cannot be recommended until more accurate measures of androgenic activity emerge **GRADE B**

8. **SEX HORMONES AND NEUROTRANSMITTERS**

Fluctuations in estradiol levels during perimenopause have been linked to irritability, tearfulness, anxiety, depressed/labile mood, lack of motivation/energy, poor concentration and interrupted sleep [189]. Neurotransmitters and steroid hormones appear to have a modulatory function on each other, and changes in one system may have a dramatic effect on the other [190]. For instance, recent longitudinal data suggest that the transition to menopause is strongly associated with new onset depressed mood among women with no history of depression [191]. Clinical and experimental data in addition to new imaging techniques such as PET, SPECT, spectroscopy and functional and structural MRI have confirmed a large part of earlier animal studies: the major neurochemical systems involved in sexual behavior consist of pathways involving neurotransmitters and hormones including dopamine, serotonin, norepinephrine, prolactin, oxytocin, melancortins and endogenous opioids. Some of these substances are substantially influenced by gonadal steroid hormones and/or interact among each other [190,192]. In rodents, estrogen receptor type beta (ERβ) has been found in populations of gonadotropin-releasing hormone, corticotropin-releasing hormone, vasopressin, oxytocin and prolactin containing neurons in the hypothalamus [193]. As noted earlier, steroids may also act through stimulation of rapid changes in the neuron membrane excitability.

9. **AGE VERSUS MENOPAUSE IN PREDICTING SEXUAL PROBLEMS**

When exploring the influence of menopause on sexual response, separating age-related effects from hormonal changes can be difficult though it is essential. In the Melbourne Women’s Midlife Health Project, comparison between age-matched premenopausal and postmenopausal women showed that sexual desire and lubrication are affected by both menopause and aging, independently [150,152]. In a longitudinal study of 1,525 British women aged 47-54, independent effects of menopause and aging on sexual functioning were also found [194]. Health factors related to aging are known to affect sexuality. A study assessing 1,384 women and men older than 45 found that high blood pressure was linked to low sexual desire whereas diabetes, arthritis, and depression were not [195]. Age was strongly associated with a decline in desire but not for all women. In 22% of women with higher levels of desire, an association was found with the
belief that sexual activity is important for quality of life, disagreeing with the belief that “sex is only for younger people”, and the presence of a partner. In a multiple regression analysis, psychological variables were more predictive of desire than any biological factor [195]. The Global Study of Sexual Attitudes and Behaviors (GSSAB) conducted in 27,500 men and women aged 40-80 across 29 countries, found low sexual desire was related to age in women, and was associated with the belief that aging reduces sexual desire [50]. Reduced lubrication was also age-related but curvilinear in that symptoms decreased in the oldest cohort of women.

A 2003 review of all population-based studies exploring sexuality after menopause found that sexual problems were more common in older women, but more distressing for the younger cohorts [196]. This phenomenon (sexual problems greatest, but least distressing in older women) has been replicated in larger, more recent studies [31,197]. The Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking Study (PRESIDE) was conducted in 31,581 US women aged 18 and older. Desire, arousal, and orgasm problems were found in 27.2% of women aged 18–44 years, compared with 44.6% of women aged 45-64, and 80.1% of 65 years or older, although the prevalence of having a distressing sexual problem was far less (10.8%, 14.8% and 8.9% respectively) [31].

**Recommendations:**

Teasing apart age-associated versus menopause associated contributions can be difficult although practitioners should make and effort to do so. Age and menopause are both significantly associated with desire and arousal problems in women, however, the presence of distress appears not to be. Whereas sexual complaints increase with age, the associated distress appears to diminish. Psychosocial aspects of aging and menopause contribute more to difficulties than hormonal contributions and should therefore be the focus of assessment and treatment **GRADE B.**

**10. SURGICAL MENOPAUSE AND DESIRE/AROUSAL COMPLAINTS**

The contribution of surgical (via bilateral salpingo-oophorectomy; BSO), as opposed to natural menopause, has been extensively studied but with inconsistent findings. The WISHes study recruited 4,517 women from France, Germany, Italy, the United Kingdom, and the USA [197,198] (Level 3). In this study, a greater proportion of surgically menopausal women had low sexual desire compared with age-matched premenopausal or naturally menopausal women. Surgically menopausal women aged 20 to 49 years were significantly more likely to experience distress about their condition. Of note, no subgroup analysis comparing estrogen-replete to non-estrogen-replete women was done. Another recent cross-sectional study assessed prevalence of low sexual desire with and without distress in 2,207 US women aged 30-70 [199]. The highest prevalence of low sexual desire was found in naturally menopausal women (52.4%) rather than surgically menopausal women (39.7%) when compared to premenopausal women (26.7%). Low desire plus distress (HSDD) was found to be nearly twice as prevalent among surgically menopausal women (12.5%) than in premenopausal women (6.8%), especially if women were younger than 45. Women receiving exogenous hormones were less likely to complain about low desire but had slightly more distress than women not using hormones (Level 3).

Prospective studies have not confirmed sexual dysfunction subsequent to surgical menopause for benign disease. Aziz et al. found no correlation between ovarian removal and reduced sexual function in a study of 362 perimenopausal women undergoing elective hysterectomy with and without BSO [200] (Level 2). In this study the women were evaluated for sexual function within 2 months before the surgery and one year after. Importantly, women were the ones who chose either to undergo BSO or not, after receiving information on its potential advantages and disadvantages (e.g., change in hormonal milieu with possible negative effects on sexuality and psychological well-being vs. prevention of ovarian cancer and avoidance of future surgery for benign adnexal mass). Teplin et al. prospectively compared sexual function among 112 premenopausal women who underwent hysterectomy with and without BSO. BSO was performed at the patients' request or to treat intraoperative ovarian pathology. Assessment was carried out at 4 weeks, 6 months, and 2 years after the surgery. There were no statistically significant differences in measures of sexual functioning between the groups at any follow-up visit [201] (Level 2). A more recent study collected data prospectively for 3 years from 257 women undergoing hysterectomy and 57 women undergoing hysterectomy with BSO. The proportion of sexually active women in either group after the surgery and the prevalence of vaginal dryness did not differ [409] (Level 2). No data on sexual desire or interest were presented.

**Conclusion:**

Distress associated with low desire, but not low desire per se, is most prevalent among surgically as opposed to naturally menopausal women. Among prospective trials of elective BSO, sexual function did not appear to differ from a control group. Sexual distress should always be assessed when there are complaints of low desire. **GRADE B**
11. DIAGNOSIS AND FORMULATION

On the basis of a thorough biopsychosocial assessment of partners individually and together (when available and possible), and the relevant physical, physiological, or hormonal assessments, the clinician determines a diagnosis and formulation of a woman’s sexual problem(s). Assessment does not end when treatment begins; emerging information continues to inform treatment, and outcomes from interventions may in turn modify the diagnosis and formulation. Patient rapport is facilitated if a cogent formulation is presented and explained to the patient. Historical details, direct observation of the couple, couple interactions and attitudes, and response to initial treatment interventions modulates the formulation. The initial formulation may well change as patient visits continue. With the publication of DSM-V in 2013, it is likely that diagnostic criteria may evolve even further [28].

The type, frequency, and severity of sexual complaints must be determined as well. Using the DSM-IV-TR system, one might apply a diagnosis of HSDD and/or FSAD. The recommended diagnoses and criteria set out by the AUAF (Table 1) offer an improvement over the DSM-IV-TR with less pathologizing diagnostic criteria. Some find it useful to include both diagnostic schema. With the publication of DSM-V in 2013, it is likely that diagnostic criteria may evolve even further [28].

Part of the formulation also includes relevant information from self-report questionnaires, interviews, and relevant physical or physiological examinations and testing. Graham and Bancroft describe a “three windows” approach helpful for contextualizing factors influencing the sexual complaint [202] (Level 3) (Figure 2). The first window describes aspects of the woman’s current situation, e.g., are poor communication, relationship difficulties, fatigue, or lack of privacy responsible for the desire or arousal concerns? The woman plagued with fatigue might benefit from a course of sleep hygiene therapy prior to (or instead of) sex therapy. In the second window, Graham and Bancroft suggest looking at individual vulnerability factors influencing the presentation of complaints. Does the woman display persistently negative attitudes about herself and her body? Does she have a high need to maintain control in all life and sexual situations? Is there a past history of sexual abuse or trauma such that flashbacks to the prior abuse are frequent and intrusive when she is attempting to be sexual? If such individual vulnerability factors are present, she may benefit from a cognitive behavioral (CBT) treatment focused on that vulnerability factor (e.g., Cognitive Processing therapy for sexual assault, CBT for perfectionism, etc). The third window invites the clinician to consider health-related factors influencing the sexual response. One aspect of this domain would include mental health, such as depression or anxiety. This window also explores physical health related factors, such as problems in the neural control of desire and arousal, problems in vascular supply to the genitals, endocrine dysfunction, and metabolic problems. The presence of any of these physical health related factors significantly impacts the formulation of the sexual complaint (as being due to a general medical condition). An important aspect of this third window includes the influence of both over-the-counter and prescription medications on sexual response. These ‘windows’ echo the descriptors recommended by the AUAF committee [41] and are depicted in Figure 2.

Although objective duration and severity criteria are not features of either the DSM-IV-TR or the AUAF systems of classification, such information can be a very useful adjunct in the formulation. The DSM-IV-TR text for HSDD indicates that “occasional problems with sexual desire that are not persistent or recurrent or are not accompanied by marked distress or interpersonal difficulty are not considered to meet criteria for HSDD” [1]. Notably, data on the required frequency or intensity of low desire for designating desire disorder and the specific duration of complaints have not been reported on in the empirical literature. In the FSFI [203] --the most commonly used self-report measure of sexual response in women--the desire domain is assessed as a composite of one question assessing the frequency of sexual desire and another question about the level (degree) of sexual desire (from very low to very high). Whether a reduction in sexual desire is experienced more often in terms of reduced frequency or reduced intensity, however, has never been empirically tested. It has been recommended that only problems lasting for a minimum of 6 months duration be considered for diagnosis [28,29,204]. This time duration was chosen given the finding of the NATSAL survey [49] that lack of interest in sex for the past one month was significantly more common (40.6%) than lack of interest lasting for six months (10.2%). Short term complaints that might be attributable to transient changes in the woman’s health or relationship should not be diagnosed as a sexual dysfunction. Whether the problem is lifelong or acquired and generalized versus situational can be coded as specifiers if one uses the traditional DSM-IV-TR classification scheme. However, in clinical practice, a sexually distressing problem that is only situational is rarely diagnosed as a dysfunction, although treatment of that problem might still take place (Level 4).

Recommendations:

A formulation of the diagnoses is recommended. The formulation integrates all information obtained from (sometimes a series of) assessments of the woman with and without a partner, and any relevant physical examinations, blood analyses, and self-report questionnaires completed. On the basis of the formulation, a diagnosis is applied, possibly using
both the DSM-IV-TR as well as the AUAF systems. The clinician also continues to modify the formulation as information emerges during treatment. The “three windows” approach can be very helpful for considering the many biopsychosocial factors that influence the woman’s sexual complaints. An effort should be made to determine the duration and severity of symptoms. **GRADE C**

**12. TREATMENT INGREDIENTS RELEVANT TO ALL SEXUAL PROBLEMS IN WOMEN**

General issues related to improved well-being, such as diet, exercise, possible alcohol and chemical substance abuse, and sleep should be addressed in all women. Advising on all prescription and non-prescription medications, vitamins and herbal supplements, and recreational drugs is important as well. Providing women relevant information on improving general health related to each of these domains may also be a component of care, and referral to appropriate medical or specialty providers may be necessary. The early stage of treatment might also include providing information on basic genital anatomy and physiology, and a discussion of sexual stimulation and sexual activities other than intercourse. Women should be encouraged to use techniques that enhance arousal, including enhancing the context within which her sexuality is expressed and the stimuli she receives. **GRADE C**

**III. ISSUES SPECIFIC TO LOSS OF DESIRE**

**1. BIOLOGICAL ASPECTS OF LOW SEXUAL DESIRE AND LOW SUBJECTIVE AROUSAL**

The biology of desire and subjective arousal is not yet well known and understood. It seems that the instinctual part is rooted in thalamic, hypothalamic and limbic brain regions. Sexual desire may be conceived of as being connected to other basic emotional systems like fear-anxiety, in that it is a highly adaptive response to an emotionally competent stimulus [205] (Level 4). In this perspective, the subjective experience of desire may be the conscious awareness of the automatically generated bodily responses to the stimulus (i.e., arousal) which produces the sensation of “wanting” [206] (Level 4). The subjectively experienced state of desire may thus be the final result of a complex interplay of driving and inhibiting forces [207] (Level 4). The biological factors mentioned below may hamper responses to “sexually competent stimuli”. The most important neurotransmitters involved in desire and subjective arousal are norepinephrine, dopamine, melanocortins, oxytocin, serotonin acting via 5 HT_{1A} and 5 HT_{2C} receptors—being prosexual, and prolactin, GABA and serotonin acting via other receptors—being inhibitory or negative [46] (Level 4). The actions of
these substances are modified and influenced by the endocrine milieu provided by estrogen, progesterone and testosterone (Level 4). Here we briefly consider the influence of chronic disease, the postpartum, and oral contraceptives on sexual desire.

Chronic diseases may have an important negative impact especially on desire and arousal, and are covered more thoroughly in Chapter 9. The mechanisms involved can be separated into biological changes that interfere directly with the physiology of the central and peripheral sexual response on the one hand, and the psychological consequences of being ill (coping with the illness, depressive reaction etc.) on the other [208] (Level 2 and Level 3). The chronic conditions listed in Table 8 have been found to be positively correlated with the incidence of HSDD. Table 9 provides recommendations for assessment questions specific to the sexual complaints among women with chronic disease.

Research suggests that a woman’s interest in sexual relations changes after childbirth; 47-57% of women interviewed at three months postpartum noted a decreased sexual interest. Lower libido has been attributed to fatigue, pain, and concern over injury. Despite any potential changes in desire, more than 80% of women resume coitus by six weeks postpartum [209] highlighting the disconnect between sexual desire and sexual activity frequency.

Combined oral contraceptives containing ethinylestradiol increase SHBG and thus decrease available free testosterone. This has been purported to contribute to a lack of desire and subjective arousability [210] (Level 3). Due to the fact that oral contraceptives display manifold psychological and biological actions, some of which may have a positive impact on sexuality (reduce anxiety about unwanted pregnancy, diminish dysmenorrhea, attenuate acne etc.), it is very difficult to discern the clinical effect of the diminution of free testosterone in users of oral contraceptives [211] (Level 3).

2. PSYCHOLOGICAL ASPECTS OF LOW SEXUAL DESIRE AND SUBJECTIVE SEXUAL AROUSAL DISORDER

A woman’s sense of personal well-being is important to sexual desire. Low perceived levels of physical and emotional satisfaction and a sense of unhappiness correlate with low sexual desire [31,33,46,212] (Level 3).

Psychological factors may contribute to desire and subjective arousal in manifold ways, including motivational and cognitive pathways. The motivation to engage in sexual activity may be the wish to be emotionally close to the partner, to satisfy the partner, to feel feminine, to feel powerful and accepted [26]. Cognitive pathways refer to the meaning given to the sexual activity which implies previous experiences provided by episodic memory. There are many factors that may have a negative impact on motivation and cognition.

There is very little evidence-based research in this field. The observations about facilitating and impeding factors for the development of sexual health are mainly theoretical, clinical and anecdotal. The most frequent applied research methodologies in this field are correlational and ecological studies.

Some major groups of predisposing factors have been found to be clinically relevant for desire and arousal difficulties and these include:

a) Sexual abuse and emotional neglect in childhood:

Several studies have shown variable midterm and long-term effects on the female adult’s sexuality after childhood abuse and neglect. One of the possible sequelae is low desire and sexual aversion [213-219] (Level 2 and 3).

b) Traumatic experiences during puberty:

Research among adolescents has shown that first negative sexual experiences and especially humiliation and offense may have long-term consequences for the internal sexual script which determines positive and negative attributions to one’s sexual life [220] (Level 3).

Other psychological factors may act as predisposing and maintaining factors:

a) Perceived stress:

Some observational studies have shown that psychosocial stress in general may reduce the motivation to become sexually active. Apart from cognitive processes there may be an incremental effect of a stress induced cortisol secretion [31,221] (Level 3). There is one experimental study on the effect of (acute and chronic) psychological stressors on genital and subjective sexual arousal [222]. To investigate whether psychological stressors inhibit sexual responding, sexually functional women were randomly assigned to an experimental condition in which acute psychological stress was induced by a frustrating computer task or to a control condition. After the acute psychological stress or control induction women were exposed to an erotic stimulus. Genital sexual arousal was assessed with VPA. Women in the acute stress condition responded with lower levels of genital and subjective sexual arousal to an erotic stimulus than women in the control condition. Women were post hoc divided into a ‘low’ and a ‘high’ chronic stress group, based on their pre-assessment scores on a chronic daily stress questionnaire. Those with high levels of chronic stress responded with lower levels of genital sexual arousal to an erotic stimulus than women with low levels of chronic stress. Chronic stress did not affect the level of subjective sexual arousal (Level 3).
Table 8: Association of chronic medical illness and sexual desire difficulties in women and levels of evidence (LOE) across studies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Association with low desire</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyper and Hypothyroidism</td>
<td>Increase in lubrication and orgasm problems in dysthyroidal women compared to age matched controls, with an increase in depressive symptoms. No significant difference in desire [390]</td>
<td>3</td>
</tr>
<tr>
<td>Urinary Incontinence</td>
<td>Prevalence rates of sexual dysfunction from 0.6-64%. [391] In a case control study women with urinary problems had significantly lower desire, more arousal difficulties and pain [392]</td>
<td>3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Different prevalence rates of FSD are reported due to the methodological difficulties and possible confounders (Type of Diabetes, age, treatment, complications etc) The predominant symptoms seem to be low desire, arousal dysfunction and decreased lubrication, although estrogen deficiency could be a possible confounder and not all studies show significant differences to controls. A significant correlation between number of complications but not type of complication was found and a significant correlation with depression. Low desire seems more depression and relationship related in female diabetic patients than disease related [393-398]</td>
<td>2, 3</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Higher incidence of sexual arousal disorder but not HSDD in women [399]</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>The impact of hypertension or treatment of hypertension in women is not clear. One cross sectional found decreased desire compared to the control group [400,401]</td>
<td>3</td>
</tr>
<tr>
<td>Arthritis</td>
<td>This disease may lead to a dramatic decrease in mobility and to chronic pain and thus impair sexual function [402]</td>
<td>3</td>
</tr>
<tr>
<td>Spinal cord injuries, MS, neuromuscular disorders</td>
<td>Direct impact on the neuromuscular and neurovascular elements of the sexual response. The effect on desire is in general indirect mediated by other dysfunctions and pain [403,404]</td>
<td>2, 3</td>
</tr>
<tr>
<td>Parkinson’s disease, Dementia, Schizophrenia</td>
<td>Hypothalamic sexual centres are connected to central nervous neurotransmitter pathways and may be influenced by disturbances of dopaminergic, serotoninergic, adrenergic and gabaergic action. May result in decreased desire but also in increased desire and hypersexual behaviour. Sexual dysfunction is estimated to affect 30-80% of patients with schizophrenia and is a major cause of poor quality of life. [406-408]</td>
<td>3</td>
</tr>
</tbody>
</table>
b) Distraction/Attention:
Distraction has been shown to be detrimental to female sexual arousal, especially subjective arousal and desire [91,223,224] (Level 3). Attention has been investigated as it relates to sexual arousal. In two subgroups, which were differentiated on the basis of their initial preconscious attentional bias for sexual cues, a different sexual response profile was found. In an initially low-attention group, preconscious attentional bias for sexual cues increased under a testosterone condition. In these women, the combination of supra physiological testosterone and vardenafil caused an improvement in genital response and subjective indices of sexual functioning. In the group that had initially a high attention for sexual cues, preconscious attentional bias for sexual cues decreased under the condition of testosterone. In these women, the combination of testosterone and vardenafil had no effect on any of the indices of their sexual functioning [225] (Level 3). An earlier pilot study found similar results [226] (Level 3).

c) Self-focused attention:
Self-focused attention may negatively impact genital and subjective sexual arousal. In a recent study, state self-focus was induced by switching on a TV camera that pointed at the participant’s face and upper torso in sexually functional women. Induction of state self-focus per se did not affect genital responses, but an interaction effect between self-focus and participants’ level of trait sexual self-focus was revealed. Compared with women with low scores on this trait, women with high scores exhibited smaller genital responses when state self-focus was induced. Both groups did not differ when no self-focus was induced. Increase of state self-focus did not affect subjective sexual arousal, but participants with a high level of trait sexual self-focus reported stronger subjective arousal, compared with those with low trait level [227] (Level 3).

d) Anxiety:
The model of performance anxiety was largely derived from male patients with erectile dysfunction. For women sexual performance concerns have a different focus because the signs of sexual arousal are less publicly evident. For women there is a large array of sexual concerns (worries about pleasing her partner, fear of partner rejection, fear of pregnancy and STI, unease related to the ability

Table 9: provides recommendations for assessment questions specific to the sexual complaints among women with chronic disease.

<table>
<thead>
<tr>
<th>Question</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Danger (Threat)</td>
<td>How does the patient experience the threat of the disease to her life?</td>
</tr>
<tr>
<td>Destruction</td>
<td>Does the disease or treatment have a direct impact on the integrity of sexual organs?</td>
</tr>
<tr>
<td>Disfigurement</td>
<td>Does the disease lead to a change in the body’s outer appearance with a possible negative emotional impact?</td>
</tr>
<tr>
<td>Disability and pain</td>
<td>Is the disease causing chronic pain and motor disability which may impact on the patient’s capacity to enjoy the bodily expression of her sexuality?</td>
</tr>
<tr>
<td>Dysfunction</td>
<td>Does the disease lead to an impairment of the sensorimotor and sensovegetative innervation of the physiological processes involved in the human sexual response?</td>
</tr>
<tr>
<td>Dysregulation</td>
<td>Does the pathophysiology of the disease have an impact on the neurobiological and neuroendocrine processes involved in the central or peripheral regulation of the sexual response cycle?</td>
</tr>
<tr>
<td>Disease load</td>
<td>Is the disease accompanied by an impairment of intimate physical mechanisms like micturition and defecation?</td>
</tr>
<tr>
<td>Drugs</td>
<td>What is the impact of the drugs used for the treatment of the disease?</td>
</tr>
<tr>
<td>Depression</td>
<td>Has the disease process lead to depression as a independent comorbidity</td>
</tr>
<tr>
<td>Debility</td>
<td>Is the disease accompanied by severe cognitive impairment</td>
</tr>
<tr>
<td>Loss of Independence</td>
<td>Is she now dependent on others for basic daily functioning and is the caretaker also the woman’s intimate partner?</td>
</tr>
</tbody>
</table>

Note: This information is covered more fully in Chapter 9.
to reach orgasm) that may interrupt her experience of sexual desire [228] (Level 3). Anxiety has been conceptualized as consisting of a chronic somatic component of overactivation, a cognitive component focusing on perceived lack of control, and a shift of attention to internal somatic cues. In terms of the subjective experience, anxiety can be characterized as a condition of anxious apprehension [229] (Level 3). Research examining the role of anxiety in sexual dysfunction has included both clinical studies and controlled laboratory investigations. Early psychodynamic theories placed a heavy emphasis on anxiety as an important etiological predictor of sexual dysfunction. In Kaplan’s influential model of etiology [230], performance anxiety was both a consequence of sexual activity, and a cause of sexual dysfunction, and reflected the failure of psychic defenses to prevent the emergence of anxiety (Level 4). Based completely on clinical experience, anxiety and sexual arousal were thought to be incompatible with each other. The empirical literature, however, suggests such conclusions to be overly simplistic.

The role of anxiety as a key etiological agent in the genesis of sexual disorders has been highlighted in a number of clinical research studies. One review found high levels of anxiety in sexually dysfunctional individuals [231] (Level 2) however, there was a high degree of variability in the amount and quality of anxiety across individuals with different sexual disorders [232,233] (Levels 2 and 3). Sexual aversion tends to correlate highly with acute anxiety [234] (Level 3). More recent studies on women with general sexual dysfunction [235], (Level 2) as well as those with low sexual desire [236], find higher rates of depression and anxiety compared to sexually healthy women (Level 3). Worry, on the other hand, while it is associated with many psychiatric disorders and especially anxiety, did not appear to be a risk factor for sexual desire [237] (Level 3).

Whereas most of the research examining the relationship between anxiety and sexuality has explored anxiety in women with sexual dysfunction, some research has looked at sexuality in men with anxiety disorders. The literature suggests a higher incidence of sexual difficulties in women with anxiety disorders compared to non-anxious women. For example, women with panic disorder [238,239] and obsessive compulsive disorder [239] show lower sexual desire than healthy controls (Level 2). Women with OCD are more likely to experience sexual difficulties, in particular avoidance of sexual activity, than women with generalized anxiety [240] (Level 2). Social anxiety has also received attention as it relates to sexual function. Compared to women with panic disorder, a small retrospective study found that those with social phobia have more difficulties with orgasm than sexual aversion [241] (Level 3). However, in a very large sample of college students [242], as well as in a clinical sample of 40 socially phobic women [243] social anxiety was very strongly related to sexual difficulties, fewer sexual partners, and greater unhappiness in sexual encounters (Level 2). Looking at the causal relationship of panic disorder and sexual dysfunction, data indicate that there is either a coincidence of panic syndrome and sexual phobia/aversion or, more often, a panic experience during sexual arousal. The results tend to confirm hypotheses claiming that sexual phobics with panic syndrome are not really afraid of sexuality, but rather of panicking and losing control [244]. Van den Hout and Barlow (2000) reviewed the empirical literature on sexual disorders and anxiety disorders. In general they found that anxious patients tend to selectively attend towards perceived threat whereas patients with sexual dysfunction focus their attention away from relevant cues [245] (Level 2).

The notion that anxiety is associated with sexual dysfunction has been challenged by a number of well-controlled laboratory investigations. Different techniques for manipulating and inducing anxiety have been explored, and sexual arousal has been assessed by both subjective (e.g., self-report questionnaire) and psychophysiological (e.g. vaginal photoplethysmograph) techniques. In sexually healthy women, anxiety-inducing techniques have been found to significantly increase psychophysiological sexual arousal [246-249] (Level 2). Anxiety’s mechanism of action may be via increased sympathetic nervous system (SNS) activity given that exercise [250] and other methods of SNS-facilitation [251] enhance physiological sexual arousal (Level 2). This explanation of the above findings was recently challenged by Bancroft [252] (Level 3), who argued that sexual arousal is the result of a complex interaction of sympathetic and parasympathetic processes, varying according to the response being controlled and the part of the body affected. The Meston et al. findings may be better explained by ‘excitation transfer’ [253]. Subjective sexual arousal, however, has been shown to be increased [246], decreased [248], and unaffected [92,250,251] by these techniques (Level 2). In women with heterogeneous sexual difficulties, anxiety significantly improved genital sexual congestion [248,249,254] (Level 2).

e) Depression:

DeRogatis and colleagues administered the Symptom Check-List Revised 90 (SCL-90R) to 325 male and female outpatients seeking treatment for sexual dysfunction [255] (Level 3). Of the 126 women, 50% were assigned a psychiatric diagnosis. Specifically, major depression was found to be a feature of women with FOD and sexual pain disorder. In an older study, women with impaired sexual de-
sire were compared to sexually healthy controls on current and lifetime affective symptoms [256] (Level 2). Although no patient met criteria for major depression at study entry, women with impaired desire were twice as likely as controls to have a history of major depressive disorder. Interestingly, the major depressive episode always either coincided with or preceded the sexual dysfunction onset.

Compared to the literature on anxiety and sexual function, a strong and clear relationship exists between depressed mood and sexual dysfunction in women. However, the literature on sexual function of depressed individuals is complicated by the influence of antidepressant medications. However, in a detailed review of the literature, it was concluded that loss of desire is a consistent consequence of major depression, regardless of antidepressant use [257] (Level 2). In older studies, sexual desire was found to be associated with depression in Finnish women in their 60s [258] and with Bipolar disorder [259] (Level 3). Most recently, Kennedy and colleagues examined a consecutive series of 79 women with Major Depression and found that half the sample experienced problems with sexual desire and arousal [260] (Level 3). Frohlich and Meston compared depressed to nondepressed college women using the Beck Depression Inventory. The depressed group showed higher rates of desire for sexual activity alone, despite more problematic sexual arousal, orgasm, pain, satisfaction, and pleasure. This novel finding was explained by the speculation that masturbation may reflect a reliable form of pleasure compared to partnered sexual activity [261] (Level 2).

Given the retrospective design in the studies reviewed, it is difficult to determine the order of causality, however, some have speculated that depression may play a causal role in the development of female sexual dysfunction. Even in the absence of a diagnosis of Major Depressive Disorder, women with HSDD are more likely to have a “vulnerable self-system” characterized by more depressed thoughts and lower self esteem compared to controls [262] (Level 3).

f) Personality variables:

Some authors have speculated that mood or affect-related difficulties are deep-rooted as opposed to acute reactions to the sexual difficulty. Women with histrionic personality disorder were compared to non-histrionic women and were found to have significantly lower sexual assertiveness, greater erotophobic attitudes toward sex, lower self-esteem, and greater marital dissatisfaction [263] (Level 2). Despite lower sexual desire, more sexual boredom, and greater orgasmic dysfunction, this group displayed higher sexual esteem and increased likelihood of entering into an extramarital affair compared to non-histrionic women. Women with borderline personality disorder show a similar pattern in that despite sexual depression and dissatisfaction, there were higher rates of sexual esteem and sexual assertiveness compared to non-borderline personality disorder women [264] (Level 2). Sensation seeking, a characteristic of individuals with narcissistic personality, has been found to be related to increased sexual desire and arousability, but is not associated with marital or sexual satisfaction [265] (Level 2). In an extensive review which included individual differences pertaining to women’s sexuality, Andersen and Cyranowski [266] report that developmental factors are important to consider when examining the relationship between personality and sexuality. Specifically, older women seeking treatment for mixed sexual dysfunctions had higher Neuroticism scores [267] whereas in younger women, the trait of Extraversion was more prominent [268] (Level 2).

From the available literature it is apparent that personality features of low/fragile self-regulation and self-esteem, as well as histrionic personality relate to impaired sexual desire. Cluster B traits of histrionic and borderline personality are associated with increased sexual esteem, despite impaired sexual desire and dissatisfaction. Additionally, developmental factors must be taken into account when considering the role of personality in women’s sexual function and dysfunction.

g) Body image self-consciousness:

Body image self-consciousness has negative effects on female sexual function, above and beyond actual body size or general body image dissatisfaction [269,270] (Level 3). In the laboratory setting, desire in response to viewing erotic stimuli was positively correlated with higher body esteem [271] (Level 2). Interestingly, inducing a state of increased body awareness while exposed to a sexual stimulus resulted in significant enhancement of physiological and subjective sexual arousal [272] (Level 2). Another recent study in 320 men and women found that body concerns negatively affect sexual pleasure and promote sexual problems [273] (Level 2). Women were significantly more likely to report appearance concerns than men across sexual and non-sexual contexts. The relationship between body shame and sexual pleasure and problems was mediated by sexual self-consciousness during physical intimacy, that is, body shame was related to greater sexual self-consciousness, which in turn predicted lower sexual pleasure and sexual arousability.

Recommendations:

Screening for and treatment of anxiety disorders is recommended. Overall, the empirical results provide evidence of a significant relationship between anxiety and sexual difficulties. Sexual disorders including impaired arousal, desire and satisfaction are common complications of various anxiety
disorders. A strong and clear relationship exists between depressed mood and sexual dysfunction in women, although it is difficult to determine the order of causality. Given that personality factors (i.e., trait of an individual) are much less amenable to change than psychological reactions (i.e., state of an individual), assessment of personality as it might influence sexual health is important but there may be limits to what the clinician can do in terms of improving these aspects of the woman’s personality disposition. Body concerns are found to have negative effects on sexual function in women and should be assessed. **GRADE C**

### h) Relationship factors

Evidence based research about relationship factors contributing to desire and arousal concerns is scant, but clinical experience and correlational studies show a close link between relationship and sexual satisfaction, although there is not a strict interdependence (both domains can operate independently meaning that couples with a good quality of their relationship may have severe sexual problems and couples with marital difficulties may function sexually in a positive way).

Another difficulty in the clinical evaluation of relationship factors is the question about cause and effect. Sexual dissatisfaction which leads to relationship problems or couple maladjustment then leads to sexual dysfunction. Additionally in some couples one problem may be unconsciously used to "resolve" or "disguise" another problem, which is experienced as even more threatening than the sexual dysfunction [274] (Level 4). There is a strong association between sexual function/satisfaction and feelings for a partner [33,275].

1. **Partner’s sexual dysfunction:**

A considerable number of studies have shown that sexual dysfunction of the male partner, especially erectile dysfunction and premature ejaculation have a negative impact on the female partner’s sexual desire [276] (Level 2 and 3) and successfully addressing the former restores the woman’s sexual quality of life [277] (Level 2). However, there are also qualitative data showing women’s dissatisfaction with not being involved in treatment decision making when their male partner’s sought treatment for erectile difficulties, and that they would have welcomed a couple approach that equally emphasized her own sexuality and pleasure [278]. A medically-induced erection has also been found to lead to resistance in some women as it is perceived that the erection is unrelated to her partner’s desire for her [279].

2. **Duration of the relationship and routine:**

Some community surveys have shown that the duration of relationship is inversely correlated to sexual desire and arousal [280] (Level 3).

3. **Global dissatisfaction with the relationship:**

Compared to women without HSDD, women with HSDD report poorer dyadic adjustment, greater dissatisfaction with conflict resolution in their relationship, and less attraction to and emotional closeness with their partners. Furthermore these women found that relationship factors were major contributors to their sexual desire problems [280] (Level 3).

4. **Communication deficits:**

Difficulties expressing sexual needs, wishes and fears between partners are frequently an immediate and direct factor which impacts negatively on the woman’s desire to engage in sexual activity. Men seem to have more inhibitions to talk about emotional and sexual issues [281-283] (Level 2 and 3).

5. **Cultural issues:**

Sexual desire is significantly lower in East Asian compared to Euro-Candian/American samples, and increasing acculturation to the mainstream culture is associated with higher levels of sexual desire [284-286]. This relationship between culture and sexual desire appears to be mediated by sexual guilt [287] in that the link between being an East Asian woman and having lower sexual desire is mediated by higher levels of sex guilt. Moreover, as sexual desire increases with increasing westernization, there is a concomitant decline in sex guilt (Level 3). The extent to which these findings apply to other ethno/cultural groups remains to be determined.

**Recommendations:**

The above mentioned biological and psychosocial factors have been discussed as separate entities. In clinical practice they usually interact in the individual patient with HSDD and FSAD and it is the task of the clinician to disentangle these factors, assess their pathogenetic importance and their accessibility to change. A biopsychosocial approach, advocated by many experts is recommended. In this approach (see **Table 4**) the factors are grouped into biological, psychosexual, and contextual, and are subdivided along a timeline in predisposing, precipitating, and maintaining considerations. A fuller diagnostic workup using this model is likely to help clinicians to come to a further understanding of the patient’s desire and arousal difficulties. **GRADE C**

3. **Treatment issues specific to low desire**

The general lifestyle approaches to improving sexual desire (e.g., diet, sleep, appropriate exercise, improved general health) as well as psychoeducation on the normality of age- and relationship duration-associated declines in sexual drive are a logi-
cal first step in treating the woman with distressing low sexual desire. Using a circular model of women's sexual desire that emphasizes the responsive nature of women's desire (Figure 1), the clinician provides psychoeducation and explains our current understanding of how desire is triggered [131]. That women provide a variety of reasons and incentives for engaging in sexuality is also emphasized [25-26]. Encouraging women to consider their own reasons for sexual activity and challenging their belief that “sex should only happen when I am ’in the mood’” can be therapeutic. For women with a DSM-IV-TR diagnosis of HSDD but who retain the ability to become sexually excited during the sexual encounter, this process of discussing incentives for sexual activity is especially important [288]. For some women, these steps are sufficient for improving their sexual desire and sexual well-being (Level 4). For other women, however, more intensive strategies will be required. These can be divided into: psychosexual, hormonal, and non-hormonal medications.

a) Psychosexual treatments for low desire

Unfortunately there have been very few psychological outcome studies of treatments focusing specifically on low desire. When the low desire is better accounted for by depression, poor body image, sexual assault sequelae, or other more general personality or relationship factors, then those factors must be addressed either in conjunction or before the low desire itself is targeted.

CBT is an extremely versatile treatment modality used across a variety of psychological conditions. It is based on the theory which states that thoughts, feelings, and behaviors interact and mutually influence one another. By targeting negative or maladaptive thoughts, both behaviors and affect will improve. The behavioral component includes attending to a problematic sexual context or behaviours in either partner which reduce attractiveness or trust and ability to focus on the sexual stimuli and feelings. The cognitive component of CBT targets maladaptive thoughts that foster negative emotions and maintain problematic behavior such as avoidance. This may include identifying and challenging beliefs that she is unattractive, idealizing an unrealistic mode of sexual response portrayed by media, or challenging beliefs that unless she feels a high level of desire all the time, then she is dysfunctional. Group CBT improves sexual desire disorder in 74% of couples and this effect was maintained in 64% at one year [289] (Level 2). A modified Masters and Johnson sex therapy was also found to improve sexual function in 57% of women with sexual desire disorder [290] (Level 3). Other psychological modalities have also been investigated and may target more distant factors in the woman's history such as unresolved themes from childhood including abuse or neglect, control issues, low sexual self image. There has been only one published study utilizing such an approach, however, there was a benefit to sexual desire in women [291] (Level 3).

More traditional sex therapy approaches, with their origins in the work of Masters and Johnson [292] and Kaplan [293,294] have also been studied. This includes sensate focus exercises consisting of exchanging physical touch, moving from non sexual to sexual areas of the body, with partners taking turns and giving feedback. Among the very limited available empirical literature, one study showed that 65% of 365 married couples improved by clinical judgment at the end of therapy [295] (Level 3).

Most recently, a mindfulness-based CBT administered to women with mixed HSDD and FSAD has also been explored in an uncontrolled trial. Mindfulness is an eastern practice with roots in Buddhist meditation which focuses on present moment, non-judgmental awareness. Women were taught in-session mindfulness exercises and encouraged to practice approximately 5 hours every 2 weeks of mindfulness between sessions. A mindfulness-based CBT administered in group format to women with HSDD and FSAD resulted in significant improvements in sexual desire and many other domains of sexual response and mood [296] (Level 3).

Recommendation:

Psychological approaches to low desire have a long history and have been found to be effective immediately after treatment with sustained improvements over time. Moreover, they are without adverse side effects. Newer cognitive-behavioural treatments which integrate mindfulness meditation have shown excellent promise for sexual desire problems but await randomized controlled testing. There is also evidence that brief cognitive behavioural interventions are helpful for improving desire. Overall there is an urgent need for more randomized controlled investigations of psychological therapy for low desire in women.

GRADE C

b) Hormonal treatments for low desire

Testosterone has been used in the treatment of low sexual desire since the 1930s; however, systematic study of it is only relatively recent. This topic is covered more thoroughly in Chapter 23. Briefly, although the US Food and Drug Administration has not approved testosterone for this purpose, it is commonly prescribed off-label, despite recommendations against doing so by the American Endocrine Society (due to lack of long-term safety data). Studies in surgically menopausal estrogen-replete women who reported a decline in their desire for sex since BSO have found, in general, a benefit of testosterone administered via a 300µg/day patch,
but no significant beneficial effect of either 150 µg/day or 450 µg/day compared to placebo [297-299] (Level 2). Similar effects were found among naturally menopausal, estrogen replete women [300].

A review of testosterone trials among estrogen replete surgically and naturally menopausal women found that those women receiving the 300 µg/day patch reported an increase in sexually satisfying events of 1.9 per month. Interestingly, a significant benefit was also found across placebo groups of approximately 0.9 events per month [301]. Among 814 naturally and surgically postmenopausal women with HSDD and not receiving estrogen, there was a significant beneficial effect of 300 µg/day patch, but not of 150 µg/day patch on sexually satisfying events. When natural versus surgical menopausal women were compared, this beneficial effect was only seen in the naturally menopausal women. Both testosterone doses produced a significant increase in desire for sex, above placebo. Importantly, 30% of the testosterone group experienced androgenic side effects, and there were 4 new cases of breast cancer in the testosterone but not placebo group [302]. In contrast, among estrogen-deplete cancer survivors with HSDD, testosterone treatment was found to be without benefit on any measure of sexual response or activity [303].

Most recently, testosterone among premenopausal, estrogen-replete women has been studied. When 260 premenopausal women (aged 35-46yrs) with HSDD were given a transdermal testosterone spray for 16 weeks (or placebo), only the 90 microL spray (the middle dose used) led to a significant increase in sexually satisfying events over placebo [304]. In addition, the level of free testosterone was supraphysiological in the majority of women. Notably, in all of these testosterone trials, a strict entry criterion was a certain baseline frequency of sexual activity and most women experienced 2-3 sexually satisfying episodes per month. Compared to the majority of women seeking treatment for sexual difficulties, where sexual frequency may take place on a once every several month basis, women recruited for research trials have a much higher level of sexual response and frequency. It is unknown if testosterone therapy would be of benefit to the large majority of women seeking treatment for sexual desire concerns.

Despite its lack of approval, many women seek out testosterone therapy for problematic low desire. In such instances, the clinician and patient should engage in a careful discussion of the benefits and hazards of such treatment. In light of the finding of increased prevalence of breast cancer when estrogen-depleted menopausal women are receiving testosterone [302], an informed discussion about the potential risk of breast cancer must take place. This is especially important given the finding in an epidemiological review that endogenous androgen levels are associated with risk for breast cancer [305] (Level 2). This area is open to debate given that there has been another study showing antiproliferative effects of testosterone [306]. Other risks of testosterone therapy include the link with cardiovascular health. Estrogen is required with testosterone administration given that women with high endogenous testosterone-to-estrogen ratios have more cardiovascular disease and insulin resistance [307,308] (Level 3) although estrogen use is also not without risks [309] (Level 1).

The androgenic, progestogenic, and estrogenic synthetic hormone, tibolone, is available in Europe and has been investigated in a Dutch study of women with various sexual complaints. Scores on the FSFI among the sample of 400 women were lowest for the desire domain suggesting that many of them may have met criteria for HSDD. Twenty-four weeks of tibolone resulted in a significant increase in all scores on the FSFI and there were no differences from women treated with combined transdermal estradiol/norethisterone (50 µg/140 µg) [310] (Level 1). An earlier placebo-controlled cross-over study in 38 Dutch postmenopausal women, heterogeneous with respect to sexual functioning, found that tibolone 2.5 mg/day was associated with significant increases in sexual desire, and the frequency of arousability and sexual fantasies compared with placebo [93] (Level 1).

Vaginal lubrication was significantly improved on tibolone. In addition, tibolone significantly increased baseline VPA levels and VPA response to sexual fantasy but not to visual stimulation, suggesting two possible pathways of sexual response (an androgen-dependent and an androgen-independent pathway). A recent study found that tibolone increases the risk of recurrence in breast cancer patients (HR 1.44), while relieving vasomotor symptoms and preventing bone loss [311] (Level 1).

