CHAPTER 1

Historical Highlights of Erectile and Sexual Dysfunction
An Illustrated Chronology

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INTRODUCTION

This short introductory chapter is to give very selected impressions on some historical milestones from the field of erectile and sexual function and dysfunction. These highlights are arranged in chronological order and are not including the developments of the most recent years.

The idea for this chapter was born by the author and Prof. Alain Jardin - both members of the Historical Committee of the European Association of Urology (EAU) - during the 2nd International Consultation held in Paris in summer 2003. The concept was immediately supported by the board of the consultation.

Every reader who is familiar with the history of sexual medicine will realize that many dates and names have not been mentioned in this brief overview. So hopefully, the 3rd International Consultation will come up with an extended and complete research of all fields and aspects of the history of sexual medicine and not only a collection of selected spotlights.

PREHISTORIC PERIOD

An early wall painting in the caves of Lasceaux, France, from the Late Stone Age (left) already depicts a man with an erect penis positioned beside a bison. Hunting as well as human reproduction were elemental tasks for prehistoric men and the basis for the survival of mankind. Both aspects are united in this painting as well as in a similar hunting scene from a Neolithic rock painting from Mongolia (right).
Ithyphallic depictions – like that of the god Min in the Temple of Luxor (left) - are frequently found in ancient Egyptian culture as the erect penis was a sign of good fortune and masculine strength. Prescription 663 of the famous Papyrus Ebers (right) offers a variety of remedies for the cure of male impotence. Other passages of this Papyrus also address several contraceptive recipes for women.

Square columns with the head of a man and an erect phallus – called “Hermes” (left) - were set up besides roads, public places or at private houses to provide protection from robbery or other evil events. During the famous fertility festivals, named after the god Dionysos, large erected penises were exhibited and played a major role (right).

In “De aëre aquis et locis” Hippocrates (5th-4th century BC) (left) 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 B.C.) - like the other Greek authors - outlined the physiological concept of “pneuma” (= wind, air) as the initiator of erection (right).
The Greek god Priapos – son of Dionysos and Aphrodite – was always depicted with a gigantic and erected phal-lus (left) and became also very popular in later Roman culture. Poets like Catullus, Horace or Martialis wrote obscene verses – the “Priapea” and the famous wall painting of the “phallus weigher” in the House of Vettii in Pompeii (right) most likely also represents Priapus.

Many cultures used ithyphallic symbols for fertility rites and other reasons. The antropomorphic terracotta vase (left) from the Mochica culture (Peru, 100 BC – 600 AD) depicts a priest with an exaggeratd phallus. The Swedish god Freyr (right) is represented with an erected penis in this small bronze figure (Södermanland, 9th – 10th century AD).

The “Kama Sutra” (Aphorisms on Pleasure) is the earliest surviving example of a comprehensive love manual in the history of the world. It was compiled by the Indian scholar Vatsayana between 330 and 369 A.D. The descriptions of many lovemaking postures (illustrations shown here from 18th century) is only one aspect of the Kama Sutra besides the many psychological insights into the interactions and scenarios of love.
Leonardo da Vinci (1452-1519) – the great artist of the Renaissance - can not only be considered as the founder of modern medical illustration but is also the first author to describe the blood filling of the penis as the cause of erection. He drew this conclusion from his own observations in human corpses.

Although the “Musculi erectores penis” (i.e. Mm. bulbospongiosi and ischicavernosi) had already been described by Galen in the 2nd century A.D., 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.

In respect to sexual medicine the famous Avicenna (980-1037 A.D.) - also known as ABU ALI AL HUSAIN IBN ‘ABD ALLAH 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.
AMBROISE PARÉ

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 how to diagnose pregnancy, how to follow pregnancy and finally how to conduct delivery.

THE FIRST PENILE PROSTHESIS?

Paré also 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.

REGNIER DE GRAAF I

In his male book “Tractus de virorum organis generationi inservientibus, de clysteribus et de usu siphonis in anatomia” (1668) the Dutch physician Regnier de Graaf (1641-1673) 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.
Spermatorrhoea and the involuntary loss of semen was an important aspect of the masturbation hysteria that coursed through western medicine following the publication, in 1758 of “De l’Onanisme, Dissertation sur les Maladies Produites par la Masturbation” (left) by the illustrious Swiss physician Simon Auguste David Tissot (1728-1797). A variety of preventive devices (right) and therapies emerged over the next 150 years.

**SPERMATORRHŒA AND MASTURBATION**

His book on the female genital organs “De mulierum organis generationi inservientibus” (left) published four years later (1672) in many ways is astonishingly precise in explaining female sexual function and human reproduction. As to the function of the ovaries (right) the “Graafian follicles” were named after him.

**REGNIER DE GRAAF II**

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.

**PEYRONIE’S DISEASE**
JOHN HUNTER

The famous surgeon and anatomist John Hunter (1728-1793) 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”.

THE AGING MALE IN 1813!

The clinical features of this disorder have already been described adequately in the article “On the climacteric disease” from 1813 by Sir Henry Halford (1766-1844) from London. One of his statements is the following: “…I will venture to question, whether it be not, in truth, a disease rather than a mere declension of strength and decay of the natural powers.” Halford seems to be the first to connect the term “climacteric” with the symptoms observed in some men aged between 50 and 75 years.

FEMALE GENITAL MUTILATION IN VICTORIAN TIMES

Clitoridectomy, a part of female circumcision in many African and Eastern cultures, was also performed by certain doctors in Western society mainly in the 19th century in order to cure the serious consequences of masturbation in women. The main protagonist was the gynecologist Isaac Baker Brown (1812-1873) from London who started this procedure in 1859 and published his results in 47 patients in 1866. One year later he was dismissed from the fellowship of the Obstetrical Society of London.
In 1863 the German physiologist Conrad Eckhard (1822-1905) from Giessen published his results on animal experiments inducing penile erections by applying electrical stimulation at different levels of the nervous system. More detailed contributions were made by J.N. Langley and H.K. Anderson from England in the mid 1890’s.

**FIRST NEUROPHYSIOLOGIC EXPERIMENTS ON ERECTION**

![Image of Francesco Parona](image1)

**FRANCESCO PARONA**

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 (left). 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 (right).

**THE BIRTH OF ANDROGEN THERAPY**

The famous self-experiment of the French physiologist Charles Edouard Brown-Séquard (1817-1894) at the age of 72 years with several subcutaneous injections of a mixture of blood from the testicular veins, semen and juice extracted from crushed testicles of young and vigorous dogs and guinea pigs in 1889 was a first milestone of androgen therapy in the aging male although his “pharmaceutical” prescription must have been equivalent to a placebo.
In 1896 (left) 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 (right).

THE FIRST ORAL DRUG FOR ERECTILE DYSFUNCTION

Through the discovery and development of the psychoanalysis as an important psychotherapeutic school Sigmund Freud (1856-1939) from Vienna had great influence on sexual medicine. 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 Freud deals directly with male erection disorders.

HOMOSEXUALITY AND THE “THIRD GENDER”

Homosexuality, also addressed as the “Third Gender” in modern times (left, lay press publication against homosexuality from 1904), is documented in most cultures at all times but scientific interest in this issue only developed at the end of the 19th century. In 1897 the German sexologist Magnus Hirschfeld (1868-1935) founded the “Wissenschaftliche-humanitäre Comitée” (scientific-humanitarian committee) dedicated to the study of homosexuality and edited a related yearbook (right).

ERECTILE DISORDERS AND PSYCHOANALYSIS

This image contains text that is not fully visible or legible. It appears to be discussing the history of erectile dysfunction and psychoanalysis, including references to chemist Leopold Spiegel's work on yohimbine and Sigmund Freud's essay on degradation in erotic life.
The curative application of negative pressure to different parts of the body was well established in 19th century medicine (left). 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 (right); long before Geddings D. Osbon constructed his device in 1960.

**VACUUM DEVICES FOR THE TREATMENT OF ERECTILE DYSFUNCTION**

At the turn of the century the physiologist Eugen Steinach (1861-1944) from Vienna started animal experiments to study the sexual differentiation of the organism and the hormonal function of the gonads. Later he postulated that an increased hormonal production follows the cessation of the secretory output of the gonads after surgical ligation of the seminal ducts. In the 1920’s Steinach’s “autoplastic" treatment of aging., i.e. vasoligation, became very popular and was performed by many surgeons worldwide.

**REJUVENATION I**

At the beginning of the 20th century the transplantation or implantation of either human or animal testicular tissue was another appealing form of androgen therapy in hypogonadal and aging males. The most important protagonist in Europe during the 1920’s was the Russian Serge Voronoff (1866-1951) who worked in Paris and transplanted sliced monkey glands in hundreds of his patients who visited him from all over the world. According to his reports, hormonal secretion lasted for about one or two years and was then slowly decreasing due to fibrosis of the grafted tissue.

**REJUVENATION II**
Since the early 1930’s Oswald S. Lowsley (1884-1955) from New York was the main protagonist of surgical treatment for corporoveno-occlusive 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 INSTITUTE OF SEXOLOGY IN BERLIN
In 1919 Magnus Hirschfeld (left, 1868-1935) established the “Institut für Sexualwissenschaften” (right) in Berlin. It was the first center of public information and education, treatment of patients and scientific research. Many scientist worked at the institute, 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 Hirschfeld left Germany in 1930 and the institute was plundered and the library destroyed by the Nazis in 1933.

THE SURGICAL MANAGEMENT OF MALE-TO-FEMALE TRANSSEXUALISM
In 1931 Felix Abraham (left), a physician at the Hirschfeld Institute in Berlin, published the first scientific report on two complete male-to-female transsexual operations including penectomy, orchiectomy, and the creation of a neovagina with a Thiersch’s graft (right). After the war in 1952 the American Christine Jorgensen underwent sex-change surgery in Denmark and although she was not the first patient this caused a sensational media circus and public awareness of transsexualism.