**Recommendations:**

Testosterone therapy is effective for estrogen-replete naturally menopausal women, and marginally effective for premenopausal women, though it produces supraphysiological levels in the latter. Among estrogen-depleted women, there are conflicting data with no effect among cancer survivors with HSDD but a positive effect among menopausal women without cancer. The long-term risks of testosterone therapy on breast cancer, insulin resistance, and metabolic syndrome are unknown,
so a careful discussion with patients evaluating the potential hazards must take place before any testosterone supplementation is considered. Because positive studies of testosterone have required women to be engaging in sexually satisfying events 2-3 times per month, the efficacy of testosterone on women in the larger population of treatment-seekers is unknown. Future research should aim to use stricter inclusion criteria for low desire. GRADE B.

c) Non-hormonal medications for low desire

Non-hormonal medications that have been investigated for low sexual desire have typically had a mechanism of action that was centrally-acting. In non-depressed women with HSDD, the antidepressant bupropion, which blocks norepinephrine and dopamine reuptake, was found to significantly improve sexual arousal and orgasm, but not sexual desire [312] (Level 2). In women with SSRI-associated mixed sexual symptoms, 4 weeks of treatment with the addition of bupropion led to a significant increase in self-reported feelings of desire and sexual activity, but no significant effect on sexual thoughts [313] (Level 1). The most recently investigated of the centrally-acting agents for HSDD has been fibanserin. Fibanserin's mechanism of action is not yet fully understood but it acts as a 5-HT1A serotonin receptor agonist and 5-HT2A serotonin receptor antagonist. At present, no peer-reviewed publications concerning efficacy of fibanserin on women's sexual desire are available, but results of three large US and European RCTs with fibanserin 100mg taken daily were made public at the European Society of Sexual Medicine annual meeting in November 2009 and summarized at the Boehringer Ingelheim website[314] (level1). Of note, Boehringer Ingelheim categorizes HSDD as a medical disease, but unclear is how it was established that the complaints were of medical etiology and not resulting from other sources. The primary endpoint was frequency of satisfying sexual events(SSE) following 24 weeks of treatment, or the number of sexual events (defined as sexual intercourse, oral sex, masturbation or genital stimulation by the partner) which were satisfying for the woman (i.e. gratifying, fulfilling, satisfactory and/or successful), irrespective of whether women had an orgasm or whether the event was satisfying for the partner. The pooled analysis of 1,378 premenopausal US women showed a statistically significant increase in the frequency of SSEs in women taking fibanserin (from 2.8 at baseline to 4.5), versus placebo (2.7 at baseline increasing to 3.7), an increase in the FSFI total score and a reduction in FSDS-R sexual distress. An analysis of the 634 premenopausal European women showed women taking fibanserin 100mg had statistically significant improvements in their level of sexual desire as measured by the eDiary and a reduction in FSDS-R sexual distress but not significant change in SSEs. Most adverse drug reactions with fibanserin 100mg were mild to moderate and included dizziness, nausea, fatigue, somnolence and insomnia. Given that fibanserin's mechanism of action is not understood, it is as yet unclear which women, in the long run, may or may not benefit from its use, whether long term use will prove to be safe, and whether, on a long term basis, fibanserin is the best treatment for women with no/low sexual desire.

Recommendation:

Centrally acting agents show promise for targeting low desire in women but published RCTs are required and an evaluation of their safety remains to be studied. GRADE A

IV. ISSUES SPECIFIC TO LOSS OF AROUSAL

1. COMPONENTS OF SEXUAL AROUSAL, INCLUDING PSYCHOPHYSIOLOGICAL MEASUREMENT

An ideal protocol for the assessment of FSAD should be constructed following theoretical and factual knowledge of the physiological, psychophysiological, and psychological mechanisms involved. The protocol would describe the most parsimonious route from presentation of complaints to effective therapy. Unfortunately, we are at present far from a consensus on the most probable causes of FSAD. Despite this disagreement, at least two diagnostic procedures should be considered. Firstly, assessment of sexual dysfunction in a biopsychosocial context should start with a verification of the chief complaints in a clinical interview. The aim of the clinical interview is to gather information concerning current sexual functioning, onset of the sexual complaint, the context in which the difficulties occur, and psychological issues that may serve as etiological or maintaining factors for the sexual problems, such as depression, anxiety, and personality factors, negative self- and body image, feelings of shame or guilt that may result from religious taboos. Sexual problems are common complications of anxiety disorders and impair sexual desire, arousal and satisfaction. Laboratory studies suggest potential enhancement of genital arousal by some types of anxiety, but the precise cognitive, affective, or physiological processes by which anxiety and women's sexual function are related have as yet to be identified [46]. The ongoing work of Bancroft and colleagues exploring a dual control model of sexual excitation and inhibition in men as well as in women, may clarify the role of anxiety in women's predisposition to sexual inhibition and to sexual excitation [315]. Like men, in women close to normal distributions of sexual inhibition...
and excitation are found. Such distributions lend support to the idea that variation in excitation and inhibition proneness is normal, and that the midpoint of the range represents adaptive levels of inhibition. There is some suggestion that sexual inhibition is associated with difficulty experiencing orgasm [6], evidence that would fit their basic inhibitory model. However, this study involved a nonclinical sample of women; future research should involve clinical samples of women.

One of the most important but difficult tasks is to assess whether inadequate sexual stimulation is underlying the sexual problems, which requires detailed probing of (a variety of) sexual activities, conditions under which sexual activity takes place, prior sexual functioning and sexual and emotional feelings for the partner. Several studies have shown that negative sexual and emotional feelings for the partner are among the best predictors for sexual problems [33,316]. The clinician should always ask if the woman has ever experienced sexual abuse, as this may seriously affect sexual functioning [217-219] (Level 2 and 3). Some women do not feel sufficiently safe during the initial interview to reveal such experiences; nevertheless, it is necessary to inquire about sexual abuse to make clear that traumatic sexual experiences can be discussed. The initial clinical interview should help the clinician in formulating the problem and in deciding what treatment is indicated. An important issue is the agreement between therapist and patient about the formulation of the problem and the nature of the treatment. To reach a decision to accept treatment, the patient needs to be properly informed about what the diagnosis and the treatment involve.

If psychophysiological tools are available (although these are typically reserved for the research setting), observation of the genital arousal response to adequate stimulation by means of audiovisual, cognitive (fantasy) and/or vibrotactile stimuli, may be useful. However, it is important to note that this often does not correlate with the woman’s subjective report of (impaired) sexual arousal. Although psychophysiological testing to date is not a routine assessment, such a test may be crucial in establishing the etiology of FSAD for two reasons. A recent study by Laan and colleagues demonstrated how difficult it is to rule out that sexual arousal problems are not caused by a lack of adequate sexual stimulation [44]. In addition, they showed that impaired genital response cannot be assessed on the basis of an anamnestic interview. Women with sexual arousal disorder may be less aware of their own genital changes, with which they lack adequate proprioceptive feedback that may further increase their arousal. If a genital response is possible, even when other investigations indicate the existence of a variable that might compromise physical responses, an organic contribution to the arousal problem of the individual women is clinically irrelevant. They argued that sexual arousal problems in medically healthy women are most likely more often related to inadequate sexual stimulation due to contextual and relational variables than to somatic causes. For estrogen deplete women, care must be taken not to simply facilitate painless intercourse in the nonaroused state with a lubricant, but to consider the possibility that estrogen lack has unmasked long-term lack of sexual arousal that is of contextual etiology [45]. Of note, nonresponse in the psychophysiological assessment does not automatically imply organicity. The woman may have been too nervous or distracted for the stimuli to be effective, or the stimuli offered may not have matched her sexual preferences. This problem of suboptimal sensitivity is not unique to this test, many other well established diagnostic tests of this nature have a similar disadvantage [317].

Two other procedures could be used to corroborate findings from the clinical interview and the psychophysiological assessment. The first is the use of self-report measures to supplement the clinical interview. The Female Sexual Function Index [203] (Table 5) is currently the most often used measure. Diagnostic cutoff scores were developed by means of sophisticated statistical procedures [318]. Together with a Female Sexual Distress Scale [32] score of 11 or higher, indicating distress, there is some evidence to suspect sexual dysfunction [319]. Use of self-report measures alone are not very useful for clinical purposes because they lack sensitivity and specificity with regard to causes of the individual patient’s dysfunction.

Secondly, a careful focused pelvic exam is needed when there is a complaint of loss of genital response. Normal findings can be therapeutic by directing the woman to focus on what goes on in her mind rather than assuming she has a genital abnormality. As well an exam is essential when lack of arousal is accompanied by complaints of pain or vaginistic response during sexual activity. Common (e.g. vulvo vaginal atrophy) or rare diseases such as connective tissue disorder, can be identified. Often, the purpose of the exam may be more educational than medical, for instance to observe the consequences of pelvic floor muscle activity [46,317]. In women with neurological disease affecting pelvic nerves or with a history of pelvic trauma a detailed neurological genital exam may be necessary, clarifying light touch, pressure, pain, temperature sensation, anal and vaginal tone, voluntary tightening of anus, and vaginal and bulbocavernosal reflexes [46]. The clinician should be aware of the emotional impact of a physical examination and the importance of the timing. When a woman is very anxious about being examined it may be appropriate to wait until she feels more secure. In case of women who are not familiar with self-examination of their genitalia,
it is preferable to advise self-examination at home before a doctor carries out an examination [320]. It is recommended that the procedure is explained in detail, what will and what will not take place, and the woman’s understanding and consent obtained. It is important to realize that any medical exam is not able to examine function, because the genitalia are examined in nonaroused state. As such, a medical exam can never replace a careful detailed interview. Psychophysiological assessment may be an integral part of the clinical assessment in the future.

Recommendation:

A thorough assessment of FSAD must include an in-depth personal interview during which adequacy of sexual stimuli is assessed. Psychophysiological tools may be helpful though, at present, are reserved primarily for the research setting. Self-report measures may corroborate information obtained from an interview. A carefully focused genital/pelvic examination is necessary when there are complaints of loss of genital sensitivity or pain or vaginistic reactions. GRADE C

2. TREATMENT ISSUES SPECIFIC TO LOW AROUSAL

a) Psychological treatments

Currently, we are in a climate that overlooks and dismisses psychological treatments [321]. One of the reasons for this may be that due to sociocultural pressure in the medical and larger culture, psychological treatments are seen as superior [322]. The emphasis on impaired genital responsiveness in the DSM-IV definition of FSAD and the success of pharmacological treatments for men’s erectile dysfunction have undoubtedly contributed as well.

Prior to publication of Masters and Johnson’s seminal book on sex therapy [292], sexual problems were seen as consequences of (nonsexual) psychological conflicts, immaturity, and relational conflicts. Masters and Johnson proposed to directly attempt to reverse the sexual dysfunction by a kind of graded practice and focus on sexual feelings (sensate focus). If sexual arousal depended directly on sexual stimulation, that very stimulation should be the topic of discussion (masturbation training). A sexual dysfunction was no longer something pertaining to the individual; rather, it was regarded as a dysfunction of the couple. It was assumed that they did not communicate in a way that allowed sexual arousal to occur when they intended to “produce” it. Treatment goals were associated with the couple concept: the treatment goal was for orgasm through coital stimulation. This connection between treatment format and goals was lost once Masters and Johnson’s concept was used in common therapeutic practice. People came in for treatment as individuals. Intercourse frequency became the gold-standard indicator of sexual function. Male orgasm through coitus adequately fulfills reproductive goals, but it is not very satisfactory for many women because they do not easily reach orgasm through coitus [35,323] What has remained over the years since 1970 [292] is a direct focus on dysfunctional sex and a focus on sexual sensations and feelings as a vehicle for reversal of the dysfunction.

Psychological treatment of sexual arousal problems generally consists of sensate focus exercises and masturbation training, with the emphasis on becoming more self-focused and assertive [324]. A lack of meaningful treatment goals for women, the difficulty in obtaining adequate control groups, and the lack of clear treatment protocols, may explain the paucity of well-controlled randomized trials of psychological therapy.

Almost all of the data on psychological treatments were collected in the mid-1980s or earlier. The high success rates published by Masters and Johnson have never been replicated. There are no randomized controlled trials of psychological treatments for FSAD. Instead, as described in the earlier section on low desire, there is mounting evidence from two uncontrolled trials that a mindfulness-based cognitive behavioral intervention is helpful for women with HSDD and/or FSAD [296,325]. In these studies, the eastern practice of mindfulness, or non-judgmental, present moment awareness, was combined with cognitive therapy of dysfunctional thoughts associated with poor arousal (e.g., “my body is incapable of being aroused”), as well as behavioral techniques (e.g., sensate focus, exploration of a woman’s body and her genitals) and was found to lead to significant improvements in self-reports of sexual arousal as well as a marginal improvement in physiological sexual arousal (Level 3). Although promising, these data await replication in a randomized controlled trial.

Recommendations:

Despite our support for evidence-based practice, care for people with sexual problems, according to the rules of “good clinical practice”, must continue, even without solid proof of efficacy. There clearly is a great need for controlled efficacy studies in this area. From our review that the majority of sexual arousal problems in healthy women are not related to impaired genital responsiveness it follows that we recommend psychological treatments for FSAD. GRADE C

b) Hormonal Pharmacotherapy for FSAD

1. Testosterone

A limited number of studies have investigated potential beneficial effects of testosterone on sexual arousal. In a placebo-controlled study in hypogonadotropic hypogonadal women, treatment with tes-
testosterone undecanoate, 40 mg orally per day during an 8-week period, enhanced genital arousal as measured by VPA [326] (Level 2). Because women swallowed the capsules each morning, while the measurements were performed in the afternoon, it was assumed that this effect on genital sexual responding could be caused by a time-dependent effect of testosterone. To test this hypothesis, eugonadal and sexually functional women were administered a single dose of testosterone sublingually (0.5 mg). Such pulsed testosterone delivery produces supraphysiological testosterone levels 15 minutes after treatment, with levels returning to normal within 1.5 hours [327]. A 4-hour delay effect of testosterone on VPA was demonstrated [327,328]. This finding was replicated in another laboratory [329] (all four studies Level 2).

2. Estrogen

There is evidence that treatment with local and systemic estrogen benefits vulvo-vaginal atrophy and relieves vaginal dryness and dyspareunia [330,331] (Level 1).

3. Selective Tissue Estrogenic Activity Regulator (STEAR):

Tibolone. Tibolone is a 19-nor testosterone derivative which is metabolized into three main metabolites: the 3α-hydroxy and the 3β-hydroxy, which are estrogenic, and the 8-4 isomer, which has progestagenic and androgenic properties. Tibolone is a selective tissue estrogenic activity regulator (STEAR). In postmenopausal women, it acts as an estrogen on brain, vagina, and bone, but not on endometrium and breast.

A randomized, double-blind, cross-over study was conducted in 38 postmenopausal women who received tibolone 2.5 mg/day and placebo. Vaginal blood flow during erotic stimulation was measured using a vaginal photoplethysmograph and subjects completed sexual function questionnaires and daily diaries. Women receiving tibolone showed a significant increase in VPA in response to erotic fantasy but not during erotic film stimulation. Tibolone was associated with significant increases in sexual desire, and the frequency of arousability and of sexual fantasies compared with those with placebo. Vaginal lubrication was significantly improved on tibolone [93]. In another study, 72 women were randomized to treatment with either tibolone or continuous combined conjugated equine estrogens 0.625 mg/day and medroxyprogesterone acetate 5 mg/day (CEE/MPA). After 6 months of treatment, both groups were associated with significant self-reported improvements in sexual function, but women receiving tibolone had significantly higher sexual desire, sexual excitement, intercourse frequency and vaginal dryness scores [332] (Level 2).


A Selective Estrogen Receptor Modulator was originally defined as a compound that binds with high affinity to the estrogen receptor (ER), without significant binding activity to any other nuclear receptor; which induces “estrogen agonistic” activities in some tissues, and “estrogen antagonistic” activities in others. Emerging data show that the interaction between a particular SERM and the ER results in a response in a given tissue which cannot necessarily be characterized simply as either “agonistic” or “antagonistic”. Each SERM may have a unique set of clinical responses, which are not always predictable from those seen with another SERM. Ospemifene (formerly named FC-1271a) is a novel SERM developed for the treatment of vaginal atrophy in postmenopausal women (which also shows promise in the prevention and treatment of osteoporosis). The effects of ospemifene on urogenital atrophy in postmenopausal women are currently being assessed in Phase III studies [333].

5-Hormone Precursor Replacement Therapy (HPRT): DHEA

A recent phase III prospective RCT studied the effect of the vaginal application of 0.25%, 0.50% or 1.0% DHEA on signs and symptoms of vaginal atrophy in 216 postmenopausal women. All three doses induced a rapid beneficial change in the maturation of the vaginal epithelial cells and vaginal pH [334]. In addition, the beneficial effects induced by DHEA in the vagina had parallel positive consequences in sexual desire/interest, sexual arousal, orgasm and pain as measured by validated sexual function questionnaires [335]. This effect is attributed to the tissue specific local conversion of the inactive precursor DHEA into androgens as well as estrogens, exerting benefits on all the three layers of the vaginal wall. Preclinical data obtained in the rat have shown beneficial effects of androgens made locally from DHEA on collagen fibers of the lamina propria and on the muscularis [336]. While local DHEA was found to be an efficient treatment, all serum steroids (DHEA and its 11 metabolites) measured by validated mass spectrometry remained within the reference range observed in postmenopausal women, indicating a strictly local action with no systemic exposure to sex steroids [337]. On another note, a recent study has shown a fivefold increase in serum estradiol measured by mass spectrometry assays, in postmenopausal women using local vaginal formulations after 1 week of daily treatment [338] (Level 1).

c) Non-hormonal Pharmacotherapy for FSAD

In the relatively short time span (compared to psychological treatments) that pharmacological treatments have become available for men in 1998, the effect of pharmacological treatments in women
with sexual arousal problems has been investigated in several controlled and uncontrolled studies. To date, none of the treatments that are listed in Table 10 have been approved.

1. Phosphodiesterase Inhibitors.

Sildenafil is the first pharmacological treatment that has been investigated on a reasonable scale in controlled studies with female subjects. In the very first laboratory study, which was done on sexually healthy women, 50mg sildenafil produced an increase in physiological but not subjective sexual arousal [339]. In a large study of diagnostically heterogeneous women, 10-100mg sildenafil similarly showed no benefit on subjective sexual response [340]. In general, the literature has conflicting findings with some studies showing a benefit [341-343] and others failing to find a significant benefit over placebo, and one study showing that the benefit depending on psychophysiolologically-measured impairments in sexual arousal [43]. In small studies of women with impaired genital arousal due to spinal cord injury [42] or diabetes [344] there does appear to be a significant beneficial effect of sildenafil.

A new approach to the study of efficacy of PDE5-inhibitors is combining this drug with testosterone. The rationale for such an approach is that activation of central sexual mechanisms is necessary for the interpretation of stimuli as sexual, by which these stimuli can produce (behavioral) sexual responses (i.e., an increase in sexual desire and motivation; inducing sexual approach behavior). Activation of central "sexual" mechanisms is a necessary condition for activation of the nitric oxide pathway, which in turn is necessary for a PDE5-inhibitor to be effective. The authors argue that centrally working drugs will increase the sensitivity for sexual stimuli, and may induce a condition required for a PDE5-inhibitor to be effective [225,226] (Level 2). Color naming latency times in a Stroop test was the measure of preconscious attentional bias for sexual cues. In the initially low-attention group preconscious attentional bias increased with testosterone, in the other group attentional bias decreased with testosterone. Only in the former group did the combination of (0.5 mg sublingual) testosterone (producing high supraphysiological levels) and (10 mg) vardenafil cause an improvement in genital response (VPA) and subjective indices of sexual functioning, supporting the idea that testosterone sensitizes the brain, paving the way for vardenafil to be effective [225]. The high dose of testosterone administered in this study limits the generalizability of the findings.

In 2004 Pfizer ended their program of testing sildenafil in women, perhaps resulting from the conflicting findings in medically healthy women [345]. It would be theoretically and clinically meaningful to investigate which factors may have been responsible for these inconsistent findings. Possible candidates are: inadequate sexual stimulation (sildenafil will not be effective without sexual stimulation that is useful—i.e., that causes subjective arousal to trigger the genital response); inadequate outcome measures; wrong patient group (e.g. women with sexual problems unrelated to genital responsiveness); estrogen depletion, although in larger studies of sildenafil, the majority of participants were premenopausal (estrogen-replete) women. In most studies prior to this decision, women excluded from the trials. That may have been an unfortunate choice. Women with various medical conditions, and not medically healthy women [44], may have an impaired genital response and may therefore have more to gain from a genital arousal enhancing agent such as sildenafil. PDE5-inhibitors combined with testosterone may have a beneficial effect over placebo in certain groups only [225,226].

2. L-Arginine

The nitric oxide precursor L-arginine was investigated in a double-blind, placebo-controlled study combined with yohimbine, an adrenergic antagonist, in women with FSAD [346] (Level 2). The combination significantly enhanced VPA but had no effect on subjective measures of arousal or affect.

3. Prostaglandins

One placebo-controlled, single-blind, dose response study of alprostadil found no significant benefit over placebo [347] (Level 2) whereas another small trial in postmenopausal women found a significant benefit on genital sensation, subjective sexual arousal, and sexual satisfaction [348].

4. Phentolamine

Two controlled studies have investigated the effect of alpha-1 and alpha-2 adrenergic receptor antagonist phentolamine based on the hypothesis that, as in men, the smooth muscle surrounding the vaginal arterial vascular bed is mainly alpha adrenergically innervated. In a small study of six postmenopausal women with FSAD, it showed a positive effect on subjective and genital sexual arousal (VPA) [349] (Level 3). In the second, a placebo-controlled administration of both oral and vaginal applications in 41 estrogenized and non-estrogenized postmenopausal women found a benefit to genital response and subjective sexual arousal but only in the estrogenized women [349,350] (Level 2). It should be noted that the pharmaceutical company previously sponsoring these trials of phentolamine has no longer sponsored additional (larger) trials. Also, it is important to note that most women who present with sexual arousal concerns have normal genital congestion when measured in the laboratory [44].
### Table 10: Pharmacotherapy trials and their levels of evidence (LOE)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Findings</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil in 12 healthy premenopausal women [339]</td>
<td>Women randomized to 50mg sildenafil or placebo across two sessions. Significant increase in vaginal engorgement (VPA) during erotic stimulus conditions but no effect on subjective sexual arousal.</td>
<td>2</td>
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<tr>
<td>Sildenafil in 557 estrogenized and 204 estrogen deplete pre- and post-menopausal women with mixed sexual dysfunctions [340]</td>
<td>Women randomized to 10-100mg sildenafil for at-home use. No significant improvement on subjective sexual arousal and subjective perception of genital arousal, as assessed by several different measures.</td>
<td>2</td>
</tr>
<tr>
<td>Sildenafil in women with FSAD and no complaints of desire disorder [341]</td>
<td>Significant benefit of sildenafil beyond placebo.</td>
<td>2</td>
</tr>
<tr>
<td>Sildenafil in premenopausal women with FSAD [342]</td>
<td>Significant improvement in subjective sexual arousal, pleasure, orgasm, and frequency of orgasm. However, unvalidated questionnaires used.</td>
<td>3</td>
</tr>
<tr>
<td>Sildenafil in sexually healthy women [343]</td>
<td>Significant improvement over placebo on arousal, orgasm and enjoyment, now with a validated questionnaire.</td>
<td>2</td>
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<tr>
<td>Sildenafil in 34 postmenopausal women with genital FSAD and/or FOD [43]</td>
<td>Only those women with impaired genital arousal, as assessed with a vaginal photoplethysmograph, showed a significant benefit of 50mg sildenafil.</td>
<td>2</td>
</tr>
<tr>
<td>Sildenafil in women with spinal cord injury and FSAD [42]</td>
<td>Significant beneficial effect of sildenafil on genital (VPA) and subjective sexual arousal. The beneficial effects of sildenafil over placebo were most evident in the strongest stimulus condition of both visual and manual stimulation.</td>
<td>2</td>
</tr>
<tr>
<td>Sildenafil in 30 women with diabetes Type 1 [344]</td>
<td>Sildenafil significantly improved subjective indices of arousal, and improved orgasm, sexual enjoyment and dyspareunia compared to placebo. Clitoral blood flow (using clitoral Doppler ultrasonography) was higher with sildenafil compared to placebo and compared to baseline.</td>
<td>2</td>
</tr>
<tr>
<td><strong>Table 10: Pharmacotherapy trials and their levels of evidence (LOE)</strong></td>
<td></td>
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<tr>
<td><strong>Alprostadil in a single-blind trial in women with FSAD [347]</strong></td>
<td>No significant difference beyond placebo. A comparison of the lowest with the highest dose did show some effects in the expected direction, but these effects were estimated by visual inspection by an MD. It is unknown whether that MD was also blinded to treatment.</td>
<td>2</td>
</tr>
<tr>
<td><strong>Alprostadil in postmenopausal women [348]</strong></td>
<td>Significant benefit over placebo on genital sensation, subjective sexual arousal, and sexual satisfaction.</td>
<td>2</td>
</tr>
<tr>
<td><strong>Phentolamine administered orally in postmenopausal women with FSAD [349]</strong></td>
<td>Significant positive effect on subjective and genital sexual arousal (VPA).</td>
<td>2</td>
</tr>
<tr>
<td><strong>Phentolamine in a placebo-controlled trial administered both orally and vaginally to estrogenized and non-estrogenized postmenopausal women [350]</strong></td>
<td>Subjective sexual arousal was significantly higher than placebo with the highest doses of both applications of phentolamine (in estrogenized women only).</td>
<td>2</td>
</tr>
<tr>
<td><strong>Levodopa in a placebo-controlled study of sexually healthy men and women. [351]</strong></td>
<td>No significant enhancement of Achilles tendon reflex in men (a measure of somatic motor preparation).</td>
<td>2</td>
</tr>
<tr>
<td><strong>Apomorphine administered daily to premenopausal women with HSDD and FSAD [352]</strong></td>
<td>Significant improvement in sexual function.</td>
<td>2</td>
</tr>
<tr>
<td><strong>Bremelanotide administered to postmenopausal women with FSAD [354]</strong></td>
<td>Significant increase in desire but not arousal.</td>
<td>2</td>
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</table>
5. Dopamine Agonists

Dopaminergic drugs might be interesting because other than the previously discussed drugs, they have a direct effect on the brain and may therefore have a positive influence on sexual arousal and desire. Levodopa significantly enhanced the Achilles tendon reflex in men, indicating somatic motor readiness [351]. However, apomorphine significantly improved sexual function in 44 women with HSDD and FSAD. Side-effects were mainly nausea, vomiting, and dizziness [352]. Sumanireole is a dopamine agonist that specifically targets D2-receptors. The effect of this drug in women with complaints of sexual arousal and desire were studied in an unpublished, placebo controlled laboratory study where no effects on genital or subjective sexual arousal were found.

6. Buproprion

Buproprion was used in one uncontrolled study to counteract the sexual side-effects of selective serotonin reuptake inhibitors. Keeping in mind that no adequate control was used, the authors concluded that the results point to relief of the sexual complaints [353] (Level 4).

7. Bremelanotide

Bremelanotide is an analogue of the naturally occurring peptide alpha-melanocyte-stimulating hormone (alpha-MSH). A single intranasal dose of this melanoctin receptor agonist resulted in increased reports of sexual desire and arousal in premenopausal women with sexual arousal disorder [354]. After this initial favorable result, studies were suspended due to undesirable side-effects.

d) Physical aids for FSAD

In the past 10 years, a new, non-pharmacological approach to FSAD was developed. The EROS Clitoral Therapy Device (CTD) consists of a small cup that can be placed over the clitoris, and a pump that creates a vacuum over the clitoris. A study in 20 women with FSAD and 12 healthy controls found improvements in genital sensation, vaginal lubrication, ability to reach orgasm, and sexual satisfaction relative to pretreatment [355] (Level 3). The authors speculated that “the increased vaginal lubrication resulting from clitoral engorgement with the EROS-CTD is due to activation of an autonomic reflex that triggers arterial vasodilatation with subsequent increases in transudate and lubrication”. This ‘medical’ device again demonstrates that, if proven effective in larger groups of women with sexual arousal difficulties, many if not most sexual arousal problems are due to a lack of adequate sexual stimulation.

Recommendations:

Although testosterone showed a beneficial effect on sexual arousal as measured with a vaginal photoplethysmograph, these are supraphysiological levels with an unknown long-term safety profile. There is no evidence for increased subjective excitement or pleasure. Currently, no recommendation for pharmacotherapy for FSAD can be made due to lack of efficacy and/or unwanted side-effects. Women with various medical conditions rather than medically healthy women may have an impaired genital response and may therefore gain from peripheral, genital arousal enhancing agents. GRADE C

IV. ISSUES SPECIFIC TO LOSS OF ORGASM

1. DEFINITION OF ORGASMIC DISORDER IN WOMEN

In the recent Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE) study, a cross-sectional population-based survey of female adults in the United States, 18 years and older, FOD was present in 20.5% of the 31,581 respondents, being a distressing problem in 4.7% [31]. Cross-cultural data of women aged 40-80 show an incidence of 16%, with the greatest prevalence in Asia and the lowest in Northern Europe [50].

In the DSM-IV, FOD is defined as: “Persistent or recurrent delay or absence of orgasm following a normal sexual excitement phase” [1]. The international committee assembled in 2003 by the AUAF proposed an alternative definition of Women’s Orgasmic Disorder (Table 1) that emphasized that the diagnosis could only be made if high levels of sexual arousal were able to be attained by the woman [41]. In other words, according to these definitions, the woman who does not experience orgasm but also does not experience a sufficiently high level of sexual arousal (presumably to facilitate orgasm) would not be given a diagnosis of FOD, but rather just FSAD. With the publication of DSM-V in 2013, there have been proposed new criteria for FOD[356]. The main difference between DSM-IV - TR and proposed criteria for DSM-V is the addition of “markealy reduced intensity of organic sensation”.

2. ETIOLOGY OF ORGASM DISORDER

Orgasm has been the subject of interest and research for many years. Both the study of the biological aspects, the subjective appraisal of the events and the correlation between the two have been examined. While the early studies contemplated physiological parameters such as heart rate, blood pressure, contraction of “target organs” [10,357], later studies have focused on the involvement of the peripheral nervous system, spinal cord pathways and brain areas engaged, as well as neuroendocrine influences.
An extensive review of the literature has been published following the previous 2003 International Consultation on Sexual Dysfunctions [358] and at the time of this publication, there are no significant new data on the subject except what is briefly discussed below.

The pathophysiology of orgasmic disorders involves biological as well as psycho-social predisposing and precipitating factors. A genetic influence on variation in female orgasmic function has been assumed, since the intra-class correlation for frequency of orgasm during intercourse and masturbation has been found higher for monozygotic twins (31% and 39%, respectively) than for dizygotic twins (10% and 17%; p=0.0001) [359] (Level 3). Moreover, the heritability for orgasm problems in intercourse is approximately 31%-34% and for orgasm problems with masturbation is approximately 37%-45% [360,361] (Level 3). Data from a recent twin registry database on 2,035 British women indicate that some measures of personality (e.g., introversion, emotional instability, not being open to new experiences) and emotional intelligence were associated with orgasmic dysfunction in women [362,363] (Level 3) though these data need to be replicated.

In their 1997 review, Heiman and Meston concluded that only Directed Masturbation treatment for primary anorgasmia fulfills the criteria of “well-established”, and Directed Masturbation studies for secondary anorgasmia fall within the “probably efficacious” group [364]. This conclusion is still valid up to date. Directed Masturbation in conjunction with sex education, anxiety reduction techniques and CBT remain the main therapeutic tools. No effective pharmacological treatments have been found to date for FOD [365].

In 98 women with SSRI-induced FOD who were recruited over four years across 7 American treatment centers, half were randomized to receive 50 or 100mg sildenafil and the other half the placebo pill [366]. Those in the treatment group had significantly fewer negative sexual side effects. However, the highly specific inclusion criteria calls into question the generalizability of the findings.

**Recommendations:**

There are no significant new data on FOD since the 2003 International Consultation meeting. There are some preliminary genetic research from twin registries showing a significant heritability factor to orgasmic problems with intercourse and masturbation. There is one published RCT of sildenafil showing positive effects on orgasmic disorder in a highly selective sample of women with SSRI-induced FOD. **GRADE C**

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**V. THE PLACEBO RESPONSE**

It has become increasingly apparent in pharmaceutically sponsored RCTs that there is a notable placebo response among women randomized to the placebo arm of a drug trial. For example, in studies of sildenafil, the placebo response was at least 40% [340,341]. In recent testosterone trials, there is also a notable placebo response. For example, among estrogen depleted postmenopausal women, the increase in sexually satisfying events in the placebo group (0.7 units) was no different than the increase seen in the 150µg group (1.2 units) – although both groups were lower than the 300µg testosterone group [302]. Among surgically menopausal women, the placebo response was comparable to the increase in sexually satisfying events seen in both testosterone groups. Among premenopausal women, 43.5% of women in the placebo group experienced a significant increase in sexually satisfying events which was comparable to the proportion experiencing benefit in the one 56-µL spray (46.2%), one 90-µL spray (57.8%), and two 90-µL spray (54.7%) groups [304].

Recently, there has been a systematic effort to better understand the placebo response in pharmacological trials for female sexual dysfunction and there have been three studies by Bradford and Meston to this effect.

In a review of 16 placebo-controlled pharmacological trials in women’s sexual dysfunction, Bradford and Meston attempted to quantify the degree of placebo response [367] (Level 3). Their review focused on trials of women seeking treatment in which a placebo effect could be calculated. Studies employing a retrospective design and/or studied postmenopausal women, and studies focusing on sexual desire (as opposed to sexual arousal) endpoints were more likely to show placebo effects.

Bradford and Meston [368] (Level 2) then examined correlates of the placebo response among 16 women receiving the placebo arm in one of their randomized controlled trials of gingko biloba. The pre- to post-treatment change in overall FSFI scores was 4.66, representing a large effect size of d = 0.73. Age, length of relationship at baseline, and changes in relationship adjustment, were all significantly correlated with the placebo response whereas psychological symptoms, baseline sexual function, and baseline relationship adjustment scores were not. Married women showed a stronger placebo response whereas SSRI use was associated with a smaller effect. There were no significant differences in the magnitude of the placebo response based on ethnicity or based on diagnosis (either FSAD or FOD).

In an unpublished examination of placebo effects, 50 women participating in a pharmaceutically-sponsored trial of Cialis versus placebo for FSAD, Bradford and Meston found that the strongest predictor of the pla-
As well as spontaneous orgasms in some cases. Vaginal contractions, throbbing, pressure and pain, include clitoral tingling, irritation, vaginal congestion, sexual interest or desire. Complaints by sufferers genital arousal occurring in the absence of subjective distress [369] although improvements in sexual satisfaction also correlated with the placebo response. In fact, this study found no significant difference in improvements in sexual frequency between the placebo and treatment groups. Interestingly, this study also found that the placebo group resulted in a significant increase in genital stimulation received by a partner.

In speculating about the potential mechanisms by which the placebo response occurs, Bradford and Meston [367] reasoned that expectancies may partially explain this effect (e.g., expecting an enhanced sexual response). However, it is also possible that other mechanisms, such as desirable responding, regression to the mean, and effects of repeated measurement may have underlined this effect. Study design related factors, such as investigator effects, assessment strategy, duration of treatment, dosing schedule, selection criteria, and treatment procedures, may also have affected the placebo response [367] and the finding that studies which employ identical methodologies show comparable rates of placebo effects supports this possibility. The authors also speculated that enrolling in a treatment trial that requires a minimum number of sexual events per week may enhance communication between partners and subsequently enhances sexual response [368]. However, they also acknowledged that enhanced sexual response may have facilitated emotional intimacy and communication between the partners.

**Recommendations:**

Clearly, statistical significance is not a sufficient indicator for determining treatment response between placebo and active treatment arms of a particular trial. Instead, the magnitude of placebo effects is important to consider as well as the clinical meaningfulness of the group differences. In the future, the magnitude of placebo effects and the correlates of the placebo response may also be used to guide thinking about a particular sexual dysfunction’s etiology. **GRADE B**

**VI. PERSISTENT GENITAL AROUSAL DISORDER**

1. **WHAT IS PERSISTENT GENITAL AROUSAL DISORDER?**

Persistent Genital Arousal Disorder (PGAD) is a perplexing condition characterized by high levels of genital arousal occurring in the absence of subjective sexual interest or desire. Complaints by sufferers include clitoral tingling, irritation, vaginal congestion, vaginal contractions, throbbing, pressure and pain, as well as spontaneous orgasms in some cases. Attempts to quell the genital arousal by engaging in masturbation or sexual activity usually provides only temporary relief or even more arousal and activation. Although it is not a formal category of dysfunction in the DSM-IV-TR, PGAD might currently be diagnosed as a Sexual Dysfunction Not Otherwise Specified.

The diagnosis of PGAD is made based on the presence of all five of the following features: (a) the physiological responses characteristic of sexual arousal (genital vasocongestion and sensitivity) persist for an extended period of time (hours to days) and do not subside completely on their own; (b) the genital arousal does not resolve completely despite one or more orgasms; (c) the persistent genital arousal is experienced as unbidden, intrusive and unwanted; (d) the persistent genital arousal may be triggered not only by sexual activity but by nonsexual stimuli as well (e.g. vibrations from a car) or triggers may not even be apparent; and most importantly, (e) there is at least a moderate or greater feeling of distress associated with the experience [370]. Hypersexual states often associated with mania, sexual compulsivity or stimulating social drugs preclude a diagnosis of PGAD.

2. **PGAD PREVALENCE**

Leiblum and her colleagues have published three internet based studies on PGAD using data from women who completed web-based surveys concerning the condition [370-372] (Level 3). These research reports found high levels of stress and anxiety among sufferers as well as a greater incidence of obsessive-compulsive and somatization symptoms in PGAD women. Unlike women who met some, but not all features of the condition (a non-PGAD group), PGAD women reported that the genital arousal they experienced was more intense, continuous, unwanted and distressing than that of the non-PGAD women, many of whom enjoyed the unsolicited genital arousal.

Although in many cases, the dysphoric mood of PGAD sufferers preceded their first experience of unsolicited genital arousal, the unremitting nature of the symptoms coupled with the lack of relief predisposes some women to become severely depressed and even suicidal [373]. The distress associated with the disorder is compounded by the fact that many women feel embarrassed and humiliated about revealing the condition to intimate partners and health care providers. The shame and embarrassment attached to the symptoms has most likely contributed to the phenomenon going unrecognized and underreported. As a result, there are currently no reliable figures on the prevalence of PGAD, although it may not be as rare as initially described.

3. **PGAD ETIOLOGY**

At this time, there is little consensus regarding the etiology of PGAD. Based on individual case reports or
small series of cases, Goldstein [374] has suggested the following major etiological possibilities: (i) central neurological changes (e.g., post-injury, specific brain lesion anomaly) (ii) peripheral neurological changes (e.g., pelvic nerve hypersensitivity or entrapment) (iii) vascular changes (e.g., pelvic congestion), (iv) mechanical pressure against genital structures, (v) medication-induced changes, and (vi) psychological changes (stress) or some combination of all of the above. There have been case studies that document the onset of PGAD secondary to neurological pathophysiology [374]. Leiblum and Goldmeier [375] note that some women have associated the onset of PGAD symptoms with the initiation of treatment with SSRIs and other mood stabilizers. Other possible triggers that have been identified include the cessation of treatment with antidepressant medication, beginning menopause, physical inactivity, and severe stress [373]. A recent study found an association between restless leg syndrome and PGAD and suggested that the pharmacological treatment of the former may be helpful to women with PGAD [375].

From a psychological perspective, Leiblum and Chivers [376] have postulated that women with PGAD may be more vigilant in monitoring small changes in their physical well-being than women who simply report unsolicited but untroubling genital arousal. This tendency may reinforce a possible underlying pathophysiological mechanism, and lead to perpetuation of the arousal. It is not known at this time whether the distress experienced by PGAD patients as compared with non-PGAD women stems from the kind, intensity or duration of the genital sensations, or how these women label and account for the arousal.

4. PGAD TREATMENT

While there is no generally accepted treatment for PGAD, current interventions [377,378] focus largely on symptom management (Level 4). Guidelines have been published but notably they are based on case reports and not on RCTs [379]. Psychoeducation and social support are often the first steps as patients are relieved to discover that they are not alone in their experience and become aware of the stimuli which exacerbate symptoms. In addition, a first step should involve reducing or eliminating any identifiable factors which have exacerbated the symptoms. Anesthetizing agents or ice may be used to numb the area. Pelvic massage or stretching exercises are sometimes helpful in reducing pelvic tension. Medication management is largely achieved by trial and error as certain medications may be associated paradoxically with either alleviation or activation of the symptoms. Mood stabilizing, anti-seizure medications such as valproic acid (Depakote) have helped some women, while others report relief with SNRIs (Selective Norepinephrine Reuptake Inhibitors). Cognitive-Behavioral interventions have been used to enhance coping skills and assist in interrupting the cycle of anxiety and catastrophizing of the symptoms. Mindfulness based intervention has also helped since anxiety worsens symptoms by leading to more autonomic nervous system activation, and often, more genital arousal [379] (Level 4).

5. FUTURE DIRECTIONS WITH PGAD

More research is clearly needed to investigate the etiology, causes and treatments of PGAD. In addition to extensive medical histories and psychological evaluations, the collection of comprehensive physiological data including gynecologic examinations, thermograph measurement of the genital area, pelvic floor muscle tone data, the measurement of hormone levels, fMRI brain scan information, evaluation of the sensitivity of the genital tissue areas, etc., will be key in elucidating the disorder. Since little is known about the range and diversity of women’s sexual response, investigations into PGAD will likely shed light on the dynamics of arousal, desire, and female sexual functioning.

Recommendations:

PGAD is a distressing intrusive condition that is relatively new to the sexual dysfunction lexicon. Data on prevalence, pathophysiology, and treatments is very scant and there are no randomized controlled trials on any available treatment method. Psychoeducation and support are important in the early stages of intervention. There may be relief with medications (e.g., mood stabilizers, SNRIs), anesthetizing medications, pelvic floor physiotherapy, psychological therapy, and mindfulness may be helpful for the condition and may be tried alone and/or in combination with one another. **GRADE C**

7. Subjective excitement, pleasure, and relationship satisfaction should be targeted endpoints
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Women’s Sexual Pain Disorders

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I. INTRODUCTION

The sexual pain disorders, dyspareunia and vaginismus, have provided special challenges to health professionals. The primary challenge, perhaps, has been the continuing controversy concerning how to conceptualize and treat sexual pain. Robert Latou Dickinson noted this as early as 1933 by writing:

"The surgeon thinks of difficult coitus in terms of a knife passed through muscles in spasm; the psychiatrist thinks of dyspareunia as a mental knot to be disentangled by analysis; the gynecologist who is weary of patching - poor and late patching - begins to think in terms of prevention through routine premarital examination and instruction"[1].

This continuing uncertainty about treatment is complicated by the clinical challenge of dealing with highly distressed patients. Sims [2] described this in the following way:

"From personal observation I can confidently assert that I know of no disease capable of producing so much unhappiness to both parties of the marriage contract... ([2] p. 361).

The combination of professional uncertainty and patient distress often makes standard examinations and interviews lengthy and difficult. Understandably, many professionals have avoided treating and investigating dyspareunia and vaginismus. Although there has been increased clinical and research attention in the last 10 years, there is still much basic missing information.

1. TERMINOLOGY

The term "vaginismus" was coined by Sims in the second half of the 19th century and continues to be used today by gynecologists, mental health professionals, sexologists and physicians in general. By contrast, a very large number of labels and classification terms have appeared which describe painful intercourse or dyspareunia without known pathological causes. These include terms such as (generalized, localized, dysesthetic, essential or (hemi) vulvodynia, clitorodynia, vulvar dysesthesia, focal vulvitis, vulvar adenitis, vulvar vestibulitis, (provoked/unprovoked/generalized/localized) vestibulodynia, burning vulva syndrome, pelvic pain, etc. In recent years, there has been an increased emphasis in describing and classifying vulvar pain whether or not it is linked to a pathological state. The International Society for the Study of Vulvar Disease (ISSVD) has recently published updated versions of their classifications of vulvar pain [3]. There has not been parallel activity in describing and classifying deeper vaginal/pelvic pain. For many women who complain of pain during intercourse, there is a combination of superficial (vulvar) and deeper (vaginal/pelvic) pain. For many women who complain of pain during intercourse, there is a combination of superficial (vulvar) and deeper (vaginal/pelvic) pain. In addition, it is often unclear whether the pain can or should be attributed to a disease process or not. The term "sexual pain" was introduced in the DSM-III-R and refers to both dyspareunia and vaginismus when they are not directly caused by physical pathology. The rationale for the introduction of this term is not clear [4].

While such nosological and terminological confusion is not uncommon in the health sciences especially when multiple disciplines are involved, it has impeded research and clinical communication. In this chapter, we will for convenience sake continue to use the traditional mental health terms vaginismus.
and dyspareunia. When there is a focus on vulvar pain and the literature warrants it, we will use diagnostic terms such as “provoked vestibulodynia” (PVD) as suggested by the new ISSVD classification. Developing a uniform, comprehensive and reliable nosology remains a challenge.

2. CLASSIFICATION AS A SEXUAL DYSFUNCTION, DISEASE OR PAIN SYNDROME

The diagnostic operationalization of vaginismus by Sims (1861) as a spasm of the pelvic floor muscles remained virtually unchallenged until recently [2]. The presumed etiology of this spasm, however, has been attributed to varying causes, ranging from a psychosomatic fear of sex and/or vaginal penetration to the repeated or imagined experience of pain during intercourse. Typically, once anatomical and disease-related causes of pain or difficulties in penetration were excluded, vaginismus was considered by most authorities and classification systems as a sexual dysfunction. While the ICD-10 continues in this tradition, it also allows for the classification of vaginismus as a pain syndrome.

Dyspareunia has traditionally been conceptualized either as the direct result of physical and anatomical factors or as a reflection of psychological/sexological difficulties. Some recent research and theorizing suggests that these two views might be usefully combined under the rubric of pain syndrome, though many consider this approach controversial [5].

Whichever conceptualization one adheres to for the understanding of “sexual pain”, it is clear that both vaginismus and dyspareunia are frequently comorbid with DSM-IV sexual dysfunctions such as hypoactive sexual desire disorder, female sexual arousal disorder and orgasmic disorder.

3. SEXUAL PAIN AND EVIDENCE-BASED REPORTING

The Oxford system of levels of evidence is unfortunately not well suited to this literature since there are not many high quality studies or systematic reviews. Nonetheless, each relevant study cited in this chapter is graded according this system. This will allow for comparisons of the quality of evidence concerning dyspareunia and vaginismus with other problems covered in this volume. In comparing the number and quality of studies available for this chapter as compared with those available for the 2004 version, it is encouraging that there are many new studies and several replications of previously reported findings. It is also very encouraging that the first randomized controlled trial (RCT) for the treatment of vaginismus has been published [6]. These developments bode well for the future of the field.

II. NEUROBIOLOGY OF THE PELVIS

A basic understanding of the neurobiology of the pelvic floor is paramount to gain further insight into the pathophysiology of urogenital disorders (which are characterized by disturbances of sensation and motility) and to develop effective clinical management strategies for patients presenting with these syndromes [7].

Over the last 15 years, the basic neurobiology of the pelvic floor, despite its complexity, has come to be a reasonably well-developed discipline owing to an increasingly refined knowledge of principles pertaining to the neuroanatomy and neurochemistry of pelvic functions [8].

It is important to note that this summary attempts to derive as much information as possible from investigations involving humans although some generalizations are necessarily taken from animal studies, recognizing that much research in this field is still in its infancy. Many of the animal studies concerned with the characterization of the autonomic outflow to the pelvis (unless they were specifically designed to assess the female reproductive tract) have primarily been conducted in male animals. This caveat is important since there is some evidence to suggest that pelvic floor and perineal innervation may differ between men and women [9].

1. NEUROANATOMY OF THE PELVIS AND PELVIC FLOOR

The pelvis and pelvic floor are innervated by both divisions of the autonomic nervous system, the sympathetic and parasympathetic divisions, as well as by the somatic motor and sensory nervous systems (Grade A). In a broad anatomical view, dual projections from the thoracolumbar and sacral segments of the spinal cord carry out this innervation, converging primarily into discrete peripheral neuronal plexuses before distributing nerve fibers throughout the pelvis (Figure 1). Interactive neuronal pathways routing from higher origins in the brain through the spinal cord add to the complexity of neuronal regulation in the pelvis. While it is important to appreciate the influence of supraspinal centres in the coordination of pelvic organ activities, it is beyond the scope of this review to discuss these interactions in further detail [10-16].

The nomenclature of the various plexuses, ganglia, and nerves in the pelvic cavity is varied and sometimes confusing, presenting designations from both Nomina Anatomica and clinical usage [17, 18]. In this review, we have used the anatomical nomenclature, the clinical usage is given in brackets: superior hypogastric plexus (presacral nerve), hypogastric plexus (hypogastric nerve), inferior hypogastric plexus (pelvic plexus) and pelvic splanchnic nerve (pelvic nerve).

a) Pelvic Autonomic Innervation

Within the pelvis, the inferior hypogastric plexus is regarded to be the major neuronal integrative center [19]. Neuropathological studies have confirmed its retroperitoneal location adjacent to each lateral aspect of the rectum, with interconnections between the left and right inferior hypogastric plexuses at the posterior aspect of the rectum [20-22]. It innervates multiple pelvic organs, including the urinary bladder, proximal urethra, distal ureter, rectum and internal anal sphincter, as well as genital and reproductive tract structures [23]. The anterior part of the inferior hypogastric plexus, associated with the distal extent of the hypogastric plexus (hypogastric nerve), is referred to as the paracervical ganglia. These ganglia are situated in the parametrium lateral to the cervix and the upper part of the vagina, and they distribute nerve fibers to the corpora cavernosa of the clitoris, vagina, and periurethral tissues [24].

Neuronal input to the inferior hypogastric plexuses involves sympathetic and parasympathetic systems. Sympathetic nerves originate in the thoracolumbar segments of the spinal cord (T10-L1) and condense into the superior hypogastric plexus located just inferior to the aortic bifurcation. Pre-ganglionic efferents originate largely in the intermediolateral cell column, whereas afferents have their cell bodies located in dorsal root ganglia of these segments. Nerve fibers project from the superior hypogastric plexus as paired hypogastric plexuses (hypogastric nerves) and fuse distally before diverging bilaterally into branches destined for the inferior hypogastric plexuses. Additional sympathetic innervation to genitourinary organs may involve pre-ganglionic nerves which synapse on postganglionic nerves originating in sympathetic chain ganglia; these postganglionic nerves join sacral nerves and course to their destinations via pelvic somatic neuronal pathways (see description below) [25]. Parasympathetic preganglionic nerve efferents are thought to arise from cell bodies of the sacral parasympathetic nucleus located in the intermediolateral gray matter of the sacral spinal conus (S2-S4) and fuse as the pelvic splanchnic nerve before entering the inferior hypogastric plexus [26, 27]. Parasympathetic afferents have cell bodies located in the S2-S4 dorsal root ganglia and course also within the pelvic splanchnic nerve. In addition to its parasympathetic efferent and afferent component, the pelvic splanchnic nerve also receives postganglionic axons from the caudal sympathetic chain ganglia [28].

A distinctive distribution of pelvic autonomic innervations is recognized at the urogenital organ level. In women, it involves inferior hypogastric plexus projections deriving primarily from the paracervical ganglia part of the plexus. Conspicuous nerve trunks run in the adventitia of the vagina parallel to its long axis, sending off anterior branches that course to the clitoris and periurethral tissues and local branches which enter the vaginal smooth muscle walls [18, 29]. A network of nerve fibers tends to follow vascular distributions and conspicuously terminates at the junction between the subepithelial connective tissue and the vaginal epithelium as well as within the epithelium. Nerve density is observed to be greater in the distal vagina compared with proximal regions and in the anterior vaginal wall as compared to the posterior vaginal wall [29, 30]. These regional differences in vaginal innervation are supported by psychophysical studies, which have identified a relative sensitive position to electrical stimuli in the anterior vaginal wall as compared to other vaginal areas [31]. A network of nerves rather than discrete nerves...
pierce the urogenital diaphragm to supply the vulvar tissues which engorge with sexual arousal.

Recent research data from spinal cord transected rats and women with spinal cord injury suggest that the vagus nerves can convey genital sensory input directly to the brain, completely bypassing the spinal cord [32-35]. Vaginal-cervical mechanical self-stimulation in women diagnosed with spinal cord injury at the T10 level resulted in activation of brain regions to which the vagus nerves project, the Nucleus of the Solitary Tract, as demonstrated in PET [33] and fMRI [35] studies.

**b) Somatic Innervation**

Somatic efferent and afferent innervation to the pelvis is generally understood to involve the sacral nerve roots (S2-S4) and their ramifications. Somatic efferents arise within Onuf's nucleus situated in the ventral horn of the S2-S4 spinal conus, and afferents reach the dorsal horn with their cell bodies in dorsal root ganglia of these segments [36]. Central projections of somatic afferents overlap with pelvic nerve afferents within the spinal cord, which theoretically allows coordination of somatic and visceral motor activity [25].

The sacral nerve roots emerge from the spinal cord forming the sacral plexus, from which the pudendal nerve diverges (S2-S4, with the S3 segment providing the largest contribution) along with the sciatic nerve diverging (S2-S4, with the S3 segment providing the largest contribution) along with the sciatic nerve. The pudendal nerve divides into upper and lower trunks [38]. The lower trunk or both trunks and provides innervation to the ischiocavernous, bulbocavernous and superficial transverse perineal muscles and the striated urethral sphincter and labial skin [38].

Many anatomical texts have described that the pelvic floor muscles receive a dual innervation by the pudendal nerve and direct branches of the third and fourth sacral motor nerve roots [42-44]. However, a study in female cadavers published in 2002 found that a nerve directly originating from sacral foramina S3 to S5 crosses the superior surface of the pelvic floor to innervate the three levator ani muscles: ilio- coccygeal,pubococcygeal, and puborectal muscles [38]. No pudendal nerve branch that innervated the levator ani muscles could be identified in this study. Branches of S4-S5 nerve roots forming the coccygeal plexus distribute to perineal, perianal, and labial (or scrotal) skin [40].

**c) Innervation of the Vulvar and Vaginal Area - Clinical Relevance**

Most studies on vulvar/vaginal innervation have been derived from animal studies [7, 45]. Compared to other areas of neuroscience little is known about the functional neural correlates that signal the wide range of sensations from the vulvar and vaginal area ranging from pleasure to pain. The vulva is densely innervated by branches of the pudendal nerves (somatic nerves), conveying information about gentle and intense mechanical stimulation to the sacral spinal cord (S2-S4). The vagina is innervated by the pelvic nerves (parasympathetic nerves). The cervix and adjacent fornix region of the vagina are innervated more densely than the rest of the vagina by the pelvic and hypogastric nerves. Information arriving from the vulva, vagina, and cervix is conveyed to widespread regions of the CNS, implying that stimulation of these regions can affect a wide range of physiological and perceptual functions [15, 46-48]. Fibers innervating the vagina are activated by both gentle and intense mechanical stimulation, including noxious stimuli [46, 49]. Mechanical probing (non-noxious stimuli) of the vagina and/or cervix has produced antinociceptive effects in rats and analgesia in women [50, 51]. The urogenital sinus of the embryo differentiates into the adult urachus, bladder, urethra, and vestibule, which in the adult comprises a shallow funnel of endodermal origin, sandwiched in between the (ectodermally derived) vulva and vagina proper [52-55]. The human vulvar vestibule contains free nerve endings but has no specialized nerve endings such as Meissners or Pacinian corpuscles [30]. The first survey of the innervation pattern in the human vagina using a pan-axonal marker was published in 1995 [29]. Free intraepithelial nerve endings were only detected in the introitus vaginae region. These very superficial free nerve endings are considered to
be nociceptive or thermoceptive [56]. Studies in rats have demonstrated, as the extent of the vaginal innervation varies as a function of the gonadal hormonal status [57]. This plasticity of the innervation is not restricted to the vagina, but has been reported in other parts of the female reproductive tract as well: remodeling of the innervation has been described in the rodent and human uterus during the estrous cycle and during gestation. Estrogen seems to be a major factor, but not the only one, determining the level of innervation during the reproductive cycle [58]. Interestingly, four independent studies reported vestibular neural hyperplasia in women with vulvar vestibulitis, which might provide a morphological explanation for the vestibular hyperalgesia reported by these patients [54, 59-61]

d) Sexual Pain

Pain arising from within the pelvis and pelvic floor involve diverse neuronal mechanisms, although there are some general characteristics. In general, sensations from the pelvic viscera are conveyed within the sacral afferent parasympathetic system, with a far lesser afferent supply from thoracolumbar sympathetic origin [62]. Receptive fields in the perineum are understood to be carried out primarily by sensory-motor discharges associated with pudendal nerve afferents [62, 63]. Entrapment of the pudendal nerve has been considered as one of the causes of urogenital pain [64]. While the interactions of sensory afferents are quite complex, likely possibilities by which these pathways exert effects on autonomic efferent function include mediating effects on spinal cord reflexes and modulatory effects on efferent release in peripheral autonomic ganglia and in peripheral organs.

2. NEUROCHEMISTRY

An elaborate neurochemical coordination of all components of the central and peripheral nervous systems is necessary for the performance of autonomic and somatic events in the pelvis. As indicated previously, the inferior hypogastric plexus represents the major neuronal center in the pelvis providing a relay station for interconnecting nerve pathways, but it also represents a critical integrative site for the neurochemical influences operative in the pelvis [36, 63, 65]. The structure contains multiple subpopulations of cells, defined by their putative neurotransmitter contents, and displays a highly specialized synaptic organization and system of signal processing. For example, while cholinergic preganglionic neurons provide a primary excitatory input to cholinergic postganglionics, postganglionic nicotinic receptors can provide feedback inhibition on preganglionic acetylcholine release. Similarly, noradrenergic sympathetic fibers synapsing on cholinergic postganglionic neurons or interneurons in the inferior hypogastric plexus impede cholinergic synaptic transmission [63]. In fact, neuropeptides, purines, kinins, monoamines, and amino acids, as well as local factors such as prejunctional muscarinic receptors and non-neuronal endothelins, may all serve as co-transmitters or neuronal modulators of classical neurotransmitter (acetylcholine and norepinephrine) release. A major sensory role for urothelially released ATP acting via P2X3 receptors on a subpopulation of pelvic afferent fibers has been documented in P2X3 knockout mice [66].

Surprisingly, there had been little focus on neurotransmitters in the vulvo-vaginal area. However, recently several reports have been published both in animal models and in humans. In rabbits hypothalamic neuropeptides have a contractile and relaxant effect on vaginal strips and arteries [67]. In female rats estradiol down-regulates estrogen-receptor alpha and up-regulates progesterone-receptor expression in the vagina [68]. Several studies have focused on steroid receptor expression in the vaginal epithelium and in the vulvar vestibular mucosa as a function of hormonal contraceptives and the menstrual cycle. Steroid-receptor expression in human vaginal epithelium was altered by long-term use of depot medroxyprogesterone acetate injections. The relation to other types of contraceptives did not show a clear picture and there were no differences observed between the follicular and luteal phase samples [69]. Estrogen-receptor beta was more abundant in the vulvar vestibular mucosa of women using combined oral contraceptives (COC) than in women without COC use. During the menstrual cycle, progesterone-receptor B was more abundant in the stromal tissue of the vulvar vestibular mucosa in the follicular phase than in the luteal phase in healthy women [70]. In women with PVD, there was a higher expression in estrogen-receptor alpha in the vulvar vestibular mucosa, but the epithelial morphology seemed unaffected [71].

CGRP, a neuropeptide known to exist in nociceptive afferent nerves, was the only neuropeptide detected in the superficial nerves of the vestibular epithelium in an earlier study by Bohm-Starke et al [72]. Afferent nerve distributions within the vascular and nonvascular smooth muscle of the vagina contain the neuropeptides galanin, and substance P [65, 73] while extensions into the epithelium and between epithelial cells primarily contain substance P and CGRP [73]. Studies using vestibular biopsy tissue from patients with PVD have demonstrated an increase in vanilloid receptor TRPV1 (a receptor expressed by nociceptors) innervation as compared to controls [74].

Clitoral and vaginal vasodilation is generally associated with parasympathetic vasodilator mechanisms, among which acetylcholine, VIP, and nitric oxide appear to be contributing neurotransmitters [73, 75]. Flaccid genital organ states appear to be tonically governed by adrenergic and possibly peptidergic sympathetic mechanisms [76]. It is contended that parasympathetic mechanisms also account for
vaginal fluid transudation, which accompanies vaginal vasodilatation, and that neuropeptides are primary candidates for this regulatory function [65, 77, 78].

These recent studies on neurochemical substrates in the female urogenital area provide a basis for future research on peripheral neurochemical mechanisms involved in the etiology of the sexual pain and sexual arousal disorders. There is already an impressive body of literature on visceral nociceptive processing and potential novel drug targets [79, 80]. Future studies could extend these findings to sexual pain and arousal disorders and might lead to the identification of peripheral targets for treatment.

**III. CHRONIC PAIN PHYSIOLOGY AND SEXUAL PAIN DISORDERS**

1. CURRENT NEUROMATRIX THEORY OF PAIN

Pain is a complex sensation involving sensory-discriminative (localization of the stimuli, detection of intensity and quality discrimination), affective-motivational (encompassing emotional reactions, an arousal and selective attention to the painful stimuli) and cognitive-evaluative aspects (anticipation, attention to the painful stimuli and comparison with past experience) (Grade C) [81].

The classical pain theory that has been established over the last 40 years states that there are two parallel pain processing systems operating at a cortical and subcortical level; the lateral and medial pain systems [81]. The lateral pain system, comprising the lateral projections of the spinothalamic tract, is also termed the neospinothalamic pathway. This pathway projects to the lateral thalamic nuclei and subsequently to the primary and secondary somatosensory cortex, and also to the parietal operculum and the insula. By contrast, the medial pain system, also termed the paleospinothalamic pathway, projects to the intralaminar and medial thalamic nuclei and further to the anterior cingulate cortex, insula, amygdala, hippocampus, and hypothalamus; the spinoreticular tract projects to the parabrachial nucleus and the locus coeruleus, and the spinomesencephalic tract projections to the periaqueductal grey matter. Whereas the lateral pain system is mainly associated with the sensory-discriminative aspects of pain processing, the medial pain system plays a crucial part in the motivational-affective and cognitive-evaluative aspects of pain processing, memory for pain, and the autonomic-neuroendocrine responses [82, 83].

The neuromatrix theory of pain proposes that pain is a multidimensional experience produced by characteristic “neurossignature” patterns of nerve impulses generated by a widely distributed neural network the "body-self neuromatrix" in the brain. This theory suggests a new conceptual framework for understanding chronic pain disorders. It proposes that the output patterns of the body-self neuromatrix activate perceptual, homeostatic, and behavioral programs after injury, pathology, or chronic stress. Therefore, pain results from the neural network in the brain rather than directly by sensory input evoked by injury, inflammation, or other pathology (Grade C) [84].

2. NEUROGENIC INFLAMMATION

It is of interest that there are several urogenital and pelvic pain syndromes in which pain seems to be related to an inflammatory etiology: interstitial cystitis, irritable bowel syndrome, prostatodynia (prostatitis) and PVD. However, despite numerous research efforts, no causes for such inflammatory changes have been identified thus far. It has been suggested that the pathological changes in PVD occur at three interdependent systems (See Figure 2) including the vestibular mucosa, pelvic floor muscles and central nervous system (Grade B) [85].

![Figure 2](image_url)

**Figure 2.** Neurogenic inflammation is thought to be involved in the pathogenesis of numerous conditions including chronic pain such as osteoarthritis, migraine, dental disease, pancreatitis, virus-associated respiratory infection, nonproductive cough, allergic rhinitis, asthma, chronic bronchitis, sarcoidosis, inflammatory bowel disease, rheumatoid arthritis, and painful conditions in general [86-91]. Recent evidence indicates that neurogenic inflammation plays a role in the development of pelvic pain disorders (e.g., interstitial cystitis [92-95]), which suggests that PVD is probably multifactorial.

The relationship between the inflammatory process and the nervous system is two-fold. The nervous system is activated by inflammation processes which cause inflammatory pain. Conversely, the nervous system reacts to the peripheral process by activating primary afferent fibers and subsequent neurogenic
inflammation. In these conditions, an initial nervous system dysfunction or injury may trigger the neural release of inflammatory mediators and subsequent neurogenic inflammation. This neuro-inflammatory process is believed to be mediated by the release of vasoactive peptides such as substance P, neurokinin A, and calcitonin-gene-related peptide (CGRP). These inflammatory mediators trigger vasodilatation, extravasation of proteins, and release of bradykinin and nitric oxide. These mediators can also cause degranulation of peripheral mast cells which, in turn, releases histamines and serotonin, causing a long-lasting lowering of nociceptive thresholds (i.e. peripheral sensitization [96]).

Given that there is no direct evidence for inflammatory changes in PVD and that, under certain circumstances, non-noxious stimulation evokes pain, it is possible that additional mechanisms are involved. Recent studies suggest that such pain syndromes are associated with hypersensitivity to both visceral and somatic stimuli (Grade B). Thus, enhanced or altered pain sensitivity arising from within the viscus at the peripheral or central level may play a role. Over time, afferent signals from both primarily affected viscera and secondarily sensitized nociceptors lead to increased afferent excitability and central sensitization to facilitate chronic pain disorders [97, 98]. It may be assumed that such inflammation-evoked processes lead to plasticity in pain modulation pathways and chronic pain.

In visceral pain conditions, neurogenic inflammation may also appear to be an important mechanism in referred pain [99]. For example, pain of acute myocardial infarction may sometimes induce a left scapulohumeral periarthritis, an inflammatory condition in the referred zone [100]. It could be hypothesized that neurogenic inflammatory mechanisms in the referred zone might play a role in interstitial cystitis and vulvodynia, vulvodynia, or pelvic pain in which an inflammatory painful condition develops in the referred zone (the urogenital floor) of the urinary bladder or the pelvis. Evidence for neurogenic inflammation in the somatic referred zone triggered by inflammation of a viscus has been demonstrated in an animal model of uterine pain in the rat, supporting the above hypothesis [101]. In humans, the increasing evidence that most of the urogenital and pelvic pain syndromes occur together in some women over time support also this hypothesis [102]. Neurogenic inflammation may result from changes at the local/peripheral level but also reflect changes at the central level. Quantitative sensory testing (QST) studies that involved the application of various modalities of experimental noxious stimuli to evaluate A-β fiber function revealed altered pain processing in visceral pain conditions. According to most of these studies enhanced pain perception at the local as well as the systemic level exists [103, 104]. Local hypersensitivity was found in PVD women via increased innervations and/or sensitization of thermoreceptors and nociceptors in their vestibular mucosa [105-107] add more references). Nevertheless, more and more studies support the role of enhanced systemic pain response to noxious stimuli applied to remote body areas, indicating that there might be general hypersensitivity in those patients. In this line, low pain thresholds, high magnitude estimation of supra-threshold stimuli and altered central sensory processing have been observed [108-111]. Enhanced response to punctate hyperalgesia and dynamic allodynia evoked by capsaicin injection extending far beyond the anatomic location of the primary complaint provide an additional support for the role of systemic hypersensitivity in PVD [112]. In this line, the augmented pain response to supra-threshold stimuli applied to the forearm in PVD women has been also found to be associated with lower efficacy of treatment [113]. Moreover, Bohm-Starke et al. [114] noted increased vestibular pain thresholds, reduced dyspareunia, and improved bodily pain in women with PVD versus control women in response to various treatments. However, despite the improvement of the superficial dyspareunia the general hypersensitivity was not affected by the treatment. These studies suggest that pain mechanisms in PVD (and probably other pelvic pain disorders) cannot be solely attributed to neurogenic inflammation occurring at the local level (Grade B).

Ness et al [115] also suggests altered central mechanisms in the processing of sensory events from the bladder of interstitial cystitis (IC) patients who demonstrated hypersensitivity to somatic stimuli applied to deep tissue at the forearm and the bladder. Similarly, generalized cutaneous hypersensitivity to thermal or vibratory stimulation among painful bladder syndrome (PBS) patients has been found [98]. Warren et al. examined IC/PBS patients and concluded that multiple sites of pain (including pain in the genital area) in the same patient could be attributable to a single illness [116]. Central sensitization probably explains the multiplicity of pain sites in patients with IC/PBS.

The role of alterations in central pain processes is also supported by other psychophysical studies. Recently, a brain imaging study using functional magnetic resonance imaging (fMRI) in PVD women indicated that painful genital stimulation led to increased activation of brain areas associated with pain modulation (limbic and sensory brain regions) as compared to control women [111]. In addition, a second study by the same group [117] showed morphological alterations in supra-spinal pain modulation areas in women with PVD. Specifically, women with PVD had greater gray matter density in the parahippocampal gyrus/hippocampus and basal ganglia as compared with non-affected women.
3. NEUROPATHIC PAIN: CENTRAL AND PERIPHERAL MECHANISMS

The accumulative reports that suggest systemic hypersensitivity to noxious stimuli raise the issue of whether pain that is attributed to neurogenic inflammation can also be considered as part of neuropathic pain. It may be assumed that nerve injury associated with neurogenic inflammation leads to non-reversible changes that represent the clinical picture of neuropathic pain. There is experimental evidence from several QST studies, suggesting that neuropathic pain mechanisms might be involved in PVD [105, 107, 112, 114, 118, 119]. Nevertheless, most of the PVD patients report spontaneous or provoked pain with no other symptoms of neuropathic pain such as paraesthesias and dysesthesias. It may be assumed that PVD (and other related pain conditions) encompass both mechanisms of neurogenic inflammation as well as neuropathic pain, the combination of which may lead to the development of these disorders in patients with less efficient pain modulation processing.

There is general consensus today that both peripheral and central nervous system mechanisms play a role in neuropathic pain [120]. Briefly, neuropathic pain is typically characterized by spontaneous paraesthesias, dysesthesias, and by evoked pain (for example, pain provoked by mechanical stimuli, such as the pain elicited by tampon insertion or sexual intercourse in patients with PVD). Under normal conditions, pain is experienced when impulses reach the brain via A-delta-fiber or C-fiber nociceptive afferents. Minor tissue injuries can cause a reduction in the threshold of nociceptors, resulting in “peripheral sensitization”. This change in threshold is caused by the release of chemical inflammatory mediators into the tissue. Sensitized nociceptors respond to weak, non-noxious stimuli - a clinical phenomenon called “alldynia”. Further, noxious stimuli result in an exaggerated pain response - “primary hyperalgesia”, in which the magnitude of pain sensation no longer matches the intensity of the noxious stimulus. Psychophysical tests reveal lower pain thresholds at the vestibule. In addition, the differences between threshold and supra-threshold pain sensitivity at the vestibulum region among women with moderate and severe PVD support the clinical picture of peripheral sensitization, suggesting that PVD is compatible with the definition of neuropathic pain condition [107, 121].

The clinical phenomena of alldynia and hyperalgesia can also be due to abnormal signal amplification of dorsal horn cells in the CNS, a process called “central sensitization”. In the presence of central sensitization, signals entering the CNS via non-nociceptive A-β touch afferents may evoke pain. The exact mechanisms that lead to increased descending excitatory signals and/or decreased inhibitory signals and their role are unclear. Although most PVD women are characterized more by provoked pain and less by paraesthesias, and dysesthesias, the role of a neuropathic pain origin should be considered in the pathogenesis of this pain disorder.

It is not clear whether an enhanced or altered systemic pain response leads to greater neurogenic inflammation response after stress or injury at the local level, or if an exposure to noxious events leads to central sensitization that, in turn, leads to greater pain sensitivity. The typical initiation and exacerbations of the pain of PVD after severe stressful life events fits the model of central sensitization [117]. The existence of pain in other body sites and the reports of other idiopathic pain disorders in PVD patients emphasizes the complexity of this issue [122].

A major modulation process of endogenous analgesia is exerted by the descending endogenous analgesia system, and includes the spinal-bulbo-spinal pain inhibition mechanism which is responsible for the ‘pain inhibits pain’ phenomena termed ‘diffuse noxious inhibitory control’ (DNIC). Impairment of DNIC (obtained via experimental pain tests) has been suggested in various chronic pain conditions with a female predominance, such as fibromyalgia and temporomandibular disorders. The role of dysfunctional central pain modulation and altered mechanisms of endogenous analgesia has been also been proposed in PVD. Recently, Johannesson et al., [123] suggested a systemic hypersensitivity in women with PVD that may support the role of altered endogenous pain modulation in PVD women. A similar approach has been reported in patients with IC [124]. Thus, it may be assumed that the less efficient pain modulation processing contributes to the development of hypersensitivity and to chronic neuropathic changes which characterize pelvic pain disorders.

IV. VULVOVAGINAL DISORDERS AND SEXUAL PAIN

1. INTRODUCTION

Disorders of genital skin and mucous membranes are common and many interfere with sexual contact causing pain (Grade A). Most of these painful disorders are transient and are caused by inflammation from acute genital infections. Infections that most commonly cause vulvo-vaginal inflammation include acute episodes of candidiasis, trichomonas, genital herpes, human papilloma virus infection (HPV), furuncles, and infection of the greater vestibular glands. The cause of the acute inflammation usually is readily discernable by the clinician and treatment usually resolves both the inflammation and the pain.
Chronic genital pain is more problematic because the causes are often difficult to discern. A comprehensive review provides a systematic approach to vulvar disease and offers a detailed list of diseases to consider [125]. Vulvar dermatoses are chronic inflammatory conditions, frequently affecting the vulvar skin and mucosa. A deficiency in the autoimmune system is thought to be the major etiologic factor (Grade B) and most dermatoses respond to topical corticosteroids [126]. However, depending on what area of the vulva is affected and the severity of the condition, pain and dyspareunia are common symptoms. Genital infections such as candidiasis, herpes and bacterial vaginosis have high recurrence rate and might also lead to chronic pain and discomfort in young sexually active women.

Unfortunately, iatrogenic inflammation of the vulvar skin is common from self-treatment or contact with irritants [127]. Nearly all women with chronic vulvar symptoms first use over-the-counter anti-fungal medication (Grade B). This self-treatment may be associated with increased duration of symptoms, which suggests a detrimental effect from the medication [128, 129].

2. VULVODYNIAS

a) Generalized Vulvodynia

Generalized vulvodynia may be provoked or unprovoked. The pain is usually described as burning and may affect the major part of the vulva [3, 130, 131]. In the unprovoked form, pain is not aggravated by physical or sexual contact. Here all the vulvar structures are of normal appearance and no obvious underlying causes are found. Women with generalized vulvodynia are often older than women with PVD, but data on incidence and prevalence are scarce. Furthermore, these data are often included under the general term vulvodynia, not separating the generalized and localized form [132, 133]. As compared to PVD, less research has been conducted and the underlying pain mechanisms are not fully understood. The symptoms of continuous burning pain and discomfort share many common features with neuropathic pain conditions. The syndrome might be difficult to treat. Therapies using tri-cyclic antidepressants or anticonvulsants usually offer alleviation, but not always a resolution for the pain [134].

b) Provoked Vestibulodynia (PVD)

PVD represents one of the most common causes of genital pain and pain with intercourse in premenopausal women. Pain is usually noticed with attempted vaginal penetration, although in more severe cases, pain will be present with other activities like sitting or running as well. Besides pain, a sensation of vulvar burning may occur. These symptoms cause physical, sexual, and psychological distress (Grade B) [135]. Primary PVD is defined as superficial dyspareunia ever since first intercourse attempt, whereas secondary PVD occurs after a period of pain free vaginal penetration. It has been suggested that these two subgroups differ in etiological, clinical and genetic variables (Grade C) [108, 136-139].

Community studies suggest vulvar pain is common, but the prevalence varies widely from 3-18% [133, 140]. PVD has been described in up to 15% of gynecologic outpatients and was thought to primarily affect Caucasian women [141-143]. A recent survey of ethnically diverse women gave similar lifetime prevalence rates of chronic vulvar burning or pain on contact [144].

Although PVD is easy to diagnose for the experienced clinician, the mean time between the onset of symptoms and diagnosis usually reaches two years or longer. Diagnostic criteria were initially defined for the former vulvar vestibulitis syndrome, but these criteria are still used for PVD: 1) pain with penetration during vaginal intercourse; 2) tenderness of the vestibular area upon even light touch with a cotton applicator; and 3) variable erythema of the vestibular area [145]. Symptom duration of at least 3-6 months is also usually included as a criterion. The areas of allodynia (sensation of pain from a light touch stimulus) are typically between 4 and 8 o'clock on the introitus, just exterior to the hymeneal ring [105]. However, in severe cases the hypersensitivity may involve the mucosa around the whole introital ring, including the openings of the Skene's ducts, and may extend laterally to labia minora [109, 118].

1) ETIOLOGY

No single causative factor has yet been identified for PVD and the etiology is considered multi-factorial (Grade B). Most probably a vast number of "triggers" may initiate the pain and if not taken care of properly, a more or less chronic pain condition might develop. A combination of causes might include psychosocial factors as well as more obvious physical trauma to the tissue such as recurrent infections. The pain mechanisms involved are in detail described in the paragraph on "Chronic pain physiology and sexual pain disorders". The most important etiological factors will here be discussed.

2) INFLAMMATORY REACTIONS

It has been proposed that PVD may represent a chronic local inflammatory condition with a wide variety of etiologic causes (Grade B). T-cell lymphocytes make up most of the inflammatory cells present in vulvar biopsies obtained from those with PVD [146, 147]. The infiltration is located in the subepithelial part of the lamina propria and is described as a non-specific chronic inflammation by pathologists. Plasma cells indicative of ongoing chronic infection are present, but not in large numbers. Mast cells and eosinophils indicative of an allergic condition are less common. However, similar infiltration of inflammatory cells
is also seen in healthy women and cannot serve as a histological indicator of PVD [60, 148]. Two studies on pro-inflammatory mediators have been published with conflicting results. Foster and Hasday found elevated tissue levels of interleukin I-ß (IL-1) and tumor necrosis factor alpha (TNF-α) in vulvar tissue of patients with PVD, but these pro-inflammatory mediators were actually at higher levels in the surrounding vulvar tissue than in the area of inflammation, confirming the clinical finding of a wider area of involvement beyond the area of erythema [149]. These results were not supported in a study by Eva et al, who did not find any differences between patients and controls regarding these mediators [150].

The two inducible enzymes nitric oxide synthase (iNOS) and cyclooxygenas 2 (COX 2) are hardly detectable in the skin and mucosa under normal conditions. However, its expression increases in response to various mediators released at the site of inflammation [151, 152]. COX 2 and iNOS are not up-regulated in biopsies obtained from the vestibular mucosa in women with PVD as compared to healthy controls. This finding is inconsistent with an ongoing cell-mediated inflammation and also explains why corticosteroids are not helpful for PVD [130, 153].

3) Infections and antigen

If a possible antigen has induced PVD for an individual, it could still be present in vulvar tissues in a small concentration, or the antigen could have stimulated an inflammatory response but be gone by the time patient usually presents with PVD. The most likely antigen candidate would be from microbes that commonly affect the vulva. Human papillomavirus (HPV) was first considered, but in multiple studies, HPV was as common in controls as women with PVD [154-157]. Herpes simplex virus (HSV) is also a common vulvar infection, but, to date, HSV does not appear to cause PVD [54, 158]. Bacterial vaginosis (BV) with an overgrowth of vaginal bacteria is also a common cause of vaginitis in young women [159]. According to case-control studies, women with PVD are more likely to report a history of BV than asymptomatic controls (Grade B) [160-162].

Candida is an antigen present in the vulva more frequently than HPV or HSV. Up to 75-80% of women develop symptomatic candidiasis during their lifetime [163]. Patients with PVD in many cases have a history of candidiasis, often recurrent [160, 164]. Candida might be identified by potassium hydroxide wet mounts, which require about 105 microbes to be positive. Candida is often isolated on culture from women with PVD, although extensive comparisons with control groups are lacking [160, 164]. Some patients with chronic recurrent vulvovaginal candidiasis (VVC) are noted to develop PVD when they are prospectively followed. Further, some women relate the onset of PVD to an acute episode of VVC and patients cured of PVD often develop recurrent genital pain when another episode of VVC occurs. Recently a new promising animal model of vulvodynia has been developed using repeated candida infections to produce dyspareunia in the mouse [165].

According to one study, a subset of PVD women is sensitized to seminal fluid. Thus, allergic reaction to seminal fluid may initiate pain symptoms in some women [166]. Undoubtedly, other microbial antigens from bacteria, viruses, or other microbes or non-microbial antigens that are present in the environment or in chemicals that come in contact with vulvar skin could also cause PVD.

4) Genetics

Recent work points to a possible genetic involvement [167, 168]. In fact, as is common for inflammatory conditions, allele 2 of the IL-1ß gene was found in significantly more women with PVD (40%) than controls (25%) [169]. In yet another study, an association of primary PVD and gene polymorphism of the mannosebinding lectin (MBL) gene was reported together with a reduced capacity for TNF-α production in response to microbial components in patients [137]. It has also been suggested that women with fair skin are more susceptible to PVD. An increased risk of PVD was found in cases with polymorphism of the melanocortin-1 receptor (MC1R) gene in a retrospective case-control study [170].

5) Hormonal influence

The first modern report of women suffering from PVD appeared in 1976, approximately 10-15 years after combined oral contraceptives (COCs) were introduced in the US. However, when reviewing historic medical texts, vulvar hypersensitivity without obvious infectious or dermatological etiology was described in the European and American textbooks of gynecology over 100 years ago [171]. Since then, COCs have been modified to contain less ethinyl estradiol and various progestins. A possible etiological correlation between COCs and PVD has been investigated in various epidemiological studies. In a clinic-based study from 2002, the results showed a 6.6 relative risk of PVD (95% confidence interval 2.5 - 17.4) for ever-users of OC compared to non-users. When OCs were used before the age 16, the relative risk reached 9.3 and increased with the duration of OC use up to 2-4 years. The relative risk was higher when the pill used was of high progestogenic, high androgenic, and low on estrogenic potency [172]. These findings were not, however, confirmed by a population-base case-control study from 2008 [173].

The hormonal effect of COCs on genital mucosa has mainly been studied in the endometrium. Recently, it was observed that the vestibular mucosa of healthy women on COCs undergoes changes compared to non-users [70]. The dermal papillae become
shallow and sparser which might result in a more fragile and sensitive mucosa [174]. It has also been reported that women without dyspareunia who use COCs have lower vestibular pain thresholds to mechanical stimuli [106]. These findings are thought to be reflective of a gestagenic effect, and they support the data of an increased risk of developing vestibular pain from using pills with gestagenic potency. However, more data are needed. The current recommendation is to continue to prescribe the pill when needed, but both users and prescribers should be aware of side-effects such as dryness, soreness and pain [174].

Results from studies investigating the expression of estrogen receptor alpha (ERα) in women with PVD are difficult to interpret. Initially, decreased expression of ERα in the vestibular mucosa was reported [175]. In a more recent but small study, biopsies were taken in the same phase of the menstrual cycle and a significant increase in ERα was found in patients compared to controls [159]. The clinical implication of these results suggests that topical estrogen might have a role in the treatment of PVD [71].

6) Psychosocial and sexual factors
Increased prevalence of comorbid psychopathology has been reported in women with PVD. In an etiological context, it is not clear how these findings relate to PVD since they might be considered either a cause or a consequence for different individuals. Psychological and sexual factors in PVD will be discussed in detail in the section on “Psychological aspects of sexual pain disorders”.

3. CHRONIC VULVAR DERMATOSES
A wide variety of chronic vulvar skin conditions can cause sexual pain both intermittently and continuously. While not common in the general population, lichen simplex chronicus, lichen sclerosis, and lichen planus can cause chronic vulvar inflammation and, hence, vulvar pain [125, 176, 177]. The diagnosis of these conditions can be easily discerned by experienced clinicians. Lichen simplex chronicus originates from chronic scratching, which produces inflammation of the skin and results in an itch-scratch cycle. The cycle can be interrupted by topical steroid and oral antihistamine therapy [178]. Lichen sclerosis is an indolent chronic condition of unknown etiology. The clinical signs are characteristic white hyperkeratotic papules and plaques of the vulvar skin. The areas most often affected are the clitoris which becomes buried, the labia minora (which disappear), and the perineum. Underlying subepithelial inflammation results in mild to intense itching and the first line treatment is potent topical steroids [179]. Erosive lichen planus usually affects the vulvar mucosa. Superficial ulcers and erosions of the superficial epithelium may develop, often resulting in intense pain and itch. Patients can have concomitant vaginal mucosal inflammation that results in a profuse, irritating vaginal discharge. Often, patients with lichen planus have evidence of inflammation in other mucous membrane areas such as ulcers of the gums, esophagus, or bowel in a Behcet-like syndrome. Prolonged topical steroid, topical tacrolimus (an inhibitor of interleukin-1) or other anti-inflammatory therapies are needed of the ulcerated and inflamed areas [180]. Raised vulvar lesions usually do not cause pain but must be accurately diagnosed and treated.

4. GENITAL INFECTIONS
a) Candidiasis
Episodic vulvovaginal candidosis is a very common genital infection in fertile women. Approximately 5-8% of women will experience recurrent vulvovaginal candidosis infections (RVVC), defined as at least 4 episodes every year [163]. The infection generates an inflammatory response in genital skin and mucosa. Cell-mediated immunity is the predominant host defense against RVVC but the innate immune system is also thought to play a major role in the defense mechanisms [181, 182]. Uncomplicated infections are treated with either topical or oral antifungal medication. Management of recurrent infections is more problematic and might require weekly administration of oral antifungals over a period of 2-3 months for clearance [125]. Candidiasis is considered risk factor for PVD, although the cause-and-effect relationship has not been proven [161, 183]. Women with PVD often report a history of vulvovaginal candidosis, and frequent use of topical and oral anti-fungal treatments has, in many cases, preceded the onset of dyspareunia. After treatment, the characteristic white sticky discharge and itch disappear, but the stinging pain at contact may remain. Lately, over-the-counter topical anti-fungals have been discussed as frequent use may cause an irritation of the vulvar tissue; furthermore, it has been shown that only one-third of women purchasing the medications actually have candida [126]. In the clinical setting, it is important to rule out or treat a concomitant candidiasis infection in women with PVD.

b) Human papillomavirus (HPV)
Detection of HPV infection in the vulva may be difficult. Condyloma acuminata is easy to detect, whereas subclinical HPV infections appearing as aceto-whitening lesions or as papillomatosis are more controversial [184]. Exophytic genital warts found predominately on the labia minora, vestibule, fourchette, perineum, and perianal areas are usually not painful. The warts are manifestation of low-risk HPV infection and may clear spontaneous after a period of time. In more persistent infections, itch and pain from fissures in the affected areas may occur. Current methods for treating HPV lesions include cryotherapy, immune
stimulation with imiquimod and laser and surgical debulking. Virtually all of these methods are painful, irritating, or both. Much caution regarding treatment choice and performance is recommended [185].

c) Herpes simplex virus (HSV)

The most common etiology of ulcers in the lower genital tract is HSV 1 and 2. Primary infection presents with multiple and painful ulcerations [125]. Inguinal lymphadenopathy, fever and malaise may coexist with the ulceration. Recurrent lesions are usually less severe, but might be more difficult to diagnose. For women with frequent recurrence, the infections may severely interfere with sexual activity. Antiviral therapy is used for acute symptoms and prophylactic treatment.

d) Bacterial vaginosis (BV)

BV is the most common cause of vaginitis in fertile women. It causes profuse and fishy-smelling discharge. The condition is characterized by decrease in hydrogen peroxidase-producing lactobacilli and an overgrowth of bacterial species that are part of the normal flora of the vagina, including Gardnerella vaginalis, Mobiluncus spp., Mycoplasma hominis and a variety of anaerobic bacteria [186]. BV may occur and remit spontaneously. Although BV requires no treatment in asymptomatic non-pregnant women, it has several serious medical consequences in pregnant women, such as preterm delivery. In addition, it increases the susceptibility to sexual transmitted diseases, including HIV [159]. Profound vaginal discharge with extensive use of hygiene pads may irritate the vulvar skin and mucosa. In three case-control studies, BV was identified as a risk factor for PVD [160-162].

5. VULVAR DYSPLASIA

During the last 30 years, the incidence of vulvar intraepithelial neoplasia (VIN) has significantly increased, particularly in younger women. The symptoms may vary from an incidental finding during a gynecological examination to pruritus, soreness and/or dyspareunia. The lesions demonstrate diversity in clinical features and may affect both the vulvar skin and mucosa. Common findings are white, slightly raised lesions, sometimes with a wart-like appearance with or without pigmentation that might be mistaken as condylomas. Most lesions are visible to the naked eye but magnification with a colposcope, using an application of 5% acetic acid, is usually helpful [187]. It has been recommended to divide VIN in two groups: VIN usual type and VIN differentiated type. The usual type occurs predominantly in younger women and is related to HPV infection. These lesions are often multifocal, causing chronic irritation and soreness. The differentiated type is less common and is seen in older women, often in association with lichen sclerosus or planus. These lesions are important to discern as they have a greater malignancy risk [188]. Lichen sclerosus lesions that do not clear should be biopsied.

VIN has an invasive potency that is likely rather low. However, many lesions need to be excised or treated. In younger women with usual type VIN, much caution should be taken in trying to avoid vulvar scarring which might cause dyspareunia.