SURGICAL TREATMENT OF ERECTILE DYSFUNCTION
Since the early 1930’s Oswald S. Lowsley (1884-1955) from New York was the main protagonist of surgical treatment for corporoveno-occlusive 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) 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.

The biologist Alfred Charles Kinsey (1894-1956) from Bloomington, Indiana performed the first epidemiologic study on human sexuality collecting sexual histories from a large number of men and women, resulting in a final sample of around 18,000. The two volumes “Sexual Behavior in the Human Male” (1948) and “Sexual Behavior in the Human Female” (1953) are milestones in the literature on the anatomy, physiology and psychology of human sexuality.

In 1948 the French surgeon René Leriche (1879-1955) 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.
THE BIOCHEMICAL BASIS OF PDE-5-INHIBITORS

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 also fundamental for the understanding of the first effective oral treatment of ED at the end of the 20th century.

THE G-SPOT

The gynecologist Ernst Gräfenberg (1881-1957) from Germany was a pioneer of intrauterine devices since the 1920’s favoring a ring of coiled silver wire (right). He emigrated to New York in 1940, where he finally published his milestone article on “The Role of Urethra in Female Orgasm” in 1950. The anatomical area described by Gräfenberg was later named after him as the G-spot.

WILLIAM H. MASTERS AND VIRGINIA E. JOHNSON: PRACTICAL SEX-THERAPY

"There is no such entity as an uninvolved partner in a marriage contending with any form of sexual inadequacy." The therapeutic approaches used by Masters and Johnson are oriented towards therapy of the "marital-unit", i.e. the couple, with a strong component of exercising, rather than focussing on verbal aspects of therapy. “Human Sexual Inadequacy” from 1970 is one of their milestone publications.
In 1973 Václav Michal (left) from Prague reported the first microsurgical treatment of vascular ED by perfor-
mimg a direct anastomosis of the inferior epigastric artery to the corpus cavernosum (right). In the 1980’s further
techniques were introduced by Michal himself, as well as by Ronald Virag from Paris and Dieter Hauri from
Zurich.

MICROSURGICAL REVASCULARIZATION OF THE PENIS

The very breakthrough of penile implant surgery was initiated by F. Brantley Scott (left) from Houston, Texas,
together with his colleagues William E. Bradley and Gerald W. Timm when they implanted the first silicone
inflatable device (right) on February 2nd, 1973.

INFLATABLE PENILE IMPLANTS

The French vascular surgeon Ronald Virag (left) from Paris discovered the proerectile effect of the vasoactive
drug papaverine when injected into the corpus cavernosum in 1982 (right). The injection of phenoxylbenzamine
was suggested by Giles S. Brindley from London the following year and Adrian W. Zorgniotti from New York
introduced drug combination of papaverine and phentolamine in 1985.

INTRACAVERNOUS INJECTION THERAPY FOR ERECTILE DYSFUNCTION

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## A. ANATOMY

### B. PHYSIOLOGY OF ERECTILE FUNCTION

#### I. REGULATION OF PENILE ERECTION BY THE CENTRAL NERVOUS SYSTEM

#### II. PHYSIOLOGICAL REGULATION OF PENILE SMOOTH MUSCLE TONE.

- **IIa. PENILE SMOOTH MUSCLE CONTRACTION**
- **IIb. INTRACELLULAR MECHANISMS REGULATING SMOOTH MUSCLE CONTRACTION**
- **IIc. PENILE SMOOTH MUSCLE RELAXATION**
- **IId. REGULATION OF THE BALANCE BETWEEN THE DILATOR AND CONSTRICTOR MECHANISMS**
The average length of the human male pendulous penis is 8.8 cm flaccid, 12.4 cm stretched and 12.9 cm erect with neither patient age nor size of the flaccid penis accurately predicting erectile length [1] In another study, erect penile length varied from 10-20 cm with an erect thickness of 3-5 cm [2]. The penis is composed of three bodies of erectile tissue; the corpus spongiosum, encompassing the urethra and terminating in the glans penis; and the two corpora cavernosa which function as blood-filled capacitors; providing structure to the erect organ [3-5]. In this section we will discuss the anatomical composition of the three erectile tissues of the penis, the nerve and blood supply and the connective tissue and fascia which together make up the intact penis.

The corpora cavernosa are a unique vascular bed consisting of sinuses (the trabeculae) whose arterial blood supply arises from the resistance helicine arteries (figure 1); which in turn are fed from the deep penile cavernosal artery [3-5] The trabeculae are drained by the subtunical venules that coalesce to form the emissary venules which in turn communicate with the cavernosal veins (figure 2). The penile arterial and venous supply are discussed in greater detail below. The trabeculae, while arterially fed, have measured blood PO2 of 20-40 mmHg when the penis is in the flaccid state [6-8]. This venous-like flaccid blood PO2 increases upon erection with dilation of the helicine arterioles to 90-100 mmHg [6] and these changes in oxygen tension directly impact both the physiologic function and trabecular structure of the corpora cavernosa (see pathophysiology section below) [9,10]. Histologically, the corpora are...
composed primarily of trabecular smooth muscle (40%-50%) and connective tissue (~50%-45%) with endothelium, fibroblasts, and nerves [3-5,9]. The corpora are separated in the pendulous penis by an incomplete septum and proximally separate into two individual corpora, terminating in the paired crura which directly attach to the ischiopubic ramus. This latter structure is particularly susceptible to pelvic trauma [11] and x-radiation during wide beam therapy for prostate cancer (see iatrogenic causes of erectile dysfunction below) [12]. Crural leakage can result in a dysfunctional veno-occlusive mechanism and erectile dysfunction [11].

The **tunica albuginea** is a multilayered structure of inner circular and outer longitudinal layers of connective tissue encompassing the paired corpora cavernosa [13-15]. An incomplete septum separates the two corpora cavernosa and anchors into the circular inner layer of the tunica albuginea. In the distal pendulous penis, intracavernous pillars anchor the tunica across the corpora cavernosa at the two- and six-o’clock positions with minor struts branching off of these pillars at the five- and seven-o’clock positions [15]. It has been demonstrated that tunical thickness varies from 1.5 to 3 mm thick depending on the circular position around the tunica [13-15]. The longitudinal outer layer which provides strength to the tunica albuginea is absent at the six-o’clock position where the corpus spongiosum fits in the indentation between the two corpora cavernosa [15]. It has been proposed that this design allows unrestricted expansion of the corpus spongiosum such that ejaculation is unimpeded during penile erection [15]. The longitudinal layer is also thinnest at the three- and nine-o’clock positions, consistent with the greatest number of traumatic penile fractures in those positions [14]. The tunica albuginea is composed of fibrillar (mainly type I but also type III) collagen in organized arrays interlaced with elastin fibers [15]. While collagen has a greater tensile strength than steel, it is unyielding. In contrast, elastin can be stretched up to 150% of its length [15]. It is the elastin content that allows the compliance of the tunica albuginea and helps to determine stretched penile length [16]. Disorganization of the circular or longitudinal layers in the tunica as well as disruption of elastin or a decrease in elastin content can result in penile deformities during erection as well as erectile dysfunction. Further, damage to the tunica albuginea can result in site-specific leakage or undermining of the draining tunical venules [17].

The **corpus spongiosum** has a similar histologic appearance to the corpus cavernosum in that it is a spongy erectile tissue, but this erectile tissue does not provide structure to the erection. The intraspongiosal pressures are one-third to one-half that of the corpora cavernosa; an advantage in that this lower pressure may prevent urethral blockage during ejaculation [5]. This may also be the reason for the absence of longitudinal tunical fibers in the six-o’clock position of the tunica albuginea, such that the urethra is not restricted during ejaculation [15].

Three sets of **peripheral nerves** have a role in erectile function: thoracolumbar sympathetic, sacral parasym pathetic, and sacral somatic (figure 3). The pelvic plexus (occasionally referred to as the inferior hypogastric plexus in humans) found in the pelvic fascia on either side of the lower genitourinary tract and the rectum is also a very important site for the integration of autonomic input to the penis via the cavernous nerves (see below). The efferent limb originates in the parasympathetic center in the sacral cord, which contributes fibers to the pelvic nerve that enters the cavernosal tissue as the cavernous nerves. Careful attention to preserving these nerve tracts has gained importance in radical pelvic cancer surgery in the potent patient.

![Figure 3: The pelvic plexus](image)

In the **brain**, several regions modulate the psychogenic component of erection, including the thalamic nuclei, the rhinencephalon, and the limbic structures, with integration of these various areas occurring in the preoptic anterior hypothalamic area [18]. Input from the brain involves descending spinal pathways and is relayed through both lumbar sympathetic and sacral parasympathetic outflows to the penis. Anti-
erectile sympathetic efferent pathways arise in paravertebral sympathetic chain ganglia and course to the penis primarily through hypogastric and pudendal nerves. Physiologic studies and the presence of cholinergic nerves in the cavernous tissue implicate the parasympathetic nervous system as the primary effector of penile erection. The neurophysiology of erection is dealt with in greater detail elsewhere in this volume.