6. UROGENITAL ATROPHY

Symptomatic estrogen deficiency affects approximately 40% of postmenopausal women (Ref). Other causes of estrogen loss than the natural menopause are bilateral oophorectomy and chemotherapy which might result in reduced ovarian steroid-hormone production. Another group of patients to be aware of are women treated with radiotherapy for gynecological malignancies. The major complaints are dryness, vaginal irritation and dyspareunia, but urinary symptoms are also common. Urogenital atrophy due to estrogen loss causes several physiological changes of the vaginal mucosa. The epithelium becomes thin and the normal rugation is lost. Vaginal fluid secretion decreases and becomes more alkaline (pH ≥ 5) and there is an increased susceptibility to infections. Systemic or local estrogen replacement treatment, if not contradicted, usually provide rapid symptomatic relief and the physiological changes can partially or completely be restored [189].

V. PELVIC FLOOR AND SEXUAL PAIN DISORDERS

NORMAL PELVIC ORGAN SUPPORT

In normal conditions, pelvic organs are supported by the pelvic floor musculo-fascial complex (See Figure 3). Pelvic floor muscles, also called levator ani muscles (LAM) are divided in an anterior part, the pubo-visceralis and pubo-coccygeus muscles and a posterior part, the ilio-coccygeal and coccygeal muscles. The vagina, urethra and anal canal pass across the genital hiatus formed by the pubo-visceralis muscle. Posteriorly, pelvic floor muscles form a horizontal shelf called the levator plate on which pelvic organs can rest. Levator ani muscles are covered on their internal surface by a layer of connective tissue called the endopelvic fascia (EPF) that supports pelvic organs and anchors them to the pelvic sidewall.

1. PELVIC ORGAN PROLAPSE (POP)

Pelvic organ prolapse (POP) happens when LAM are weakened and the EPF is distended or torn. Bladder and urethra are in close contact with the
anterior vaginal wall. Anterior vaginal prolapse is also called a cystocele or a urethrocele depending on which organ is descending. Similarly, a rectocele or posterior vaginal prolapse is caused by a defect in the posterior EPF layer. Vaginal vault prolapse is caused by a defect in apical ligaments such as uterosacral and cardinal ligaments.

POP is a prevalent condition among women, with about 10% of the female population requiring surgical correction for POP [190]. Swift et al. [191] demonstrated that about half of parous women presented some degree of vaginal relaxation. Pelvic organ prolapse symptoms include dragging pain, vaginal bulging or exteriorization and may be associated with urinary incontinence.

Anterior vaginal prolapse surgical repair involves either direct suture of the anterior EPF through an anterior vaginal incision or by reattaching lateral vagina to the pelvic sidewall. New techniques involving the insertion of a synthetic mesh or xenografts have been developed to decrease the recurrence rate.

Abdominal or laparoscopic sacrocolpopexy is one of the most efficient procedures to treat vaginal vault prolapse [192]. It involves placement of a synthetic mesh between the vaginal apex and the sacral promontory. Complications include erosion of the adjacent organs such as the rectum or ureter. Other procedures have been described through the vaginal route involving a suture between the vaginal wall and the sacro-spinous ligament [193], the pre-spinous fascia [194] or the utero-sacral ligaments [195]. The vaginal route is preferred when correction of other compartments is required.

Correction of the posterior compartment involves a repair of the posterior EPF and reinforcement of the perineum. The perineum is repaired by suturing the perineal membrane (perineorrhaphy) or by levator ani muscle plication. The latter gives excellent anatomic results at the expense of a high rate of dyspareunia [196]. Use of mesh in the posterior compartment is controversial given the excellent results (85-90%) of traditional repairs. A randomized trial by Milani et al. [197] comparing the traditional levator plication with and without mesh reinforcement concluded that dyspareunia was significantly more frequent after mesh usage, although other authors found opposite results in non-randomized trials [198].

2. DYSPAREUNIA

a) Sexual function in women with POP and/or urinary incontinence (UI)

A few studies have specifically addressed the issue of sexual function in patients with pelvic floor dysfunction [199-203]. In these studies the proportion of sexually active patients varied from 56 to 68.6%. Sexual function does not seem to be affected by POP. Age is found in two studies to be the major factor impacting on declining sexual function. Dyspareunia did not vary by grade of prolapse although increasing grade of prolapse predicted interference with sexual activity. UI significantly affects sexual function especially when coital incontinence is present (45% of patients with UI).

b) Sexual function after pelvic floor surgery

A multicenter prospective trial [204] comparing sexual function measured by the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ) score [205] before and after surgery for UI (82.4%) and/or POP (76.5%) in 75 patients found that despite an improvement in continence, PISQ total scores declined significantly. While 29% of women had an improvement in sexual function, 71% reported lower
sexual function was improved in both groups [211]. Frequent in the posterior repair group although global repair with those who did not. Dyspareunia was more for PoP and compared those who had a rectocele.

More recently, a study compared patients operated plication to reconstruct the posterior compartment. From 18% to 27% postoperatively used levator authors reporting an increase in dyspareunia after defect specific or midline fascial plication. The latter procedure has been reported by several authors to create narrowing of midvagina with a high percentage of postoperative dyspareunia [208-210]. Dyspareunia appears to be improved from a mean of 31.8% preoperatively to 18.5% postoperatively either after defect specific or midline fascial plication. The only authors reporting an increase in dyspareunia from 18% to 27% postoperatively used levator plication to reconstruct the posterior compartment. More recently, a study compared patients operated for POP and compared those who had a rectocele repair with those who did not. Dyspareunia was more frequent in the posterior repair group although global sexual function was improved in both groups [211].

c) Anterior POP repair

One study [206] comparing three surgical techniques of anterior colorrhaphy found a reduction of dyspareunia from 30% preoperatively to 22% postoperatively. Colombo [207] found that 13 of 23 patients (56%) who had an anterior repair for urinary stress incontinence and cystocele had mild to severe dyspareunia after eight years follow up. However, all the patients also had a posterior colporrhaphy and perineorrhaphy at the same time so it is impossible to conclude that any one procedure is to blame. Care needs to be taken in combining anterior and posterior repair as this can cause mid-vaginal stenosis and create dyspareunia.

d) Posterior POP repair

Reconstruction of the perineum is an important part of posterior repairs. It involves either an approximation of the superficial perineal musculature or a LAM plication with suture of the pubovisceralis muscle. The latter procedure has been reported by several authors to create narrowing of midvagina with a high percentage of postoperative dyspareunia [208-210]. Dyspareunia appears to be improved from a mean of 31.8% preoperatively to 18.5% postoperatively either after defect specific or midline fascial plication. The only authors reporting an increase in dyspareunia from 18% to 27% postoperatively used levator plication to reconstruct the posterior compartment. More recently, a study compared patients operated for POP and compared those who had a rectocele repair with those who did not. Dyspareunia was more frequent in the posterior repair group although global sexual function was improved in both groups [211].

e) Vault prolapse

Vaginal vault prolapse can be repaired by the vaginal or abdominal route (sacrocolpopexy). Sacrospinous fixation is the most popular vaginal procedure. Sexual function after sacrospinous fixation can be altered either because of pain, vaginal narrowing or pudendal nerve function alteration.

Baessler and Schussler [212] found that dyspareunia ceased after sacrocolpopexy in all but one of nine patients (n=31) presenting with prolapse related dyspareunia preoperatively. At the same time, two patients developed pain at the mesh fixation points. Pilsgaard and Mouritsen [213] reported that none of the three patients (n=35) with preoperative coital impairment complained of this symptom postoperatively, whereas Virtanen et al. [214] found that 44% (7/16) complained of dyspareunia 3 years after abdominal sacrocolpopexy.

Two RCTs compared vaginal and abdominal approach for vaginal vault suspension with conflicting results. Benson [215] found that 15 of 26 (58%) patients in the sacrospinous group developed dyspareunia compared to 0 of 15 patients in the abdominal group, although this difference was not statistically significant. In contrast, Maher et al. [216] found no difference between the two groups (n=95), with 28% and 21% of patients who were not sexually active preoperatively resuming sexual activity. Preoperative dyspareunia was resolved in 56% and 43% in the abdominal and vaginal group, respectively. Dyspareunia developed de novo in two women in the abdominal and three women in the vaginal group.

Abdominal sacrocolpopexy seems to be superior to sacrospinous fixation regarding post operative dyspareunia.

f) Use of mesh for pelvic organ prolapse repair

Mesh erosions, mesh shrinkage and extensive fibrosis around the mesh may cause pain and dyspareunia. Synthetic and donor grafts are being increasingly used to reinforce vaginal repair to improve the long-term results and prevent prolapse recurrence. Dwyer and O'Reilly [198] reported their results using polypropylene mesh to reinforce anterior and posterior compartment repair in 97 women with recurrent or large vaginal prolapse. Dyspareunia decreased significantly postoperatively from 26% of women to 6% at 6 months, 8% at 12 months and 9% at 24 months. In three patients, the dyspareunia occurred de novo following surgery. These results are in contradiction with those of Milani et al. [197] who found a 20% increase in dyspareunia following anterior repair and 63% after posterior repair reinforced by polypropylene mesh. Several studies have shown increased or de novo dyspareunia happening after mesh usage for vaginal repair [217, 218]. To date, there is no evidence of clear benefit for the use of mesh in pelvic floor repair surgery. Dyspareunia seems to be a real concern and patients should be aware of this complication before surgery (Grade B) [219, 220].

g) Conclusions

POP is a frequent condition and may be associated with UI. Treatment should aim at improving quality of life rather than to restore anatomy so that conservative management should be offered before surgery. Patients should be thoroughly informed about potential deleterious impacts of the surgery on sexual function.
3. VAGINISMuS
Vaginal or pelvic loor muscle contraction or spasm
has long been considered the distinctive symptom
allowing for the differential diagnosis of vaginismus
from dyspareunia. However, this difference is debated
as several studies have shown that these entities
are dificult to distinguish [221, 222]. This has led to
a new deinition suggested by Basson et al. [223]:
“persistent or recurrent dificulties of the woman to
allow vaginal entry of the penis, a inger, and/or any
object, despite the woman’s expressed wish to do
so. There is variable (phobic) avoidance, involuntary
pelvic muscle contraction and anticipation/fear/
experience of pain. Structural or other physical
abnormalities must be ruled out/addressed”.
This new deinition encompasses dyspareunia
and vaginismus as a global entity although the
notion of muscular contraction is acknowledged.
The etiology of muscular spasm is not clear. Van
der Velde suggested that involuntary contraction
of pelvic loor muscles occur during exposure to
threatening situations [224] rather than to sexual
situations. Muscular contraction also takes place
in other muscle groups suggesting that it is part of
a global reaction to a situation felt as threatening.
Reissing showed that vaginal muscle spasm does
not characterize vaginismus and that different pro-fessionals diagnose spasm very differently [225].
Treatment of vaginismus has long been directed
towards relief of vaginal spasm by progressive
dilatation of the tightened vagina. Several meth-ods have been described including combinations
of systematic desensitization together with the use
of graded dilators; sex therapy, in which a gradual
approach is taken to overcoming the disorder, in-cluding education and cognitive therapy, relaxation
therapy, looding where the patient watches in a mir-ror while the therapist and then the subject inserts
a inger into the vagina. Other approaches include
pharmacotherapy, hypnotherapy, and Botulinum
toxin injections have also been reported. In review
of the Cochrane database about interventions for
vaginismus, only three controlled studies could be
included for analysis. They compared two forms of
systematic desensitization. In one study [226] both
groups received information and relaxation exer-cises. In the irst group, the physician introduced an
appropriately sized dilator. In the second group, the
physician provided verbal instruction for introducing
the dilator. The program included a desensitization
exercise and journal entries after each exercise. The
patients were told to perform the exercise for 10 to
15 minutes, ive times per week. Therapy sessions
were conducted every two weeks to follow and sup-port the progress made in the treatment. Throughout
sexual therapy, the patients were advised to refrain
from coitus. No difference was found between the
two forms of treatment. Until recently, there was only

limited evidence from uncontrolled trials and one con-trolled trial which lacked a waiting list group as con-trol to suggest that desensitization is an effective and
recommendable method to treat vaginismus [227].
A recent prospective trial [228] investigated the
effectiveness of therapist-aided exposure for
lifelong vaginismus. 10 women were evaluated
during 24 weeks. During exposure, patients
performed vaginal penetration exercises on
themselves, in the presence of a female therapist.
Nine of 10 participants reported having intercourse
after treatment, and in 5 of 9, intercourse was
possible within the 1st week of treatment. The
results were sustained at 1-year follow-up.
Botulinum toxin has been advocated by some
authors [229, 230] as an effective mean of relieving
muscular spasm associated with vaginismus. In one
uncontrolled study, Botulinum toxin (150-400 mIU)
was injected into the puborectalis muscles in 3 sites
on each side of the vagina to treat moderate to severe
cases according to the Lamont classiication [231].
Twenty-three patients (95.8%) had a vaginal
examination that showed no or little resistance, 18
(75%) achieved satisfactory intercourse after the
irst injection, 4 (16.7%) had mild pain, and 1 was
cured after a second injection. only one controlled
study [232] compared injection of 25 IU of botulinum
toxin into each of the bulbo-spongiosus muscles in
8 patients to saline in 5 patients. All the patients in
the botulinum toxin group improved with couples
achieving intercourse compared to none of the
control group. No complications were reported in
either study. Botulinum toxin may have a place
in the treatment of vaginal spasm associated with
vaginismus although many questions remain
regarding the dose, the injection sites and the need
for other form of support.

VI. FEMALE GENITAL MuTILATION
Female genital mutilation (FGM) means partial or
complete non-therapeutic removal or injury of each
of the female genitals for religious or cultural reasons.
Four types of FGM are described (See Figure 4):
Type I (also called Sunna): Removal of the clitoris
foreskin.
Type II Removal of the clitoris with partial or total
excision of the labia minora.
Type III (“Inibulation” or “pharaonic circumcision”)
Removal of the clitoris and the labia minora and
majora, sewing up of the oriicium vaginae, leaving
only small opening for urine or menstruation blood.
Type IV other types like pricking, piercing, stretch-ing of clitoris or vulva, scraping of the vagina.

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FGM affects about 130 million women or girls in the world, with about 2 million girls undergoing the procedure every year [233]. Instruments used for FGM may be sterilized instruments when performed by doctors or midwives, but any cutting instruments such as razors or piece of broken glass are often used. Consequences depend on the experience of the operator and the hygienic conditions. Heavy bleeding, causing anemia or death, may occur. Local infection, infection of the uterus and adnexae, tetanus, gangrene, or sepsis may also result. After type III FGM, the risk of infertility is around 25-30% because of tubal obstruction or tightness of the vagina preventing intercourse.

There is a general assumption made that all women who have undergone FGM suffer from pervasive sexual dysfunction and a total loss of sexual pleasure. However, recent evidence does not support this idea in all women. For example, 250 patients of Maternal and Childhood Centers in Ismailia (of whom 80% were circumcised) were examined and interviewed to investigate their psychosexual activity. Results indicated that, although the circumcised group complained significantly more frequently of dysmenorrhea (80.5% vs. 56%), vaginal dryness during intercourse (48.5% vs. 30%), lack of sexual desire (41.5% vs. 16%), less initiative during sex (11% vs. 22%), experiencing less pleasure from sex (44% vs 14%), and being less orgasmic (29% vs. 44%) than uncircumcised women, other psychosexual problems, such as loss of interest in foreplay and dyspareunia, did differ significantly between groups [234]. However, other studies demonstrate that sexual pain and dysfunction are significant issues among women who have undergone FGM. For example, dyspareunia was reported among almost one-third of circumcised women in an Egyptian sample, and 23% of these women perceived personal distress related to their sexual problems [235]. Additional evidence exists that when dyspareunia is present, it is most commonly reported with first intercourse and/or in the initial period after marriage, and with attempts made after re-infiltration [236]. Thus, FGM may not affect all aspects of sexual function in a persistent and uniform manner [237]. Further research is needed in order to determine the outcomes of FGM, specifically of the FGM subtypes, as wide variations in the type, depth, and extent of tissue damaged/excised may range from minimal to severe. Damage to any of the neural networks associated with the vulvar and perineal areas may alter genital sensation [237], resulting in pain and other sensory outcomes.

VII. PSYCHOLOGICAL ASPECTS OF SEXUAL PAIN DISORDERS

1. OVERVIEW AND DATABASE

The following psychological factors associated with the sexual pain disorders will be discussed:

a. Psychological vulnerability factors for developing sexual pain; specifically, empirical findings with regard to individual differences on personality traits, personality disorders, and psychiatric comorbidity are reviewed.

b. Characteristics of the sexual relationship of women with sexual pain disorders, compared with asymptomatic women.

c. Psychological variables that are found to predict outcome of treatment of sexual pain disorders.

The evidence for psychological factors associated with the sexual pain disorders is grouped into the following categories:

I. Psychometric data, showing differential presence of psychopathology and personality levels (state and trait) in patients and non-patient comparison groups (Table 25.1a,b,c). Note that psychopathology and impaired psychological functioning found in observational or cross-sectional studies may be a cause as well as an effect of the various forms of sexual pain;

II. Experimental data on sensory perception and cognitive-affective processes (Table 25.2);

III. Outcome data of treatment studies of sexual pain disorders, and psychometric data that predict treatment outcome (Table 25.3); These data will be reviewed in the following subParagraphs as they pertain to, respectively, PVD (see Table 25.1a), superficial dyspareunia not identified as PVD (DYS; see Table 25.1b), and vaginismus (VAG; see Table 25.1c). Asterisks are added in the text to provide an index of the robustness of the findings that are mentioned: **: If more than one study with results pointing in the same direction are retrieved; *: if only single study results were retrieved.
2. PROVOKED VESTIBULODYNIA (PVD)

a) Individual Psychological And Personality Characteristics

1) PSYCHOPATHOLOGY

Higher rates of psychopathology in women with PVD were found with regard to depression** and anxiety disorders* through assessment using both structured interviewing and self-report instruments (Grade B; see Tables 25.1 & 25.4). As to self-reported symptoms of depression, state anxiety, phobic anxiety, social anxiety, and obsessive-compulsive behavior, results are conflicting, finding both higher** and equal** scores compared with normative groups.

2) PERSONALITY CHARACTERISTICS

Using self-report measures (see Table 25.1a), several differences on continuous dimensions were found between women with PVD and asymptomatic women. Women with PVD scored higher on trait anxiety**, shyness*, hysterical personality*, perfectionism*, reward dependency**, low self-esteem*, fear of negative evaluation, and harm avoidance**.

In contrast with the deviant scores on these primarily social- and evaluation anxiety-related aspects of personality, other personality features in women with PVD were indistinguishable from asymptomatic women. Scores on neuroticism of women with PVD were in the normal range in most studies**. Women with PVD had normal scores on extraversion*. With some exceptions, women with PVD had normal scores on hostility**, obsessive-compulsive problems**, paranoid ideation**, and psychoticism**. Results on interpersonal sensitivity, novelty seeking*, and somatization** are equivocal, with studies finding both higher and equal scores than non-affected women.

With regard to personality traits more directly related to the domain of sexuality, women with PVD scored higher on erotophobia*, and had more self-reported difficulties with sexual arousal and vaginal lubrication during partner interaction** as compared to their functioning during masturbation*. They were also found to lack sexual pleasure more often*.

Women with PVD have more catastrophic thoughts** about the pain they (will) experience during sexual interaction, and about other, problem-related issues, such as the negative consequences of the pain problem for the partner and the threat that it poses for the (longterm) durability of the relationship. The strength of positive* and negative sexual selfschemas* was equal to normative groups*. There are indications that the population of women with PVD may consist of different subtypes of women with primary vs secondary PVD [108], characterized by different physical aspects (e.g., systemic pain sensitivity, lower pain threshold) and aspects of personality (e.g., somatization, pain catastrophizing, trait anxiety) [238-241]. These findings require further replication studies.

b) Sexual Relationships Of Women With PVD

Women with PVD were found to have more negative feelings about sexual partner contact**. Their marital satisfaction regarding non-sexual aspects of the relationship was equal to normative groups**. The level of pain ratings in PVD patients is predicted by their level of marital adjustment*, where lower marital adjustment is associated with higher pain ratings.

c) Psychological and Psychophysical Processes in Women with PVD

Heat pain thresholds and unpleasantness thresholds in women with PVD are lower compared with asymptomatic women** (See Table 25.2, and perceived pain during suprathreshold heat stimulation is higher in women with PVD*. The thresholds for tactile (pressure) sensitivity at several vestibular sites, over the labia minora, and on the deltoid muscle are lower in women with PVD* compared with asymptomatic women. This lowered sensitivity is stable over time. Pressure pain thresholds at vestibular sites, over the labia labia minora, and on the deltoid and voral forearm are lower in women with PVD*. Women with PVD report higher distress for sustained suprathreshold pressure, and tolerate less pressure than controls*. Higher suprathreshold pain ratings are associated with stronger traits of harm avoidance and reward dependence in women with PVD*.

Using fMRI-recording, women with VVS had significantly higher activation levels in the insular and frontal cortical regions than control women during pressure described as painful [111].

Stronger attentional bias toward pain-related stimuli is demonstrated in women with PVD* compared with asymptomatic women, suggesting hypervigilance for pain-related stimuli*. The level of hypervigilance is largely accounted for by state and trait anxiety levels. Speeded detection of sexual pain-related stimuli, reflecting attentional bias towards such stimuli, has also been investigated with other methodologies. When using a modified pictorial Affective Simon Task (a reaction time task that assesses the strength of automatic associations of stimuli with positive vs. negative valence), women with superficial dyspareunia were not different from asymptomatic women indicating the absence of an automatic affective bias. On the self-report level, however, deliberate affective associations with sex cues were significantly more negative for women with dyspareunia than for asymptomatic women [242].

Compared with asymptomatic women, women with PVD respond with equal levels of genital sexual arousal, but with lower levels of subjectively experienced sexual arousal** [243, 244]. This pattern was
Table 25.1a Psychological characteristics (including psychopathology) of women with PVD (continue)

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<tr>
<td>Erotophobia</td>
<td>SSS</td>
<td>Reissing, 2003 [252]</td>
<td>2b</td>
<td></td>
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<td>Positive sexual self-schema</td>
<td>SSS</td>
<td>Reissing, 2003 [252]</td>
<td>2b</td>
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<tr>
<td>Sexual desire problems</td>
<td>SHF</td>
<td>Reissing, 2003 [252]</td>
<td>2b</td>
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</table>
### Table 25.1a Psychological characteristics (including psychopathology) of women with PVD (continued)

<table>
<thead>
<tr>
<th>Psychological characteristic</th>
<th>Instrumenta</th>
<th>Authorb, year</th>
<th>LOEc</th>
<th>Instrumenta</th>
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<th>LOEc</th>
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<tr>
<td>Lack of sexual pleasure</td>
<td>SHF GRISS</td>
<td>Brotto, 2003 [261]</td>
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<td>Negative feelings about sexual interaction</td>
<td>Campion Q.</td>
<td>Reissing, 2003 [252]</td>
<td>2b</td>
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</tbody>
</table>

*a Instrument: see list. c Author: only first author listed. d LOE = Level Of Evidence according to OCEMLe.

### Table 25.1b Psychological characteristics (including psychopathology) of women with superficial dyspareunia, not identified as PVD

<table>
<thead>
<tr>
<th>Psychological characteristic</th>
<th>Instrumenta</th>
<th>Authorb, year</th>
<th>LOEc</th>
<th>Instrumenta</th>
<th>Authorb, year</th>
<th>LOEc</th>
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<td>Neuroticism</td>
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<td>van Lankveld, 1995 [222]</td>
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<tr>
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<td>SCL-90</td>
<td>van Lankveld, 1995 [222]</td>
<td>2b</td>
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<td></td>
<td>BSI</td>
<td>Meana, 1997 [251]</td>
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<tr>
<td></td>
<td>HAD Scale</td>
<td>Dunn, 1999 [268]</td>
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<tr>
<td></td>
<td>CIDI</td>
<td>van Lankveld, 2000 [249]</td>
<td>2b</td>
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<td>SCL-90</td>
<td>van Lankveld, 1995 [222]</td>
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<td>SCL-90</td>
<td>van Lankveld, 1995 [222]</td>
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<td>BSI</td>
<td>Meana, 1997 [251]</td>
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<td>CIDI</td>
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<td>Social phobia</td>
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<td>van Lankveld, 2000 [249]</td>
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<tr>
<td>Eating disorder</td>
<td>CIDI</td>
<td>van Lankveld, 2000 [249]</td>
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<td>SCL-90</td>
<td>van Lankveld, 1995 [222]</td>
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<td>Erotophobia</td>
<td>SOS</td>
<td>Meana, 1997 [251]</td>
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<td>Marital problems</td>
<td>LW-MAS</td>
<td>Meana, 1997 [251]</td>
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<td></td>
<td>(maladjustment, dissatisfaction)</td>
<td>SPQ</td>
<td>Dunn, 1999 [268]</td>
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*a Instrument: see list. c Author: only first author listed. d LOE = Level Of Evidence according to OCEMLe.
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<th>Instrument[^a]</th>
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<th>LOE[^d]</th>
<th>Instrument[^a]</th>
<th>Author[^c], year</th>
<th>LOE[^d]</th>
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<td>van Lankveld, 1995 [222]</td>
<td>2b</td>
<td>EPQ</td>
<td>Kennedy, 1995 [269]</td>
<td>3b</td>
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<td>van Lankveld, 2000 [249]</td>
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<td>Extraversion</td>
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<td>Hysterical personality</td>
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<td>Kennedy, 1995 [269]</td>
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<td>Disgust propensity</td>
<td>DS</td>
<td>De Jong, 2007 [271]</td>
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<tr>
<td>Positive sexual self-schema</td>
<td>SSS</td>
<td>Reissing, 2003 [252]</td>
<td>2b</td>
<td>(positive sexual self-schema lower than no-pain control women)</td>
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<tr>
<td>Negative sexual self-schema</td>
<td>SSS</td>
<td>Reissing, 2003 [252]</td>
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<td>Marital problems (maladjustment, dissatisfaction)</td>
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<td>Reissing, 2003 [252]</td>
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<td>Less sexual self-stimulation</td>
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<td>Reissing, 2003 [252]</td>
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<td>Sexual desire problems</td>
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<tr>
<td>Sexual arousal problem during sexual interaction</td>
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<td>Reissing, 2003 [252]</td>
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<td>Lubrication problem during sexual interaction</td>
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<td>van Lankveld, 1996 [260]</td>
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<td>Lack of sexual pleasure</td>
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<td>Reissing, 2003 [252]</td>
<td>2b</td>
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</table>

[^a]: Instrument: see list, ^[^c]: Author: only first author listed. ^[^d]: LOE = Level Of Evidence according to OCEMLE.
Table 25.2. Sensory processes and cognitive-affective processes in sexual pain disorders in women: Results of experimental investigations (continued)

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Dysfunction type</th>
<th>N</th>
<th>Design</th>
<th>Assessment</th>
<th>Process findings</th>
<th>Level of evidence (Oxford system)</th>
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<tbody>
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<td><strong>Sensory processes</strong></td>
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<tr>
<td>Granot, Friedman, Yamitsky &amp; Zimmer, 2002 [110]</td>
<td>PVD</td>
<td>N(PVD)=44; N(Contr.)=41</td>
<td>Administration of heat pain stimuli to volar forearm; threshold assessment; assessment of suprathreshold pain magnitude with increasing temperature (1°C/sec); blood pressure and heart rate on 1 min suprathreshold heat pain stimulation</td>
<td>Perceived pain threshold; Visual Analog Scale of perceived pain intensity and unpleasantness</td>
<td>Heat pain threshold lower in PVD vs. controls (42.2°C ± 2.5 vs 43.6°C ± 1.9). Unpleasantness threshold lower in PVD women (40.2°C ± 2.9 vs 41.7°C ± 2.3). Higher perceived pain (VAS) with suprathreshold stim. (with 47°C: 88.3 ± 14.9 vs 70.8 ± 14.9; with 48°C: 96.1 ± 7.3 vs 84.6 ± 14.8)</td>
<td>1b</td>
</tr>
<tr>
<td>Khalife, Amsel &amp; Abbott, 2002 [118]</td>
<td>PVD</td>
<td>N(PVD)=13; N(Contr.)=13</td>
<td>Controlled comparison of tactile and pain threshold in comparison groups, using graded calibrated filaments. Testing sites were vestibular, thigh, labium minus, deltoid, forearm and tibia</td>
<td>Thresholds for tactile sensitivity, pain, pressure-pain tolerance</td>
<td>Tactile thresholds were lower in PVD at all vestibular sites, labium minus and deltoid. Lowered tactile sensitivity was stable over time in PVD. Pain thresholds were lower in PVD, at all vestibular sites, labium minus, deltoid and forearm. PVD women gave higher distress ratings for sustained suprathreshold pressure. Women with PVD tolerated less pressure than controls.</td>
<td>1b</td>
</tr>
<tr>
<td>Pukall, Binik &amp; Khalife, 2004 [304]</td>
<td>PVD</td>
<td>N(PVD)=14; N(Contr.)=14</td>
<td>Controlled comparison of vulvar tactile and pain threshold in comparison groups, using the vulalgesiometer.</td>
<td>Thresholds for tactile sensitivity, pain</td>
<td>Women with VVS have significantly lower vestibular pain thresholds compared with control women. Tactile thresholds were not different.</td>
<td>1b</td>
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<tr>
<td>Pukall, Baron, Amsel, Khalife, &amp; Binik, 2006 [239]</td>
<td>PVD</td>
<td>N(PVD)=16; N(Contr.)=16</td>
<td>Tender point examination by palpation of 9 bilateral nonvulvar areas by a blinded rheumatologist</td>
<td>Perceived pain threshold</td>
<td>Women with PVD had significantly more painful TPs than nonaffected women; they reported significantly higher pain intensity and unpleasantness ratings and displayed more pain behaviors than controls (P&lt;0.05).</td>
<td>1b</td>
</tr>
<tr>
<td>Pukall, Young, Roberts, Sutton &amp; Smith, 2007 [121]</td>
<td>PVD</td>
<td>N(PVD)=15; N(Contr.)=15</td>
<td>Controlled comparison of vulvar tactile and pain threshold in comparison groups, using the vulalgesiometer.</td>
<td>Thresholds for tactile sensitivity, pain</td>
<td>Women with VVS have significantly lower vestibular pain thresholds compared with control women. Tactile thresholds were not different.</td>
<td>1b</td>
</tr>
<tr>
<td>Authors, year</td>
<td>Dys-func-tion type</td>
<td>Design</td>
<td>Assessment</td>
<td>Process findings</td>
<td>Level of evidence (Oxford system)</td>
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<td>Burrows, Klingman, Pukall &amp; Goldstein, 2008 [241]</td>
<td>Vestibulo-dynia</td>
<td>N(Primary VD)=22; N(Second. VD)=16; N(Contr.)=8</td>
<td>Controlled comparison of vulvar and umbilical tactile and pain threshold in comparison groups, using the vulalgesiometer.</td>
<td>Women with primary vestibulodynia demonstrated higher umbilical sensitivity and lower pain threshold, compared with women with secondary VD and control women. No difference in higher umbilical sensitivity was found between women with secondary VD and control women.</td>
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<tr>
<td>Sutton, Pukall &amp; Chamberlain, 2009[262]</td>
<td>PVD</td>
<td>N(PVD)=25; N(Contr.)=25</td>
<td>Controlled comparison of vulvar tactile, pain, and thermal threshold and tolerance in comparison groups, using the vulalgesiometer.</td>
<td>Thresholds for tactile sensitivity, pain, and thermal sensitivity, and pain and heat tolerance.</td>
<td>1b</td>
<td></td>
</tr>
<tr>
<td>Meana, Binik, Khalifé &amp; Cohen, 1998 [305]</td>
<td>DYS, PVD</td>
<td>N=76; N(PVD)=33; N(DYS)=19</td>
<td>Correlational study: Assessment of predictability of pain ratings by scores of depression, anxiety, marital adjustment, and organic pathology</td>
<td>Significant correlations of pain ratings with anxiety (r = .36; p &lt; .01), marital adjustment (r = -0.351; p &lt; .01), and depression (r = .251; p &lt; .05); pain rating in PVD predicted by marital adjustment (r = -0.24; p &lt; .02); pain rating in DYS predicted by depression (r = 0.26; p = .03)</td>
<td>2b</td>
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<tr>
<td>Payne,Binik, Amsel &amp; Khalifé, 2005 [256]</td>
<td>PVD</td>
<td>N=34; N(PVD)=17; N(Contr.)=17</td>
<td>Controlled comparison of context-specific hypervigilance with pain-related stimuli, using an emotional Stroop test with pain words, social threat words, positive words, and neutral control words</td>
<td>Reaction time to Stroop words</td>
<td>1b</td>
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<tr>
<td>Wouda, Hartman, Bakker, Bakker, van der Weij &amp; Weijmar Schultz, 1998 [246]</td>
<td>DYS</td>
<td>Controlled comparison of DYS and Contr. women on sexual arousal response to different erotic stimuli; kissing, caressing, manual stimulation, oral stimulation, and penile-vaginal intercourse</td>
<td>Average Spectral Tension (AST) for genital arousal; subjective arousal with mechanical lever</td>
<td>AST response differed between various stimuli. Both groups responded with equal AST, but AST response differed between DYS and Control women when viewing intercourse. Subjective arousal during various stimuli did not differ between groups.</td>
<td>1b</td>
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</table>

**Cognitive-affective processes**

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<th>Authors, year</th>
<th>Dys-func-tion type</th>
<th>Design</th>
<th>Assessment</th>
<th>Process findings</th>
<th>Level of evidence (Oxford system)</th>
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<tbody>
<tr>
<td>Meana, Binik, Khalifé &amp; Cohen, 1998 [305]</td>
<td>DYS, PVD</td>
<td>N=76; N(PVD)=33; N(DYS)=19</td>
<td>Correlational study: Assessment of predictability of pain ratings by scores of depression, anxiety, marital adjustment, and organic pathology</td>
<td>Significant correlations of pain ratings with anxiety (r = .36; p &lt; .01), marital adjustment (r = -0.351; p &lt; .01), and depression (r = .251; p &lt; .05); pain rating in PVD predicted by marital adjustment (r = -0.24; p &lt; .02); pain rating in DYS predicted by depression (r = 0.26; p = .03)</td>
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</tr>
<tr>
<td>Payne,Binik, Amsel &amp; Khalifé, 2005 [256]</td>
<td>PVD</td>
<td>N=34; N(PVD)=17; N(Contr.)=17</td>
<td>Controlled comparison of context-specific hypervigilance with pain-related stimuli, using an emotional Stroop test with pain words, social threat words, positive words, and neutral control words</td>
<td>Reaction time to Stroop words</td>
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<tr>
<td>Wouda, Hartman, Bakker, Bakker, van der Weij &amp; Weijmar Schultz, 1998 [246]</td>
<td>DYS</td>
<td>Controlled comparison of DYS and Contr. women on sexual arousal response to different erotic stimuli; kissing, caressing, manual stimulation, oral stimulation, and penile-vaginal intercourse</td>
<td>Average Spectral Tension (AST) for genital arousal; subjective arousal with mechanical lever</td>
<td>AST response differed between various stimuli. Both groups responded with equal AST, but AST response differed between DYS and Control women when viewing intercourse. Subjective arousal during various stimuli did not differ between groups.</td>
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</table>
Table 25.2. Sensory processes and cognitive-affective processes in sexual pain disorders in women: Results of experimental investigations (continued)

<table>
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<tr>
<th>Authors, year</th>
<th>Dysfunction type</th>
<th>N</th>
<th>Design</th>
<th>Assessment</th>
<th>Process findings</th>
<th>Level of evidence (Oxford system)</th>
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<tr>
<td>Meana, Binik, Khalifé &amp; Cohen, 1997 [251]</td>
<td>DYS</td>
<td>N/(DYS)=100</td>
<td>Groups of patients with either psychosocial or physiological attribution of sexual pain cause were compared on ratings of pain experience, sexual attitude, sexual function, psychological adjustment</td>
<td>Pain rating (MPQ), sexual attitudes (SAI), sexual function (SOS), psychological adjustment (BSI, L-W MAS)</td>
<td>Women with psychosocial attribution scored higher on sensory and evaluative pain dimensions, lower on sexual attitudes, more aversive to sex, higher on depression, interpersonal sensitivity, anxiety, phobia, paranoid ideation, psychoticism, and lower on marital adjustment.</td>
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<tr>
<td>Van der Velde &amp; Everaerd, 1999[306]</td>
<td>VAG</td>
<td>N=110 N/(VAG)=67; N/(Contr.)=43</td>
<td>Controlled comparison of ability to voluntarily control and relax pelvic floor muscles; 6 short flick contractions; 3 10-sec holding contractions</td>
<td>Intravaginal surface EMG; additional EMG of adjacent muscle groups</td>
<td>No baseline difference in intravaginal surface EMG; No EMG difference in performance of exercises</td>
<td>1b</td>
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<tr>
<td>Van der Velde &amp; Everaerd, 200a [307]</td>
<td>VAG</td>
<td>N=29 N/(VAG)=22; N/(Contr.)=7</td>
<td>Controlled comparison of pelvic floor muscle response to threatening, erotic, neutral, and non-threatening film excerpts</td>
<td>Intravaginal surface EMG; affective response poststimulus with Likert scales; experienced threat monitor using mechanical lever</td>
<td>No EMG differences or experienced threat between VAG and Control women. No EMG changes during neutral and erotic stimuli. Significant correlation of pelvic floor muscle activity and experienced threat.</td>
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<tr>
<td>Van der Velde &amp; Everaerd, 2001b[224]</td>
<td>VAG</td>
<td>N=77 N/(VAG)=45; N/(Contr.)=32</td>
<td>Controlled comparison of pelvic floor muscle response to threatening, erotic, neutral, and non-threatening film excerpts</td>
<td>Intravaginal surface EMG; trapezius EMG</td>
<td>No EMG differences between VAG and Control women. Threatening and sexual-threatening excerpts produced increase in (involuntary) pelvic floor and trapezius EMG, compared with erotic and neutral.</td>
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<tr>
<td>Reissing, Binik, Khalifé Cohen &amp; Amsel, 2004 [225]</td>
<td>PVD VAG</td>
<td>N/(PVD)=29; N/(VAG)=29; N/(Contr.)=29</td>
<td>Comparative study</td>
<td>Gynecological examination, physical therapist evaluation, vaginal EMG; McGill Pain Questionnaire, Pain Catastrophizing Scale</td>
<td>Vaginals spasms higher in women with PVD and VAG than in Contr. No difference between women with PVD and VAG.</td>
<td>1b</td>
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<tr>
<td>Brauer, Laan &amp; ter Kuile, 2006 [243]</td>
<td>DYS</td>
<td>N/(DYS)=50; N/(Contr.)=25</td>
<td>Exposure to two erotic films, depicting oral sex vs. coitus</td>
<td>VPA, subjective sexual arousal, negative and positive affect</td>
<td>No differences between women with DYS and Contr. women.</td>
<td>1b</td>
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</table>
### Table 25.2. Sensory processes and cognitive-affective processes in sexual pain disorders in women: Results of experimental investigations (continued)

<table>
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<tr>
<th>Authors, year</th>
<th>Dysfunction type</th>
<th>N</th>
<th>Design</th>
<th>Assessment</th>
<th>Process findings</th>
<th>Level of evidence (Oxford system)</th>
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<tr>
<td>Brauer, ter Kuile, Janssen &amp; Laan, 2007 [245]</td>
<td>DYS</td>
<td>N(DYS)=48; N(Contr.)=48</td>
<td>Manipulation of pain-related fear (electrocutaneous ankle shock) vs. neutral condition</td>
<td>VPA, subjective sexual arousal, skin conductance, negative and positive affect</td>
<td>General suppressing effect of pain-related fear on genital and subjective sexual arousal: no differences between women with DYS and Contr. women. More negative affect in DYS women.</td>
<td>1b</td>
</tr>
<tr>
<td>Brauer, de Jong, Huijding, Laan &amp; ter Kuile, 2009 [308]</td>
<td>DYS</td>
<td>N(DYS)=50; N(Contr.)=25</td>
<td>Manipulation of negative (pain threat) vs. positive (sexual enjoyment) vs. neutral appraisal</td>
<td>VPA, subjective sexual arousal, negative and positive affect</td>
<td>General suppressing effect of negative appraisal on genital and subjective sexual arousal: no differences between women with DYS and Contr. women.</td>
<td>1b</td>
</tr>
</tbody>
</table>

Dysfunction type: DYS = dyspareunia; PVD = provoked vestibulodynia; VAG = vaginismus. BSI = Brief Symptom Inventory; L-W MAS = Locke-Wallace Marital Adjustment Scale; MPQ = McGill-Melzack Pain Questionnaire; SAI = Sexual Arousability Inventory; SOS = Sexual Opinion Survey.