**Neural innervation of the penis** may be divided into autonomic (parasympathetic and sympathetic) and somatic (sensory and motor) [3,5,18]. Parasympathetic preganglionic fibers originate from the second to fourth sacral vertebra and proceed to the pelvic or hypogastric plexus. This plexus serves as a relay station for preganglionic and postganglionic fibers to the penis. The cavernous nerve begins at the pelvic plexus and travels through the pelvic fascia to the prostatic capsule where it goes across the posterolateral aspect of the prostate. Distal to the membranous urethra, branches of the cavernous nerve penetrate the tunica albuginea of the corpus spongiosum. Other branches enter the crura of the corpus cavernosa along the pudendal artery and exiting cavernous veins. The remaining branches proceed down the dorsal nerve to innervate distal portions of the penis. Sympathetic preganglionic fibers arise preganglionic neurons from ninth thoracic and fourth lumbar vertebra. These neurons interface with sympathetic chain neurons at level of the spinal cord and proceed downward to the superior hypogastric plexus. This plexus divides into the right and left hypogastric nerve. One of these branches then interfaces with the pelvic plexus. Sensory stimuli elicited in the glans, penile, and other perineal and inguinal areas are originated in sensory receptors whose nerve fibers converge to form the dorsal nerve of the penis. This nerve joins other pelvic nerves to become the internal pudendal nerve, ascending to the dorsal root of the second, third and fourth sacral vertebra. are eventually carried by the dorsal penile and other sensory nerves to the sacral spinal cord via the pudendal nerve. Motor innervation of the penis derives form the second, third and fourth sacral vertebra within the sacral nerves which lead to the pudendal nerve and the bulbocavernous and ischiocavernous muscles. Contraction of the later muscle is important in the rigid erection phase by constriction and compression of the corpora cavernosa while rhythmic contraction of the bulbocavernous muscle is important for the expelling of semen during ejaculation [3,5,18].

The arterial blood supply of the penis is primarily via the hypogastric artery [3-5] (figure 4). The internal pudendal artery branches off of the hypogastric artery and proceeds through Alcock’s canal becoming the common penile artery. However, accessory internal pudendal arteries arising from the obturator or other pelvic arteries are not uncommon. The internal pudendal artery splits into the bulbourethral, dorsal, and cavernosal arteries. The bulbourethral artery supplies the urethra and the glans while the cavernosal arteries enter the corpora cavernosa at a point where the two crura converge. As the cavernosal arteries proceed proximally, they lie in the middle of the corporal bodies. The cavernosal arteries give rise to the helicine resistance arterioles which in turn feed the individual trabeculae. The paired dorsal penile arteries proceed down the penis in the eleven- and one-o’clock positions along with the dorsal nerves and supply superficial structures in the penis as well as potentially supplying the corpora cavernosa via circumflex arteries. Thus the dorsal penile artery can supply the cavernous tissue with multiple branches along the shaft of the penis as normal variant. There also can be rich anastomotic networks of vessels between the arteries of the pelvic area, and one side may also supply both corporeal spaces as a normal variant.

![Figure 4: Arterial blood supply of the penis](image)
The **venous drainage system** of the penis occurs on three levels: superficial, intermediate, and deep [3-5]. The superficial venous system, which lies above Buck’s fascia and primarily drains the penile skin, can also have anastomotic connections to the deep dorsal vein. This superficial system drains into the femoral vein via the saphenous and the external pudendal veins. The intermediate system consists of the deep dorsal and circumflex veins. The trabeculae of the corpora cavernosa drain into a system of sub-tunical venules that coalesce on the outer surface of the cavernous tissue just beneath the tunica albuginea of the corpus cavernosum [3-5]. These venules form a number of veins transversing the tunica albuginea called emissary veins which usually drain into the circumflex veins on the outer surface of the tunica albuginea. The circumflex veins in turn drain into the deep dorsal vein of the penis shaft between the dorsal arteries lying usually just laterally adjacent, all beneath Buck’s fascia. Occasionally, the deep dorsal vein consists of more than one trunk on the most distal shaft of the penis, and occasionally the deep dorsal vein receives direct emissary veins from the cavernous tissue in the dorsal midline. The deep dorsal vein near the glans penis also is initially constituted by numerous trunks from the glans and many of the circumflex vessels anastomosis with small tributaries from the spongiosum. The deep penile drainage system consists of the cavernosal and/or crural veins that drain the deeper cavernous tissue. The cavernosal veins are in fact extensions of emissary veins from the infrapubic cavernous tissue that drain directly into the pelvic plexus or the internal pudendal veins. The deep penile drainage system consists of the cavernosal and/or crural veins that drain the deeper cavernous tissue. The cavernosal veins are in fact extensions of emissary veins from the infrapubic cavernous tissue that drain directly into the pelvic plexus or the deep dorsal vein in the deep infrapubic area. The crural veins are direct emissary veins from the antero- to posterolateral surface of the crura of the cavernous tissue that usually drains into the internal pudendal veins or the pelvic plexus.

The **penile skin** is continuous with that of the abdominal wall and continues over the glans penis as the prepuce to reattach at the coronal sulcus [4]. The underlying Colles’ fascia is continuous with Scarp’s fascia of the lower abdominal wall. The deep layer of penile fascia, Buck’s fascia, covers both corpora cavernosa and the corpus spongiosum in separate fascial compartments. This fascia layer has a dense connective tissue structure and is attached proximally to the perineal membrane and distally to the corona-

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**B. PHYSIOLOGY OF ERECTILE FUNCTION**

**I. REGULATION OF PENILE ERECTION BY THE CENTRAL NERVOUS SYSTEM**

**1. OVERALL ORGANIZATION**

The study of the neurophysiology of human sexual response has progressed steadily but it is a vast and complex subject. The knowledge of central nervous system (CNS) control of sexual function appears to lag far behind the understanding of local physiological, biochemical, genomic processes. The understanding of disease and treatment in the CNS aspects of sexual function is correspondingly in its infancy. However, while there should be an acute awareness of these current limitations, there should be no doubt that it is in the CNS that the keys to improving many dimensions of sexual response will be found. There is currently a realization of the parallels between vascular and endothelial disease and erectile dysfunction and its implications for therapy. It has taken perhaps 10 years for these parallels to reach the mainstream of thinking in ED. So, when the diagnostic and therapeutic tools become available it will be possible
to understand the essential elements of CNS involvement and incorporation of its management will joint the mainstream.

There are many primary sources that piece together these complex CNS systems. Most are derived from animal modeling which increases the detail while decreasing the direct applicability of the information to the human situation. Especially in the area of sexuality the complexity of human sexual response places some severe limitations on the relevance of animal studies. A few excellent detailed reviews of the neural substrates of female [19] and male [20] sexual function are available.

There are a number of models that can be constructed to explain the CNS and sex – the finer the resolution the greater the complexity and the greater the uncertainty. The neural control of sexual function including penile erection and female genital arousal may, on a practical basis, be conceptualized into three main areas: local neural pathways, midbrain and spinal cord pathways, and higher brain centers. Local neural pathways incorporate genital and pelvic nerves and plexi (parasympathetic, sympathetic and sensory). The emphasis in these is in ‘cable’ function – the connection of genital structures with central organization and control. Within these there is limited self regulation of the signal for instance by feedback loops. Although at many points there is ample opportunity to change the signaling in local neural pathways through pharmacological, hormonal or traumatic/surgical means. In the midbrain and spinal cord there are many complex pathways with extensive interconnections and many possibilities for signal modulation or conditioning. It is through the spinal cord that reflexive erections can take place. The coordination of genital, hemodynamic, erectile and ejaculatory responses depends on the midbrain and spinal cord. Higher brain centers provide the awareness, the sensory and motor function, the imagery/memory, the strategy – the highs and lows of human sexual response.

2. LOCAL NEURAL PATHWAYS

Clitoral and vaginal responses and erections occur through motor efferents that originate in the sacral parasympathetic center and pass through the pelvis as the pelvic nerves (preganglionic neurons from the intermediolateral cell column through S2, 3 and 4). These neurons together with fibers from the inferior hypogastric (sympathetic) nerves form the pelvic plexus. This major pelvic ganglion, also called the paracervical ganglion or the uterine cervical gan-
rone and nerve growth factors in maintaining neuronal structure and function in vivo [24]. Age has been shown experimentally to induce degenerative changes in the pelvic nerves. The sympathetic and parasympathetic preganglionic neuronal populations change in aged rats differentially [25].

2. MIDBRAIN AND SPINAL CORD

The first level of reflex organization for signals supporting sexual function is in the lumbar spinal cord. Nerve tracing studies using neurotropic viruses clearly show that pelvic and sexual reflexes depend on the central grey region for coordination and generation of sexual responses including erection, arousal and orgasm [26].

Using the local neural connections (efferent and afferent), and including the vital spinal cord connections, there are a number of examples of spinal reflexes. These may be activated by pudendal (penile or clitoral skin) and the bulbocavernous reflex (BCR) is an obvious example. Stimulation of the glans penis evokes a contraction in the bulbocavernous muscles and the equivalent in the female manifests as contraction of elements of the pelvic floor [27]. Stimulation of the clitoris and vagina inhibits bladder activity – a response appropriate to sexual activity [28].

These spinal reflexes can be vitally regulated by descending signals from the midbrain and higher centers. Spinal reflexes rest in an inhibited state – the efferent side is tonically directed to non-sexual function (flaccidity, lack of engorgement, baseline lubrication). Local sensory input and descending spinal signals can change the balance and activate a pro-sexual cascade of parasympathetic activity, reduced sympathetic activity and somatic muscular support. The preference for particular pathways and components of the diffuse innervation in the periphery with types of stimulation is not fully worked out. For instance experimentally it can be shown that reflexive erections can be modulated by learning and opportunity (here correctly labeled ‘psychogenic’) and that this modulation does not depend on the hypogastic nerves [29].

A critical recent addition to the understanding of the importance of spinal events in sexual function comes from a study where a population of lumbar spinothalamic cells has been found to be essential in the generation of ejaculatory behavior [30]. These cells, which express neurokinin-1, relay ejaculation-related signals from reproductive organs to the brain. If this population of cells is destroyed no aspects of sexual behavior other than ejaculation are altered. Further work is needed to establish the human implications of this concept and how central and peripheral efferent and sensory signals integrate with the experience of ejaculation.

Sensory information is conveyed cephalad through spinothalamic (fast fibers serving the penis and clitoris), spinoreticular (slower) and vagal (extra spinal) pathways. Electrophysiological studies have revealed that the thalamus has significant inputs from the male genitalia that are relevant to various aspects of penile sensation associated with sexual response [31].

The nucleus paragigantocellularis (nPG) receives ascending sensory input [32] and also has neurons that innervate the penis [33]. The nPG appears to have a role in orgasm but is not vital to erection. The most common neurotransmitter identified through staining techniques in the nPG is serotonin. The nPG, in common with other central sites of sexual function is not exclusively employed in regulating sexual response. In fact the major output from the midbrain that effects sexual response is autonomic and it is appropriate that sites that regulate cardiorespiratory homeostasis and other pelvic functions that are also autonomic should be found in the same regions.

One such region is the periaqueductal gray (PAG) and this area has a large number of connections with hypothalamic sites involved in sexual response [34]. The paraventricular nucleus (PVN) has a major role in controlling genital responses. PVN neurons send direct projections via the nPG onto neurons that innervate the penis [35]. The PVN has direct projections to pelvic and autonomic efferents and is reciprocally connected to the medial pre-optic area (MPOA). Experiments indicate that penile erections, associated with the largely dopaminergic, and oxytocinergic, receptor population of the PVN, are eliminated by lesioning [36]. PVN activation has also been shown to be critical in models of female response [37].

The MPOA has been shown in many studies to have a vital role in controlling sexual behavior (in addition to blood pressure and respiratory control) and is well connected through reciprocal links with the nPG and PAG. Much of this pathway has been shown to have the potential for sex hormone modulation [38]. Neurons in the MPOA have been shown to regulate timing aspects of female rat copulatory behavior.
The MPOA likely does not regulate motivation of performance but may have a critical role in mate selection.

3. HIGHER BRAIN CENTERS

Behavioral studies in rats combined with stereotactic lesioning and direct brain injection studies have shown that the medial amygdala has a role in acquisition and recognition of an appropriate partner and sexual arousal [40]. Simple peptide neurotransmitters, vasopressin and oxytocin, are closely associated with these mechanisms.

The impact of imagination on human sexual behavior has been measured. In healthy middle and older married couples imagination (about other women), wife’s desire for sex and erectile competence were universal determinants of sexual activity [41]. Imagination, known as creative-dynamic image synthesis (CDIS), has been compared with the benefit of yohimbine and placebo in men with erectile dysfunction of no evident organic cause [42]. Measures of potency were found to improve more with CDIS than with yohimbine or placebo. In many men, enhancing the central pro-erectile signal, by enhanced imagination or pharmacological means will reasonably be expected to enhance the erection. More neural signal at the level of the peripheral vasculature causes better erection as is seen in post-prostatectomy patients (where 2 nervi erigentes are better than one or none), reversible nerve lesioning experiments and with graded stimulation (imagination < VSS < vibratory stimulation) [43].

The four major categories of sexual stimulus have been said to be tactile sensation, visual input, imagination and olfactory input. The effects of male, female and neutral fragrance on provoked sexual response in women have been assessed. Erotic fantasy was enhanced by male scent during the follicular phase – and these effects occurred independent of any effects on mood [44].

Functional magnetic resonance imaging (fMRI) and derivative techniques have assisted in identifying areas of the brain relevant to sexual function (figure 5). Sexual (pleasant) imagery is primarily associated with activation in the dominant or L > R brain hemisphere [45]. Visual sexual stimulation (VSS) activates the occipital cortex, inferior frontal lobe, cingulate gyrus, insula gyrus, corpus callosum, thalamus, caudate nucleus, globus pallidus, and inferior temporal lobe. Other studies have shown evidence of activation associated with penile tumescence in the right sub-insular region including the claustrum, left caudate and putamen, right middle occipital and middle temporal gyri, bilateral cingulate gyrus, right somatosensory and pre-motor regions and in the right hypothalamus [46]. PET and MRI techniques show activation of the somatosensory thalamus and in the region of the nucleus of the solitary tract, which is the brainstem nucleus to which the vagus nerves project. This can be seen in women with complete SCI at the midthoracic level suggesting that vagus nerves can convey genital sensory input directly to the brain in women [23].

The new technologies that enable the mapping of

Figure 5: Functional magnetic resonance imaging (fMRI) during sexual arousal (A) and cocaine craving (B). Anterior Cingulate Gyrus is activated in both circumstances.
4. CNS NEUROTRANSMITTERS

The complexity of the types and subtypes of neurotransmitters that have potential involvement in sexual function is vast and increasing. There are reasonably established roles for a few that are currently clinically important. Dopamine (DA) clearly has a role in the PVN and MPOA in facilitating erections and there may be activity in the spinal cord. Increased levels of dopamine in the MPOA increase both reflexive and noncontact erections in rodents [47]. Human evidence of the effects of dopamine agonism in the erectile pathway derives from clinical trial responses to sub-lingual apomorphine [48]. Centrally and experimentally, dopamine also has an impact on the perception of reward (more is better) and the implications of this in the context of sexual pleasure or reward in human males and females are not yet fully investigated although apomorphine has no impact on conventional measures of male sexual desire in men with normal desire [49].

In general terms, DA is supportive of copulation and 5-HT is inhibitory. DA is released in the MPOA at the time of ejaculation (5-HT is not) and changes in DA and 5-HT in different areas of the brain may promote copulation and sexual satiety, respectively [50]. Testosterone enhances DA release in the MPOA at rest and with sexual challenge possibly by upregulating NOS, which increases NO thereby increasing DA release. The same pattern of copulatory activity promoting DA release in the MPOA and the enhanced effect of the presence of sex hormones is seen in female rats. Longer lasting changes may be seen through the post-copulatory effects of gene expression and this expression increases with increased sexual experience – effectively changing the phenotype of certain cells in sexually experienced animals.

Cells of the MPOA have high densities of \( \alpha_2 \)-noradrenergic receptors, as well as DA receptors and the effects of DA in the MPOA are most likely facilitated by the activation of \( \alpha_2 \) (inhibition) and \( \alpha_1 \) (excitation) adrenoceptors due to cross talk within CNS catecholamine systems [51].

Gamma aminobutyric acid (GABA) activity in the paraventricular nucleus provides a mechanism to balance (inhibit) pro-erectile signaling [52]. GABAergic (A) receptor agonism in the PVN can reduce both pharmacologically (apomorphine) and physiologically induced (NCE) erections.

Serotonin (5-HT) and thyrotropin-releasing hormone (TRH) are other candidates for inhibitory control. Both 5-HT and TRH (intrathecal) exhibit inhibitory effects on penile erection through common or parallel sets of neurons [53]. 5-HT and TRH activity modulation may therefore be expected to have potential benefit for erectile function if suitable compounds and routes of delivery can be found.

Oxytocin is well known to be associated with reproductive and erectile pathways and has been shown to be capable of inducing erection when introduced into the hippocampus (rat). Intracavernous (systemic) oxytocin is not effective [54]. The potential for oxytocinergic compounds that cross the blood-brain barrier and can be delivered readily has yet to be fully explored.

The expression of inducible NO synthase (iNOS) increases with age in the PVN and MPOA and in regions known to control the synthesis and release of gonadotropin releasing hormone (GnRH) and oxytocin. iNOS, and hence increased NO, may impact serum testosterone, spermatogenesis, and copulatory function in the aging male animal [55].

Nitric oxide (NO) is a physiological mediator of penile erection at the level of the paraventricular nucleus of the hypothalamus [56] and at other levels of the neural pathway supporting sexual response. The presence of NO and the soluble guanylyl cyclase needed to generate the second messenger cyclic GMP (cGMP) are present throughout the human brain. The NO/cGMP pathway is affected by aging in the human brain and offers a potentially significant but unexplored site for mediating the deleterious effects of age on sexual function [57]. Testosterone or its metabolite DHT down-regulates NO synthase (NOS) activity and mRNA expression, and the number of neuronal NOS+ neurons [58]. Direct evidence of the importance of NO in central signaling related to erectile function resulted from a series of experiments designed to alter CNS NO activity [59]. Manipulation of NO or cGMP levels altered MPOA triggered intracavernous pressure response through CNS not peripheral mechanisms.

The melanocortins have relevance to central control of sexual function and the MC4 receptor (MC4R) appears to be most responsible for the stimulation of penile erection (and appetite control). Small molecule analogs active at the MC4R have been assessed.
and one such is the second modern centrally active compound to enter formal human studies [60]. These are believed to work through the familiar hypothalamic pathways.

Galanin, when administered by intracerebroventricular injection to mice appeared to enhance motivational aspects of sexual function. No other changes in sexual performance were identified [61]. Further investigation of the galanin system has failed to reveal any important natural role.

5. MIND AND BRAIN

There is a convention of dividing erectile dysfunction into organic and psychogenic etiologies. There are problems with this dichotomy because of its lack of precision and its reliance on old concepts of mind and body distinctions. There is now a good understanding of the neurobiology of psychological disorders and the implication to the patient that it is all in his mind is not helpful. Psychogenic has been misused to imply either the imaginary nature of the problem or that drugs have little or no role. Diagnosis by exclusion denies this neurobiological understanding and also limits the ‘organic’ label to only that which is obvious and measurable by today’s methods. Since the distinction between organic and psychogenic is not clearly defined it is not testable and the distinction does not advance diagnosis, treatment or research in ED. An alternative view, supported by the Nomenclature Committee of the International Society for Impotence and Sex Research, contrasts organic and situational ED, a class reserved for episodic occurrences of ED clearly due to particular attributes of sexual encounters. The organic category now includes several of the causes of ED previously thought to be psychogenic [62]. Looking forward one can imagine that with the current level of sophistication in science the understanding of neurobiological disease will grow rapidly and with great diversity at the same time as cardiovascular understanding reaches many significant goals. This understanding will have great implications for sexual dysfunction management and the interface between sexual biology and behavior [63].