### Table 25.3. Outcome of treatment studies of women with sexual pain disorders, including psychological predictors of treatment outcome (continued)

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Dysfunction type</th>
<th>N</th>
<th>Design</th>
<th>Assessment</th>
<th>Process findings</th>
<th>Level of evidence (Oxford system)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scholl, 1988 [309]</td>
<td>VAG</td>
<td>N(VAG)=23</td>
<td>Variables associated with positive treatment outcome were assessed in a behavioral treatment of unlimited duration, employing increasing size dilators, Kegel exercises, relaxation exercises, and ban on intercourse.</td>
<td>Dichotomous assessment of intercourse success; unvalidated interview ratings of predictor variables.</td>
<td>Twenty patients (87%) continued in therapy and had successful outcomes in terms of successful intercourse. Length of therapy was related to duration of vaginismus, patient’s causal attribution of etiology, history of operative treatment, motivation factors, partner’s acceptance of vaginismus, previous organic abnormalities, extent of sexual knowledge, fear of STIs, parental attitudes towards sex, and patient’s attitude to her genitalia. Dropouts all had previous operative treatment and exclusive somatic attributions.</td>
<td>3b</td>
</tr>
<tr>
<td>Hawton &amp; Catalan, 1990 [310]</td>
<td>VAG</td>
<td>N(VAG)=30</td>
<td>Treatment provided was sex therapy, vaginal self-examination (first with mirror, then with fingers), and Kegel exercises. Later: digital penetration with partner’s fingers before penile-vaginal containment was reintroduced.</td>
<td>Four-point rating of outcome by therapist (sexual intercourse without difficulty to no change). Predictor variables: therapist ratings of treatment compliance, patient motivation, global general and sexual relationship.</td>
<td>80% had positive outcome and gains were sustained at 3 months follow-up. Treatment success was positively related to therapist-rated compliance to homework assignment by third session, and to woman-rated low tension in the relationship.</td>
<td>3b</td>
</tr>
</tbody>
</table>
### Table 25.3. Outcome of treatment studies of women with sexual pain disorders, including psychological predictors of treatment outcome (continue)

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Weijmar Schultz, Gianotten, van der Meijden, van de Wiel, Blindeman, Chadha &amp; Drogendijk, 1996 [248]</td>
<td>PVD</td>
<td>N(CBT)= N(CBT+Surgery)=</td>
<td>RCT for first 14 participants, other participants could choose between CBT and CBT+Surgery (vestibulectomy).</td>
<td>Subjective pain during intercourse. Scoring range: 1-5; 1 = complaints fully disappeared; 2 = diminished; 3 = unchanged, but less of a problem; 4 = unchanged; 5 = complaints worsened. Score of 1, 2, or 3 = ‘positive result’.</td>
<td>Randomized study part (n=14): subjective pain score: CBT = 1.86; CBT + surgery = 1.57. Unrandomized study part: CBT = 2.14; CBT + surgery = 1.67. Both treatments were equally effective (p &gt; .05).</td>
<td>2b</td>
</tr>
<tr>
<td>Schnyder, Schnyder-Lüthi, Ballinari &amp; Blaser, 1998 [226]</td>
<td>VAG</td>
<td>N(VAG)=44</td>
<td>Behavioral sex therapy involving daily home exercises with insertion of vaginal dilator after demonstration of insertion by therapist (in vivo) or therapist’s verbal explanation only (in vitro), participants randomized to treatmen</td>
<td>Dichotomous assessment of intercourse success; unvalidated interview ratings of predictor variables.</td>
<td>Forty-three (97.2%) of the patients were able to have sexual intercourse after an average of 6.3 therapeutic sessions. Success tended to occur more often in the absence of sexual desire disorders. No correlations were found between success and patients’ sexual history variables.</td>
<td>2b</td>
</tr>
<tr>
<td>Schover, Youngs &amp; Cannata, 1992 [257]</td>
<td>PVD</td>
<td>N(PVD)=45</td>
<td>Uncontrolled prospective study. Treatment: localized vestibuloplasty, offer of sexual counseling, Kegel exercises, vaginal dilation and couple therapy.</td>
<td>Outcome: therapist rated on 5-point scale: very much improved to very much worse. Predictor variables: Sex History Form, Dyadic Adjustment Inventory, Brief Symptom Inventory, structured interview for DSM-IIIR disorders and sexual history.</td>
<td>Of the 32 women who had both surgical excision of vulvar lesions and contact with the psychologist, 50% were much improved in perceived pain, 41% were somewhat improved, and 9% were unimproved. Predictive for better outcome were: higher socioeconomic status, childlessness. Psychological factors at pain onset and test scores were not predictive. Willingness to be psychologically evaluated was highly predictive, as was cooperation of patient in postoperative counseling. More localized introital pain was predictive of better treatment outcome, as opposed to diffuse genital pain.</td>
<td>2b</td>
</tr>
<tr>
<td>Bergeron, Binik, Khalifé, Pagidas, Glazer, Meana &amp; Amsel, 2001 [247]</td>
<td>PVD</td>
<td>N(Vest.)=22 N(CBT)=28 N(EMG)=28</td>
<td>Prospective RCT: vestibuloplasty vs. CBT vs. EMG feedback.</td>
<td>Gynaecological examination, structured interview, MPQ, vestibular pain index, pain during intercourse, SHF, frequency of intercourse, DSFI, BSI.</td>
<td>Compared with pretreatment, study completers of all treatment groups reported statistically significant reductions on pain measures at posttreatment and 6-month follow-up. The vestibuloplasty group was significantly more successful than the two other groups. Seven women who had been assigned to vestibuloplasty withdrew before the operation was carried out. All groups improved regarding psychological adjustment and sexual function from pretreatment to 6 month follow-up. Reduction of pain during intercourse at posttreatment and 6-month follow-up. Vestibuloplasty &gt; CBT = EMG. Larger dropout rate for vestibuloplasty.</td>
<td>1b</td>
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</table>
Table 25.3. Outcome of treatment studies of women with sexual pain disorders, including psychological predictors of treatment outcome (continued)

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</tr>
</thead>
<tbody>
<tr>
<td>Bergeron, Brown, Lord, Oala, Binik &amp; Khalilé, 2002 [311]</td>
<td>PVD</td>
<td>N(PVD)=35</td>
<td>Retrospective study: physical therapy (pelvic floor muscle rehabilitation + biofeedback) was provided with a mean of 7 sessions. Length of follow-up = 2-44 months; mean = 16 months.</td>
<td>Intravaginal dyspareunia (7-point scale from a lot worse to complete relief), current pain during intercourse, and sexual functioning.</td>
<td>Physical therapy yielded complete or great improvement for 51.4% of participants, moderate improvement for 20.0% of participants, and little to no improvement for the other 28.6%. Treatment resulted in a significant decrease in pain experienced both during intercourse and gynecological examinations; it also resulted in a significant increase in intercourse frequency and levels of sexual desire and arousal. Successful responders were less educated than unsuccessful responders.</td>
</tr>
<tr>
<td>Bohm-Starke, Brodda-Jansen, Linder, &amp; Danielsson, 2007 [114]</td>
<td>PVD</td>
<td>N(EMG)=17; N(lidocaine)=18; N(Contr.)=30</td>
<td>Prospective RCT: topically applied lidocaine (2% gel or 5% ointment) on the vestibule 5 times per day for 4 months vs. surface EMG biofeedback, using a portable instrument for 10 minutes’ practice twice a day for 4 months according to a standard Protocol. No untreated comparison group. Length of follow-up = 6 months.</td>
<td>Pressure pain thresholds (PPTs) in the vestibule measured with vulvalgesiometer. General pain thresholds on the upper arm and leg (pressure algometer); functional impairment (SF-36); estimated overall response to treatment (worse, no change, improved, or completely cured).</td>
<td>Vestibular pain thresholds increased from median 30 g before to 70 g 1b after treatment in the anterior vestibule (P&lt;0.001) and from median 20 to 30 g in the posterior vestibule (P=0.001). PPTs on the leg and arm were lower in the patients as compared with controls both before and at the 6-month follow-up. Patients reporting total cure were 3/35; 25/35 were improved. The number of patients who frequently reported of other bodily pain was reduced after the treatment. The patients had lower scores for SF-36 (General Health, Vitality) before treatment, which was restored at the 6-month follow-up. No differences in outcome measures were observed between the 2 treatments. No predictors were investigated.</td>
</tr>
<tr>
<td>van Lankveld, ter Kuile, de Groot, Melles, Nefs &amp; Zandbergen, 2006 [6]</td>
<td>VAG</td>
<td>N(Contr.)=38</td>
<td>Prospective RCT: cognitive-behavioral treatment vs. waiting-list. CBT both as group therapy and bibliotherapy</td>
<td>Self-report questionnaire: behavioural endpoints, penile-vaginal penetration and other types of penetrative behaviour (with finger, self or partner’s). Questionnaires: FSFI, MMQ, GRISS.</td>
<td>Waiting-list participants did not improve re. successful intercourse. At follow-up assessment (1 yr posttreatment) 21% of bibliotherapy, and 15% of group therapy CBT were successful re. intercourse. Outcome of both treatments did not differ. No effects of treatment on other aspects of sexual or marital functioning.</td>
</tr>
<tr>
<td>ter Kuile, van Lankveld, de Groot, Melles, Nefs &amp; Zandbergen, 2007 [250]</td>
<td>VAG</td>
<td>N(Contr.)=36</td>
<td>Prediction study on outcome of cognitive-behavioral treatment vs. waiting-list. CBT both as group therapy and bibliotherapy. The same subjects were investigated as in the previous reference.</td>
<td>Self-report questionnaire: behavioural endpoints, penile-vaginal penetration and other types of penetrative behavior (with finger, self or partner’s). Fear of sexuality Questionnaire, STAI.</td>
<td>Changes during treatment in fear of intercourse, and fear of non-penetrative sexual behaviour predict successful outcome of CBT for lifelong vaginismus.</td>
</tr>
</tbody>
</table>
Table 25.3. Outcome of treatment studies of women with sexual pain disorders, including psychological predictors of treatment outcome (continued)

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Dys-func-</th>
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<th>Assessment</th>
<th>Process findings</th>
<th>Level of evidence (Oxford system)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pukall, Kandyba, Amsel, Khalifé &amp; Binik, 2007 [312]</td>
<td>PVD</td>
<td>N(PVD)=8</td>
<td>Uncontrolled prospective trial of hypnosis.</td>
<td>Pain ratings during gynecologic examination, vestibular pain thresholds, McGill Pain Questionnaire and PCS, intercourse-related and nonintercourse-related pain, FSFI, STAI, BDI, BSI.</td>
<td>Gynecologic examination pain and intercourse pain decreased, nonsignificant increases of the pain threshold. Some indices of noncoital vulvar pain decreased. Overall sexual function, particularly sexual satisfaction, increased at posttreatment.</td>
<td>3b</td>
</tr>
<tr>
<td>ter Kuile &amp; Weijenborg, 2006 [313]</td>
<td>PVD</td>
<td>N(PVD)=76</td>
<td>Uncontrolled prospective trial of cognitive-behavioral group therapy.</td>
<td>Pain intensity during intercourse, level of perceived pain control, SCL-90, MMQ, GRISS.</td>
<td>Pain intensity during intercourse decreased, vestibular pain and vaginal muscle tension. Perceived pain control, sexual satisfaction increased. Marital satisfaction and level of distress (SCL-90) were not affected. 9 women dropped out before completion of treatment.</td>
<td>3b</td>
</tr>
<tr>
<td>Bergeron, Khalifé, Glazer &amp; Binik, 2008 [314]</td>
<td>PVD</td>
<td>N(PVD)=51</td>
<td>Follow-up study (6 mth – 2.5 yr) of originally randomized women with PVD to vestibullectomy, CBT, or EMG-biofeedback.</td>
<td>1) a gynecologic examination involving the cotton-swab test, 2) a structured interview, and 3) validated pain and sexual functioning measures.</td>
<td>All three treatments yielded significant improvements at 6-month follow-up. Vestibulectomy more pain reduction compared with other treatments. Participants had less pain at the 2.5-year follow-up than at the previous 6-month follow-up. Sexual functioning measures remained unchanged between 6-month and 2.5-year follow-up. No group differences on sexual functioning measures. Higher pretreatment pain intensity predicted poorer outcomes at the 2.5-year follow-up for vestibullectomy (P&lt;.01), biofeedback (P&lt;.05), and cognitive-behavioral therapy (P&lt;.01). Erotophobia also predicted a poorer outcome for vestibullectomy (P&lt;.001).</td>
<td>1b</td>
</tr>
<tr>
<td>Backman, Widenbrant, Bohm-Starke &amp; Dahlof, 2008 [315]</td>
<td>PVD</td>
<td>N(PVD)=27</td>
<td>Uncontrolled prospective trial of combined physical and psychosexual therapy, including mucosal desensitization. (topical cream application + finger penetration exercises).</td>
<td>Unvalidated self-report questionnaire.</td>
<td>19 women considered themselves cured or greatly improved (increased frequency of intercourse, reduced coital pain). 3 women dropped out before completion of treatment.</td>
<td>3b</td>
</tr>
</tbody>
</table>
Table 25.3. Outcome of treatment studies of women with sexual pain disorders, including psychological predictors of treatment outcome (continued)

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Dysfunction type</th>
<th>N</th>
<th>Design</th>
<th>Assessment</th>
<th>Process findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldfinger, Pukall, Gentilcore-Saulnier, McLean &amp; Chamberlain, 2009 [316]</td>
<td>PVD</td>
<td>N(PVD)=13</td>
<td>Uncontrolled prospective trial of physical therapy, including intravaginale manual techniques (e.g., trigger point release, massage), biofeedback therapy, insertion of vaginal dilators, and ban on intercourse during treatment.</td>
<td>Vestibular pain index, cotton-swab test, QST, FSFI, Sexual Esteem subscale of the Sexuality Scale (SS-SE) [317]</td>
<td>Following treatment, participants had significantly higher vestibular pain thresholds and lower pain ratings during the gynecological examination; significant reductions in pain intensity during intercourse and were able to engage in more pain-free activities. Overall sexual function improved, but various components of sexual function and frequency of intercourse did not. Participants’ mental health did not significantly improve. Pain catastrophizing and pain-related anxiety significantly decreased.</td>
</tr>
</tbody>
</table>

Dysfunction type: PVD = provoked vestibulodynia; VAG = vaginismus; PCS = Pain Catastrophizing Scale; FSFI = Female Sexual Function Index, STAI = State-Trait Anxiety Inventory, BDI = Beck Depression Inventory-II, BSI = Brief Symptom Inventory, SCL-90 = Symptom Checklist-90, MMQ = Maudsley Marital Questionnaire, GRISS = Golombok-Rust Inventory of Sexual Satisfaction, MPQ = McGill Pain Questionnaire, SHF = Sexual History Form, DSFI = Derogatis Sexual Functioning Inventory.
found both with stimuli depicting intercourse and nonintercourse erotic stimuli. In two studies, women with dyspareunia responded with equal genital arousal to nonintercourse erotic stimuli, but with a lower genital response to stimuli depicting intercourse [245, 246]. When fear of pain was induced during visual erotic stimulation, both women with PVD and asymptomatic women responded with decreased genital sexual arousal [245].

d) Psychological Variables and Treatment Outcome (Grade C)

The psychological treatment of PVD has been evaluated in three controlled trials [114, 247, 248]. Significant improvement in experienced pain and in intercourse frequency and other measures of sexual functioning was reported after cognitive-behavioral therapy (CBT) and CBT combined with vestibulotomy, and these results were found to be maintained over time. Electromyographic biofeedback treatment and topically applied lidocaine were equally effective regarding pain reduction [114]. Prediction of treatment outcome by means of psychological or psychosocial variables (see Table 25.3) has been investigated in women with PVD. Psychosocial variables predictive for positive outcome were: higher socioeconomic status*, lower education*, and childlessness*. Psychological and relational factors at treatment onset and psychological test scores (marital adjustment, neuroticism, psychopathology) were not predictive*. Willingness to be psychologically evaluated was highly predictive for positive outcome of limited vestibulotomy*, as was cooperation of patient in postoperative counseling*, low erotophobia score*, and lower pretreatment pain intensity*. High scores on instruments measuring fear of negative evaluation by others, phobia related to vaginal entry and the Personality Assessment Screener have been associated with poor outcome. No replications of prediction models have yet been reported.

e) Conclusions Regarding Women with Dyspareunia Resulting From PVD

In sum, in women with PVD, increased prevalence of comorbid psychopathology was found, specifically depression and anxiety disorders. These findings were not consistently reported and only one study [249] employed an instrument producing DSM-IV diagnoses. The crosssectional design of the relevant studies precludes conclusions regarding the causal direction of the association between affective disorders and PVD.

Furthermore, both more problematic and non-affected psychological functioning have been reported in women with PVD. Although this could reflect differences in study samples and instrumentation, it could also indicate true heterogeneity of women with PVD. Increased trait anxiety, pain catastrophizing, reward dependency and harm avoidance in women with PVD, however, have consistently been found in multiple studies, and may represent a complex of stable characteristics that suggest an important contribution to the etiology of PVD of avoidant, dependent, and obsessive-compulsive personality features.

Single study findings of women with PVD included elevated rates of shyness, perfectionism, low self-esteem, and negative feelings towards sexual interaction, erotophobia, and problems with subjective sexual arousal and lubrication during sexual interaction with partner, but not during masturbation. Women with PVD have been found to be more sensitive to thermal, pain, and tactile stimulation, reflected in lowered thresholds for sensitivity, and they experience heightened pain in response to painful stimulation as compared with non-affected women. An etiological element may be the deficits in information processing, i.e., hypervigilance for pain-related stimuli. These latter findings require replication in future studies.

3. SUPERFICIAL DYSpareunIA NOT IDENTI FIED AS PVD (DYS)

a) Individual Psychological And Personality Characteristics

It is not known whether or not participants in studies of superficial dyspareunia not identified as PVD (DYS) meet the clinical criteria for PVD. Higher rates of psychopathology in women with DYS were found with regard to depression** and anxiety disorders*, more specifically: generalized anxiety disorder*, simple phobia*, obsessive-compulsive disorder*, and social phobia*. Equal rates of psychopathology in women with DYS, compared with healthy controls, were found with regard to posttraumatic stress disorder* and eating disorder* (see Table 25.1b).

Frequency of (childhood) sexual trauma was found equal in women with DYS** compared with the general female population or asymptomatic women, such as women seeking routine gynecological examination. On self-report measures (see Table 25.1b), women with DYS were found to have higher scores on neuroticism*, depression** and state anxiety**. Phobic anxiety in women with DYS was found higher**, as were obsessive-compulsive behaviors**, and social phobia (interpersonal sensitivity)**. This pattern of results is strikingly different from that of women with PVD; however, an unknown proportion of women with PVD may have in fact been included in the samples of these studies. Scores on most psychological features that were investigated in women with DYS were elevated, whereas comparisons of women with PVD with control women on the same variables yielded equivocal findings.

Women with dyspareunia also reported more symptoms of hostility**, more (psycho)somatic complaints...
(somatization)*, higher paranoid ideation*, and more psychotic symptoms*.

**b) Sexual Relationships in Women With DYS**

With regard to personality traits more closely related to the domain of sexuality, women with DYS are found to score higher on erotophobia* than healthy control women. With regard to sexual functioning, they also appear to have lower sexual arousal** in response to sexual intercourse stimuli. Furthermore, they more often report relationship discordance**.

**c) Psychological Processes InWomen With DYS**

With respect to psychological processes that cause or maintain dyspareunia (see Table 25.2), the level of pain ratings in dyspareunia patients is predicted by their level of depression*, where higher depression scores are associated with higher pain ratings.

The role of low sexual response, potentially (but not empirically demonstrated to be) accompanied by lack of vaginal lubrication in medically unexplained superficial dyspareunia, may be seen as pivotal in our understanding of the etiology of this invalidating condition in women. In a first experimental study [246], genital response in women with DYS was compared with that of asymptomatic women. In women with DYS, genital response was lower to audiovisual representation of penile-vaginal penetration*, compared with stimuli depicting other forms of sexual activity (oral heterosexual stimulation). Subjective sexual arousal did not differ between women with and without dyspareunia*.

However, in more recent studies [242, 243, 245], women with DYS and healthy control women were found to exhibit equivalent genital responses to, respectively, 1. stimuli depicting oral sex vs. penile-vaginal penetration, 2. induction of pain-related fear, and 3. induction of negative vs. neutral vs. positive appraisal of a situation in which they viewed erotic films. Both groups of women showed identical patterns of genital sexual arousal, but several differences were found regarding subjectively experienced sexual arousal, and negative and positive affect.

Neither psychological treatment of superficial dyspareunia (not identified as PVD) nor prediction of treatment outcome by psychological or psychosocial variables has been investigated in controlled comparisons.

**d) Conclusions Regarding Women with Superficial Dyspareunia Not Identified As PVD (DYS)**

In summary, women with DYS were found to have elevated rates of clinically relevant comorbid depression and anxiety disorders. Sexual traumatization appears not to play a significant role in etiology. Self-report measurement of psychological characteristics corroborates the presence of depressive and anxious symptoms, both on the experiential and the behavioral level. Experiential and behavioral signs of hostility and psychotic symptoms also appear to be more frequently present. With respect to sexual functioning, women with dyspareunia are found to be more erotophobic, reflecting negative and conservative attitudes towards sex, and aversion to engage in sex. Findings with regard to sexual arousal problems in women with DYS have thus far been contradictory. Relationship discord was found to be increased in women with DYS.

Lower genital response during laboratory investigation to specific sexual stimulation (audiovisual representation of penile-vaginal intercourse vs. oral sex) in women with DYS, compared with control women, was found in one study, whereas more recent studies found absence of genital response differences between these groups, whereas subjective arousal and other affective responses were different between these groups.

The controversy that has arisen regarding the role of low vaginal vasocongestion and lubrication response to erotic stimulation in women with DYS warrants further study.

**4. VAGINISMUS**

**a) Individual Psychological and Personality Characteristics**

Higher rates of psychopathology in women with vaginismus were found with regard to agoraphobia without panic disorder* and obsessive-compulsive disorder* (see Table 25.1c). In women with vaginismus, when compared with the general female population, equal frequency* of childhood sexual trauma was found in one study, whereas another study found elevated frequency*.

On self-report measures (see Table 25.1c), many conflicting findings were reported. Women with vaginismus were found to have equal and higher scores on neuroticism**, depression**, state anxiety**, phobic anxiety**, social phobia**, obsessive compulsive behavior**, paranoid ideation*, psychoticism**, somatization**, and hostility**. Compared with asymptomatic women, women with vaginismus had increased catastrophic thinking* both for non-genital and genital pain. Compared with both women with dyspareunia (including PVD) and asymptomatic women, women with vaginismus had higher disgust propensity*.

With respect to dispositional traits, women with vaginismus were equal to the normal population on extraversion** and negative sexual self-schema*. They showed elevated traits of low self-esteem*, less positive sexual self-schema*, and hysterical personality*. 
b) Sexual Relationships of Women with Vaginismus

Rates of marital discord were equal to the general population*. With regard to their sexual functioning, women with vaginismus reported less self-stimulation*, and more problems with sexual desire* and arousal*.

c) Psychological Processes in Women with Vaginismus

With respect to psychological processes causing or maintaining vaginismus (see Table 25.2), women with and without vaginismus are found not to differ in baseline pelvic floor muscle tension*, or in the ability to control pelvic floor muscles while performing exercises (short flick contractions and 10-sec holding contractions)*. Women with vaginismus and asymptomatic women do not differ in their EMG measured pelvic floor muscle response to physically-threatening or sexually-threatening stimuli*. Compared with control women, women with vaginismus (28%) had higher incidence of vaginal spasm*. Visual erotic stimulation does not increase the pelvic floor muscle activity in women with vaginismus. However, subjectively experienced threat of the stimuli correlates significantly with EMG-measured muscle activity*. A randomized controlled trial of standard cognitive-behavioral treatment for vaginismus yielded better response of CBT (27% successful intercourse) compared to a waiting-list control condition (0%) [6]. Reduction of penetration-related fears was found to mediate positive response to treatment [250].

d) Prediction of Treatment Outcome (Grade B)

Prediction of treatment by means of psychological, psychosexual and psychosocial variables has been investigated in vaginismus in three non-controlled studies and one RCT of CBT (see Table 25.3).

Psychological variables predictive for better outcome were: attribution of problem to psychological causes*, positive attitude towards own genitalia*, strong wish to become pregnant*, better sexual knowledge*, good compliance with homework assignment by third treatment session*, and lower pre-treatment ratings of marital tension in the female partner*. Peri-treatment reduction of fear of penile-vaginal penetration was found to be predictive of successful intercourse after CBT*.

Negatively associated with treatment length were: pre-treatment sexual desire problems*, fear of sexually transmitted diseases*, negative parental attitudes towards sex*, having undergone previous operations for vaginismus*, and history of organic abnormality (septum, vaginitis)*.

No predictive value was found with respect to history of sexual abuse* or presence of additional sexual dysfunctions in either partner*. No replications of prediction models have been reported.

e) Conclusions Regarding Women with Vaginismus

In summary, women with vaginismus were found to have significantly increased comorbid anxiety disorders (agoraphobia without panic disorder, obsessive-compulsive disorder), while depression rates were not found to be increased. The role of childhood sexual trauma is unclear since different frequency rates were found, and the presence of increased rates of posttraumatic stress disorder has not yet been investigated. Psychological characteristics, measured with self-report instruments, only partially lend clear support to the role of anxiety symptoms in the etiology of vaginismus. Interpersonal sensitivity (social evaluation anxiety) was found increased in women with vaginismus**, although absence of difference in this respect has also been found*. Personality features found to be more often present in this group suggest the presence of pain catastrophizing cognitions, disgust propensity, and a specific fear of penile-vaginal penetration in the etiology or maintenance of vaginismus. Sexual functioning may be impaired with regard to sexual desire and arousal response during sexual activity. Experimental evidence thus far has documented the role of experienced threat in increased pelvic floor muscle tension, but did not discriminate between women with and without vaginismus. In sum, whether vaginismus is caused or maintained by psychological factors requires additional investigation. Fear of penetration, anxiety and disgust, and other aspects of negative affect may play a role.

VIII. CLINICAL PRESENTATION OF SEXUAL PAIN DISORDERS

1. PREVALENCE

Prevalence estimates for dyspareunia range from 6.5-45% in older women and from 14-34% in younger women [318-327]. Estimates vary according to several factors, such as culture [326-332], setting (population-based or clinic-based) [325, 327], the time frame specified by researchers [318], the presence of chronic disease [333, 334], the duration of menopausal status [335, 336], body mass index [335], depression [336, 337], the degree of perineal trauma experienced during vaginal delivery [325], and, most importantly, the physician's initiative to bring up the topic [338]. Therefore, in order to detect sexual concerns, explicit questions must be asked.

Prevalence rates for vaginismus are scarce, without the benefit of multiple studies on specific populations. Population-based estimates for vaginismus range from 1 to 6% [323, 339, 340].
2. PHYSICAL CONDITIONS ASSOCIATED
WITH PAIN ON ATTEMPTED OR
COMPLETED VAGINAL ENTRY

Table 25.4 summarizes various conditions that may be associated with varying degrees of chronic dyspareunia (See Table 25-X).

3. GENERAL SEXUAL HISTORY FOR SEXUAL PAIN DISORDERS

Gynecological complaints, diagnostic procedures, and/or treatment may have consequences on the sexual functioning of the patient and her partner. It is therefore advisable for health care providers to ask each patient whether she has any sexual concerns. In addition, asking about any past negative sexual experiences prior to procedures and treatments is recommended, as tailored approaches may be necessary for such patients [341]. Given that women with sexual pain may experience embarrassment, shame, guilt, low self-esteem, frustration, and other negative emotions in addition to their dyspareunia, it is crucial that the clinician uses communication skills that enhance openness, comfort, trust, and confidence within a non-judgmental context.

Obtaining a psychosexual history is recommended as it can provide invaluable information about predisposing and maintaining factors; however, of more direct relevance in the initial interview is the assessment of the pain experience itself (Grade C). Allowing the patient to describe her difficulties and reasons for seeking treatment in an open-ended manner can communicate much information about her psychological disposition toward the problem. This part of the interview is then followed by more specific questions about the pain (see Table 25.5). Questions about the properties of the pain are essential for diagnosis [251] and include questions regarding the lifetime onset and temporal pattern of the pain as well as questions on pain duration, location, quality, and severity. Questions focusing on whether the pain is exacerbated with a male partner’s ejaculation, the presence of post-coital burning, and post-coital dysuria should also be asked. In addition to this information, questionnaires may be administered in order to more formally capture scores for empirical comparison and/or to track treatment progression (see below). Second, questions about pain mediators are crucial as pain is a complex subjective experience that can be impacted by a range of factors. Thus, asking whether any factors (e.g., intercourse positions, level of arousal, time of menstrual cycle) improve or exacerbate the pain may provide clues to management [342].

Third, queries about what activities have been affected by the pain and any comorbid issues (e.g., problems with sexual function, relationship distress, psychological issues) allow for a comprehensive understanding of the patient’s experience and may lead to additional treatment avenues. Furthermore, inquiring about patients’ theories regarding their pain can be important, as research has shown that psychosocial – as opposed to physical – explanations for the pain are related to higher distress and lower relationship adjustment [251]. Fourth, questions related to previous treatments undertaken and their outcomes can be useful in treatment planning [342]. Throughout the assessment, it is important to keep in mind that sexual pain problems are embedded in a somatic, psychological, relational, and social context which must be assessed in order to make adequate decisions regarding diagnosis, treatment, or referral.

Table 25.4: Conditions associated with chronic dyspareunia

<table>
<thead>
<tr>
<th>Superficial pain</th>
<th>Deep pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vestibulodynia, dyspareunia vulvodynia</td>
<td>Estrogen deficiency</td>
</tr>
<tr>
<td>Vaginal atrophy</td>
<td>Vaginal pain</td>
</tr>
<tr>
<td>Vulvar vestibulodynia and/or vulvodynia</td>
<td>Chronic pelvic inflammatory diseases</td>
</tr>
<tr>
<td>Interstitial cysts</td>
<td>Pelvic organ prolapse</td>
</tr>
<tr>
<td>Condylomata and other sexually transmitted infections</td>
<td>Urinary tract symptoms (LUTS) with urinary incontinence</td>
</tr>
<tr>
<td>Vulvar dermatoses</td>
<td>Uterine fibroid</td>
</tr>
<tr>
<td>Urethral tenderness</td>
<td>Fixed inverted uterus</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>Gynecologic cancer treatments</td>
</tr>
<tr>
<td>Vulvovaginitis</td>
<td>Pelvic organ prolapse</td>
</tr>
<tr>
<td>Anatomic variations</td>
<td>Uterine fibroid</td>
</tr>
<tr>
<td>Urethritis</td>
<td>Fixed inverted uterus</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>Hidradenitis suppurativa</td>
</tr>
<tr>
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</tr>
<tr>
<td>Condylomata and other sexually transmitted infections</td>
<td>Congenital abnormalities</td>
</tr>
<tr>
<td>Vulvar dermatoses</td>
<td>Lower urinary tract symptoms (LUTS) with urinary incontinence</td>
</tr>
<tr>
<td>Urethral tenderness</td>
<td></td>
</tr>
</tbody>
</table>

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4. EDUCATIONAL GYNECOLOGICAL SEXOLOGICAL EXAMINATION

In order to detect or exclude physical illness or abnormalities that cause pain on (attempted) vaginal entry (Table 25.4), the patient and physician have to work together. Especially in the case of dyspareunia or vaginismus, it is not always desirable or practical to perform a medical examination right away. The patient and care provider must make decisions together about timing, who is present, and the extent of the examination. The examination technique to search for the cause of dyspareunia is more detailed and requires much more finesse than a routine pelvic examination (Grade C). When conducted correctly, it can be highly therapeutic. This is especially true when the sexual partner is also present. Often referred to as an “educational gynecological sexological examination”, the patient watches in the mirror as the doctor gathers information and tells the patient about her genital anatomy, clarifying normal (or abnormal) structures. This examination can correct misinformation and negative self-image, and can clarify how physical changes can relate to sexual problems [341].

Essentially, the patient’s personal boundaries must be respected and safeguarded throughout the process [343]. It is she who decides who is going to be present during the examination and how far the examination will proceed. Before the examination occurs, it is important to inform the patient how it will be performed and to ensure her that, during the exam, she will be told when the next step of the examination will be taken. In addition, clarifying that she can interrupt the examination at any stage – and that doing so is not considered a failure – is essential. Through the examination, the foundations are present for a meaningful discussion afterwards, in which all the findings are explained and at which time, further sexual complaints may come to light. Although based on level 5 evidence, this process is recommended to lessen the common occurrence of women having to seek multiple health care providers before an accurate diagnosis is made.

a) The Context

When dyspareunia and vaginismus are suggested by the history, the patient is told ahead of time that the use of a speculum or other means of internally examining the pelvis will not necessarily be part of the examination. It is recommended to ask the woman if there is anything she can think of that will facilitate the exam and to impart to her a sense of control with respect to what will happen in the examination. The physician should be seated comfortably and the examination couch should be adjusted for the woman to be sitting up so that she may see the examination of her genitals in a hand mirror; her wish to not watch, however, should also be respected. Verbally checking how the woman is coping with the exam during the process is recommended. Non-verbal communication – the patient’s behavior and that of her partner (if present) – are noted. In addition, the physician must also be aware of his or her own non-verbal behaviors.

1) Pain

Have you had the pain since your first vaginal penetration attempt, or did it occur after a period of pain-free vaginal penetration? Where does it hurt?

How would you describe the pain?

When does the pain first start (e.g., during initial vaginal penetration, once the object has been partially/fully inserted, etc), or is it always there? If it is always there, does vaginal penetration make it worse?

Does the pain only occur in response to touch of the area, or is it present most of the time?

How long does the pain last during intercourse (only during initial penetration, only once the object has fully entered, during thrusting, afterwards, the whole time?)

What makes the pain better or worse? Specifically ask questions related to post-coital pain, pain with ejaculation fluid, post-coital dysuria, pain with arousal, and pain with orgasm.

On a scale from 0 to 10 (where 0 is no pain at all and 10 is the worst pain felt), how would you rate the intensity of the pain?

Does touching elsewhere in the genital area cause pain?

Does the area hurt during non-penetrative activities (e.g., riding a bicycle, wearing tight clothes)?

Does other forms of penetration hurt (tampons, fingers)?

What do you believe is the cause of your pain?

2) Pelvic Floor Muscle Tension

Do you find that your body/pelvic area tenses up when you are faced with vaginal penetration activities? If so, does this tension make vaginal penetration impossible sometimes/always?

Do you experience the same tension in non-sexual situations that involve vaginal penetration (e.g., gynecological examinations, tampon insertion)?

Have you ever been able to have full vaginal penetration?

3) Arousal

Do you feel sexually excited when you engage in sexual activity?

Does your vagina feel wet?

Does your vagina feel dry before or during sexual activity?

Does the use of a lubricant help?

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the use of a lubricant help?</td>
<td>?</td>
</tr>
<tr>
<td>Does your vagina feel wet?</td>
<td>?</td>
</tr>
<tr>
<td>Does your vagina feel dry before or during sexual activity?</td>
<td>?</td>
</tr>
<tr>
<td>Does the use of a lubricant help?</td>
<td>?</td>
</tr>
</tbody>
</table>
What are your thoughts and feelings before, during, and after sexual activity?

4) CONSEQUENCES OF THE COMPLAINT

What do you do when you experience pain during sexual activities? (Continue/stop intercourse/continue to make love without intercourse?)

Do you find yourself avoiding activities (sexual/non-sexual) that involve vaginal penetration?

Do you currently engage in activities involving vaginal penetration?

What sexual activities do you engage in?

Do you express affection with your partner in non-sexual ways?

What consequences does the pain have on your sexual functioning and intimate relationships?

What consequences does the pain have on your self-image, psychological well-being, quality of life?

5) ANTECEDENTS

When and how did the pain start?

What diagnostic tests have been done?

What diagnoses have you received?

What was happening in your life at the time that the pain started (e.g., health issues, stressful events)?

What treatment/s have you tried? Which treatments helped, and which ones did not?

What other things have you done to try to alleviate the pain?

(end of Table)

b) Adequate Spreading

Permission is asked to gently spread the labia majora or the patient is asked to spread them herself with her fingers. This enables her to observe the consequences of pelvic floor muscle activity. By bearing down or coughing, she is able to see the introitus becoming larger. The vulva is carefully inspected, including the skin of the outer part of the vulva, labia minora, labia majora, the crease between the labia, the clitoral hood and clitoris, the posterior fourchette, vestibule, hymen, and hymenal edge. For women with introital dyspareunia, sites of allodynia are investigated using a cotton-swab (Q-tip), applying light pressure along the outer edge of the hymen where it meets the inner edge of the internal surfaces of the labia minora. In cases where vaginal discharge is noted, relatively pain-free samples for vaginal pH and microscopy using a cotton-swab are possible to obtain. Additional testing is indicated by clinical findings; however, routine bacterial vaginal cultures are generally not useful.

c) Internal Exam

It may be possible to proceed to the internal exam, with the woman’s permission, on this first visit when the characteristic features of vaginismus are not present in the history or during the exam. With the woman is bearing down, the insertion of physician’s finger (or if necessary, something smaller such as cotton-swab) confirms vaginal entry without pain. If possible, additional examination using a small speculum, careful palpation of the uterus and adnexa, and/or transvaginal sonographic assessment for deep dyspareunia or ovarian abnormality might be performed [344].

d) Pain Measurement In Vestibulodynia

For the purpose of diagnosis and treatment outcome, it is advisable to measure the pain in the genital region. In order to diagnose PVD, the cotton-swab test is used (Grade C) [52, 145]. The cotton-swab test consists of palpating different areas of the vulva, including the vulvar vestibule, with a cotton-swab and asking whether the pressure is painful or not. Some clinicians also ask that the patient rates the pain intensity of the pressure on numerical rating scales (e.g., from 0-10). If the cotton-swab test reveals a pattern of sensitivity in which the pain is localized to the vestibule, then the diagnosis of PVD is made. It is important to note that different health professionals conduct the cotton-swab test in different ways; however, the order of the palpations should be randomized as it has been demonstrated that sensitization may occur when adjacent areas are palpated [304]. In addition, different clinicians may apply different amounts of pressure [345]. As such, the cotton-swab test is prone to measurement error when used for experimental purposes or to measure treatment outcome. Therefore, a new mechanical device, the vulvalgesiometer (see Figure 25.5), has been developed [121, 304, 345]. The vulvalgesiometer has been shown to discriminate between women with and without PVD [111, 121, 304], and has demonstrated that, in women with

Figure 25.5: Vulvagesiometer
PVD, painful levels of stimulation replicate the quality of the pain reported during vaginal penetration (i.e., burning, sharp) [121, 304]. Although specific studies are currently lacking, the vulvalgesiometer can be used as a diagnostic tool capable of differentiating women with different types of genital pain. In addition, because of its large range of exertable pressures (3-950 g), it may aid in quantifying the severity of pain (mild, moderate, severe) experienced by these women. The vulvalgesiometer has been used to measure changes in vestibular pressure-pain sensitivity as a result of treatment [114, 312, 316, 346].

Methods to assess vaginal pressure-pain sensitivity may be useful in conditions in which vaginal dyspareunia is the main complaint. The vaginal algometer [347] assesses pressure-pain threshold on the lateral walls of the vagina with a thimble-like probe worn on the clinician’s finger. It is well tolerated by healthy women and is capable of discriminating between women with and without chronic pelvic pain [348]. Devices with which to measure genital sensitivity to other forms of stimulation (e.g., thermal, vibratory) also exist and are empirically useful; however, they may not be practical for clinical settings [342].

e) The Pelvic Floor

Involuntary contraction on the gynecology table does not infer that this response is also necessarily present at home. Conversely, some women can undergo a gynecological examination without any problem, but have vaginismic reactions in other circumstances, depending on what they find threatening. Instead of asking a patient to relax, offering her information and tools is usually more successful to decrease anxiety and hypertension of the pelvic floor muscles [341]. In many cases, the pelvic floor muscles are chronically contracted and feel like “steel cables”.

Physician assessment of pelvic floor muscle tone is imprecise but still of some value (Grade C) [349]. The physician places his or her finger between the woman’s labia just in front of the vaginal opening and applies gentle pressure. The woman is asked to bear down while the physician (slowly) moves the finger inside, keeping it dorsally curved to feel the pelvic floor muscle without touching painful areas at the vestibular margin. At the end of the examination, the finger is slowly withdrawn as the patient bears down. The use of a lubricant will facilitate the examination and prevent tissue damage.

It has been proposed that surface electromyographic (sEMG) biofeedback is a useful method to detect pelvic floor hypertension and dysfunction in women with PVD [350]. Although more recent data do not support these findings and sEMG biofeedback is no longer recommended for assessment in the routine clinical setting [351], it has been shown to be a valuable tool for restoring pelvic floor function and improving dyspareunia in PVD patients [247, 346].

5. THE USE OF SELF-REPORT MEASURES IN PATIENTS WITH DYSPAREUNIA

Measures of psychological function may also aid in treatment planning. For example, if anxiety or depression is suspected, the Beck Depression Inventory-II [272] and the Beck Anxiety Inventory [357] can be used. Additionally, the Personality Assessment Inventory [358] yields a global profile of psychological function, and it has been validated with chronic pain populations. The administration of any measure of psychological symptomatology should be prefaced with a clear explanation of its function (i.e., to investigate pain mediators); otherwise, the patient may believe that her pain is not being taken seriously [342].

IX. MANAGEMENT OF SEXUAL PAIN DISORDERS

1. GENERAL REMARKS

Sexual pain disorders are heterogeneous, multisystemic and multifactorial disorders that should be treated in a multimodal way according to etiological factors, risk profile and context. The following algorithm with three distinctive characteristics meets these requirements.

a) General Recommendations (Grade C)

A multidimensional and multidisciplinary approach with specific attention to 6 areas: the mucous membrane, the pelvic floor, the experience of pain, sexual & relationship function, psychosocial adjustment and genital mutilation/sexual abuse. There is no “one size fits all” approach and no “or-or” approach but an “and-and” approach is recommended. Simply focusing on one symptom or facet of the experience may lead to improvement in that single area; however, this sole effect may not impact other areas of function that are in need of improvement.

Individualized treatment After careful listening to her story and after she has been well informed about the condition, its natural course, and possible treatment options and management tips, a treatment plan is made.

Patient-focused approach: it is up to the woman and her partner to decide which treatment avenue they wish to pursue. If the assessment of psychological function has revealed some issues, this aspect should be treated first with psychotherapy and/or medications. By involving patients in the decision process with regard to potential treatment avenues, the clinician and patient share the responsibility for treatment choice; this involvement is known to have a positive effect on the treatment outcome [359]. Shifts in preference for a certain approach will depend on the country in question, the woman’s attitudes regarding treatment
options, the individual health care systems, and the cost effectiveness of the various modalities, e.g. for PVD, surgery, CBT, biofeedback/physical therapy, transcutaneous electric nerve stimulation (TENS) or a combination of these treatments.

b) A Counseling Model

This approach implies that the health care provider has to be familiar with the counseling model. He or she is an advisor and counselor but it is the patient who is in full command of the situation. Treatments for sexual pain disorders are time-consuming, and they require great patience and empathy, sensitivity to non-verbal signals and insight into relational interactions. The treatment provider should be able to identify any ambivalent feelings on the part of the patient regarding coitus, sexuality, her partner, her own body, and her desire to have children. The health care provider must be able to bring to light serious relational problems or severe traumatic experiences (sexual violence) in addition to recognizing that sexual pleasure may be a goal over and above that of tolerable vaginal penetration.

2. THERAPEUTIC OPTIONS

In table 25.7 the various treatment modalities for subtypes of chronic dyspareunia in women are outlined. They include chronic pain medications along with sexual and psychological counseling. In this chapter, the treatment modalities and prognostic factors of PVD and vaginismus are discussed in detail.

a) General Recommendations (Grade C)

1) MEDICAL INTERVENTION

In terms of medical intervention for PVD, there are only three level 2 placebo controlled RCTs. One examined the effectiveness of Fluconazol [378] one investigated the usefulness of Cromolyn 4% [379], and one assessed the effectiveness of botulinum toxin injections [380]; however, neither Fluconazol nor Cromolyn 4% proved to be more effective than placebo. Additionally, the botulinum toxin injections did not result in significantly greater improvements in pain, sexual function, or sexual distress as compared to the placebo (saline injections); in fact, the placebo group fared better than the botulinum toxin group in sexual distress scores from baseline to 6-month follow-up. These results are contrary to the pattern of findings in smaller uncontrolled studies examining treatment outcomes following the administration of these injections [381, 382].

Other medical interventions that have been tested are Corticosteroids + lidocaine [383, 384], Botulinum toxin [382, 385], Capsaicin [386, 387], Ketoconazole [388], lidocaine/xylocaine [389, 390], and amitriptyline or other tricyclic antidepressants [130, 258, 391]. Various medical regimens (tricyclic anti-depressants, SSNRI (Duloxetine), venlafaxine, anticonvulsants - usually carbamazepine or gabapentin) are typically recommended for neuropathic pain conditions [392]. Some of these have been found to offer some pain relief in women with vulvar and pelvic pain, but total pain resolution with these drugs appears to be infrequent [130, 393, 394]. With respect to antidepressant medications, low doses are indicated for neuropathic pain reduction whereas higher doses are recommended for improvement in depressive symptoms. It is not clear, however, whether the medications, regardless of dosage, have a dual effect in that both pain and depressive symptoms can be targeted simultaneously. Further research is needed to assess this issue. None of the studies cited above were controlled (level 3) and, apart from their methodological limitations, the results are disappointing. One confounding factor is a consistent improvement of 30-40% of patients with PVD when treated with placebo or with no therapy reflecting the highly active processes in the brain that are mediated by psychological mechanisms such as expectations and conditioning [395].

Despite this issue, many clinicians continue to include in their biopsychosexual therapeutic approaches, medical interventions of unknown efficacy. RCTs of carefully evaluated women who appear to have similar medical and psychological profiles are encouraged to establish efficacy of these commonly used medical adjuncts.

2) HYGIENE MEASURES (GRADE C)

Preventative hygienic measures (level 5) include recommending that the patient avoid the use of soap, vaginal douches, nylon underwear and pantyliners (mini pads), and other potentially irritating factors (e.g., direct vulvar contact with semen) and activities (e.g., wearing tight trousers). In addition, the patient is encouraged to drink sufficient fluids to produce approximately 1500 ml of non-concentrated urine daily. Hydration with sitz baths may help reduce inflammation and symptoms.