6. ORGASM AND EJACULATION

The literature on the neurophysiological basis for orgasm is scant. Probably on a cultural basis this is one of the least discussed aspects of male human sexual function. A majority of men still have little understanding of the relative independence of erection and orgasm. The decline in parameters and experience of orgasm and ejaculation with age is also well established but little known to patients. At the same time it is also an issue of pivotal importance to the management of sexual problems in many women. The physiological basis of aspects of sexual function that have relevance to pleasure, not merely procreation, will receive close attention now that the study of female sexual dysfunction (FSD) is receiving attention.

Orgasm is probably a spinal level reflex, it may persist after spinal cord injury (SCI), although clearly the appetitive and reward aspects of orgasm are represented at much higher levels [64]. Genital stimulation in animal models may produce a response that simulates the rhythmic activity seen in orgasm and this is associated with cavernous nerve activity. The male and female orgasm have similar electrophysiological appearances [65,66]. Positron emission tomography (PET) techniques (semi-quantitative 99mTc-HMPAO) have been applied to the study of orgasm in healthy young men. Cerebral blood flow decreases during orgasm except in the right prefrontal cortex, where the cerebral blood flow increases [67].

Plasma prolactin (PRL) concentrations (but not testosterone) increase for about an hour following orgasm (masturbation and intercourse) in both men and women. The equivalent stimulation but without orgasm leaves PRL levels within the normal, lower, range [68]. In experimental and clinical conditions elevated levels of PRL are frequently associated with reductions in sexual activity. Thus the surge in PRL post-orgasm may have a role in suppressing sexual behavior through a feedback process that is systemic but probably acts centrally - a PRL mediated neuroendocrine reproductive reflex. Orgasm increases blood pressure, heart rate, plasma catecholamines as well as prolactin. After sexual abstinence serum testosterone may be higher while no changes in other measured sex hormones have been documented [69]. Certain central structures (nucleus accumbens (NA)) are functionally altered by the experience of even just one ejaculation [70]. This may have implications in learning, sexual motivation and reward.

II. PHYSIOLOGICAL REGULATION OF PENILE SMOOTH MUSCLE TONE

The state of the tone of penile smooth muscle (arterial and trabecular) determines the hemodynamic events that maintain penile flaccidity or elicit erec-
In the flaccid penis, smooth muscle tone is heightened. Penile erection on the other hand requires a decrease in the tone of penile smooth muscle.

The contractile activity of the penile muscle (arterial and trabecular) is regulated by several factors: adequate levels of agonists (neurotransmitters, hormones, and endothelium-derived substances), adequate expression of receptors, integrity of the transduction mechanisms, calcium homeostasis, interaction between contractile proteins, and effective intercellular communication among smooth muscle cells (gap-junctions) [71]. The balance and interaction between relaxant and contractile factors determines the final outcome of the penile smooth muscle tone (figure 7).

IIa. PENILE SMOOTH MUSCLE CONTRACTION

The contraction of smooth muscle depends on the rise, relatively rapid, of the intracellular concentration of free calcium and the sensitivity of the contractile machinery to calcium. The net response of calcium sensitizing mechanisms to contractile and relaxant factors determines the tone of the smooth muscle.

1. ALPHA-ADRENERGIC MECHANISMS

Locally, the detumescence of the erect penis is mediated by adrenergic nerve terminals whose neurotransmitter, norepinephrine (noradrenaline), activates adrenergic receptors on the penile smooth muscle membrane. Contraction of human penile arteries and trabecular smooth muscle is largely mediated by $\alpha_1$ adrenergic receptors [72,73]. The $\alpha_{1d}$ and $\alpha_{1a}$ subtypes are the ones expressed with higher density in the trabecular muscle [74]. The $\alpha$-adrenergic receptors can also be stimulated by circulating catecholamines (norepinephrine as well as epinephrine). Contraction mediated by $\alpha_2$-receptors depends on the entry of calcium from the extracellular compartment while the activation of $\alpha_1$ receptors provokes the release of intracellular calcium, initially, with subsequent extracellular calcium entry for the maintenance of the contractile tone. Adrenergic stimulation causes vasoconstriction of the penile arteries and contraction of the trabecular smooth muscle which results in the reduction of the arterial inflow and in the collapse of the lacunar spaces res-
pectively. The contraction of the trabecular smooth muscle causes decompression of the drainage venules from the cavernous bodies, allowing the venous drainage of the lacunar spaces [75-77]. The administration of α-adrenoceptor blockers into the corpus cavernosum facilitates erection [78,79] and α-adrenoceptor agonists cause detumescence [80] further confirming the role of α-adrenoceptors in the regulation of penile smooth muscle tone.

1. ENDOThELIN

The peptide endothelin has been suggested to participate in the maintenance of penile flaccidity [81]. Endothelin-1 is a member of a family of three peptides [82] and is a potent constrictor synthesized by the lacunar endothelium and, possibly, by the trabecular muscle itself [81,83]. Its presence and constrictor activity in human cavernous tissue suggests the participation of this peptide in the regulation of trabecular smooth muscle contractility. It has been also demonstrated that endothelin potentiates the constrictor effects of catecholamines on trabecular smooth muscle [84]. Two receptors for endothelin, ET₄ and ET₂, mediate the biological effects of endothelin in vascular tissue. ET₄ is the principal mediator of the contraction in response to endothelin while ET₂ prevails in endothelium, mediating an endothelium-dependent vasodilator response. The mechanism of intracellular transduction for both receptors is the activation of the metabolism of inositol-phosphate, with release of intracellular calcium and activation of protein kinase C (PKC). Endothelin has also been suggested to regulate smooth muscle proliferation in the penis [85]. A recent study has shown no change in endothelin-1 concentrations in the peripheral and cavernous blood during erection [86]. Further studies are required to establish whether or not endothelin is released during neurogenic erectile stimulation.

2. ProstAnoids

Several constrictor prostanoids, including PGH₂, PGF₂α, thromboxane A₂ (TXA₂) are synthesized by the human cavernous tissue. In vitro studies have demonstrated that prostanoids are responsible for the tone and the spontaneous activity of isolated trabecular muscle [87]. Different prostanoids are generated in the human corpus cavernosum from arachidonic acid through the activity of cyclooxygenase. Production of contractile prostanoids antagonizes relaxant effects of those with relaxant capacity [88]. Functional characterization of prostanoid receptors in human trabecular and arterial penile smooth muscle revealed that only TP-receptors mediate contractile effects of prostanoids in these tissues [88]. Also it has been observed in vitro that constrictor prostanoids, simultaneously released with nitric oxide, attenuate the dilator effect of the latter [89,90]. The correlation of these in vitro findings with the physiological regulation in vivo is not yet established.

3. ANGIOTEnsin

Renin-angiotensin system could also play a significant role in the maintenance of penile smooth muscle tone. Angiotensin II has been detected in endothelial and smooth muscle cells of human corpus cavernosum, where is locally produced. [91]. Angiotensin II evokes contraction of human [92] and rabbit [93] corpus cavernosum in vitro. The contractile effects of angiotensin II are probably mediated by interaction with AT-1 subtype receptors, since the blockade
of these receptors prevents angiotensin II-induced contractions in rabbit corpus cavernosum [93]. AT-1 receptors are G-protein coupled receptors. Contractile effects mediated by these receptors involves Gq stimulation that activates phospholipase C, promoting IP3 generation and subsequent intracellular calcium increase [94]. Intracavernosal injection of angiotensin II reverses spontaneous erections in dogs, while the AT-1 receptor antagonist, losartan produces intracavernosal pressure increases in these animals [91]. Finally, intracavernosal blood levels of angiotensin II, which are higher than in systemic peripheral blood, increase in detumescence phase [95]. Thus, local production of angiotensin II could increase penile smooth muscle contractility by way of AT-1 receptors facilitating detumescence of the penis.

**IIb. INTRACELLULAR MECHANISMS REGULATING SMOOTH MUSCLE CONTRACTION**

Once the penile smooth muscle is activated by the excitatory substances (vasoconstrictors) mentioned above, intracellular free calcium concentrations ([Ca2+]i) increase. This rise in [Ca2+]i is secondary to activation of various signalling mechanisms such as phospholipase C and inositol trisphosphate (IP3) resulting in release of calcium from intracellular stores such as sarcoplasmic reticulum and/or opening of calcium channels on the smooth muscle cell membrane leading to an influx of calcium from extracellular space. This increase is usually transient where [Ca2+]i returns to near basal levels despite the fact that the constrictor activity is still present (figure 8). During this transient phase the increase in [Ca2+]i leads to activation of calcium-calmodulin dependent myosin light chain kinase (MLCK). Activated MLCK phosphorylates myosin light chain (MLC20) therefore initiates the smooth muscle contractility (96,97).

Once the [Ca2+]i returns the basal levels, the calcium-sensitizing pathways take over. One such mechanism is via activation of excitatory receptors coupled to G-proteins which can also cause contraction by increasing calcium sensitivity without any change in [Ca2+]i. This pathway involves RhoA, a small, monomeric G protein that activates Rho-kinase. Activated Rho-kinase phosphorylates and thereby inhibits the regulatory subunit of smooth muscle myosin phosphatase (SMPP-1M) preventing dephosphorilation of myofilaments which maintain contractile tone (figure 9) [98].

RhoA and Rho-kinase have been shown to be expressed in penile smooth muscle [99,100]. Interestingly, the amount of RhoA expressed in the cavernosal smooth muscle is 17 fold higher than in the vascular smooth muscle [100]. A selective inhibitor of Rho-kinase has been shown to elicit relaxation of human corpus cavernosum in vitro and to induce penile erection in animal models [101,102]. Anesthetized rats transfected with dominant negative RhoA exhibited an elevated erectile function as compared with control animals [103].

The emerging consensus is that the phasic contraction of penile smooth muscle is regulated by an increase in [Ca2+]i and the tonic contraction is governed by the calcium sensitizing pathways [104].

**IIc. PENILE SMOOTH MUSCLE RELAXATION**

Dilation of the penile arteries (cavernous artery and helicine arteries), is the first event in the development of erection. Its consequence is the increase of blood flow and pressure into the lacunar spaces. Following arterial dilation, the trabecular muscle relaxes increasing the compliance of the lacunar spaces to its expansion facilitating the accumulation of blood. The relaxation of the muscle depends on endocrine (circulating substances), paracrine (substances released from neighboring nerves and endothelium) as well as, possibly, on autocrine (substances generated within the smooth muscle) mechanisms (figure 10).

**1. MODULATION OF PENILE SMOOTH MUSCLE CONTRACTILITY BY ENDOTHELIA**

The endothelium is the key regulator of vascular physiology and has a fundamental role in the process of erection. In fact, diseases in which endothelial dysfunction develops, such as in diabetes mellitus, hypertension, hypercholesterolemia or aging, are associated with a high prevalence of erectile dysfunction [105].

Many substances that influence smooth muscle contractility are produced by the endothelium. These include substances promoting contraction (endothelin, TXA2, ...) or relaxation (NO, PGF2, ...) of the adjacent smooth muscle. However, preservation of the endothelial function is usually associated to the maintenance of adequate relaxation of vascular
smooth muscle and to the modulation of contractile responses. In response to humoral or paracrine stimuli, the endothelium releases factors that promote smooth muscle relaxation. Endothelium-dependent vasodilators (acetylcholine, bradykinin,...) produce vascular smooth muscle relaxation by acting on specific endothelial receptors that provoke an increase of intracellular Ca$^{2+}$ in the endothelial cell. This Ca$^{2+}$ increase triggers the activity of endothelial enzymes which are responsible for the synthesis of local mediators that relax neighboring vascular smooth muscle. Intracavernous injection of acetylcholine induces erection, as it has been demonstrated in animal models [106,107].

In human corpus cavernosum, nitric oxide (NO) is the only mediator of endothelium-dependent relaxation while in human penile resistance arteries, endothelium-dependent relaxation is mediated by NO and by another mechanism that does not involve NO synthesis or cyclooxygenase activity. This process is mediated by Ca$^{2+}$-activated K$^+$-channels and is attributed to endothelium-derived hyperpolarizing factor (EDHF) [108].

2. NITRIC OXIDE AND THE cGMP PATHWAY

Nitric oxide (NO) is a free radical (the molecule has an unpaired electron); therefore it is a highly reactive and chemically unstable molecule. It is now known that this molecule is synthesized in different types of cells in mammals and that it is involved in the regulation of diverse physiological processes including smooth muscle relaxation, platelet reactivity, central and peripheral neurotransmission, and the cytotoxic actions of immune cells [109,110].

Nitric oxide synthase (NOS), uses the amino acid L-arginine and molecular oxygen to produce NO and the amino acid L-citrulline. This reaction requires tetrahydrobiopterin and NADPH. Three distinct isoforms of NOS have been identified which share 50-60% homology. Two constitutive forms, neuronal NOS (nNOS) and endothelial NOS (eNOS), are present in the nervous system and vascular endothelial cells respectively. Both isoforms require calcium and calmodulin for activity. A third calcium-independent isoform, inducible NOS (iNOS) can be isolated from a variety of cells following induction with inflammatory mediators and bacterial products [109,110].

nNOS and eNOS are expressed in the cholinergic nerves and endothelium of the penis, respectively [111-116]. Under physiological conditions iNOS is not expressed in the penis, however following an exposure to inflammatory mediators iNOS has been shown to be expressed in the urogenital smooth muscle [117].

Postganglionic parasympathetic (cholinergic) nerves which have nNOS in their structure and release NO as a co-transmitter with acetylcholine are now termed as nitrergic nerves [113,118]. Stimulation of cavernous nerve activates nitrergic nerve fibres therefore elicits NO release [119,120] at the nerve terminals which causes relaxation of penile smooth
muscle (figure 11). In various animal models penile erection induced by stimulation of cavernous nerves or spinal cord can be inhibited by NOS inhibitors [111,121-123]. Moreover in vitro non-adrenergic non-cholinergic (NANC) stimulation of penile blood vessels or corpus cavernosum leads to nitrergic relaxation responses which can be blocked by NOS inhibitors [119,124-127].

Another source of NO is eNOS which is present in the sinusoidal endothelium in the corpus cavernosum and in the endothelium of penile blood vessels (figure 11). Three theories can be put forward for the involvement of eNOS in erectile function. Firstly acetylcholine released from postganglionic cholinergic nerves may evoke release of NO from endothelium. Indeed exogenous administration of acetylcholine produces endothelium-dependent relaxation in the isolated corpus cavernosum or penile arteries [89,128]. However atropine or neostigmine does not inhibit cavernous nerve-induced penile erection [111,129]. Furthermore, neurogenic relaxation of corpus cavernosum does not require a functional endothelium [126,130]. A second possibility for involvement of eNOS can be due to the activation of eNOS by shear stress [131]. During erection the expansion of vascular and sinusoidal lumen can cause shear stress which may lead to activation of protein kinase Akt (also known as PKB) and subsequent phosphorylation and activation of eNOS, facilitating NO release from the endothelium [132]. Thirdly, substances in plasma, such as bradykinin, and oxygen may trigger NO production by the endothelium upon the entrance of oxygenated blood in the corpora cavernosa. Therefore the emerging consensus is that NO derived from nNOS in the nitrergic nerves is responsible for the initiation and majority of the smooth muscle relaxation whereby NO from eNOS contribute to the maintenance of the erection.

The activity of nNOS can be affected by the binding of additional factors such as the protein inhibitor of NOS (PIN) [133], the NMDA receptor (NMDAR) [134], or the carboxy-terminal PDZ ligand of nNOS (CAPON) [135] to an N-terminal PDZ sequence in nNOS. Although these nNOS modulators have been
shown to be expressed in the penis [136,137] their role in the regulation of penile erection remains to be established.

Although the role of nNOS in mediating penile erection is well established, genetically engineered nNOS knock-out mouse is fertile and has intact neurogenic NO production in the penis [138]. This contradiction has later been resolved by the finding of the expression of a variant of nNOS (penile nNOS; PnNOS) in the penis of nNOS knock-out mice [139]. Interestingly central nervous system variant of nNOS (CnNOS) is not found in substantial amounts in the rat penis, therefore it may be inferred that the PnNOS is the main nNOS variant responsible in this animal [139]. Further studies will be required to identify human variants of nNOS in the penis and their potential for gene-therapy approaches to erectile dysfunction [140].

The activity of nNOS in the penis has been found to be regulated by androgens. Castration of adult rats reduces the erectile response to stimulation of cavernosal nerve, and the activity of nNOS in the penis; both changes are prevented by androgen administration [141-144]. Whether or not androgens affect the expression of the nNOS protein and mRNA is disputed [141-144]. Further investigation is necessary to explain the molecular mechanisms involved in erectile dysfunction due to androgen deficiency in elderly men and due to anti-androgen treatment in benign prostatic hyperplasia.

Unlike many other regulatory substances, such as the classic neurotransmitters (e.g. acetylcholine, norepinephrine), NO does not have a specific receptor on the cellular membrane. NO crosses cell membrane targeting the enzyme soluble guanylate cyclase (sGC) in the cytoplasm. The binding of NO to sGC produces a conformational change in the protein and increases its activity [145]. Activated sGC catalyzes the conversion of guanosine-5'-triphosphate (GTP) to guanosine 3', 5' cyclic monophosphate (cGMP) (Figure 4). cGMP signals via three different ways in eukaryotic cells; ion channels, phosphodiesterases and protein kinases. Through these interactions the increase in intracellular cGMP concentrations sets in motion a cascade of intracellular events which induce a loss of contractile tone. These include: hyperpolarization, closure of voltage activated calcium channels, sequestration of calcium by intracellular organelles, prevention of an increase in intracellular calcium and desensitization of contractile apparatus (figure 12).

Nitrergic nerve stimulation or administration of exogenous NO causes an increase in intracellular cGMP concentrations in the penile corpus cavernosum [125,146,147]. Selective inhibitors of sGC have been shown to inhibit nitrergic relaxation responses of the penile smooth muscle [148-150]. All these findings confirm that nitrergic neurotransmission operates via stimulation of sGC and elevation of cGMP concentrations in the penile smooth muscle.

One of the targets of cGMP is cGMP-dependent protein kinases (cGK) of which two different isoforms have been identified in mammals: cGKI and cGKII [151]. The abundant isoform in the smooth muscle is cGKI [152]. cGKI knock-out mice have very low

Figure 12 : Schematic representation of the mechanisms involved in penile smooth muscle relaxation by the cGMP pathway. GC, guanylate cyclase; IP3, inositol triphosphate; PKA, protein kinase A; PKG, protein kinase G; PLB, phospholipase B; PLC, phospholipase C; NO, nitric oxide.
ability to reproduce and their corpora cavernosa fail to relax on activation of the NO-cGMP pathway [153]. This suggests that cGMP-independent (i.e. VIP, cAMP) and cGK-independent (i.e. direct action of cGMP on ion channels) pathways play a minor role in erectile physiology.