3) RECOMMENDATIONS REGARDING SEXUAL ACTIVITY (GRADE C)

As long as the pain predominates, avoidance of vaginal penetration is recommended in addition to ensuring that semen does not come into contact with the sensitive vulvar areas. Some women may feel guilty about their restricted sexual activities, which may lead to frustration in their partners. Education about the effects of sexual pain on the sexual response cycle (consisting of desire, arousal, and orgasm) is needed, as many women with sexual pain will also suffer from comorbid decreases in sexual function, in particular, lower desire and arousal which can also negatively impact orgasmic frequency. Additionally, the partner may develop lower desire and issues of his/her own in response to creating pain for the patient during sexual activity.
### Table 25.7: Subtypes of chronic dyspareunia in women and therapeutic options

<table>
<thead>
<tr>
<th>Medical Disorder</th>
<th>Type of dyspareunia</th>
<th>Findings on physical examination</th>
<th>Therapeutic options and general comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvovaginal atrophy: associated with renal failure, chemotherapy-induced menopause, hypothalamic or pituitary disease, bilateral oophorectomy, or hyperprolactinemia.</td>
<td>Introital pain and with penile-vaginal movement. Possible postcoital burning. Deeper dyspareunia when vaginal atrophy advanced.</td>
<td>Pallor, dryness, increased fragility and thinning of vulvovaginal epithelium, vaginal shortening, loss of rugae, narrowing, or urethral caruncle.</td>
<td>Local oestrogen therapy is highly recommended. In case of breast cancer: local intravaginal application of DHEA achieves beneficial effects on different aspects of sexual functioning without significant systemic exposure to a drug, thus avoiding potential systemic risks. Frequent sexual arousal and (if necessary), nonpenetrative activity could promote genital health. Give dopaminergic drugs such as bromocriptine, cabergoline, or both to reduce prolactin; with surgery or radiation as appropriate.</td>
</tr>
<tr>
<td>Chronic (abdominal) pain: Endometriosis; Chronic PID; IBS; Crohn’s disease; Ulcerative colitis; Ovarian tumour; Abdominal wall pain.</td>
<td>Deep dyspareunia. IBS is also associated with introital pain from comorbid PVD.</td>
<td>General tenderness to deep bimanual examination.</td>
<td>Sexual dysfunction is highly prevalent in such patients. Women report deep dyspareunia. Organic disorders should be treated accordingly but sexual dysfunction may still need to be specifically managed. Irrespective of the organic or functional nature of the pain, a history of possible negative sexual experiences should be queried before any procedures or treatment.</td>
</tr>
<tr>
<td>Lower Urinary Tract Symptoms (LUTS) with urinary incontinence.</td>
<td>Introital and deep dyspareunia or vulvar burning after sexual intercourse.</td>
<td>Perineal and vulvar inflammation.</td>
<td>Voiding dysfunction, recurrent bacterial cystitis, hypoactive sexual desire, and sexual pain disorders are highly correlated. For recurrent cystitis give local OT; antibiotic self-treatment or preventative treatment, and recommend postcoital micturition (based on CE). In case of prolapse, surgical treatment can be curative but can also have undesired effects on sexual functioning.</td>
</tr>
<tr>
<td>Pelvic radiation.</td>
<td>Introital and deep dyspareunia.</td>
<td>Thinning and fragility of vaginal epithelium, loss of elasticity, stenosis, or foreshortening.</td>
<td>Preventive measures such as transposition of the ovaries to prevent ovarian failure. Therapeutic options based on CE include couple counselling about non-penetrative sexual activity, topical estrogen, lubricants, vaginal inserts, and vaginal reconstruction.</td>
</tr>
<tr>
<td>Chronic vulvovaginal candidiasis associated with diabetes and HIV.</td>
<td>Introital dyspareunia and with penile vaginal movement.</td>
<td>Erythema, swelling of vulva, and thick white or pale yellow vaginal discharge.</td>
<td>Oral agents recommended for recurrent symptomatic candidiasis.</td>
</tr>
<tr>
<td>Provoked vestibulodynia (PVD) associated with IBS, fibromyalgia, interstitial cystitis (IC), and other pain syndromes.</td>
<td>Superficial vulvovaginal pain on (attempted) penetration, pain on non-penetrative vulvovaginal touching, postcoital burning, or burning from partner’s ejaculation fluid.</td>
<td>Variable erythema of the vestibule. Allodynia typically located between 4 and 8 o’clock on the introitus, just exterior to the hymenal ring but can involve the skin around the openings of the Skene’s ducts or the whole introital rim. Hypertonic pelvic floor muscles. Pain with attempted digital or speculum entry.</td>
<td>Vaginal EMG biofeedback, pelvic floor physical therapy, (group) CBT, supportive psychotherapy, TENS and vestibulectomy have been shown to have clinical benefit, surgical and behavioural treatments even for a term of years. Based only on CE is treatment with topical estrogen, cromolyn, xylcaine, capsaicin, or botulinum toxoid injections. Based on CE, and the not yet proven assumption that neuropathic pain is at least in part responsible for the pain of provoked vestibulodynia, give TCAs or AEDs. For comorbid IC, DBPTs have shown benefit of oral intravesical pentosan polysulfate, intravesical dimethyl sulfoxide or resiniferatoxin (vallinoid). Based on CE, there may also be benefit from antihistamines, quercetin, intravesical heparin, lidocaine, or a combination.</td>
</tr>
</tbody>
</table>
### Table 25.7: Subtypes of chronic dyspareunia in women and therapeutic options

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Generalized vulvodynia.</strong></td>
<td>Introital dyspareunia and pain with penile-vaginal movement. The pain is always/almost always constant, covers the entire vulvar area, and may or may not be present/increased upon provocation.</td>
<td>None.</td>
<td>Vulvar burning and pain that causes sexual and psychological distress accompanied by the complete absence of any physical abnormality on examination, in biopsies or culture. Based on CE, TCAs or AEDs can be of partial benefit.</td>
</tr>
<tr>
<td><strong>Female genital mutilation (FGM).</strong></td>
<td>Introital pain and with penile-vaginal movement and deep dyspareunia.</td>
<td>Type I: all or part of the clitoris and its prepuce or skin excised. Type II: clitoris excised, labia minora partially or totally removed. Type III: all external genitalia excised, vaginal opening closed except for a match-sized hole to allow urine and blood to escape.</td>
<td>Experienced by an estimated 130 million women, in particular from north Africa, the middle east, and southeast Asia. Most of the studies do not support the hypothesis that FGM destroys sexual function or precludes enjoyment of sexual relations. Based on CE, use a respectful approach and provide information about health consequences. Offer sexual counselling, psychotherapy, and support groups. Offer to repair the vulva, vagina, or both. Involve the partner, the family, or both in decisions. Clarify the legal and ethical responsibility of the physician, who must decline any request to re-infibulate after childbirth. Offer specific management of sexual dysfunction as needed.</td>
</tr>
<tr>
<td><strong>Dermatological diseases.</strong></td>
<td>Can be introital dyspareunia (eg. eczema) or deep (eg. lichen planus affecting vagina.</td>
<td>Benign non-STI: can be atopic eczema, contact dermatitis (including iatrogenic), lichen simplex, lichen sclerosis, lichen planus, psoriasis, hidradenoma, fox-fordyce, chronic vestibular gland infection, pediculosis pubis, pin worm infections, Behçet’s, aphthous ulcers, cicatricial pemphigoid, pyoderma gangrenosum, anorectal Crohn’s, burn, or trauma. STD can be HSV, syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale, condylomata acuminate, or molluscum contagiosum. Neonoplasia can be VIN, vulvar Paget’s, or melanoma.</td>
<td>For a benign non-STI, based on CE, give corticosteroids (oral, topical or injectable); immunosuppressive drugs (azathioprine, dapsone, tacrolimus, pimecrolimus, thalidomide, or infliximab); immune augmentation drugs (imiquimod); surgery; behavioural and physical therapy; and biofeedback. Also offer psychosexual support for sexual problems resulting from limited skin contact, visible symptoms, disrupted self-image, inability to meet a partner, shame, lack of confidence, or a combination of these. For treatment options for STI consult Guidelines from ISTI, WHO and CDC USA. Asymptomatic shedding and further infection necessitate strong encouragement of protective measures and safe sex. For neoplasia attempt surgery, laser therapy with radiation, or chemotherapy, as appropriate. Sexual activities do not stop for most couples. Based on CE, psychosexual counselling can be of benefit, in particular in the first year after treatment.</td>
</tr>
<tr>
<td><strong>Anatomical variations.</strong></td>
<td>Introital or deep dyspareunia depending on abnormality.</td>
<td>Labial fusions, rigid hymen, vaginal septum, vaginal agenesis, or hypoplastic vagina.</td>
<td>Based on CE, in case of vaginal agenesis nonsurgical options can be highly successful. Surgical intervention is recommended for imperforate hymen, labial fusions or a painful vaginal septum.</td>
</tr>
</tbody>
</table>
AEDs=antiepileptic drugs. CBT=cognitive behavioural therapy. DBCT=double blind placebo controlled trials. OT=oestrogen therapy. HIV=human immunodeficiency virus. HS=herpes simplex. IBS=irritable bowel syndrome. PID=pelvic inflammatory disease. STDs=sexually transmitted disease. TCAs=tricyclic antidepressants. VIN=Vulvar intraepithelial neoplasia. PVD=provoked vestibulodynia


C Labrie, F.,et al., Intravaginal dehydroepiandrosterone (Prasterone), the physiological and a highly efficient treatment of vaginal atrophy. Menopause, 2009. 16(5): p. 000-000 DOI: 10.1097/gme.0b013e31819e8e2d


E Labrie, et al., Serum steroid levels during 12-week intravaginal dehydroepiandrosterone administration. Menopause, 2009. 16(5): p. 000-000. DOI: 10.1097/gme.0b013e31819e8930


S Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. MMWR Recomm Rep 2006;55:1094

T World Health Organization. European Guideline on HIV testing 2009

However, persistent lack of sexual desire in spite of significant improvement in sexual frequency has been observed [247]. Therefore, normalizing, reframing and encouraging non-penetrative sexual activity is needed since healing may take several months, and in some cases, years. It is recommended that the couple focus on positive, pleasurable and relaxing sexual activities. Counseling related to (re-)starting a sexual relationship is recommended.

4) **Vaginal EMG Biofeedback, Pelvic Floor Physical Therapy, (Group) Cognitive Behavioral Therapy, TENS and Vestibulectomy (Grade B)**

Given that a reduction in pain during intercourse might be the most relevant treatment outcome criterion for women with PVD, focusing treatment on the tense pelvic floor might be useful. Indeed, it appears that vaginal EMG biofeedback, pelvic floor physical therapy, (group) CBT, including Kegel and relaxation exercises, TENS, mulitilevel local anesthetic nerve blockade and vestibulectomy are useful interventions (level 2b-4b) [247, 248, 314, 396, 397]. Additionally, treatment gains of vestibulectomy are maintained long term [314, 398-402]. This similarity of treatment effect may indicate a non-specific treatment effect in terms of attention, validation, and feelings of control and competence. The active constituents seem to be effective on a meta-level rather than on a content level: HOW you are doing it, may be more important than WHAT you are doing. This phenomenon strongly supports a continuous biopsychosocial conceptualization while treating patients with PVD and other vulvar and pelvic pain conditions. Due to the large number of variables, there is need of an individualized multifaceted therapeutical approach: care made to measure.

5) **Prognostic Factors (Grade C) [271, 314, 385, 398, 403-406]**

The following factors indicate poorer outcome of treatment gains associated with vestibulectomy, biofeedback/physiotherapy, and CBT for PVD and should be addressed in future studies:

a. Characteristics of vaginismus before the surgery
b. Lifelong introital dyspareunia
c. Large amount of surface area involved with allodynia
d. Involvement of the Skene’s duct openings
e. Unwillingness to have sex therapy if offered.
f. The coexistence of candidiasis and vulvar pain
g. Increased pretreatment pain
h. The coexistence of depression and anxiety
i. Erotophobia: the tendency to respond with negative affect to sexual cues
j. Disgust and contamination sensitivity

b) **Vaginismus**

Although vaginismus and PVD often overlap in terms of clinical presentation and may respond to some similar treatment options (e.g., pelvic floor physical therapy, sex therapy), treatment options for vaginismus typically tend to target the muscle spasm over and above the symptom of (feared) pain. As such, the major focus of treatment tends to be vaginal dilatation combined with progressive desensitization and a variety of relaxation techniques [407]. Additional components may also be part of the treatment regimen, ranging from sex education to decreasing penetration fear and anxiety. Some literature on less commonly used adjunct components also exists, and includes educational gynecological examinations [408], the application of topical anesthetics [409], pelvic floor biofeedback [410], botulinum toxin injections [230], anxiolytic medication [411], and surgical intervention [412]. Despite claims that treatment outcome for vaginismus is generally excellent, many treatment studies are methodologically unsound. A Cochrane review concluded that there is very limited evidence for the effectiveness of treatments for vaginismus from controlled trials [227].

Recently, however, an RCT was conducted by van Lankveld and colleagues [6]. Women with lifelong vaginismus (N=117) were randomly assigned to group CBT, bibliotherapy, or a wait-list control group. At post-treatment, 14% of the treated women were able to experience vaginal penetration as compared to none in the control group. At the 12-month follow-up, 21% of the women in the CBT group and 15% of the women in the bibliotherapy group reported successful intercourse. Results also indicated that successful outcome was mediated by changes in fear of intercourse and avoidance behaviors [250]. Based on these results, the investigators conducted a smaller treatment study to determine whether direct exposure aimed at decreasing penetration fears and avoidance behaviors would be effective for women with lifelong vaginismus (N=10). The treatment consisted of a maximum of three 2-hour sessions during a one-week period involving the participant performing vaginal penetration exercises on herself, in the presence of a female therapist. Results indicated that 90% of women were able to experience intercourse after two exposure sessions, and results were maintained at 1-year follow-up [228].

Caution should be taken when dealing with women with vaginismus about their fear of penetration. Although ter Kuile et al. [228] demonstrated that exposure can lead to sustained behavioural change in women with lifelong vaginismus, some patients and health care workers may feel that this process is intrusive. Further studies must be conducted in order to make firm conclusions, especially in terms of whether women with lifelong versus acquired vaginismus would benefit from similar or different treat-
The sexual pain disorders are challenging conditions to treat. Not only do they entail distressing amounts of pain in a ‘private’ area of the body, the pain typically occurs during sexually intimate situations with a partner. Unfortunately, little is known about dyspareunia and vaginismus; the terminology is still under development, classification issues plague the topic, and the empirical literature – while improving – is of relatively low quality overall. To further complicate the picture, clinicians who are faced with affected women struggle with the multidimensional nature of the pain condition, comorbid psychosexual issues, and the often overlapping clinical presentations of dyspareunia and vaginismus.

**2. NEUROBIOLOGY**

A basic understanding of the neurobiology of the pelvic floor is essential in gaining insight into the pathophysiology of the sexual pain disorders and effective treatment options. Although research in this area is still in its infancy, some conclusions from the existing literature (mainly male animal studies) are able to be drawn. The pelvis and pelvic floor are innervated by both divisions of the autonomic nervous system (sympathetic and parasympathetic) and by the somatic motor and sensory nervous systems. Within the pelvis, the inferior hypogastric plexus is the major neuronal integrative center. It has multiple interconnections, innervates many pelvic organs, contains paracervical ganglia, and receives neuronal input from the sympathetic and parasympathetic nervous systems. In terms of the autonomic innervations of the urogenital organs in women, nerve density has been shown to be greater in the distal (versus proximal) vagina and in the anterior (versus posterior) vaginal wall. Interestingly, recent research has demonstrated that the vagus nerves can convey genital sensory input directly to the brain, completing bypassing the spinal cord. Somatic afferent and afferent innervation to the pelvis involves the sacral nerve roots (S2-4) and their ramifications. The sacral nerve roots emerge from the spinal cord, forming the sacral plexus, from which the pudendal nerve diverges. The pudendal nerve divides into upper and lower trunks; the dorsal nerve of the clitoris is derived from the upper trunk.

The vulva is densely innervated by branches of the pudendal nerves, conveying information about gentle and intense mechanical stimulation. The vagina is innervated by the pelvic nerves and responds to gentle and intense stimulation, including noxious stimuli. The cervix and adjacent fornix region of the vagina are innervated more densely than the rest of the vagina by the pelvic and hypogastric nerves. Mechanical probing (non-noxious) of the vagina and/or cervix produces antinoceptive effects in rats and analgesia in women. Importantly, information arriving from the vulva, vagina, and cervix is conveyed to widespread areas of the central nervous system, such that stimulation of these areas can affect many physiological and perceptual functions. The vulvar vestibule contains free nerve endings, and neural hyperplasia in this area has been found in women with PVD; this morphological explanation may help explain the hyperalgesia reported by these patients. Pain arising from within the pelvis and pelvic floor involves diverse structural, neuronal, and neurochemical factors. However, more empirical investigation of these factors is needed in order to fully understand the complexity of mechanisms involved in the sexual pain disorders.

**3. VULVOVAGINAL DISORDERS**

Disorders of the genital skin and mucous membranes are common and interfere with sexual contact, often by causing pain. Most of these disorders, including candidiasis, trichomonas, genital herpes, human papilloma virus infection (HPV), furuncles, recurrent vulvovaginal candidosis infections (RVVC), and infection of the greater vestibular glands are transient and caused by inflammation. Some are chronic conditions, such as lichen simplex, lichen sclerosis, and lichen planus. These inflammatory conditions are easily diagnosed and some can be adequately treated.

Vulvar dermatoses are thought to be due, at least in some cases, to an auto-immune system deficiency. Inflammation of the vulvar skin may arise in response to contact with irritant substances and use of over-the-counter products (e.g., anti-fungal creams), whether prescribed by the health professional or not.

Provoked vestibulodynia (PVD) appears to be diagnosed in the majority of women with superficial, introital pain during (attempted) vaginal penetration; it occurs in up to 18% of women in the general population. The symptoms of PVD may lead to physical, sexual, and psychological distress. It has been suggested that lifelong (primary) PVD and acquired (secondary) PVD differ in etiological, clinical, and genetic variables. The etiology of PVD is considered multi-factorial, and includes inflammatory reactions with T-cell lymphocyte infiltration of the vulvar subepithelium. Women with PVD are more likely to report histories of bacterial vaginosis and candidiasis than asymptomatic controls. The association of (a history...
of) combined oral contraceptives and PVD has met with inconsistent results in prevalence studies. Generalized, unprovoked vulvodynia has been less intensively investigated, and is considered difficult to treat.

4. CHRONIC PAIN PHYSIOLOGY

Pain is a complex sensation involving sensory-discriminative (localization of the stimuli, detection of intensity and quality discrimination), affective-motivational (encompassing emotional reactions, an arousal and selective attention to the painful stimuli) and cognitive-evaluative aspects (anticipation, attention to the painful stimuli and comparison with past experience). The current neuromatrix theory of pain proposes that pain is produced by a characteristic “neurosignature” pattern of nerve impulses generated by the “body-self neuromatrix” in the brain. It proposes that pain results from activity in the neural network rather than directly from sensory input evoked by injury, inflammation, or other pathology, and can therefore occur in the absence of an identifiable, physical cause.

It has been suggested that PVD involves abnormalities in three interdependent systems: the vestibular mucosa, pelvic floor muscles, and central nervous system. Neurogenic inflammation is believed to be involved in PVD, with a bidirectional influence of peripheral inflammation and the nervous system, and a mediating role of vasoactive peptides (substance P, neurokinin A, and calcitonin-gene-related peptide), causing vasodilatation, extravasation of proteins, and release of bradykinin and nitric oxide. These mediators can also cause degranulation of peripheral mast cells, thus releasing histamines and serotonin, and causing a long-lasting lowering of nociceptive thresholds (peripheral sensitization).

Genital pain syndromes appear to be associated with hypersensitivity to both visceral and somatic stimuli. An underlying basis for the local hypersensitivity found in women with PVD has been found in the form of increased innervations and/or sensitization of thermoreceptors and nociceptors in the vestibular mucosa. Increasingly, a widespread hypersensitivity to painful stimuli can also be found in these patients. These findings suggest that pain mechanisms in PVD cannot be solely attributed to peripheral neurogenic inflammation.

Nerve injury from neurogenic inflammation in women with PVD produces non-reversible changes representing neuropathic pain, although other symptoms of neuropathic pain (paraesthesias and dysesthesias) are not commonly reported. Lowered nociceptor thresholds likely reflect peripheral sensitization, caused by the release of chemical inflammatory mediators. Central sensitization has not been verified in experimental research, but the initiation and exacerbations of the pain of PVD after severe stressful life events fits this model.

5. PELVIC FLOOR AND SEXUAL PAIN DISORDERS

Normally, pelvic organs are supported by the pelvic floor musculo-fascial complex. Pelvic floor muscles (i.e., levator ani muscles) consist of anterior and posterior divisions. Several conditions may affect pelvic floor muscle function and result in dyspareunia. For example, pelvic organ prolapse can occur when the pelvic floor muscles are weakened and the endopelvic fascia is stretched or torn. Prolapse can affect the anterior or posterior vagina, or the vaginal vault, and can be resolved via several treatment options involving surgical procedures. However, some treatment avenues can also lead to dyspareunia and decreases in sexual function. In particular, the use of mesh in pelvic floor repair surgery does not appear to entail any clear benefit, and patients undergoing this procedure should be informed of the associated high rate of postoperative dyspareunia.

6. PSYCHOLOGICAL ASPECTS

a) Provoked Vestibulodynia (PVD)

There is evidence of substantial comorbid presence of clinical psychopathology in PVD, especially depression and anxiety. The pervasiveness of these disorders warrants a careful assessment for the purpose of treatment planning. Several studies have documented elevated levels of depression in women with PVD. In terms of anxiety, these patients demonstrate increased attentional bias for pain-related stimuli (thermal and tactile stimulation) and increased catastrophic thinking about genital pain as compared with non-affected women. The level of hypervigilance is largely accounted for by state and trait anxiety levels. In line with this finding, women with PVD report stronger negative feelings toward sexual partner contact. However, results of studies examining sexual arousal responses to erotic stimuli in women with PVD have yielded contradictory results.

Variables that predict better outcome of psychological treatment in women with PVD were higher socioeconomic status, lower education, and childlessness. Willingness to be psychologically evaluated was highly predictive for positive outcome of vestibulotomy, as were cooperation of patient in postoperative counseling, localized disease, acquired vs. lifelong symptoms, absence of vulvodynia, and non-involvement of Skene’s duct openings.

Recent evidence suggest that the two major subtypes of PVD (i.e., primary/lifelong, secondary/acquired) may differ with respect to systemic pain sensitivity, pain thresholds, and levels of pain catastrophizing and trait anxiety. Indeed, various aspects of psychological functioning in women with PVD according to subtype require further study.

b) Superficial dyspareunia not identified as PVD
Similar to PVD, there is substantial comorbid presence of clinical psychopathology in this patient group, especially of depressive and anxiety disorders, relationship discordance, and problems with hostility. The pervasiveness of these issues warrants a thorough assessment to aid in treatment planning.

Vaginismus

Psychological etiological factors underlying vaginismus are not well understood, with some studies demonstrating elevated levels of affective and anxiety-related problems, and others finding equal levels on these dimensions when compared with asymptomatic women.

Successful treatment by means of psychological or psychosocial approaches was predicted by the reduction of penetration phobia and avoidance behavior, the presence of a wish to become pregnant, and better pretreatment relational and psychological functioning. More prospective research with special attention for predictor variables is needed.

7. CLINICAL PRESENTATION

Dyspareunia and vaginismus are prevalent conditions which may arise from multiple factors and affect many aspects of psychosexual function. Unfortunately, the diagnostic process may entail negative effects to the patient and treatment may not effectively manage all the areas of complaint. It is therefore recommended to conduct a thorough assessment of physical and psychosexual factors before, during, and after treatment. Questions pertaining to the pain and affected activities are essential, as are efforts to work with the patient on parameters surrounding the gynecological examination(s).

In patients with sexual pain, the gynecological examination technique is different than that conducted as part of a routine pelvic examination. For example, it may be negotiated that an internal examination will not be performed on the first visit. Once an examination is agreed upon and before it takes place, particular details of the process must be discussed (e.g., who is present in the room, the right of the patient to stop the examination at any point, the preference of the patient to watch the examination with a handheld mirror, and what is going to happen in terms of the examination procedure). During the examination, information about the genital structures should be provided and, if things are different than would be expected, this variability can be directly demonstrated to the patient. The health care professional should also be aware of any self or patient verbal/non-verbal indicators that can hinder the process. These steps form a critical part of the educational gynecological-sexological examination.

8. MANAGEMENT

Sexual pain disorders are heterogeneous, multi-systemic and multifactorial disorders that should be treated in a multimodal way according to etiological factors, risk profile, and context. A management algorithm is proposed comprised of three characteristics.

1) A multidimensional and multidisciplinary approach that focuses on six areas:
   a. the mucous membrane
   b. the pelvic floor
   c. the pain experience
   d. sexual and relationship functioning
   e. psychosocial adjustment
   f. genital mutilation/sexual abuse

2) Individualized treatment
   a. careful history taking
   b. provision of information about the condition, its natural course, possible treatment options and management tips
   c. treatment plan

3) Patient-focused approach; the patient and her partner decide which treatment options are to be pursued:
   a. when considered significant, therapy for individual psychological disorders and/or relationship issues should be offered
   b. preference for a certain approach will depend on the country in question, the woman’s attitudes regarding treatment options, the individual health care systems, and the cost effectiveness of treatment modalities

Treatment modalities for subtypes of chronic dyspareunia in women include chronic pain medications and sexual and psychological counseling.

a) Medical interventions

Only two level 2 placebo-controlled RCTs are available. Fluconazol and Cromolyn 4% did not prove to be more effective than placebo. RCTs of carefully evaluated women who appear to have similar medical and psychological profiles are encouraged to establish the efficacy of these commonly used medical adjuncts.

b) Hygiene measures

Preventive hygienic measures (level 4) include recommendations to avoid the use of soap, vaginal douches, nylon underwear and pantyliners (mini pads), and other irritants (e.g., direct vulvar contact
with semen, wearing tight trousers). The patient is encouraged to drink many fluids to produce sufficient non-concentrated urine daily. Hydration with sitz baths may help reduce inflammation and symptoms.

c) Recommendations regarding sexual activity (Level 5)

Until the pain remits, avoidance of vaginal penetration is recommended in addition to ensuring that semen does not come into contact with the sensitive vulvar areas. Normalizing, reframing, and encouraging non-penetrative sexual activity is encouraged to avoid development of feelings of guilt.

d) Vaginal EMG biofeedback, pelvic floor physical therapy, (group) cognitive behavioral therapy,

TENS and vestibuloplasty are efficacious interventions (level 2b-4b). Treatment gains are maintained long term.

e) Prognostic factors

Poorer outcome of treatment gains associated with vestibuloplasty, biofeedback/physiotherapy, and CBT for PVD are:

- Presence of vaginismus before the surgery
- Lifelong introital dyspareunia
- Large amount of surface area involved with allodynia
- Involvement of the Skene’s duct openings
- Unwillingness to have sex therapy if offered
- The coexistence of candidiasis and vulvar pain
- Increased pretreatment pain
- The coexistence of depression and anxiety
- Erotophobia: the tendency to respond with negative affect to sexual cues
- Disgust and contamination sensitivity

Summary of conclusions and recommendations on Women’s Sexual Pain Disorders

<table>
<thead>
<tr>
<th>Grade</th>
<th>Conclusion</th>
</tr>
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<tbody>
<tr>
<td>1</td>
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### Summary of conclusions and recommendations on Women's Sexual Pain Disorders

| Grade | 
|---|---|
| 11 | In patients with sexual pain, the gynecological examination technique is different from routine pelvic examination. Once an examination is agreed upon and before it takes place, particular details of the process must be discussed with the patient. The health care professional should also be aware of any self or patient verbal/non-verbal indicators that can hinder the process. These steps form a critical part of the educational gynecological-sexological examination. |
| C | 
| 12 | Vulvar or vaginal pain can be assessed via the cotton-swab test, self-report measures, and other methods and devices. Often times, pelvic floor muscle function also needs to be gauged through manual techniques and/or by EMG and other methods. Self-report measures for pain, psychological adjustment, and sexual/relationship function can be administered in order to more carefully assess such issues, compare function to normative populations, guide treatment, and monitor therapeutic efficacy. |
| C | 
| 13 | There is evidence of substantial comorbid presence of clinical psychopathology in PVD, especially depression and anxiety. The pervasiveness of these disorders warrants careful assessment for the purpose of treatment planning. |
| B | 
| 14 | Better outcome of psychological treatment in women with PVD is predicted by higher socio-economic status, lower education, and childlessness. Willingness to be psychologically evaluated was highly predictive for positive outcome of vestibulectomy, as were cooperation of patient in postoperative counseling, localized disease, acquired vs. lifelong symptoms, absence of vulvodynia, and non-involvement of Skene’s duct openings. |
| C | 
| 15 | Successful treatment of women with lifelong vaginismus by means of psychological or psychosocial approaches was predicted by the reduction of penetration phobia and avoidance behavior, the presence of a wish to become pregnant, and better pretreatment relational and psychological functioning. |
| B | 
| 16 | Sexual pain disorders should be treated in a multimodal way according to etiological factors, risk profile, and context. A management algorithm is proposed comprised of three characteristics. 
1) A multidimensional and multidisciplinary approach that focuses on six areas: 
   a. the mucous membrane 
   b. the pelvic floor 
   c. the pain experience 
   d. sexual and relationship functioning 
   e. psychosocial adjustment 
   f. genital mutilation/sexual abuse 
2) Individualized treatment 
   a. careful history taking 
   b. provision of information about the condition, its natural course, possible treatment options and management tips 
   c. treatment plan 
3) Patient-focused approach; the patient and her partner decide which treatment options are to be pursued: 
   a. when considered significant, therapy for individual psychological disorders and/or relationship issues should be offered 
   b. preference for a certain approach will depend on the country in question, the woman’s attitudes regarding treatment options, the individual health care systems, and the cost effectiveness of treatment modalities |
| C | 
| 17 | Preventative hygienic measures that are recommended are: 
   a. avoidance of the use of soap, vaginal douches, nylon underwear and pantyliners (mini pads), and other irritants (e.g., direct vulvar contact with semen, wearing tight trousers) 
   b. daily consumption of sufficient fluid to produce sufficient non-concentrated urine daily 
   c. hydration with sitz baths may help reduce inflammation and symptoms |
| C | 
| 18 | Until the pain remits, avoidance of vaginal penetration is recommended in addition to ensuring that semen does not come into contact with the sensitive vulvar areas. Normalizing, reframing, and encouraging non-penetrative sexual activity is encouraged to avoid development of feelings of guilt. |
| C | 
| 19 | Vaginal EMG biofeedback, pelvic floor physical therapy, (group) cognitive behavioral therapy, TENS and vestibulectomy are efficacious interventions in women with PVD and vaginismus |
| B | 

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Summary of conclusions and recommendations on Women's Sexual Pain Disorders

Grade

20. Poorer outcome of treatment gains associated with vestibulectomy, biofeedback/physiotherapy, and CBT for PVD are:

a. Presence of vaginismus before the surgery
b. Lifelong introital dyspareunia
c. Large amount of surface area involved with alldynia
d. Involvement of the Skene's duct openings
e. Unwillingness to have sex therapy if offered
f. The coexistence of candidiasis and vulvar pain
g. Increased pretreatment pain
h. The coexistence of depression and anxiety
i. Disgust and contamination sensitivity

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Committee 26

Summary of the Recommendations on Sexual Dysfunctions in Men


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Keywords: Erectile dysfunction; Testosterone; Premature ejaculation; Delayed ejaculation; Peyronie’s disease; Priapism; Prostate cancer; Radical prostatectomy; Guidelines
Abstract

Introduction. Sexual health is an integral part of overall health, and sexual dysfunction can have a major impact on quality of life as well as psychosocial and emotional well-being.

Aim. To provide evidence-based and expert-opinion consensus guidelines for the clinical management of sexual dysfunction in men.

Methods. An international consultation in collaboration with major urologic and sexual medicine societies was convened in Paris in July 2009. More than 190 multidisciplinary experts from 33 countries were assembled into 25 consultation committees. Committee members established the scope and objectives for each chapter. Following an exhaustive review of available data and publications, the committees developed evidence-based guidelines in each area.

Main outcome measure. New algorithms and guidelines for the assessment and treatment of sexual dysfunctions were developed. These guidelines were based on the work of the previous consultations and on the evidence coming from the scientific literature published from 2003 to 2009. The Oxford system of evidence-based review was systematically applied. Expert opinion was based on systematic grading of the medical literature in addition to cultural and ethical considerations.

Results. Algorithms, recommendations and guidelines for sexual dysfunction in men are presented. These guidelines were developed in an evidence-based, patient-centered, multidisciplinary manner. It was felt that all sexual dysfunctions should be evaluated and managed following a uniform strategy. Thus, the International Consultation of Sexual Medicine (ICSM-5), a stepwise diagnostic and treatment algorithm for sexual dysfunction in men and women, was developed. The main goal of ICSM-5 is to unmask the underlying etiology and/or indicate appropriate treatment options according to men’s and women’s individual needs (patient-centered medicine) using the best available data from population-based research (evidence-based medicine). Specific evaluation and treatment guidelines and algorithms were developed for every sexual dysfunction in men, including erectile dysfunction; disorders of libido, orgasm, and ejaculation; Peyronie’s disease; and priapism.

Conclusions. Sexual dysfunction in men represents a group of common medical conditions that need to be managed from a multidisciplinary perspective.
1. Introduction

The 2009 International Consultation on Sexual Dysfunctions was convened in Paris in 2009. It identified the following fundamental concepts as the basis for the management of sexual dysfunctions in men and women:

- Sexual health is an integral part of overall health.
- Health care providers should seek, receive, and impart information related to sexuality. Individuals have the right to receive the highest attainable standard of sexual health, including access to sexual and reproductive health care services, as a fundamental sexual right.
- Sexual dysfunctions can have a major impact on quality of life (QoL) as well as psychosocial and emotional well-being.
- The three principles for clinical evaluation and management of sexual dysfunctions are (1) adoption of a patient-centered framework, with an emphasis on cultural competence in medical practice; (2) application of evidence-based medicine in diagnostic and treatment planning; and (3) use of a unified management approach in evaluating and treating sexual problems in both men and women.
- Sexual dysfunctions are essentially self-reported conditions. Therefore, diagnostic tests or procedures should not be recommended without controlled clinical data or research-based evidence supporting their use. The International Consultation of Sexual Medicine (ICSM-5 (Fig. 1)) is a stepwise diagnostic and treatment algorithm for sexual dysfunction in men and women. The main goal of the ICSM-5 is to unmask the underlying etiology and/or to indicate appropriate treatment options according to men’s and women’s individual needs (patient-centered medicine) using the best available data from population-based research (evidence-based medicine).

- Ignorance and knowledge gaps about sexual function and dysfunction are commonplace. Misinformation or myths may lead to uninformed sexual decisions with serious consequences. During the initial phase of assessment, physicians must discriminate among sexual concerns, difficulties, dysfunctions, and disorders.

![Fig. 1 – The steps of the International Consultation on Sexual Medicine (ICSM-5).](image)

SD = sexual dysfunction; QoL = quality of life.
• For clinical purposes, sexual dysfunctions are categorized into three types according to their etiology: type I, psychogenic; type II, organic; and type III, mixed. Types II and III differ according to the absence or presence of significant mental (cognitive) or emotional (affect) distress. In type II dysfunctions, resolution of the main symptom adequately diminishes mental and/or emotional distress, whereas in type III dysfunctions, complementary psychotherapy is indicated.

• Sexual, medical, and psychosocial history is mandatory in every case.

• Physical examination and laboratory tests are strongly recommended but not always necessary.

• Specialized diagnostic procedures for women are less advanced and less widely used than those for men. Diagnostic procedures with the highest level of evidence should be used, when appropriate.

• Improved management of sexual dysfunction depends on physicians' inclination and ability to educate patients about their sexual function and dysfunction.

These principles represent the evolution of scientific thinking in the management of sexual dysfunction in both sexes. They stem from the work done in the previous consultations and the evidence coming from the literature published from 2003 to 2009.

In this article, we report the recommendations for every sexual dysfunction described in men. To facilitate reading of this article, levels of evidence and grading for each recommendation were not included but are detailed in the various articles reporting on the work of every committee. Similarly, references are not included in this manuscript but are accessible in the articles discussing each topic.

2. Erectile dysfunction

2.1. Definition of erectile dysfunction

Erectile dysfunction (ED) is defined as a man’s consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual activity. A 3-mo minimum duration of symptoms is accepted for establishment of the diagnosis. In some instances of trauma or surgically induced ED (eg, following radical prostatectomy [RP]), the diagnosis may be made prior to 3 mo. Objective testing (or partner reports) may be used to support the diagnosis of ED, but these measures cannot substitute for the patient's self-report in classifying the dysfunction or establishing the diagnosis.

2.2. Evaluation of the patient with erectile dysfunction

The 2009 international consultation supports the view that the general framework for the evaluation of patients with any type of sexual dysfunction should follow the same basic principles. The initial steps of patient evaluation, described below, should be applied uniformly regardless of the final diagnosis.

2.2.1. Initiating the discussion

In some circumstances, a single question (eg, “Do you have questions or concerns about your sexual functioning?”) may be sufficient to clarify the patient's primary issue; in other situations, a series of questions is indicated. Sexual inquiry is most often conducted in a face-to-face interview with the patient, although paper-and-pencil questionnaires or Internet-based methods may be of value. The style or manner in which sexual inquiry is conducted is important: It should reflect a high level of sensitivity and regard for each individual's unique ethnic, cultural, and personal background.

The aim of taking a sexual history should be ascertaining the severity, onset, and duration of the problem as well as the presence of concomitant medical or psychosocial factors. It is necessary to determine whether the presenting complaint (eg, ED, anorgasmia) is the primary or major sexual problem or if some other aspect of the sexual response cycle (desire, ejaculation, orgasm) is involved. Other sexual problems may exist as concomitant disorders (eg, hypoactive sexual desire) or as secondary disorders to the primary sexual complaint.

The medical and sexual history is essential and frequently the most revealing aspect of the assessment process. A comprehensive sexual history is essential in confirming the patient's diagnosis as well as in the evaluation of the patient's overall sexual function. Questions apply specifically to the evaluation of male arousal, desire, and orgasm/ejaculation difficulties. In principle, these questions can be addressed to all patients presenting with sexual difficulties.

2.2.2. Medical history

Although not always definitive, a detailed medical history may provide suggestive evidence for or against the role of specific organic or psychogenic factors and should be obtained in all cases of sexual dysfunction. Documenting a medical history has several goals. First, the physician must evaluate the potential role of underlying or comorbid medical conditions. Sexual dysfunction may be symptomatic of an underlying medical disorder, such as
atherosclerosis or diabetes. Second, the physician must actively investigate the possible association with cardiovascular conditions to differentiate among potential organic and psychogenic causes in the etiology of a patient’s sexual problem. Third, the history helps the physician assess the use of concomitant medications. Some of these medications can either cause or contribute to the patient’s sexual difficulties, and a change in medication may result in an improvement in sexual function. Additionally, the use of certain medications may be important contraindications for specific treatments. Medical history may include all medical conditions that could interfere with sexual function.

2.2.3. Psychosocial history

Potential etiologies for sexual dysfunction include a wide range of organic and medical factors, but multiple psychological or interpersonal factors (eg, anxiety, depression, relationship distress) can also be causes. A detailed psychosocial assessment is essential in every case of sexual dysfunction. Given the interpersonal context of sexual problems in men and women, the physician should carefully assess past and present partner relationships. Sexual dysfunction may affect the patient’s self-esteem and coping ability as well as his or her social relationships and occupational performance. These aspects should be assessed in each case.

The physician should not assume that every patient is involved in a monogamous, heterosexual relationship. For this reason, it is advisable to begin the history with broad questions: “Are you sexually active at the moment?” “Do you have a regular sex partner?” Then ask a follow-up question, such as, “Is this a same-sex or opposite-sex relationship?” The early stages in the development of a problem are often of crucial significance to assessment and treatment. Were there particular times of change in the sexual relationship? If so, what events occurred in the patient’s life at those times? In addition, the physician should ask questions about other relevant aspects of the patient’s life, including interpersonal relationships, occupational status, financial security, family life, and social support.

2.2.4. Physical examination

The etiology or causal factors for sexual dysfunction may or may not be apparent from the patient’s history alone. In specific sexual dysfunctions (eg, anatomic problems, ED), further investigation by means of a physical examination and selected laboratory testing may be of value in confirming or ruling out specific etiologies or comorbidities. In most cases, the physical examination will not identify the specific etiology or cause of sexual dysfunction; however, a focused physical examination is strongly recommended. This examination should include a general screening for medical risk factors or comorbidities that are associated with sexual dysfunction, such as body habitus (secondary sexual characteristics) and assessment of the cardiovascular, neurologic, and genital systems, with particular focus on the genitalia and secondary sex characteristics.

The physical examination may corroborate aspects of the medical history and can sometimes reveal unsuspected physical findings (eg, decreased peripheral pulses, atrophic testes, penile plaque). In addition to identifying specific etiologies or comorbidities, the physical examination may provide an opportunity to inform the patient about aspects of his sexual anatomy or physiology as well as to provide reassurance about body appearance and function. It should be recognized that the physical examination can also be a source of shame, embarrassment, or discomfort for many patients. Every effort should be made to ensure the patient’s privacy, confidentiality, and personal comfort during the examination.

The physician should always review the major findings of the examination and should address any questions or concerns of the patient regarding his physical appearance or normality. In some settings, it may be advisable for the physician to perform the physical examination in the presence of a nurse or chaperone.

2.2.5. Laboratory testing

Recommended laboratory tests for men with sexual problems typically include fasting glucose, cholesterol, lipids, and a hormone profile. As with the physical examination, these tests are performed primarily to identify or confirm specific etiologies (eg, hypogonadism) or to assess the role of potential medical comorbidities or concomitant illnesses (eg, diabetes, hyperlipidemia). Additional laboratory tests (eg, thyroid function) may be performed at the physician’s discretion based on the patient’s medical history and the physician’s judgment.

2.2.6. Specialized testing for erectile dysfunction

The classical specialized tests—with the exception of pharmaco-penile duplex ultrasound and measurements of nocturnal penile tumescence or sleep-related erections—are not equipped to specifically and accurately assess cavernosal neuro-endothelial function. On the contrary, these tests frequently do not add to data already available from the medical history and assessments based on patient self-report (eg, self-administered questionnaires, event logs, patient diaries), physical examination, and laboratory testing. At best, they typically confirm an expected diagnosis. Moreover, these tests are expensive, time-consuming, invasive, prone to complications (prolonged erections), and rarely conclusive except in experienced hands. A thorough description of the available specialized test
can be found in the chapter devoted to the evaluation of patients with ED.

2.3. Treatment of erectile dysfunction

2.3.1. Psychological treatment for erectile dysfunction

Psychosexologic literature has made an important contribution to the description, etiology, and diagnosis of ED, but large, randomized, and controlled studies demonstrating the efficacy of the psychotherapeutic treatment are lacking. Psychological treatment of ED consists of a variety of interventions, including psychodynamic interpretations regarding transference or anxiety, systematic desensitization, sensate focus, couples therapy, behavioral assignments, sex education, communication and sexual skills training, and masturbation exercises. It is not clear which of these interventions in combination or alone has the greatest efficacy.

Clinical experience highlights that these interventions help the patient and/or couple to improve their relationship and sexual life. Men with acquired ED demonstrated more gains than men with lifelong ED. Four goals of psychotherapy for ED have been described:

- Reduce or eliminate performance anxiety.
- Understand the context in which men or a couple make love.
- Implement psycho-education and modification of sexual scripts.
- Identify and reduce resistance to premature discontinuation of pharmacotherapy.

2.3.2. Medical treatment for erectile dysfunction

2.3.2.1. Oral agents

Medical treatment for ED has been revolutionized by the advent of phosphodiesterase type 5 (PDE5) inhibitors (PDE5-Is), which virtually represent the unique form of oral treatment for ED. A chapter is completely devoted to discussing all medical therapies for ED, and we report only the final recommendations issued by the responsible committee.

The reason for the clinical efficacy of PDE5-Is is easily understood by considering their effect on the physiology of smooth muscle relaxation. In summary, the normal pathway for penile erection is initiated by sexual arousal, which stimulates release of nitric oxide (NO) at nerve endings in the penis (Fig. 2). Another source of NO is vascular endothelial cells. NO diffuses into vascular smooth muscle cells in the penile corpus cavernosum to cause stimulation of guanylyl cyclase and elevation of cyclic guanosine monophosphate (cGMP) in these cells. This process leads to activation of cGMP-dependent protein kinase G (PKG), phosphorylation of several proteins, and

\[ GTP \rightarrow \text{Guanosine triphosphate} \]
\[ cGMP \rightarrow \text{cyclic guanosine monophosphate} \]
\[ PKG \rightarrow \text{protein kinase G} \]
\[ ATP \rightarrow \text{ADP = adenosine diphosphate} \]
\[ PDE5 \rightarrow \text{phosphodiesterase type 5} \]

**Fig. 2 – Regulation of penile corpus cavernosum smooth muscle relaxation and effect of phosphodiesterase type 5 inhibitors.**

GTP = guanosine triphosphate; cGMP = cyclic guanosine monophosphate; PKG = protein kinase G; ATP = adenosine triphosphate; ADP = adenosine diphosphate; PDE5 = phosphodiesterase type 5.
either lowering of cell calcium or reducing sensitivity to calcium, finally resulting in smooth muscle relaxation. The increased accumulation of blood in the corpus cavernosum caused by this relaxation is the underlying basis for penile erection.