3. The cAMP pathway

Vasoactive intestinal peptide (VIP), in the autonomic nerves, prostaglandin E (PGE1 and PGE2), prostacyclin, synthesized by the smooth muscle and endothelium, and neural or circulating catecholamines, stimulate specific receptors coupled to Gs proteins with stimulation of the adenylate cyclase (AC), that catalyzes the formation of adenosine 3’, 5’ cyclic monophosphate (cAMP) (figure 13). As mentioned above AC-cAMP pathway might have a minor role in the physiology of erectile function however when stimulated exogenously (i.e. PGE1 administration for the treatment of erectile dysfunction) it proves to be an efficient route for the relaxation of the penile smooth muscle.

During the 80’s great attention was given to VIP as the possible mediator of erection. This proposal was based on the observation of nerve fibers that contained VIP in cavernous tissue and that exogenous VIP was a potent relaxant of the smooth muscle of the penis [154,155]. Furthermore, the intracavernosal administration of VIP caused tumescence and rigid erection in some individuals [156]. VIP and nNOS have been shown to co-localize in nerves within the corpus cavernosum [157]. VIP has been assumed to be released at high frequency nerve stimulation; however VIP-antagonists and peptidases have failed to inhibit these relaxation responses [158,159]. Therefore the exact role of VIP in the penis and whether or not it is released during erectogenic nerve stimulation still remain to be established.

Prostaglandin E1 and E2 are the most abundant prostanoids synthesized by the smooth muscle of the penis [160,161]. The receptor(s) that mediates relaxation to PGE is designated as the EP receptor. Four subtypes of EP receptors exist, but only EP2 and/or EP4 subtypes are present, at the functional level, in arterial and trabecular penile smooth muscle [88]. These receptors are coupled to Gs proteins, which stimulate adenylate cyclase. Prostacyclin (PGI2) is also produced in human corpus cavernosum [162]. This prostanoid produces relaxation of vascular smooth muscle by means of specific IP receptors which are also coupled to Gs proteins. In human corpus cavernosum smooth muscle, PGI2 fails to produce any relaxant effect, probably due to the lack of functional IP receptors in this tissue. However, this is not the case for human penile arteries were IP receptors co-exist with EP2/EP4 receptors. Indeed, PGI2 cause vasodilation in human cavernous artery [163] as well as in penile resistance arteries [88].

Finally, the stimulation by catecholamines of β-adrenergic receptors, causes relaxation of arterial and trabecular smooth muscle [72,164]. The β2 subtype is probably the most important receptor mediating these effects [165]. However the density of β-adrenoceptors is only one-tenth of the density of α-adrenoceptors in the corpus cavernosum [166].
ver, since neurogenic relaxation is not affected by \(\beta\)-adrenoceptor antagonists [167] and intracavernosal injection of \(\beta\)-agonists does not induce full erection in humans [129], \(\beta\)-adrenoceptors seem to be of less importance among the actions of noradrenergic neurotransmission in the urogenital tract. There is evidence in the vascular system that the expression of \(\beta\)-adrenergic receptors decreases with age, giving way progressively to the constrictor mechanisms (\(\alpha\)-adrenergic) which would prevail [168]. Whether or not a similar change during aging occurs in the penile smooth muscle remains to be established.

4. Phosphodiesterases

Phosphodiesterases (PDEs) are the enzymes that breakdown cGMP and cAMP, and therefore regulate the levels of these compounds in tissues. In the penis, nitric oxide (NO) released in the nerve terminals upon sexual stimulation activates guanylyl cyclase to synthesize cGMP which in turn stimulates protein kinase G (PKG) to phosphorylate myosin and eventually triggers a reduction in intracellular Ca\textsuperscript{2+} that induces the relaxation of the corpora cavernosa smooth muscle. The maintenance of a high cGMP concentration is therefore essential for erectile function, and this may be achieved by selective inhibitors of PDE5, a cGMP-dependent PDE, such as sildenafil, tadalafil or vardenafil. cGMP may also cross-activate cAMP pathways such as PKA [169] or interconvert with cAMP [170]. Since the development of this compound for the treatment of erectile dysfunction a considerable number of studies have been published regarding the detection, purification, sensitivity to selective inhibitors, and enzymatic activity of PDEs in the penis, but naturally, they have been mainly focused on PDE5 [171,172]. As a result, comparatively little information is available on the tissue localization and regulation of expression of PDEs in the penis, and surprisingly, even on PDE5. This is perhaps a reflection of the immediate needs to characterize the therapeutic efficacy of these compounds on erectile dysfunction, but at the same time neglects the possible functional significance of other PDEs present in the penis, such as 1,2,3,4, and 9, some of which have been shown to be essential for the control of blood flow in the penis [173-175], and, more recently, for the counteraction of fibrosis in the tunica albuginea [176]. This section will focus on the molecular biology and functional significance of PDEs in the penis and will not address the clinical aspects of PDE inhibitors unless relevant to this discussion.

The PDE class I in mammals comprises 10 families designated with numbers from 1 to 10, with either one or several genes per family, named with letters from A to D, and some with subtypes of splicing variants, differentiated with numbers, e.g., PDE5A1 [177-179]. Families are classified according to their absolute specificity in the catalytic and regulatory domains for cAMP (PDE4,7,8), cGMP (PDE5,6,9), or mixed cAMP/cGMP (PDE1,2,3,10) and their response to well characterized inhibitors, such as in the case of PDE7 and 8, that are insensitive to rolipram and IBMX, respectively. They comprise a series of proteins that share a 270 amino acids catalytic domain located carboxy terminal to its regulatory domain that includes an allostERIC site.

The main approaches used to study the PDEs expressed in the penis are as follows:

a) Biochemical detection and enzyme purification from corpora cavernosa extracts.

Conventional protein purification techniques, such as anion exchange chromatography, HPLC, calmodulinagarose affinity resin, and other procedures, combined with the detection in the different elution fractions of PDE enzyme activity based on the hydrolysis of cAMP or cGMP, the effect of Ca\textsuperscript{2+}/calmodulin [177], and catalytic inhibitors were initially utilized to characterize PDE5, the target of sildenafil, tadalafil or vardenafil effects, and identify which other penile PDE enzymes may be affected by these drug. This is shown on figure 14, where the profile of elution for PDEs in a human penile extract indicates the presence of a low-salt elution peak for PDE-5 accompanied by cAMP-dependent PDE2.

![Figure 14](image-url)
and 3, in the order of salt concentrations, but no other enzyme activities were resolved [177]. This procedure also allowed to demonstrate that there is a species specificity, since no PDE3 was detected in the rabbit penis (activity insensitive to milrinone), whereas PDE1 and 2 were found to be present, with PDE5 [178,179]. However, the presence of PDEs7 to10 was not investigated. In any case, caution needs to be exercised in extrapolating data on PDE content in the penis from the animal models to the human penis.

b) Application of selective inhibitors in corpora cavernosa strips or tissue homogenates.

This approach has been the most used because it satisfies simultaneously the primary interest of pharmacological characterization of the response of the erectile mechanism to the selected inhibitors, while detecting indirectly the types of PDE activities affected in the penis by compounds whose mechanism of action was already known. For instance, the presence of PDE-5 has been confirmed not only by the sensitivity of the relaxation of corpora cavernosa strips to sildenafil [180], or the increase in the levels of cGMP by this compound [181-184], but also by other inhibitors such as zaprinast, whose specificity of action on PDE-5 had been demonstrated in other non-penile tissues [185-188]. For instance, by applying rolipram and milrinone, specific PDE4 and PDE3 inhibitors, respectively, it was shown that this isoform is also present in human penile arteries and veins [189], the relaxation appears to be endothelium-independent, and these agents act at lower concentrations than sildenafil. Rolipram elicits an erectile response in the rabbit, and milrinone relaxes the human corpora cavernosa as potently as sildenafil, and induces erections in men comparable to the human corpora cavernosa and vardenafil (0.7 nM in bovine corpora cavernosa) and vardenafil (0.7 nM in bovine PDEs) are much more potent than zaprinast, and IBMX, and rolipram. In turn, the IC₅₀ has been determined for each of these inhibitors with preparations of several PDEs, in order to ascertain their specificity for each PDE enzyme [180-184], and compare it with the relative potency.

Some of these in vitro characterizations have been confirmed in vivo in the rat and rabbit by measuring the erectile response of the penis to the effect of the selective inhibitors under suboptimal electrical field stimulation of the cavernosal nerve in anesthetized dogs or rats [190-192], or in the conscious rabbit model receiving sodium nitroprusside as NO donor [193].

c) Detection of PDE mRNAs in total RNA from the corpora cavernosa.

The comparatively simple and highly sensitive procedure of RT/PCR has been applied to detect PDEs in the penis that may be poorly expressed or have not been detected in other studies at the protein level. A single comprehensive identification of the penile PDE mRNA profile has been recently published [194], where a total of 13 genes were found to be expressed in human corporal biopsies, belonging to all families except for PDE3B and PDE10A, where primers were not available, and for PDE6. The advantage of this technique is that it allows to detect each individual splicing or alternate promoter usage variant for every isoform, a pattern that would be virtually impossible to obtain for their putative encoded proteins. The main shortcoming is obviously that expression of a given mRNA does not necessarily indicate that it is translated into the respective protein.

A similar RT/PCR approach combined with a procedure named rapid amplification of cDNA ends (RACE)/PCR was applied by Lue’s group to the human corpora cavernosa, but using variant-specific primers exclusively for PDE5 [195,196]. They identified PDE5A2 and PDE5A1 in this order of abundance in the human cavernous tissue, followed by PDE5A3, which is expressed only in tissues with substantial amounts of smooth muscle. In addition, expression of the latter variant was absent in some patients. The numbers identify the PDE5 exons in the order they are located in the gene (figure 15). Expression of the recombinant constructs in a cell line showed that the Km for cGMP was around 6 µM for the three variants, although the IC₅₀ for sildenafil was higher (13-28 nM) than for the native protein. However, in the rat penis, only PDE5A1 and 2 could be detected [197].