Lack of proper cGMP elevation could be the result (at least in part) of insufficient release of NO from nerve endings or endothelium. PDE5-Is enhance erectile function during sexual stimulation by penetrating into smooth muscle cells and inhibiting PDE5, which is an enzyme that degrades cGMP. This results in decreased degradation of cGMP, which maintains higher cellular levels of cGMP in both corpus cavernosum and the vessels supplying it. This decreased degradation increases relaxation of the smooth muscle, which dilates the corporeal sinusoids, resulting in increased blood flow and allowing an erection to occur. The pathway shown in Figure 2 may not work properly if the cGMP level in corpus cavernosum smooth muscle cells is not elevated sufficiently or if relaxation of smooth muscle in the tissue is deficient or incomplete.

In most countries, the PDE5-Is are the initial form of pharmacotherapy for men with ED. Three such drugs—sildenafil, tadalafil, and vardenafil—are licensed for use around the world. A number of other phosphodiesterase inhibitors are available in a few countries ( udenafil, mirodenafil), and still others (avanafil, lodenafil, SLx-2101) are currently under development (Table 1).

There is robust evidence that PDE5-Is are effective, safe, and well-tolerated therapies for the treatment of men with ED. Most currently available evidence relates to sildenafil, tadalafil, and vardenafil. PDE5-Is are first-line therapy for most men with ED who do not have a specific contraindication to their use. There is no evidence of significant differences in efficacy, safety, or tolerability among the PDE5-Is, but it is important to recognize that patients who are using nitrates cannot use PDE5-Is at the same time.

### Table 1 – Pharmacokinetics of the phosphodiesterase type 5 inhibitors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tadalafil, 20 mg</th>
<th>Sildenafil, 100 mg</th>
<th>Vardenafil, 20 mg</th>
<th>Udenafil, 100 mg</th>
<th>SLx-2101</th>
<th>Avanafil, 100 mg</th>
<th>Mirodenafil, 100 mg</th>
<th>Lodenafil, 160 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;, ng/ml</td>
<td>378</td>
<td>450</td>
<td>20.9</td>
<td>416.2</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>157</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;, h</td>
<td>2</td>
<td>0.8</td>
<td>0.7–0.9</td>
<td>1.1.5</td>
<td>1</td>
<td>0.5–1.5</td>
<td>1.25</td>
<td>1.2</td>
</tr>
<tr>
<td>T1/2, h</td>
<td>17.5</td>
<td>3–5</td>
<td>4–5</td>
<td>11–13</td>
<td>9–14</td>
<td>&lt;1.5</td>
<td>2.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>–</td>
<td>40%</td>
<td>14.5%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

C<sub>max</sub> = maximum plasma concentration; T<sub>max</sub> = time to maximum plasma concentration.

### 2.3.2.2. Local therapies

The dawn of the age of pharmacologic treatment began 25 years ago with the recognition that vasoactive drugs, when injected into the penile erectile tissue, were capable of initiating and maintaining erection. Currently, alprostadil, papaverine, and the combination phenolamine plus vasoactive intestinal polypeptide are the main licensed agents for intracavernosal injection (ICI) therapy. Alprostadil is also available as an intrarectal suppository.

Both ICI and intrarectal therapy with alprostadil are effective and well-tolerated treatments for men with ED. It is recognized that the intrarectal route of administration is less effective than the intracavernosal route. Local therapies are considered second-line therapy and should be considered in patients in whom PDE5-Is are not effective and in men who have contraindications to their use. ICI should not be used in men with conditions that predispose them to priapism—most notably, men with sickle cell disease, multiple myeloma, and leukemia. Anticoagulation, however, is not a contraindication to ICI.

### 2.3.3. Vacuum constriction devices

Vacuum constriction devices (VCD) are ED treatment devices that use negative pressure to engorge the penis with blood while constriction rings artificially trap blood in the penis. VCDs are a safe and effective form of therapy for men with ED. The British Society for Sexual Medicine Guidelines, an evidence-based guideline for the diagnosis and treatment of ED, concluded that oral pharmacotherapy with PDE5-Is and VCDs are the first-line therapy for ED. However, one has to recognize that a number of studies have reported that erections obtained with a VCD are unnatural and therefore are distinctly different from physiological erections. The most common VCD side effects are painful ejaculation, inability to ejaculate, generalized pain, petechiae, bruising, and numbness.
Serious complications from VCD use are rare but include penile skin necrosis, urethral varicosities, capture of scrotal tissues within the penile shaft, development of Peyronie’s disease, and Fournier’s gangrene. The importance of proper patient selection improves outcome results, as confirmed by the experience of a number of authors. VCDs may be offered preferentially to elderly patients who partake in limited intercourse attempts versus younger patients, who document lower preference for VCDs because of unnatural erections and cumbersome application.

2.3.4. Surgical treatment for erectile dysfunction

2.3.4.1. Arterial revascularization

Many retrospective studies report outcome data for penile revascularization surgery for arteriogenic ED. These studies are limited by variable inclusion and exclusion criteria, short length of follow-up, and lack of objective follow-up data. Young men who have sustained traumatic arterial lesions appear to have better outcomes compared to elderly patients.

No comparative prospective, randomized studies have assessed the outcome of penile revascularization surgery for arteriogenic ED. Based on the evidence within the literature, this surgery may be offered to men younger than 55 years of age who are nonsmokers and nondiabetic, who have no evidence of venous leakage, and who demonstrate an isolated stenosis of the internal pudendal artery.

2.3.4.2. Surgery for cavernous veno-occlusive dysfunction

At the time of this writing, cavernous veno-occlusive dysfunction (CVOD) surgery in the management of ED remains controversial, and the weight of available evidence is contrary to routine use as a treatment option for ED. CVOD surgery, as it is practiced today, does not conform to the desiderata of good clinical practice or evidence-based medicine. The normal diagnostic values for available tests, universal diagnostic criteria for case selection for surgery, and consensus on choice of operation in a given patient have not been unequivocally established. This said, although CVOD surgery is still considered investigational, it may be offered in special situations, such as for young patients with site-specific congenital, post-traumatic, or postinflammatory venous leaks. If CVOD surgery is undertaken, the physician should be required to follow an operated patient long term (48 months).

2.3.4.3. Penile prosthetic surgery for erectile dysfunction

A patient would currently be considered a good candidate for a penile prosthesis if he had failed medical therapy or if medical therapy were contraindicated and the other therapies (eg, penile injections, intraurethral therapy, VCDs) have also failed or do not satisfy the patient. Patients who eventually opt for an implant are usually highly motivated to continue with sexual activity.

In many instances, the physician helps the patient decide which prosthesis type to choose. This decision is usually based on the physician’s comfort with the surgical approach, assessment of body habitus, manual dexterity of the patient, and overall cost. Patients with a larger penis will be best served by a three-piece inflatable device, as these devices deliver the best rigidity. Similarly, patients with shorter penises often choose the three-piece device because semirigid rods and two-piece implants are more difficult to conceal. Patients with limited manual dexterity or those who have difficulty manipulating hydraulic devices are directed toward a semirigid rod. An exception to this rule is when a motivated partner manipulates the hydraulic device for the patient.

It is important for the patient receiving a three-piece inflatable implant to understand that the postimplant size of his penis will invariably be slightly shorter than his natural erection when he was fully potent. Also, unlike a normal erection, the prosthetic erection does not result in an increase in the size of the glans. Preoperative consultation with the implant candidate should explain this loss of length but emphasize that the girth of the penis may be greater than a natural erection and that girth, not length, is responsible for penile rigidity.

Sensitivity of the penis, ejaculatory abilities, and sexual drive are for the most part unchanged following placement of a prosthesis. The patient needs to clearly understand that penile implants only restore the ability to penetrate. They do not restore any special sensitivity or sexual drive that may have been present in earlier years. If the cylinders are removed at a later date, the capsule remains, and the empty space will partially fill with proliferating scar tissue. This may make it difficult for the patient to respond adequately to other treatments, such as medication or a VCD.

It is important that the patient have realistic expectations for his penile prosthesis. Along this line of reasoning, the patient should be informed of the following possible complications related to the prosthesis prior to implantation: infection and its consequences, pain, mechanical failure, penile shortening, and autoinflation. Numerous studies have shown high satisfaction rates for both patients and partners.
2.4. Clinical correlates between erectile dysfunction and coronary artery disease

When dealing with the ED patient, the following considerations should be always discussed in detail: (1) ED and coronary artery disease (CAD) share the same risk factors, (2) sexual activity for couples in a stable relationship does not increase cardiac events, (3) sex is not an undue stress to the heart, (4) men with ED should have their CAD risks assessed and treated, (5) sexual activity safety can be assessed using noninvasive stress testing, and (6) exercise stress testing and computed coronary angiography can be used to detect occult CAD.

The correlation between ED and the metabolic syndrome should also be considered with attention and discussed with the ED patient taking the following points into account: ED is closely linked to the metabolic syndrome, and the metabolic syndrome is associated with hypogonadism and reduces the effectiveness of PDE5-Is. Testosterone should be measured when the metabolic syndrome is present.

2.5. Clinical correlates between testosterone deficiency and erectile dysfunction

Testosterone deficiency (TD) is a clinical and biochemical syndrome frequently associated with age and comorbidities and is characterized by a deficiency in testosterone and relevant symptoms. It may affect the function of multiple organ systems and result in significant detriment to QoL, including alterations in sexual function. The clinical manifestations of TD are variable. Sexual dysfunction, particularly hypoactive sexual desire, ED, and delayed ejaculation, are prominent and often the presenting symptoms. Visceral obesity is often associated, and muscle mass and very likely bone mineral density are diminished. Diminished strength and alterations in spatial cognition and mood may be associated.

Physical examination is frequently unhelpful, but small testicular size, alterations in testicular consistency and hair distribution, gynecomastia, and small prostate size can be detected. It is important to recognize that cardiovascular disease is often associated with low testosterone. All men with TD as well as all men over 40 years of age or those younger with a strong family history should have their cardiovascular risk factors assessed and addressed.

Although a number of questionnaires have been proposed to support screening for or diagnosing TD, they typically show good sensitivity but low specificity. The diagnosis of TD must be based on both symptoms and serum testosterone values. Although there are no generally accepted lower limits of normal total testosterone (TT), there is general agreement that TT >12 nmol/l (3.5 ng/ml or 350 ng/dl) does not usually require substitution, whereas men with TT <8 nmol/l (2.3 ng/ml or 230 ng/dl) usually benefit from testosterone treatment. Between these levels, measuring free testosterone by equilibrium dialysis or calculating it from TT and sexual hormone-binding globulin levels may be helpful. A lower limit of 225 pmol/l (65 pg/ml) is accepted by many experts.

The indication to start testosterone therapy must be based on a clear clinical picture together with evidence of hypogonadism. Absence of an appropriate response after adequate testosterone treatment for 3–6 months calls for further investigation to rule out associated comorbidities.

Current commercially available preparations of testosterone (with the exception of the 17α-alkylated options) are safe and effective. The treating physician should have sufficient knowledge and adequate understanding of the advantages and drawbacks of each preparation. Finally, the patient should be given the opportunity to actively participate in the choice of testosterone formulation. The contraindications and cautions for the use of testosterone remain controversial. Testosterone therapy is contraindicated in men with clinical evidence of prostate cancer (PCa) until more evidence on safety is available; that said, there is no compelling evidence that testosterone treatment causes PCa or PCa progression in noncastrated men. Men with significant erythrosis (hematocrit >52%) or severe symptoms of bladder outlet obstruction should not start testosterone therapy without prior improvement in the comorbid condition.

2.6. Clinical correlates between erectile dysfunction and radical prostatectomy

It is becoming increasingly recognized that a number of sexual dysfunctions may occur after RP, the most commonly used treatment for clinically localized PCa. These dysfunctions include ED, libido reduction, changes in orgasm, anejaculation, penile size changes, and possibly Peyronie’s disease. These sexual dysfunctions should be extensively discussed with the patient prior to surgery.

It is recommended that physicians use a validated instrument with recognized cut-offs for normality and severity in their preoperative and postoperative evaluation of erectile function in their patients. Physicians should discuss the recognized predictors of erectile function recovery: patient age, baseline erectile function, and nerve-sparing status. It should also be pointed out to patients that other factors such
as comorbidity status and surgeon experience have been shown to be significant contributors to recovery. Physicians must provide patients with a realistic time frame for recovery of erectile function.

**Penile rehabilitation** is defined as the use of a medication, a combination of medications, or devices (alone or in combination with medication) in the early stages after RP. The goal of rehabilitation is to maximize preservation of all components of the local erectile mechanism and optimize recovery of erectile function. It is recommended that based on the strong animal and basic science evidence, understanding the strengths and weaknesses of the existing human studies and the negative consequences of long-term ED after RP, physicians should discuss with patients that penile rehabilitation has significant potential benefits for the patient or partner and should be considered after RP.

No specific recommendations regarding the structure of the optimal rehabilitation regimen can be given. Unfortunately, numerous variables remain undefined with regard to the ideal rehabilitative approach. These variables include defining the best time to start rehabilitation after RP; the frequency of medication use, specifically daily versus on-demand exposure, the best dosing schedule (low dose vs maximum dose), the duration of rehabilitation after its commencement, and the strategies used (PDE5-Is, ICI, transurethral prostaglandin suppository, vacuum therapy). Unfortunately, no definitive evidence exists favoring one rehabilitation strategy over another.

### 3. Orgasm and ejaculation disorders in men

#### 3.1. Premature ejaculation

##### 3.1.1. Definition of premature ejaculation

In August 2007, the International Society for Sexual Medicine convened a panel of experts to review criteria for premature ejaculation (PE; Table 2). This panel proposed the following evidence-based definition of lifelong PE: “ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences such as distress, bother, frustration and/or the avoidance of sexual intimacy.” The panel concluded that there was insufficient evidence to propose definitions for acquired PE, although it is recognized that men with acquired PE have acquired this disorder at some point after experiencing normal ejaculatory latencies and that onset may be either sudden or gradual. The appearance of PE may be the result of urologic dysfunctions, thyroid dysfunction, or psychological or relationship problems.

The possibility that other sexual problems coexist with PE should be investigated routinely. Although most men with lifelong PE do not suffer from concomitant ED, PE coexists in about one-third of patients complaining of ED. In some instances, PE and ED may form a vicious cycle in which a man trying to control his ejaculation instinctively reduces his level of excitation (which can lead to ED) or a man trying to achieve an erection basically attempts to do so by increasing his excitation and arousal (which can lead to PE). Although reduced time to ejaculation is only rarely an early manifestation of ED, it may occur when the man has an unstable erection because of a fluctuation in penile blood flow. In this case, the man may reach ejaculation quickly to compensate for the weak erection.

##### 3.1.2. Evaluation of premature ejaculation

Men with PE should be evaluated with a detailed medical and sexual history; a physical examination; and appropriate investigations to establish the true presenting complaint, identify obvious biologic causes such as medication or recent pelvic surgery, and uncover sufficient detail to establish the optimal

| Table 2 – The four premature ejaculation syndromes |
|-----------------|-----------------|-----------------|-----------------|
| Variable        | Lifelong PE     | Acquired PE     | Natural variable PE |
| IELT            | (<1–1.5 min)    | (Very) Short IELT (<1.5–2 min) | (3–8 min)          |
| Frequency       | Consistent      | (In)consistent  | Inconsistent     |
| Etiology        | Neurobiologic and genetic | Medical psychological and/or Normal variation of ejaculatory performance |
| Treatment       | Medication with or without counseling | Medication psychotherapy and/or Psycho-education, reassurance |
| Prevalence      | Low             | Low             | High             |

PE = premature ejaculation; IELT = intravaginal ejaculation latency time.
treatment plan (Fig. 3). The following relevant information should be obtained from the patient:

- A basic medical history, including the use of prescribed and recreational medications
- The cultural context and developmental history of the disorder, including whether the PE is global or situational, lifelong or recent in its development
- Quality measures of each of the three phases of the sexual response cycle (desire, arousal, and ejaculation); the desire and arousal phases may affect the ejaculatory response
- Details about the ejaculatory response, including the patient’s subjective assessment of his intravaginal ejaculatory latency time (IELT) and sense of ejaculatory control, the level of sexual dissatisfaction and distress, and the frequency of sexual activity
- The partner’s assessment of the situation, including whether the partner suffers from female sexual dysfunction
- Assessment of the sexual and overall relationship

3.1.3. Treatment of premature ejaculation
3.1.3.1. Psychological therapy

Present-day psychotherapy for PE is an integration of psychodynamic, systems, behavioral, and cognitive approaches within a short-term psychotherapy model. The guiding principles of treatment are to learn to control ejaculation while understanding the meaning of the symptom and the context in which it occurs. Besides teaching self-control techniques to delay ejaculation, modern psychosexual therapies try to achieve the following aims:

- Help the patient recover his self-confidence and confidence in his sexual performance.
- Reduce performance anxiety.
- Solve relational problems.
- Increase communication between the partners.
- Resolve interpersonal issues that precipitate and maintain the dysfunction.

In addition, psychotherapists seek to modify rigid sexual repertoires and help the couple remove

Figure 3 – Management algorithm for premature ejaculation.

*IELT = intravaginal ejaculatory latency time; PE = premature ejaculation; ED = erectile dysfunction.*
3.1.3.2. Medical treatment for premature ejaculation

The efficacy and safety of off-label daily dosing of selective serotonin reuptake inhibitors (SSRI; paroxetine, sertraline, citalopram, fluoxetine) and the serotonergic tricyclic, clomipramine, and off-label on-demand dosing of clomipramine for the treatment of PE is well established. Within this group of drugs, a meta-analysis of published data suggests that paroxetine (an SSRI) exerts the strongest ejaculatory delay. The use of SSRIs is limited by the lack of approval by the US Food and Drug Administration, the European Medicines Agency, or other regulatory agency and therefore must be prescribed off label. Recently, dapoxetine has been officially approved in Europe and other extra-European countries for the on-demand treatment of PE. The efficacy and safety of dapoxetine is well established. The decision to treat PE with either current off-label SSRI daily dosing or on-demand dosing of dapoxetine must be based on the treating physician’s assessment of individual patient requirements.

The efficacy and safety of off-label on-demand topical anesthetic agents in the treatment of PE has also been shown. The efficacy and safety of off-label on-demand or daily dosing of PDE5 is has been shown in the treatment of lifelong PE in men with normal erectile function, although the level of evidence is lower. There is no evidence to suggest that selective dorsal nerve neurotomy or hyaluronic acid gel glans penis augmentation are effective treatments for PE. Surgery may be associated with permanent loss of sexual function and is contraindicated in the management of PE.

3.2. Orgasmic dysfunction

3.2.1. Definition of orgasmic dysfunction

Orgasmic dysfunction is the inability to achieve an orgasm or markedly diminished intensity of orgasmic sensations; it can also be the marked delay of orgasm during any kind of sexual stimulation. There can be self-report of high sexual arousal or excitement in this disorder, and orgasmic dysfunction can occur together with ejaculatory function.

Delayed ejaculation (DE), retarded ejaculation, and inhibited ejaculation (IE) are probably the least common, least studied, and least understood male sexual dysfunctions. Yet, the impact of these conditions is significant in that they typically result in a lack of sexual fulfillment for both the man and his partner, an effect further compounded when procreation is among the couple’s goals for sexual intercourse. Problems with “difficulty” in ejaculating may include varying delays in the latency to ejaculation as well as the complete inability to ejaculate (anejaculation). Reductions in the volume, force, and sensation of ejaculation may occur. At the extremes are anejaculation (time) and retrograde ejaculation (direction) but IE and DE are more commonly encountered. Partially retarded ejaculation (PRE) is sometimes observed in men who attempt to control ejaculation by suppressing the muscular contractions associated with ejaculation. These men experience diminished pleasure and sensation as semen is released during emission, and the ejaculatory sensations are dulled through attempted suppression of striate muscle response. PRE is sometimes observed in men with PE as they first attempt to consciously delay their orgasm. A final disorder, anorgasmia, refers to a perceived absence of the orgasm experience, independent of whether any or all of the physiologic concomitants of ejaculation have taken place. In this paper, we briefly summarize the main principles in the management of DE (Fig. 4).

3.2.2. Evaluation of delayed ejaculation

Treatment should be etiology specific and should address the issue of infertility in men of a reproductive age. If a man has difficulty with ejaculation, a small volume of ejaculate, or absent ejaculation, it must first be established whether the problem is congenital or acquired and whether organic factors are implicated. Assessment begins by reviewing the conditions under which the man is able to ejaculate—for example, during sleep, with masturbation, with stimulation of the partner’s hand or mouth, or infrequently with varying coital positions. The course of the problem is documented, and variables that improve or worsen performance are noted. Questions concerning the man’s ability to relax, sustain, and heighten arousal and the degree to which he can concentrate on sensations are posed.

If orgasmic attainment had been possible previously, the life events and circumstances temporarily related to orgasmic cessation are reviewed. The events in question may be pharmaceutical or related to congenital problems, illness, trauma, or a variety of life stressors and other psychological factors (eg, following his wife’s mastectomy, the man is afraid of hurting her and therefore is only partially aroused). Societal and religious attitudes that may interfere with excitement are noted, such as the spilling of seed as a sin. Finally, questions
concerning the quality of the nonsexual relationship are posed and problems explored. This assessment, in conjunction with appropriate physical examination and laboratory results, will provide understanding and help determine an appropriate treatment path.

3.2.3. Treatment of delayed ejaculation

As indicated previously, before considering a psychological or behavioral approach toward the treatment of DE, physicians need to exclude probable iatrogenic and pathophysiologic causes. They should be alert for various medical conditions as well as medications that might delay ejaculation and, in the case of antidepressants, consider a reduction in dose or use of an antidote (Table 3). Vascular or neuropathic damage that causes DE is usually irreversible; therefore, the patient might be counseled to seek alternative methods to achieve mutual sexual satisfaction with his partner. Androgen deficiency—another potential cause for DE—requires appropriate testosterone replacement therapy.

Regardless of whether a clear pathophysiologic cause is present or absent, patients might be counseled to consider lifestyle changes, including enjoying more time together to achieve greater intimacy; minimizing alcohol consumption; making love when not tired; and practicing techniques that maximize penile stimulation, such as pelvic floor training. Patient education regarding existing factors that can exacerbate DE is an important first step and may represent a segue into either short-term or long-term counseling. Treatment of DE or IE with pharmaceuticals has met with limited success. No drugs have been approved by regulatory agencies for this purpose, and most drugs that have been identified for potential use have limited efficacy, impart significant side effects, or are considered experimental in nature.

4. Priapism

4.1. Definition of priapism

Priapism is an uncommon medical condition in men that is defined as an unwanted erection not associated with sexual desire or sexual stimulation and lasting for more than 4 hours. Three different types of priapism are recognized, although there may be some overlap among these categories. Ischemic
or veno-occlusive priapism is the most common form of priapism and is associated with a failure of detumescence, increasing anoxia, and ultimately necrosis of the cavernous muscle if untreated. It is an example of the compartment syndrome and requires urgent treatment. Nonischemic or high-low priapism is less common than the first type and often occurs following blunt straddle injury of the penis. It may also be congenital or idiopathic in origin. The third type, recurrent or stuttering priapism, commonly occurs in men with sickle cell disease but is not confined to them. Such priapism is usually starts with a high-flow state but may become typical ischemic priapism.

4.2. Diagnosis of priapism

Careful history and physical examination are sufficient in most cases to make the diagnosis and classification of priapism. The physical examination should focus on the rigidity of the penis, the severity of pain, and the presence of potential causative or comorbid factors, such as secondary tumors in the penis.

An initial corporal blood aspirate is essential to differentiating ischemic from nonischemic priapism. A corporal blood gas test (if this technology is available) on the initial aspirate is recommended in the emergency evaluation of priapism. Color Doppler ultrasonography (if this technology is available) of the penis and perineum is recommended in the evaluation of priapism when the history or examination suggests penile trauma.

4.3. Ischemic priapism (veno-occlusive)

4.3.1. Treatment of ischemic priapism

The recommended initial treatment for ischemic priapism is the decompression of the corpora cavernosa by aspiration. Aspiration immediately softens the erection and relieves pain, and it should be repeated until no more dark blood can be seen coming out of the corpora and fresh, red blood is obtained. This process of repeated aspiration leads to a marked decrease in the intracavernous pressure and resuscitates the corporal environment, removing anoxic, acidic, and hypercarbic blood.

Aspiration should be followed by the intracavernous injection of a sympathomimetic drug. Worldwide availability of adrenergic agents varies, and effective reversal of priapism has been documented with dilute injections of ephedrine, epinephrine, etilefrine, metaraminol, or phenylephrine. Regardless of the intracavernous sympathomimetic agent chosen for the management of ischemic priapism, physicians should consult their pharmacies and develop clear mixing and dosing protocols for safe administration. Some sympathomimetic drugs are activators of both α- and β-adrenergic receptors. Significant α-

<table>
<thead>
<tr>
<th>Drug</th>
<th>Symptom</th>
<th>Dosage</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>As needed Daily</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Anorgasmia</td>
<td>100–400 mg (for 2 d) 75–100 mg bid or tid</td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td></td>
<td>libido</td>
<td>prior to coitus</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Anorgasmia</td>
<td>75–150 mg</td>
</tr>
<tr>
<td>Buspirone</td>
<td>Anorgasmia</td>
<td>15–60 mg</td>
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<tr>
<td>Cyproheptadine</td>
<td>Anorgasmia</td>
<td>4–12 mg</td>
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<td></td>
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<tr>
<td></td>
<td>libido</td>
<td>On demand</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>Anorgasmia</td>
<td>5.4–10.8 mg</td>
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<tr>
<td></td>
<td>libido</td>
<td>5.4 mg tid</td>
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ED = erectile dysfunction; bid = twice daily; tid = three times daily.

Table 3 – Adjunctive drug therapy for selective serotonin reuptake inhibitor–induced sexual dysfunction

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mediated effects on peripheral vasculature and β-mediated ionotropic and chronotropic effects on the heart may occur.

During ICI of sympathomimetic drugs, the physician should monitor the patient for subjective complaints and objective findings consistent with known undesirable effects of sympathomimetic agents: headache, chest discomfort, acute hypertension, reflex bradycardia, tachycardia, palpitations, and cardiac arrhythmia. Patients (and parents of child patients) should be informed about these potential complications. Blood pressure monitoring is recommended if repeated sympathomimetic dosing is given in an attempt to reverse ischemic priapism. In patients with significant cardiovascular risks, a medication history should be taken, and electrocardiogram monitoring is recommended.

Ischemic priapism associated with sickle cell disease requires intracavernous treatment. A hematologist may provide concurrent systemic therapies, but the best resolution rates are achieved with therapies directed at the penis. Oral therapy is not recommended for the treatment of acute ischemic priapism.

Shunt surgery should be considered for all cases of veno-occlusive priapism failing aspiration and ICI of sympathomimetics. Patients should be counseled that erectile function outcomes decline significantly when priapism has lasted longer than 24–36 hours and that complete ED is anticipated if priapism persists for longer than 36 hours. In men presenting with ischemic priapism longer than 48 hours in duration or failing interventions for up to 48 hours, severe ED is inevitable. Consideration may be given to implantation of a penile prosthesis after 48–72 hours of unresolved ischemic priapism.

4.3.2. Treatment of stuttering ischemic priapism

The goals of managing a patient with stuttering ischemic priapism are prevention of future episodes, preservation of erectile function, and balancing of risks versus benefits of various treatment options. A trial of either daily oral sympathomimetic therapy (α-adrenergic) or PDE5-I therapy may be used in the management of patients (adults and children) with stuttering ischemic priapism associated with hemoglobinopathies. Androgen ablation therapy is also an effective therapy. Dosing efficacy should be monitored and may need adjustment.

4.4. Nonischemic priapism (high-flow, arterial)

In the management of nonischemic priapism, corporal aspiration has only a diagnostic role. Aspiration with or without injection of sympathomimetic agents is not recommended as treatment. Color Doppler ultrasonography (if this technology is available) of the penis and perineum is recommended in the evaluation and management of high-flow priapism. The initial management of nonischemic priapism may be observation. Immediate invasive interventions (embolization or surgery) can be performed at the request of the patient but should be preceded by a thorough discussion of the chances for spontaneous resolution, the risks of treatment-related ED, and the lack of significant consequences expected from delaying (immediate) interventions. Penile arteriography should be reserved for the management of high-flow priapism when embolization is elected.

Selective arterial embolization is recommended for the management of nonischemic priapism in patients who request treatment. Autologous clot and absorbable gels, which are not permanent, are preferable to coils and ablative chemicals, which are permanent.

5. Peyronie’s disease

5.1. Definition of Peyronie’s disease

Peyronie’s disease is considered a wound-healing disorder that presents with a fibrous inelastic scar of the tunica albuginea; it is currently believed to occur in genetically susceptible individuals following some form of trauma to the penis. A palpable scar develops in the flaccid state and causes a variety of deformities in the erect state, including curvature, shortening, narrowing, and hinge effect. In the early phase, an inflammatory component often causes pain. This inflammatory pain tends to resolve with time, but because of the deformity, intercourse may be compromised or impossible. Peyronie’s disease is also frequently associated with ED and a variety of other comorbid disorders, including diabetes, hypertension, dyslipidemia, and low testosterone.

5.2. Evaluation of Peyronie’s disease

The diagnosis of Peyronie’s disease is usually apparent from the patient history and penile examination. A detailed history should be obtained focusing on onset, duration, pain, deformity, and presence of ED. This data collection can be facilitated by using a disease-specific questionnaire. Plaque measurement is inaccurate by any modality and is operator dependent; therefore, it is not a reliable assessment for treatment response. An assessment of the curvature on erection is best made by an ICI of a vasoactive agent. This test is more accurate than a home photograph or a vacuum-assisted erection
test. Dynamic duplex ultrasound—a useful but unnecessary test—provides assessment of plaque calcification, vascular flow parameters, and objective measures of deformity. It is imperative that the stretched penile length be measured preoperatively so that the patient realizes that the length loss postoperatively is mainly the result of the disease itself, not the surgery.

5.3. Treatment of Peyronie’s disease

5.3.1. Nonsurgical treatment

Men with early-phase disease (ie, longer than 12 months in duration) manifest by unstable or progressive deformity and painful erections as well as those men not psychologically ready or interested in surgery may be considered candidates for nonsurgical therapy. In general, nonsurgical treatment has limited evidence of benefit, but multiple reports of deformity stabilization or reduction make it reasonable to offer electromotive drug administration and/or intralesional injection of verapamil or interferon and/or traction therapy.

5.3.2. Surgical treatment

Surgery remains the gold standard for correcting erect penile deformity in the man with stable disease. Surgical reconstruction is indicated for the man who has had stable disease for more than 6 months, painless deformity, compromised ability or inability to engage in coitus secondary to deformity, and/or inadequate rigidity when there is extensive plaque calcification as well as for the man who desires the most rapid and reliable result. Preoperative consent is critical to setting proper outcome expectations for the patient. It is imperative to have a discussion about the risks of persistent or recurrent curvature, loss of erect length, diminished rigidity, and decreased sexual sensation. Several surgical algorithms have been published, with general agreement that for men with adequate preoperative rigidity, some form of tunica plication procedure is best for those with curvature of less than 60° and with no hourglass deformity resulting in a hinge effect. For those with more severe deformity (more than 60° and/or hourglass) and good preoperative rigidity, incision or partial excision and grafting is recommended. Penile prosthesis implantation with additional maneuvers to correct the deformity is recommended when there is preoperative ED that is not responsive to oral medication (PDE5-Is).

6. Penile trauma

6.1. Definition of penile fracture

Penile fracture is defined as the traumatic rupture of the tunica albuginea. It usually occurs during sexual intercourse when the erect penis is thrust against the partner’s symphysis pubis or perineum.

6.2. Evaluation of penile fracture

A careful history and physical examination are essential. The classical presentation includes a cracking sound at the moment of injury, a sharp pain, detumescence, swelling, and ecchymosis. The typical appearance has been described as eggplant deformity or aubergine sign by some authors. A palpable defect in the tunica albuginea can occasionally be felt, but usually the swelling conceals this sign. It is important to remember that a concomitant urethral injury—partial or complete—may occur in 2–20% of patients. Imaging (cavernosography, ultrasound, or magnetic resonance imaging) can be used for localization of the injury, whereas retrograde urethrogram (preoperative or perioperative) can be performed if a urethral injury is suspected. The ultimate decision for surgery is based on clinical findings; once diagnosed, there is no indication for conservative management.

6.3. Treatment of penile fracture

Conservative management of a penile fracture with catheterization, compression dressings, analgesia, antibiotics, and erection-inhibiting agents should be avoided. Once penile fracture is diagnosed, surgical exploration is widely accepted as the gold standard therapeutic option, even in the event of a delayed presentation (48 hours after injury).

7. Penile augmentation and lengthening surgery

This area of research and practice is controversial because an increasing number of patients now present with an anatomically normal penis that the patient perceives to be inadequate in size. The risk of performing unjustified surgery in these cases is obvious.

Both penile lengthening and augmentation techniques have been described with variable success rates. A critical analysis of the pertinent literature, however, does not reveal proven efficacy outcome data. On the contrary, findings clearly demonstrate that the complications related to these procedures may be significant. Stretching devices may be viable alternative treatment options, whereas liquid silicone injection should be discouraged. It is mandatory to recommend that the patient to undergo a thorough psychological assessment prior to considering any surgical approach.

A penis with stretched length of <7 cm should be
considered a micropenis. These patients should undergo a thorough multidisciplinary assessment. Many surgical techniques are recommended for these rare cases.

### 8. Sexually transmitted infections

There is a paucity of state-of-the-art information about sexually transmitted infections (STIs) affecting sexual function. The problem is underscored by high prevalence rates: It is estimated that 35% of adult men suffer from sexual dysfunctions and that 340 million people live with STIs.

Patients with HIV frequently suffer from sexual dysfunctions due to both pathology (ie, HIV lipodystrophy and HIV neuropathy/encephalopathy) and HIV therapies (ie, highly active antiretroviral therapy). HIV-associated sexual dysfunction is ideally addressed by a multidisciplinary team, and the importance of education as a protective factor against HIV must be emphasized.

PDE5-Is prescribed for ED, as well as recreational drugs and unprotected sexual behavior, may play a role in HIV transmission among HIV-infected and HIV-negative men having sex with men. Disclosure of HIV status among partners should be encouraged (especially with newly regained erectile function following PDE5-I or sexual-aid use), and stigmatizing attitudes should be discouraged to promote voluntary counseling and testing. Male circumcision will reduce the risk of acquisition of HIV in heterosexual men and is not associated with high-risk sexual behavior (disinhibition).

Patients with frequent recurrences of genital herpes should be evaluated on a regular basis for coexisting psychological and psychosexual illness and given appropriate treatment including possible continuous antiviral medications. *Chlamydia trachomatis*, gonorrhea, and human papillomavirus may also be associated with sexual dysfunction, but more information is needed before causality can be established.

Prostatitis and chronic pelvic pain syndrome (CPPS) are associated with sexual dysfunction. The severity of the pain and illness in acute bacterial prostatitis interferes with sexual function. Chronic bacterial prostatitis (CBP) and CPPS are frequently associated with ejaculatory pain or premature ejaculation (77%) as well as with ED in 15–72% of cases. The efficacy of PDE5-Is for amelioration of the symptoms of prostatitis in patients with CBP or CPPS and disturbed sexuality remains unclear.

### 7. Conclusion

The 2009 International Consultation on Sexual Dysfunctions in men convened all the recognized experts in the field and produced evidence-based guidelines and an evaluation-treatment algorithm. It is recognized that most patients with any of the known sexual dysfunctions should be approached in a multidisciplinary fashion. The contemporary sexual medicine expert must be knowledgeable in many scientific areas, including urology, andrology, endocrinology, and internal medicine. The patient's psychological perspective remains a key parameter to be considered for successful management of these conditions.
Committee 27

Recommendations for Women’s Sexual Dysfunction

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**Keywords:** Female sexual dysfunction, diagnosis and treatment of women's sexual dysfunction, desire disorder, arousal disorder, orgasm disorder, sexual pain disorder

**ABSTRACT**

**Introduction:** Women's sexual dysfunction includes reduced interest/incentives for sexual engagement, difficulties with becoming subjectively and/ or genitaly aroused, difficulties in triggering desire during sexual engagement, orgasm disorder and sexual pain.

**Aim:** To update the recommendations published in 2004, from the 2nd International Consultation on Sexual Medicine pertaining to the diagnosis and treatment of women's sexual dysfunctions.

**Methods:** A 3rd International Consultation in collaboration with the major sexual medicine associations assembled over 186 multidisciplinary experts from 33 countries into 25 committees. Twenty one experts from 6 countries contributed to the Recommendations on Sexual Dysfunctions in Women.

**Main Outcome Measure:** Expert opinion was based on grading of evidence-based medical literature, widespread internal committee discussion, public presentation and debate.

**Results:** A comprehensive assessment of medical, sexual and psychosocial history is recommended for diagnosis and management. Indications for general and focused pelvic genital examination are identified. Evidence based recommendations for further revisions of definitions for sexual disorders are given. An evidence based approach to management is provided.

**Conclusions:** There remains a need for more research and scientific reporting on the optimal management of women’s sexual dysfunctions including multidisciplinary approaches.

**Keywords:** Female sexual dysfunction, definition, diagnosis and treatment of women’s sexual dysfunction, desire disorder, arousal disorder, orgasm disorder, sexual pain disorder

**Running Title:** Recommendations for Women’s Sexual Dysfunction
Recommendations for Women’s Sexual Dysfunction

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JACQUES VAN LANKVELD PHD, LORI BROTON PHD

I. INTRODUCTION

The current conceptualization of women’s sexual function emphasizes the responsive component of women’s desire. The circular model depicted in Figure 1 explains our current understanding of how desire is triggered during the sexual engagement thereby adding to any initial desire. Research confirms that women provide a variety of reasons and incentives for engaging in sexual activity. Sexually competent stimuli are integral to a sexual response and must always be assessed when considering a diagnosis and formulation of dysfunction. Women’s sexual dysfunction includes reduced interest/incentives for sexual engagement, difficulties with becoming subjectively aroused and/or genetically aroused and difficulties in triggering desire during sexual engagement. Frequently, all of these aspects are involved. Orgasmic disorder denotes sexual experiences consistently associated with high arousal but absence of orgasm. Other dysfunctions include pain and difficulty with attempted or completed intercourse or any attempts at vaginal penetration.

II. DEFINITIONS OF SEXUAL DISORDER IN WOMEN

The available evidence suggests that there are problems with existing definitions of sexual desire, arousal, and orgasmic disorders in women. The proposed definitions that were sponsored by the AUAF in 2003 present alternative criteria for these disorders: currently these are recommended for the clinical setting. Given the upcoming publication of the DSM-V in 2012, it is likely that the current diagnostic criteria for these disorders will change. GRADE B

1. SEXUAL DESIRE/INTEREST DISORDER
   (OR HYPOACTIVE SEXUAL DESIRE DISORDER; HSDD IN THE DSM-IV-TR)

There are absent or diminished feelings of sexual interest or desire, absent sexual thoughts or fantasies and a lack of responsive desire. Motivations (here defined as reasons/incentives) for attempting to

FIGURE 1: Circular sexual response cycle of overlapping phases may be experienced many times during any one sexual encounter. Desire may or may not be present initially: it is triggered by the arousal to sexual stimuli. The sexual and nonsexual outcomes influence future sexual motivation.

Copied with permission from Lippincott Williams & Wilkins from Figure 2: R. Basson. Female Sexual Response: The role of drugs in the management of sexual dysfunction. The American College of Obstetricians and Gynecologists 2001;98(2):350-352.
become sexually aroused are scarce or absent. The lack of interest is considered to be beyond the normative lessening with lifecycle and relationship duration.

Apparently innate desire (or experienced desire where the stimuli are not evident to the woman) present before sexual engagement begins is sometimes present for women, especially early in relationships and sometimes associated with menstrual periods. However, this definition of sexual desire disorder argues that its absence does not equate to dysfunction.

**a) Arousal disorder (or Female Sexual Arousal Disorder; FSAD in the DSM-IV-TR)**

Somatically-healthy women diagnosed with sexual arousal disorder usually show a normal vasocongestive response in the genitalia in response to erotic sexual stimulation, when tested in a controlled laboratory environment. Thus, it is these women’s lack of subjective arousal that is key to their distress, rather than failure of genital congestion.

It is recommended that subtypes of sexual arousal disorder are recognized: subjective sexual arousal disorder, genital sexual arousal disorder, combined genital and subjective arousal disorder and persistent genital arousal disorder. Of note, it is the woman’s self-report of absent or impaired genital congestion and lubrication that is the basis of these definitions and psychophysiological testing would be necessary to identify any actual reduction of congestion.

**b) Subjective arousal disorder**

There is absence of or markedly diminished feelings of sexual arousal (sexual excitement and sexual pleasure) from any type of sexual stimulation. Vaginal lubrication or other signs of physical response still occur.

**c) Genital sexual arousal disorder**

There are complaints of impaired genital sexual arousal. Self-report may include minimal vulvar swelling or vaginal lubrication from any type of sexual stimulation and reduced sexual sensations from caressing genitalia. Subjective sexual excitement still occurs from non-genital sexual stimuli.

A woman diagnosed with the genital subtype of arousal disorder indicates that she can still be subjectively aroused by, for instance, viewing an erotic film, or pleasuring her partner, being kissed or receiving breast stimulation. She complains of the marked loss of intensity of any genital response including orgasm. Awareness of throbbing/swelling/lubrication is absent or markedly diminished. Moreover, loss of sexual quality of sensations despite apparently adequate engorgement can occur and is poorly understood.

**d) Combined genital and subjective arousal disorder**

There is absence of or markedly diminished feelings of sexual arousal (sexual excitement and sexual pleasure), from any type of sexual stimulation as well as complaints of absent or impaired genital sexual arousal (vulval swelling, lubrication). It is the lack of the subjective excitement from any type of sexual stimulation that distinguishes these women from those with genital arousal disorder.

**e) Persistent genital arousal disorder**

There is spontaneous, intrusive and unwanted genital arousal, e.g. tingling, throbbing, and pulsating, in the absence of sexual interest and desire. Any awareness of subjective arousal is typically but not invariably unpleasant. The arousal is unrelieved by one or more orgasms and the feelings of arousal persist for hours or days.

The disorder is poorly understood but becoming a more frequently recognized syndrome. More research is needed on its prevalence, etiology, and effective treatments.  

2. **WOMEN’S ORGASMIC DISORDER (OR FEMALE ORGASMIC DISORDER; FOD IN THE DSM-IV-TR)**

Despite the self-report of high sexual arousal/excitement, there is either lack of orgasm, markedly diminished intensity of orgasmic sensations or marked delay of orgasm from any kind of stimulation.

3. **DYSPAREUNIA (DYSPAREUNIA IN THE DSM-IV-TR)**

There is persistent or recurrent pain with attempted or complete vaginal entry and/or penile vaginal intercourse.

It is recommended the experience of women who cannot tolerate full penile entry and the movements of intercourse because of the pain, be included in the definition of dyspareunia. Clearly, it depends on the woman’s pain tolerance and her partner’s hesitancy or insistence.

4. **VAGINISMUS (VAGINISMUS IN THE DSM-IV-TR)**

There are persistent or recurrent difficulties for the woman to allow vaginal entry of a penis, a finger, and/or any object, despite the woman’s expressed wish to do so. There is often (phobic) avoidance, involuntary pelvic muscle contraction and anticipation/fear/experience of pain. Structural or other physical abnormalities must be ruled out/addressed.
III. RECOMMENDATIONS REGARDING FURTHER CHANGE TO DEFINITIONS

Recommendation for HSDD:
The currently accepted definition of HSDD in women is highly problematic and the emphasis on sexual fantasies and desire for sexual activity is not applicable to all sexually healthy women. We recommend that desire be regarded as the result of an incentive (sexually competent stimulus) which activates the sexual system where subjectively perceived desire is one of many components. GRADE C

Recommendation for FSAD:
The focus on “lubrication/swelling response” in the DSM-IV-TR definition of FSAD is highly problematic given that this is rarely the complaint motivating treatment seeking. Moreover, there is minimal, if any, correlation between subjective and genital sexual arousal. Given the importance of “adequate sexual stimuli” for sexual arousal and desire, this should be assessed clinically when evaluating whether or not an arousal or orgasm disorder is present. GRADE C

IV. ASSESSMENT OF WOMEN’S SEXUAL DYSFUNCTION

The framework for assessment of sexual dysfunction is to assess predisposing, precipitating and maintaining factors. When there is a current sexual relationship (and if appropriate), both partners need to be evaluated to understand the aforementioned factors. A biopsychosocial approach is recommended. Current contextual factors are commonly etiologically important. For lifelong sexual dysfunctions, developmental history and past relationships are also commonly etiologically relevant.

1. MEDICAL AND PSYCHOSOCIAL HISTORY

A comprehensive medical and psychosocial history is highly recommended for all sexual dysfunctions (Table 1) GRADE C. Further assessment of the woman is recommended if she discloses a history sexual abuse. This includes assessment of the woman’s recovery from the abuse (with or without past therapy): identify any history of major depression, substance use disorders, significant anxiety, self-harm or promiscuity, any inability to trust people, especially those of the same gender as the perpetrator or an exaggerated need for control or need to please (and inability to say no). When there are concerns about residual abuse-related symptoms, assessment of the sexual dysfunctions per se are deferred temporarily.

When assessing arousal disorders, it is recommended to clarify which component(s) of arousal is absent/problematic. This will allow sub-typing of the arousal disorder so as to guide choice of therapy. For assessment of women’s arousal and orgasmic concerns it is recommended to assess the following: Is there adequate and acceptable stimulation with her partner and/or with masturbation? Is the degree of trust and safety she feels she needs present? Are orgasms wanted but absent and/or very delayed and/or markedly reduced in intensity?

In the case of dyspareunia and vaginismus, clarification of the aspects of the woman’s pain, her fear of pain, and avoidance responses are recommended. (Table 2)

A detailed medical enquiry with review of systems is highly recommended for all sexual dysfunctions (Table 1). This would include screening for depression as regardless of antidepressant use depression is consistently related to sexual dysfunction, particularly to low sexual desire. GRADE C

2. ASSESSMENT OF DYSFUNCTION IN THE CONTEXT OF CHRONIC ILLNESS

The multiple factors contributing directly or indirectly to sexual dysfunction require assessment. Included are alterations in response from the disease itself, its treatment, associated pain, immobility, fatigue as well as impairment of self image, loss of independence, of continence and of fertility and difficulties with partnerships imposed by the disease.

3. PHYSICAL EXAMINATION

The genital exam is often highly informative, can be very therapeutic, but its intimate nature demands there must be a reason for its inclusion. A focused pelvic genital exam is highly recommended in the following circumstances:

• For women with dyspareunia, especially those with lifelong pain and difficulty with penile entry, an educational exam is recommended.

• For women with vaginismus diagnosed from the history, confirmation is obtained by an exam done in progressive stages once fear of vaginal entry has lessened with therapy: an educational exam is advocated.

• For women with genital arousal disorder, information will be limited because the genitalia are in a non-aroused state, but estrogen deficiency, or more rarely, disease such as connective tissue disorder, can be identified.
### Table 1: Components of a Comprehensive Sexual, Medical, Psychosocial History

<table>
<thead>
<tr>
<th></th>
<th>BIOLOGICAL</th>
<th>PSYCHOSOCIAL</th>
<th>SEXUAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Establish current general health</td>
<td>Establish current mood and mental health.</td>
<td>Establish the sexual difficulties in her own words (e.g., cannot become aroused, always has pain with intercourse).</td>
</tr>
<tr>
<td>Present context</td>
<td>Clarify current medications/substance use, level of fatigue, presence of non-sexual pain.</td>
<td>Identify nature and duration of current relationship. Societal values/beliefs impacting the sexual problems.</td>
<td>Clarify the context when activity is attempted, including type of sexual stimulation, the woman's feelings towards her partner at the time, the safety and privacy of the situation.</td>
</tr>
<tr>
<td>Past Context</td>
<td>Establish past medical history</td>
<td>Particularly for lifelong sexual problems, it is often necessary to at least briefly clarify developmental history, particularly relationships with caregivers, siblings, traumas, and losses, and ability to form attachments.</td>
<td>Clarify past sexual experiences alone and partnered, wanted, coercive and abusive.</td>
</tr>
<tr>
<td>Onset</td>
<td>Document past medical details at time of onset of sexual problems.</td>
<td>Clarify circumstances, including relationship and psychological contributors, at time of onset of sexual problems.</td>
<td>Enquire if there was a time when the above sexual problems were not present (when was that time and what were the sexual circumstances)</td>
</tr>
<tr>
<td>Generate full picture of her current sexual response</td>
<td>If relevant medical context is present, obtain details re effects on sexual activity, e.g. cardiac compromise, or neurological deficit.</td>
<td>Evaluate personality factors including control issues, ability to express non-sexual emotions.</td>
<td>Establish the rest of the sexual response cycle (sexual interest, arousal, orgasm, satisfaction, and freedom from pain associated with sexual stimulation or intercourse)</td>
</tr>
<tr>
<td>Role of the partner</td>
<td>Clarify partner's medical health</td>
<td>Clarify partner’s mood and mental health, partner’s reaction to sexual problems</td>
<td>Establish her partner’s sexual response cycle.</td>
</tr>
<tr>
<td>Distress</td>
<td>Level of distress regarding medical issues.</td>
<td>Level of distress regarding psychosocial issues.</td>
<td>Reaction to the sexual difficulties, degree of distress</td>
</tr>
</tbody>
</table>
• For women with combined arousal disorders likely there will be no abnormality. Nothing arouses these women mentally/subjectively be it written, visual, non-genital physical stimulation and the evidence to date is that their genital response is healthy. Nevertheless, a “normal” exam is highly informative to the woman. It is also possible that a woman with combined arousal disorder goes on to become estrogen deficient – adding physical vulvar atrophy to her longstanding problems of disconnection from genital events.

2 Pelvic floor muscle tension
Do you recognise the feeling of pelvic floor muscle tension during sexual contact?
Do you recognise the feeling of pelvic floor muscle tension in other (non-sexual) situations?

3 Arousal
Do you feel subjectively excited when you attempt intercourse? Does your vagina become sufficiently moist? Do you recognise the feeling of drying-up?

4 Consequences of the complaint
What do you do when you experience pain during sexual contact? Do you still continue to include intercourse or attempts at intercourse, or do you use other ways to make love instead? If so, are you both clear intercourse will not be attempted?
What consequences does the pain have on the rest of your sexual relationship?

5 Biomedical antecedents
When and how did the pain start? What tests have been done? What treatment have you received?

* Substitute dildo/fingers for “penis” when necessary.

Table 2: Assessment of Sexual Pain

| 1 Pain | Where does it hurt? How would you describe the pain? Is the pain with penile* contact to the opening of your vagina, once the penis is partially in, with full entry, after some thrusting, after deep thrusting, with the partner’s ejaculation, after withdrawal and for how long, with subsequent micturition? Do you find your body is tensing when your partner is attempting, or you are attempting to insert his penis? What are your thoughts and feelings at this time? How long does the pain last? Does touching cause pain? Does it hurt when you ride your bicycle or when you wear tight clothes? Do other forms of penetration hurt (tampons, fingers)?
| 2 Pelvic floor muscle tension | Do you recognise the feeling of pelvic floor muscle tension during sexual contact? Do you recognise the feeling of pelvic floor muscle tension in other (non-sexual) situations?
| 3 Arousal | Do you feel subjectively excited when you attempt intercourse? Does your vagina become sufficiently moist? Do you recognise the feeling of drying-up?
| 4 Consequences of the complaint | What do you do when you experience pain during sexual contact? Do you still continue to include intercourse or attempts at intercourse, or do you use other ways to make love instead? If so, are you both clear intercourse will not be attempted? What consequences does the pain have on the rest of your sexual relationship?
| 5 Biomedical antecedents | When and how did the pain start? What tests have been done? What treatment have you received?

* Substitute dildo/fingers for “penis” when necessary.

• For women with combined arousal disorders likely there will be no abnormality. Nothing arouses these women mentally/subjectively be it written, visual, non-genital physical stimulation and the evidence to date is that their genital response is healthy. Nevertheless, a “normal” exam is highly informative to the woman. It is also possible that a woman with combined arousal disorder goes on to become estrogen deficient – adding physical vulvar atrophy to her longstanding problems of disconnection from genital events.

• For women with neurological disease affecting pelvic nerves where a detailed neurological genital exam is also necessary, clarify light touch, pressure, pain, temperature sensation, anal and vaginal tone, voluntary tightening of anus, and vaginal and bulbocavernosal reflexes.

• For women with a history of pelvic trauma.

• For women with any disease potentially affecting genital health.

• For women with acquired and lifelong orgasmic disorder even if otherwise healthy. A normal examination is of reassurance value.

• When the history indicates the opportunity for Pap smear/STI investigation should be taken.

GRADE C

A general physical exam is highly recommended as dictated by the general medical enquiry, for women with chronic illness and as part of good medical care, for example evaluation of blood pressure, breast exam etc. GRADE C

Although frequently no laboratory investigations are needed for assessment of the sexual dysfunction per se, certain situations may require laboratory testing and are guided by the general medical assessment, for example, fasting blood glucose or TSH. When an infective etiology for dyspareunia is possible, vaginal, cervical and vulval discharge microscopy/cultures should be performed. When investigational testosterone therapy is contemplated, accurate assay of baseline serum testosterone via mass spectrometry methods is recommended (see subsequent discussion).

4. PSYCHOPHYSIOLOGICAL ASSESSMENT OF AROUSAL

Psychophysiological tools are available but typically reserved for the research setting. Observation of the genital arousal response to adequate stimulation by means of audiovisual, cognitive (fantasy) and/or vibrotactile stimuli may be useful. However, it is important to note that this often does not correlate with the woman’s subjective report of (impaired) sexual arousal. Although psychophysiological testing to date is not a routine assessment, such a test may be crucial in establishing the etiology of arousal disorder. Recent study has demonstrated how difficult it is to rule out that sexual arousal problems are not caused by a lack of adequate sexual stimulation. Moreover, women with sexual arousal disorder may be less aware of their own genital changes; thus, they lack...
adequate proprioceptive feedback that may further increase their arousal. A normal genital response demonstrated in the laboratory would clarify the lesser importance of any identified organic factors potentially contributing to the arousal problem of the individual. The evidence is that sexual arousal problems in medically healthy women are more often related to inadequate sexual stimulation due to personal, contextual, and/or relational variables than to somatic causes. (Of note, nonresponse in the psychophysiological assessment does not automatically imply organicity. The woman may have been too nervous or distracted for the stimuli to be effective, or the stimuli offered may not have matched her sexual preferences.)

5. SELF REPORT MEASURES

The Female Sexual Function Index is currently the most often used measure. Diagnostic cut off scores were developed by means of sophisticated statistical procedures. Together with a Female Sexual Distress Scale score of 11 or higher, indicating distress, there is some evidence to suspect a diagnosis of sexual dysfunction. Use of self-report measures alone is not recommended for clinical purposes because they lack sensitivity and specificity with regard to etiology. Unfortunately, and contrary to evidence from epidemiological and qualitative research, current validated questionnaires are based on the assumption that (distressing) absence of sexual desire ahead of and at the outset of sexual engagement represents dysfunction in all women.

V. FORMULATION OF WOMEN’S SEXUAL DYSFUNCTIONS

Predisposing, precipitating and maintaining factors should be assessed and often the etiology is multifactorial (Table 1). Common psychosocial issues include a fear of letting go control, fear of negative outcome, inability to stay present, and lack of or inaccurate information regarding women’s sexual response. Graham and Bancroft describe a “three windows” approach helpful for contextualizing factors influencing the sexual complaint (Figure 2). These three ‘windows’ echo the descriptors recommended by the AUA committee in 2003. The first window describes aspects of the woman’s current situation (e.g., poor communication, relationship difficulties, fatigue, or lack of useful stimuli). The woman plagued with fatigue might benefit from a course of sleep hygiene therapy prior to (or instead of) sex therapy. The second window is to individual vulnerability factors influencing the presentation of complaints. These include the woman’s persistently negative

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attitudes about herself and her body, a high need to maintain control in all life and sexual situations, a past history of sexual abuse or trauma such that flashbacks to the prior abuse are frequent and intrusive when she is attempting to be sexual. If such individual vulnerability factors are present, she may benefit from cognitive behavioral (CBT) treatment focused on that vulnerability factor (e.g., it is focused on the sexual assault, perfectionism, etc.) The third window views health-related factors influencing the sexual response, importantly, depression or anxiety. Included also are problems in the neural control of desire, arousal, and pain perception, problems in vascular supply to the genitals, endocrine dysfunction, and metabolic problems as well as both over-the-counter and prescription medications. The role of deficiency in estrogens and androgens continues to be debated. There is minimal evidence that serum levels of estradiol or testosterone are linked to desire or subjective arousal but assays other than mass spectrometry have been used and these are unreliable at the low testosterone levels found in women. Future studies should measure serum testosterone by mass spectrometry methods in women with and without diagnosed sexual dysfunction GRADE C. Moreover serum levels do not reflect intracrine sex hormone production – the major source of androgen and only source of estrogen in post menopausal women. Future studies should also measure total testosterone activity by means of androgen metabolites in women with and without definite dysfunction GRADE C.

A formulation of the diagnoses is recommended. The formulation integrates all information obtained from (sometimes a series of) in-person assessments of the woman with and without a partner, and any relevant physical examinations, blood assays, psychophysiological testing, and self-report questionnaires GRADE C. On the basis of the formulation, a diagnosis is applied, preferably using both the DSM-IV-TR as well as the AUAF systems. The clinician also continues to modify the formulation as information emerges during treatment. The "three windows" approach can be very helpful for considering the many biopsychosocial factors that influence the woman's sexual complaints. An effort should be made to determine the duration and severity of symptoms and to speculate on level of insight and prognosis.

VI. MANAGEMENT OF WOMEN'S SEXUAL DYSFUNCTION

General recommendations; GRADE C

Some investigational pharmacological agents are being used to treat specific sexual disorders. The lack of long-term safety data should always be openly discussed. It is recommended that the clinician has an interdisciplinary approach. Research is needed to identify efficacious combined/integrated treatments for sexual dysfunction. Even when sexual function has been healthy prior to medical insult, there are psychological and interpersonal repercussions plus sexual adaptations that may or may not be useful: medical management alone may be insufficient.

General issues related to improved emotional and physical well-being such as addressing depression or anxiety symptoms, possible alcohol or chemical substance use, insuring adequate sleep, exercise and healthy diet should first be addressed. Advise also on prescription and non-prescription medications and supplements. Referral to appropriate medical or specialty providers may be necessary especially in the context of chronic disease or significant psychological symptoms. The early stage of treatment might also include providing education on sexual response, basic genital anatomy and physiology, and a discussion of sexual stimulation and sexual activities other than intercourse. Patients should be encouraged to use techniques that enhance arousal including enhancing the sexual context and stimuli.

VII. MANAGEMENT OF DESIRE AND COMORBID COMBINED AROUSAL DISORDERS

Discussion of the normality of age and relationship duration-associated declines in sexual drive is a logical first step in treating the woman with distressing low desire. The clinician can provide a current understanding of how desire is triggered and that women have a variety of reasons and incentives for sexual engagement, encouraging the woman to consider her own reasons for sexual activity and challenging her belief that “sex should only happen when I’m in the mood”. For women with a DSM-IV-TR diagnosis of HSDD but who retain the ability to become sexually excited during the encounter thereby triggering desire, this process of discussing incentives for sexual activity is especially important and often sufficient. For women with sexual interest/desire disorder (with associated arousal disorder) discussion of the components of women’s sexual response depicted in Figure 1, and identifying problematic areas may be sufficient to allow women and their partners to make the needed changes (Level 4). For other women, however, more intensive strategy will be required.

1. PSYCHOSEXUAL TREATMENT FOR DESIRE AND AROUSAL DISORDERS

There are few outcome studies but our general recommendation is that when the low desire is better
accounted for by depression, poor body image, sexual abuse sequelae or other more general personality, individual, or relationship factors, then those factors must be addressed initially. **GRADE C**

Psychological management of desire and arousal disorder might include cognitive behaviour techniques (CBT) and traditional sex therapy.

CBT is based on the theory that thoughts, feelings, and behaviors interact and mutually influence one another. By targeting negative or maladaptive thoughts, both behaviors and affect can improve and disrupt the dysfunctional cycle. The behavioral component includes attending to a problematic sexual context or behaviours in either partner which reduce attractiveness or trust and ability to focus on the sexual stimuli and feelings. The cognitive component of CBT targets maladaptive thoughts that foster negative emotions and maintain problematic behavior such as avoidance. This may include identifying and challenging beliefs that she is unattractive, idealizing an unrealistic mode of sexual response portrayed by media, or challenging beliefs that unless she feels a high level of desire all the time, then she is dysfunctional. Group CBT improves sexual desire disorder in 74% of couples and this effect was maintained in 64% at one year (Level 2).

A modified Masters and Johnson sex therapy was also found to improve sexual function in 57% of women with sexual desire disorder (Level 3).

Other psychological modalities have also been investigated and may target more distant factors in the woman’s history such as unresolved themes from childhood including abuse or neglect, control issues, low sexual self image. There has been only one published study using such an approach, however, there was a benefit to sexual desire in women (Level 3).

More traditional sex therapy stems from the work of Masters and Johnson and Kaplan and includes sensate focus exercises consisting of exchanging physical touch, moving from non sexual to sexual areas of the body, with partners taking turns and giving verbal and tactile feedback. Among the very limited available empirical literature, one study showed that 65% of 365 married couples improved by clinical judgment at the end of therapy (Level 3).

Most recently, a mindfulness-based CBT administered to women in group format with desire and arousal disorder has also been explored in an uncontrolled trial. Mindfulness is an eastern practice with roots in Buddhist meditation which focuses on present moment, non-judgmental awareness. Women were taught in-session mindfulness exercises and encouraged to practice for approximately 5 hours during the 2 weeks between each of the four sessions. This resulted in significant improvements in sexual desire, arousal and other domains of sexual response and mood (Level 3). One non-controlled trial of mindfulness-based CBT for women with genital arousal disorder secondary to gynecologic cancer found significant improvements in sexual response, distress, and mood (Level 3).

**2. RECOMMENDATION RE MANAGEMENT OF LOW DESIRE:**

Psychological approaches to low desire have a long history and have been found to be effective immediately after treatment with sustained improvements over time. Moreover, they are without adverse side effects. Newer cognitive-behavioural treatments which integrate mindfulness meditation have shown excellent promise for sexual desire problems but await randomized controlled testing. There is also evidence that brief cognitive behavioural interventions are helpful for improving desire. Overall there is an urgent need for more randomized controlled investigations of psychological therapy for women’s low desire/ interest disorders. **GRADE C**

**3. RECOMMENDATION RE MANAGEMENT OF LOW AROUSAL:**

Despite our support for evidence-based practice, careful management of women with sexual problems according to the rules of “good clinical practice” must continue without solid proof of efficacy. There is one noncontrolled trial showing benefit of mindfulness-based CBT for genital arousal disorder in women secondary to gynecologic cancer. There is clearly great need for controlled efficacy studies in this area. From our review we conclude that the majority of sexual arousal problems in healthy women are not related to impaired genital responsiveness: it follows that we recommend psychological treatment for arousal disorder. **GRADE C**

**VIII. HORMONAL TREATMENT OF LOW DESIRE AND LOW AROUSAL**

**1. TESTOSTERONE**

Randomized trials of transdermal testosterone have mostly targeted surgically and naturally menopausal women. Both sudden loss of ovarian androgens and the inevitable decline in adrenal sex hormone precursors might predispose to desire and arousal disorders. However the evidence is inconclusive. Prospective studies have not confirmed sexual dysfunction subsequent to surgical menopause for benign disease. Distress about low desire is more prevalent in relatively recently surgically menopausal women, but not low desire per se. The prevalence of low desire may increase with age, but low desire associated with distress changes little with age.

A review of testosterone trials among estrogen replete surgically and naturally menopausal women
found that those women receiving the 300µg/day patch reported an increase in sexually satisfying events of 1.9 per month vs. 0.9 events per month from placebo and statistically significant increase in desire for sex.

Notably, in all of the recent testosterone trials, a strict entry criterion was a certain baseline frequency of satisfactory sexual activity and most women experienced 2-3 sexually satisfying episodes per month. Compared to the majority of women seeking treatment for sexual difficulties, where sexual frequency may take place on a once every several month basis, women recruited for research trials have a much higher level of sexual response and frequency. It is unknown if testosterone therapy would be of benefit to the large majority of women seeking treatment for sexual desire concerns. Moreover, what also remains unknown is whether testosterone treatment would significantly benefit women meeting the AUAF definitions of Sexual Desire/Interest Disorder, where there is lack of interest for sexual activity but also a failure to become sexually excited during the sexual interaction to trigger same desire.

Despite its lack of approval in the USA, many women seek out testosterone therapy for problematic low desire. Formulations for men are adapted or compounded preparations are prescribed whose safety and/or efficacy have not been evaluated. Testosterone patches are approved for use in compounded preparations are prescribed whose safety and/or efficacy have not been evaluated. Testosterone patches are approved for use in surgically menopausal women in Europe. We recommend that the clinician and patient should engage in a careful discussion of the benefits and hazards of such treatment GRADE C. Whether breast cancer and cardiovascular disease would be increased is unclear GRADE C.

**Summary of recommendations on testosterone therapy**

The decision to use must be individualized and patients informed about risks and benefits Grade C. The testosterone patch appears to be effective in the short term in postmenopausal women with HSDD Grade B. Patients must be informed about lack of long term safety data Grade C. Additional studies are needed before long term use is recommended Grade C. Use of testosterone in pre- and perimenopausal women is not supported by current data Grade A. Achieving physiological testosterone levels by transdermal delivery minimizes adverse effects Grade C-D. Relative contraindications include androgenic alopecia, acne, hirsutism hyperlipidemia and liver dysfunction Grade C. Absolute contraindications include presence or high risk of breast cancer, endometrial cancer, venothrombotic episodes, cardiovascular disease Grade C.

Monitoring should include annual breast and pelvic examinations, annual mammography, evaluation of abnormal bleeding, evaluation for acne, hirsutism and androgenic alopecia. Monitor testosterone by mass spec, (SHBG, calculated free T) with goal of not exceeding normal values. Consider lipid profile, liver function tests, complete blood count. Use for more than 6 months is contingent on clear improvement and absence of adverse effects GRADE C.

2. **ESTROGEN**

There is evidence that treatment with local and systemic estrogen benefits vulvo-vaginal atrophy and relieves vaginal dryness and dyspareunia (Level 1).

3. **LOCAL DHEA**

A recent RCT of vaginal DHEA benefited vaginal atrophy and other aspects of sexual function. No increases in serum DHEA, testosterone, estradiol or androgen metabolites were detected. No recommendation can be made until this is validated by others.

4. **SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS).**

A Selective Estrogen Receptor Modulator was originally defined as a compound that binds with high affinity to the estrogen receptor (ER), without significant binding activity to any other nuclear receptor; which induces “estrogen agonistic” activities in some tissues, and “estrogen antagonistic” activities in others. Emerging data show that the interaction between a particular SERM and the ER results in a response in a given tissue which cannot necessarily be characterized simply as either “agonistic” or “antagonistic”. Each SERM may have a unique set of clinical responses, which are not always predictable from those seen with another SERM. Ospemifene is a novel SERM under trial for the treatment of vaginal atrophy in postmenopausal women.

5. **TIBOLONE**

Tibolone is a 19-nor testosterone derivative which is metabolized into three main metabolites: the 3α-hydroxy and the 3β-hydroxy, which are estrogenic, and the δ-4 isomer, which has progestagenic and androgenic properties. Tibolone is a selective tissue estrogen activity regulator (STEAR). In postmenopausal women, it acts as an estrogen on brain, vagina, and bone, but not on endometrium and breast. Sexual benefit has mostly been recorded in women recruited for reasons other than sexual dysfunction. Tibolone is available in Europe but has been declined approval in the USA.
IX. NON HORMONAL PHARMACOLOGICAL TREATMENT OF LOW DESIRE AND LOW AROUSAL

1. CENTRALLY ACTING AGENTS

In non-depressed women with HSDD, the antidepressant bupropion, which blocks norepinephrine and dopamine reuptake, was found to significantly improve sexual arousal and orgasm, but not sexual desire (Level 2). In women with SSRI-associated mixed sexual symptoms, 4 weeks of treatment with the addition of bupropion led to a significant increase in self-reported feelings of desire and sexual activity, but no significant effect on sexual thoughts (Level 1). Fibanserin is a 5-HT1A agonist/5-HT2A antagonist and was originally tested as an antidepressant. In an unpublished trial of 333 women with generalized, acquired HSDD, fibanserin showed a significant improvement over placebo on all FSFI domains, sexually satisfying events, and daily diary measures of desire (Level 1).

Centrally acting agents show some promise for targeting low desire in women but published RCTs are required and an evaluation of their safety remains to be studied. GRADE C

2. PHOSPHODIESTERASE INHIBITORS.

In a large study of diagnostically heterogeneous sexually dysfunctional women, 50-100mg sildenafil showed no benefit. In general, the literature has conflicting findings with one study showing benefit dependent upon psychophysiological-measured impairments in sexual arousal. In small studies of women with impaired genital arousal due to spinal cord injury or diabetes there was a significant beneficial effect of sildenafil.

A new approach to the study of efficacy of PDE5-inhibitors is combining this drug with testosterone. The rationale for such an approach is that activation of central sexual mechanisms is necessary for the interpretation of stimuli as sexually inviting. Then these stimuli can produce (behavioral) sexual responses (i.e., an increase in sexual desire and motivation, inducing sexual approach behavior). Activation of central “sexual” mechanisms is a necessary condition for activation of the nitric oxide pathway, which in turn is necessary for a PDE5-inhibitor to be effective. The authors argue that centrally working drugs will increase the sensitivity for sexual stimuli, and may induce a condition required for PDE5-inhibitors to be effective. Color naming latency times in a Stroop test was the measure of preconscious attentional bias for sexual cues. In an initially low-attention group, preconscious attentional bias increased with testosterone, in another initially high-attention group, attentional bias decreased with testosterone. Only in the former group did the combination of 0.5 mg sublingual testosterone (producing high supraphysiological levels) and 10 mg vardenafil cause an improvement in genital response (VPA) and subjective indices of sexual functioning, supporting the idea that testosterone sensitizes the brain, paving the way for vardenafil to be effective. The high dose of testosterone administered in this study limits the generalizability of the findings.

In summary, women with various medical conditions, but not medically healthy women, may have an impaired genital response and may therefore have more to gain from a genital arousal enhancing agent such as a PDE5-inhibitor. Similarly, other briefly studied drugs to augment genital congestion, e.g. l-arginine, prostaglandins, phentolamine are unlikely to benefit healthy women with arousal disorders. PDE5-inhibitors combined with high dose testosterone may have a beneficial effect over placebo in certain groups however, the high dose testosterone requires safety evaluation.

X. MANAGEMENT OF ORGASMIC DISORDER

In their 1997 review, Heiman and Meston concluded that only Directed Masturbation treatment for lifelong orgasmic disorder fulfills the criteria of “well-established” treatment. Directed Masturbation studies for acquired disorder fell within the “probably efficacious” group. This conclusion is still valid. Directed Masturbation in conjunction with sex education, anxiety reduction techniques and CBT remain the main therapeutic tools. No effective pharmacological treatments have been found to date for orgasmic disorder.

Ninety eight women with SSRI-induced FOD were recruited over four years across 7 American treatment centers to an RCT of 50 - 100mg sildenafil. Orgasmic function significantly improved in the treatment group. However, the highly specific inclusion criteria call into question the generalizability of the findings.

In conclusion, there are no significant new data on orgasmic disorder since the 2003 International Consultation except the one published RCT of sildenafil showing positive effects on orgasmic disorder in a highly selective sample of women with SSRI-induced orgasmic disorder. GRADE C

XI. MANAGEMENT OF SEXUAL DYSFUNCTION IN WOMEN WITH ENDOCRINE DISEASE

Recommendations on the management of sexual dysfunction in the context of neurological, renal and psychiatric illness and cancer are addressed in other manuscripts.
Endocrine disorders that alter estrogens and testosterone and precursors variably impact female sexual function. The consequences of hormone therapies in these states, including, hypothalamic amenorrhea, premature ovarian failure, surgical and natural menopause is variable but is indicative of benefits of low dose HT in individual patients. Hormonal therapy for chemically induced estrogen deficiency from selective estrogen receptor modulators (SERMs) and aromatase inhibitors has not been studied.

Hypopituitarism, hyperprolactinemia, thyroid disorders and adrenal insufficiency alter a variety of hormones, each to a variable extent. Data are limited on the effects of therapies with estrogens, testosterone and DHEA in each of these disorders, but they may provide additional model systems for future interventional trials. Studies on the effects of hormonal excess observed in PCOS, hormonally active ovarian or adrenal tumors, congenital adrenal hyperplasia and obesity induced hyperandrogenism do not suggest that excess androgens and/or estrogens per se promote normal or hypersexuality, suggesting an optimal balance of hormonal milieu is critical to normal sexual functioning. Information on the effects of diabetes and metabolic syndrome on female sexual dysfunction suggest that this is a common problem, but no data are available as to interventions to improve metabolic control and subsequent effects on female sexual function. Most importantly, the available literature emphasizes that hormones are only one component of the many factors that contribute to normal sexual function in women.

Conclusions and Recommendations

For hypopituitarism associated with E, T and DHEA deficiency consider ET and T until age of natural menopause, unless medically contraindicated **Grade B**

For hyperprolactinemia, data are lacking on any effect of prolactin on sexual function independent of effects on estrogens. We recommend further studies on effects of hyperprolactinemia and female sexual function **Grade C**

Data are lacking on thyroid dysfunction and sexual function in women and studies are recommended.

The majority of the albeit small clinical trials of DHEA in women with primary or secondary adrenal insufficiency do not show benefits on sexual function so that DHEA is not recommended for women with adrenal insufficiency **Grade A**

Interestingly, case series of women with Androgen Insensitivity Syndrome (genetic XY) show normal sexual function. This represents a model of high estrogen state without any androgen action.

Overweight but not lean women with PCOS have increased incidence of sexual dysfunction. Further research in women with PCOS needed.

Studies on women with sex hormone producing tumors are inconsistent.

Data are limited on sexual function in women with congenital adrenal hyperplasia. We recommend individualized management of signs and symptoms of androgen excess along with psychosexual counseling. **Grade C**

There is an increased incidence of sexual dysfunction in diabetes Type 1 and Type 2 which is strongly linked to comorbid depression. Glycemic control does not correlate with sexual function **Grade B. We recommend screening women with diabetes for sexual dysfunction Grade C**

There is an increased incidence of sexual dysfunction in women with metabolic syndrome. (Level3). This may be due to metabolic, vascular, neurogenic, hormonal and psychological etiologies. We recommend screening women with metabolic syndrome for sexual dysfunction. We also recommend studies of treatment interventions.

**XII. MANAGEMENT OF SEXUAL PAIN DISORDERS**

Sexual pain disorders are heterogeneous, multisystemic and multifactorial disorders. Other pain syndromes may be present. In general treatment should be multimodal taking into account etiological factors, risk profile and context.

Research of psychological function in women with Provoked Vestibulodynia (PVD) – the most prevalent type of sexual pain, has shown an increased prevalence of comorbid psychopathology, specifically depression and anxiety disorders. However, both more problematic and non-affected psychological functioning has been reported. Although this could reflect differences in study samples and instrumentation, it could also indicate true heterogeneity of women with PVD. However, increased trait anxiety, pain catastrophizing, reward dependency and harm avoidance have consistently been found in multiple studies. This may represent a complex of stable characteristics of avoidant, dependent, and obsessive-compulsive personality features which may be etiologically important. Single study findings of women with PVD included elevated rates of shyness, perfectionism, low self-esteem, and negative feelings towards sexual interaction, erotophobia, and problems with subjective sexual arousal and lubrication during sexual interaction with partner, but not during masturbation.

Women with PVD have been found to be more sensitive to thermal, painful and tactile stimulation, reflected in lowered thresholds for sensitivity. An etiological element may be a deficit in information processing, i.e. hypervigilance for pain-related stimuli. These latter findings require replication in future studies.

Women with vaginismus have been found to
have significantly increased comorbid anxiety, but not depressive disorders. The role of childhood sexual trauma is unclear since different frequency rates were found, and the presence of increased rates of posttraumatic stress disorder has not yet been investigated. Psychological characteristics, measured with self-report instruments, only partially lend support to the role of anxiety in the etiology of vaginismus. Personality features found to be more often present in this group include the presence of pain catastrophizing cognitions, disgust propensity, and a specific fear of penile-vaginal penetration.

1. TREATMENT MODALITIES FOR SUBTYPES OF CHRONIC DYS Pareunia

In table 3 the various treatment modalities for subtypes of chronic dyspareunia are outlined. They include chronic pain medications along with sexual and psychological methods.

a) Provoked Vestibulodynia (PVD)

In terms of medical interventions for PVD, there are only three level 2 RCTs. Neither fluconazole nor cromolyn 4% proved to be more effective than placebo. Botulinum toxin injections did not result in significantly greater improvements in pain, sexual function, or sexual distress as compared to a placebo (saline injections); in fact, the placebo group fared better than the botulinum toxin group in terms of sexual distress scores. Other medical interventions with some reported success include capsaicin, ketoconazole, lidocaine/xylocaine, tricyclic antidepressants, duloxetine, venlafaxine, and anticonvulsants - carbamazepine and gabapentin. Grade C/D

b) Vaginal EMG Biofeedback, Pelvic Floor Physical Therapy, (Group) Cognitive Behavioral Therapy, TENS and Vestibulectomy Grade B

Although receiving limited study, pelvic floor EMG biofeedback and physical therapy, Kegel and relaxation exercises, TENS, (group) CBT are clinically useful interventions with long term benefit. Similar benefit is also seen from multilevel local anesthetic nerve blockade and from vestibulectomy in certain (more localized and not lifelong) cases. (Level 2/3)

2. VAGINISMUS

Although ‘vaginismus’ (strictly defined as fear and difficulty with penetration with associated muscle tightening and no physical changes such as allodynia), and PVD often overlap in terms of clinical presentation and may respond to some similar treatment options (e.g., pelvic floor physical therapy, sex therapy), treatment options for vaginismus typically tend to target the muscle tightening over and above the symptom of (feared) pain. As such, the major focus of treatment tends to be vaginal accommodation/dilatation combined with progressive desensitization and a variety of relaxation techniques. Additional components may also be part of the treatment regimen, ranging from sex education to decreasing penetration fear and anxiety.

Some literature on less commonly used adjunct components also exists, and includes educational gynecological examinations, the application of topical anesthetics, pelvic floor biofeedback, botulinum toxin injections, anxiolytic medication and surgical intervention.

Many treatment studies are methodologically unsound. Recently, an RCT (N=117) was conducted comparing group CBT and bibliotherapy for women with lifelong vaginismus, and waiting list. At post-treatment, 14% of treated women were able to experience vaginal penetration as compared to none in the control group. At 12-month follow-up, 21% of the women in the CBT group and 15% of the women in the bibliotherapy group reported successful intercourse. Outcome was predicted by reduced fear of intercourse and avoidance. A recent prospective trial investigated the effectiveness of therapist-aided exposure for lifelong vaginismus. 10 women were evaluated during 24 weeks. During exposure, patients performed vaginal penetration exercises on themselves, in the presence of a female therapist. Nine of 10 participants reported having intercourse after treatment, and in 5 of 9, intercourse was possible within the 1st week of treatment. The results were sustained at 1-year follow-up.

2. MANAGEMENT OF SEXUAL DYSFUNCTION FOR THE WOMAN WITH PREVIOUS CHILD SEXUAL ABUSE

If considered necessary (see previous section), treatment for the sexual trauma should predate any treatment for sexual dysfunction. Therapy should help women understand any possible connections between past and current sexual functioning, particularly in regard to trust and being sexually vulnerable. Important aspects of therapy include:

• Encouragement that women can be in control of their sexual encounters.

• Women learning to be able to mentally and physically relax prior to and while receiving sexual stimulation.

• Women’s recognition that they need only engage in encounters with which they are fully comfortable.

• Helping women to develop verbal and non-verbal communication with their partners to limit further sexual stimulation when they feel overwhelmed, “numb” or fearful.

• Assisting women’s development of relationships where there is a healthy balance of power to minimize feelings of victimization and maximize feelings of control.
**Table 3: Management of Subtypes of Chronic Dyspareunia (continued)**

<table>
<thead>
<tr>
<th>Medical Disorder</th>
<th>Type of dyspareunia</th>
<th>Findings on physical examination</th>
<th>Therapeutic options and general comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvovaginal atrophy: associated with menopause, renal failure, hypothalamic or pituitary disease</td>
<td>Introital pain and with penile-vaginal movement. Possible post coital burning. Deeper dyspareunia when vaginal atrophy advanced.</td>
<td>Pallor, dryness, increased fragility and thinning of vulvovaginal epithelium, vaginal shortening, loss of rugae, narrowing, or urethral caruncle.</td>
<td>Local ET is highly recommended: vaginal ring or tablet. Although minimal systemic absorption is possible, there are no reports of adverse effects. Tibolone improves this disorder beyond placebo. Frequent sexual arousal and (if necessary), nonpenetrative activity may promote genital health. Recent trials of vaginal DHEA show promise.</td>
</tr>
<tr>
<td>Chronic (abdominal) pain; Endometriosis; Chronic PID; IBS; Crohn’s disease; Ulcerative colitis; Ovarian tumour; Abdominal wall pain.</td>
<td>Deep dyspareunia. IBS is also associated with introital pain from comorbid VVS.</td>
<td>General tenderness to deep bimanual examination.</td>
<td>Sexual dysfunction is highly prevalent in such patients. Organic disorders should be treated accordingly but sexual dysfunction may still need to be specifically managed. Irrespective of the organic or functional nature of the pain, a history of possible negative sexual experiences should be queried before any procedures or treatment.</td>
</tr>
<tr>
<td>Lower Urinary Tract Symptoms (LUTS) with urinary incontinence.</td>
<td>Introital and deep dyspareunia or vulvar burning after sexual intercourse.</td>
<td>Perineal and vulvar inflammation.</td>
<td>Voiding dysfunction, recurrent bacterial cystitis, hypoactive sexual desire, and sexual pain disorders are highly correlated. For recurrent cystitis give local ET, antibiotic self-treatment or preventative treatment, and recommend postcoital micturition (based on CE). In case of prolapse, surgical treatment can be curative but can also have undesired effects on sexual functioning.</td>
</tr>
<tr>
<td>Pelvic radiation.</td>
<td>Introital and deep dyspareunia.</td>
<td>Thinning and fragility of vaginal epithelium, loss of elasticity, stenosis, or foreshortening.</td>
<td>Preventive measures such as transposition of the ovaries to prevent ovarian failure. Therapeutic options based on CE include couple counselling about non-penetrative sexual activity, topical ET, lubricants, vaginal inserts, and vaginal reconstruction.</td>
</tr>
<tr>
<td>Chronic vulvovaginal candidiasis associated with diabetes and HIV.</td>
<td>Introital dyspareunia and with penile vaginal movement.</td>
<td>Erythema, swelling of vulva, and thick white or pale yellow vaginal discharge.</td>
<td>Oral anti-fungal agents recommended for recurrent symptomatic candidiasis.</td>
</tr>
</tbody>
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**Table 3: Management of Subtypes of Chronic Dyspareunia (continued)**

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<td><strong>Provoked vestibulodynia (PVD)</strong></td>
<td>Superficial vulvovaginal pain on (attempted) penetration, pain on non-penetrative vulvovaginal touching, postcoital burning, or burning from partner’s ejaculation fluid.</td>
<td>Variable erythema of the vestibule. Allodynia typically located between 4 and 8 o’clock on the introitus, just exterior to the hymenal ring but can involve the skin around the openings of the Skene’s ducts or the whole introital rim. Hypertonic pelvic floor muscles. Pain with attempted digital or speculum entry.</td>
<td>Vaginal EMG biofeedback, pelvic floor physical therapy, (group) CBT, supportive psychotherapy, TENS and vestibulectomy have been shown to have clinical benefit. Based on CE is treatment with topical estrogen, cromolyn, xylcaine, capsacin. Based on CE, and the not yet proven assumption that neuropathic pain is at least in part responsible for the pain of provoked vestibulodynia, give TCAs or AEDs. For comorbid IC, DBPTs have shown benefit of oral or intravesical pentosan polysulfate, intravesical dimethyl sulfoxide or resiniferatoxin (vallinoid). Based on CE, there may also be benefit from antihistamines, quercetin, intravesical heparin, lidocaine, or a combination.</td>
</tr>
<tr>
<td><strong>Generalized vulvodynia.</strong></td>
<td>Introital dyspareunia and pain with penile-vaginal movement. The pain is always/always constant, covers the entire vulvar area, and may or may not be increased upon provocation.</td>
<td>None.</td>
<td>Vulvar burning and pain that causes sexual and psychological distress accompanied by the complete absence of any physical abnormality on examination, in biopsies or culture. Based on CE, TCAs or AEDs can be of partial benefit.</td>
</tr>
<tr>
<td><strong>Female genital mutilation (FGM).</strong></td>
<td>Introital pain and with penile-vaginal movement and deep dyspareunia.</td>
<td>Type I: all or part of the clitoris and its prepuce or skin excised. Type II: clitoris excised, labia minora partially or totally removed. Type III: all external genitalia excised, vaginal opening closed except for a matchtip-sized hole to allow urine and blood to escape.</td>
<td>Experienced by an estimated 130 million women, in particular from north Africa, the middle east, and southeast Asia. Most of the studies do not support the hypothesis that FGM destroys sexual function or precludes enjoyment of sexual relations. Based on CE, use a respectful approach and provide information about health consequences. Offer sexual counselling, psychotherapy, and support groups. Offer to repair the vulva, vagina, or both. Involve the partner, the family, or both in decisions. Clarify the legal and ethical responsibility of the physician, who must decline any request to re-infibulate after childbirth. Offer specific management of sexual dysfunction as needed.</td>
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<td><strong>Dermatological diseases.</strong></td>
<td>Can be introital dyspareunia (eg. eczema) or deep (eg. lichen planus affecting vagina.)</td>
<td>Benign non-STI: can be atopic eczema, contact dermatitis (including iatrogenic), lichen simplex, lichen planus, psoriasis, hidradenoma, fox- fordycye, chronic vestibular gland infection, pediculosis pubis, pin worm infections, Behçet’s, aphthous ulcers, cicatrical pemphigoid, pyoderma gangrenosum, anorectal Crohn’s, burn, or trauma. STD can be HSV, syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale, condylomata accuminata, or molluscum contagiosum. Neoplasia can be VIN, vulvar Paget’s, or melanoma.</td>
<td>For a benign non-STI, based on CE, give corticosteroids (oral, topical or injectable); immunosuppressive drugs (azathioprine, dapsone, tacrolimus, pimecrolimus, thalidomide, or infliximab); immune augmentation drugs (imiquimod); surgery; behavioural and physical therapy; and biofeedback. Also offer psychosexual support for sexual problems resulting from limited skin contact, visible symptoms, disrupted self-image, inability to meet a partner, shame, lack of confidence, or a combination of these. For treatment options for STI consult Guidelines from ISTI, WHO and CDC USA. Asymptomatic shedding and further infection necessitate strong encouragement of protective measures and safe sex. For neoplasia attempt surgery, laser therapy with radiation, or chemotherapy, as appropriate. Sexual activities do not stop for most couples. Based on CE, psychosexual counselling can be of benefit, in particular in the first year after treatment.</td>
</tr>
<tr>
<td><strong>Anatomical variations.</strong></td>
<td>Introital or deep dyspareunia depending on abnormality.</td>
<td>Labial fusions, rigid hymen, vaginal septum, vaginal agenesis, or hypoplastic vagina.</td>
<td>Based on CE, in case of vaginal agenesis nonsurgical options can be highly successful. Surgical intervention is recommended for imperforate hymen, labial fusions or a painful vaginal septum.</td>
</tr>
</tbody>
</table>

AEDs=antiepileptic drugs. CBT=cognitive behavioural therapy. CE=clinical experience. DBCT=double blind placebo controlled trials. ET=oestrogen therapy. HIV=human immunodeficiency virus. HS=herpes simplex. IBS=irritable bowel syndrome. PID=pelvic inflammatory disease. STIs=sexually transmitted infection. TCAs=tricyclic antidepressants. VIN=Vulvar intraepithelial neoplasia. PVD=provoked vestibulodynia