In a recent study [176], it has been shown that expression of PDE5A is not limited to the corpora cavernosa smooth muscle as it was assumed from their localization in the arterial media, but it is also expressed in the fibroblasts of the human and rat tunica albuginea, both in vivo and in cell culture, utilizing primers common for the three splicing
variants. PDE-4 mRNA was also detected, and in this case the primers were variant-specific, so that both the A and B variants are present, but not the C.

d) Immunodetection of PDE protein and in situ localization.

There are only two reports on the detection of PDE proteins in penile tissue homogenates by western blot, and this is restricted to PDE5A in both human penile corpora cavernosa [196] and tunica albuginea [176], as well as in rat tunica albuginea [176]. The latter study showed expression of variant 3, which does not agree with the reported absence of the PDE5A3 mRNA cited above. What is even more striking is that as far as we are aware, there is no published evidence on the immunohistochemical or in situ hybridization detection of any PDE in the penis or cells derived from this tissue, with the exception of the recent demonstration of PDE5A in fibroblasts within both the human and rat tunica albuginea, in the smooth muscle of the corpora cavernosa and in cells derived from these tissues [176].

This paucity of studies probably stems from the assumption that what has already been demonstrated in the vascular system and other tissues regarding the presence of both PDE5 and PKG should logically extend to the corpora cavernosa. However, in view of the evidence with different approaches on the expression of at least PDE2, 3, 4, and 9, discussed above, more detailed investigation is needed to ascertain where these enzymes are really expressed at the protein level in the corpora cavernosa. This is particularly important in terms of the novel findings that would suggest a functional significance for PDE isoforms in the penis in tissues other than the cisternae smooth muscle for the control of blood flow through the penile arteries [189] or fibrotic processes in the tunica albuginea [176]. In addition, the role of cAMP (produced by PDEs 2-4) as compared to cGMP in penile erection is not clear, considering that PGE1 or VIP raise cAMP levels, although only PGE1 causes full erections. This may occur via PKA, or cross-activation of PKG; the latter possibility has recently been demonstrated to occur [198]. However, the cGMP-dependent kinase I deficient mice has poor reproductive ability and their corpora cavernosa fails to relax on activation of the cGMP cascade, thus suggesting that the cAMP signaling is only moderately active for penile erection [153].

e) Regulation of PDE activity and/or expression in the penis.

This is a fundamental topic, since if PDEs can be transcriptionally regulated by their substrates, cGMP or cAMP, there could be the possibility that a long-term treatment with PDE inhibitors that would enhance for sustained periods the levels of these cyclic nucleotides, could actually up- or down-regulate the levels of the PDE themselves. In the case of PDE-5, the human gene has been mapped to chromosome 4q26, and shown to span for about 100 kb with 23 exons [199,200]. The promoter region for this gene has also been cloned and shown to contain two separate promoters, one directing the synthesis of any PDE in the penis or cells derived from this tissue, with the exception of the recent demonstration of PDE5A in fibroblasts within both the human and rat tunica albuginea, in the smooth muscle of the corpora cavernosa and in cells derived from these tissues [176].

Since they contain cGMP response elements that are activated by binding cGMP, the PDE5 inhibitors could hypothetically up-regulate the synthesis of its own target, and therefore after prolonged and continuous treatment with these drugs, decrease cGMP levels when the drug is not administered.

On the other hand, regulation of PDE activity occurs by a) substrate availability; b) extracellular signals that alter intracellular signaling (phosphorylation, protein/protein interaction, Ca2+/calmodulin, etc); and feedback regulation by cAMP, allosteric cGMP, etc. Perhaps because of the pharmacological efficacy of the PDE5A inhibitors, virtually no studies have been reported on the physiological regulation of this activity.
enzyme in the penis, and whether there is a pathophysiological up-regulation associated with erectile dysfunction resembling the down-regulation occurring with the NOS system itself.

5. RELAXATION THROUGH HYPERPOLARIZATION OF THE SMOOTH MUSCLE CELL.

Hyperpolarization of smooth muscle cell causes the closure of voltage-dependent calcium channels, therefore reducing the calcium entry from the extracellular compartment, with decrease in the concentration of intracellular free calcium and subsequent relaxation of the muscle. One of the mechanisms by which the smooth muscle cell hyperpolarizes is through the opening of potassium channels (K+-channels). The opening of ATP-sensitive K+-channels (K_ATP) and Ca^{2+}-activated K+-channels (K_Ca) causes hyperpolarization and relaxation of vascular smooth muscle. The presence of these two types of channels has been revealed, at the functional level, in human corpus cavernosum smooth muscle [203]. Pharmacological stimulation of K_ATP channels induces relaxation of penile smooth muscle [204]. Furthermore, PNU-83757, an opener of K_ATP channels, has been shown to be effective to induce penile erection when intracavernosally administered in patients with erectile dysfunction [205].

The opening of large-conductance K_Ca channels, also known as maxi-K, has been found to hyperpolarize and relax human corpus cavernosum [206].

Hyperpolarization of penile smooth muscle is also important in endothelium-dependent relaxation of human penile arteries where a significant relaxation remains despite blockade of NO and prostaglandin synthesis [108]. This relaxation is prevented by K_Ca channel blockade or by precluding hyperpolarization with a high K+ concentration [108]. This activity has been attributed to the endothelium-derived hyperpolarizing factor (EDHF) that opens K_Ca channels and produces hyperpolarization and vasodilatation. The nature of EDHF remains undetermined although diverse candidates have been proposed, including arachidonic acid derivatives of cytochrome P450 oxygenase activity, hydrogen peroxide, potassium ions, anandamide and C-type natriuretic peptide. In addition, it has been suggested that agonist-induced elevation of intracellular calcium in endothelium could activate endothelial K_Ca channels, producing hyperpolarization of the endothelium that could spread through myoendothelial gap junctions to produce smooth muscle relaxation. Investigation of physiological importance of EDHF has been hampered not only by controversy over its identity, but also by the lack of specific inhibitors of its activity. Nevertheless, EDHF-mediated relaxation of human penile arteries is significantly potentiated by calcium dodecasilicate [108]. Further research is required to study the possible role of EDHF in regulating the local blood flow in the penis during detumescence and erection.

The opening of K+-channels can be stimulated by the cAMP-dependent protein kinase (PKA), by the cGMP-dependent protein kinase (PKG) or by GMPc itself. In human corpus cavernosum, K_Ca channels can be activated by the action of the PGE1 [207] and by a NO donor [208], being these effects mediated by cAMP and cGMP, respectively.

Independently of this mechanism, provoked by the action of the cyclic nucleotides, it has been proposed, in arteries, that nitric oxide can stimulate directly the opening of potassium channels as well as the Na+/K+-ATPase (the sodium pump). This last mechanism has been demonstrated in the trabecular muscle [209] (figure 12). The Na+/K+-ATPase is electrogenic due to the fact that it extracts three positive charges (3 Na+) from the cell while introducing only two (2 K+). Therefore, the cell hyperpolarizes initiating the same mechanisms of closure of calcium channels described after the activation of K+-channels. This process represents, therefore, a mechanism for relaxation that does not depend on cyclic nucleotides.

6. MOLECULAR OXYGEN AS A MODULATOR OF PENILE ERECTION.

The partial oxygen pressure (pO2) in the blood of the cavernous body during the flaccid state is similar to
that of venous blood (~35 mmHg). However, during the erection, due to the increase in arterial blood entering the lacunar spaces, the pO2 increases to approximately 100 mmHg (i.e. the corpora cavernosa are arterialized) [6].

Molecular oxygen is a substrate, together with L-arginine, for the synthesis of nitric oxide mediated by NOS. In corpus cavernosum tissue, it has been demonstrated that the synthesis of nitric oxide is directly regulated by the oxygen concentration [6].

At the low oxygen concentrations that are measured in cavernous body in the flaccid penis, the synthesis of nitric oxide is profoundly inhibited, blocking, therefore, endothelium and neurogenic relaxation of the trabecular muscle. This would help in the maintenance of penile flaccidity since it facilitates constrictor tone by suppressing relaxation.

After arterial vasodilatation, the oxygen concentration in the cavernous bodies rises providing sufficient substrate (O2) so that nitric oxide is synthesized. It has been estimated, after "in vitro" studies, that the minimal concentration of oxygen in the cavernous bodies necessary to reach a full activity of the nitric oxide synthase is between 50 and 60 mmHg.

 Inferior concentrations would induce a partial synthesis of nitric oxide with, subsequently, partial relaxation of the trabecular muscle.

Similarly to the nitric oxide synthase, the prostaglandin H synthase (the ciclooxigenase) is also a oxygenase and uses oxygen as substrate for the synthesis of prostanoids. It has been demonstrated that the oxygen concentration to which one is exposed the cavernous bodies necessary to reach a full activity of the nitric oxide synthase is between 50 and 60 mmHg.

The synthesis of the vasoconstrictor, endothelin, is also subject to modulation by the oxygen concentration. In this case, low oxygen concentrations promote its synthesis and high levels (arterial) inhibit it.

This capacity of the molecular oxygen for regulating the synthesis of endogenous vasoactive substances, make of it an important modulator of the erectile activity of the penis.

IId. REGULATION OF THE BALANCE BETWEEN THE DILATOR AND CONSTRICCTOR MECHANISMS

1. INTERACTION BETWEEN NITRERGIC AND NORADRENERGIC PATHWAYS

Nitricergic neurotransmission is known to modulate noradrenergic responses. Electrical field stimulation (EFS)-induced noradrenergic contractions are enhanced by NO synthase inhibitors in corpus cavernosum and penile resistance arteries suggesting that noradrenergic responses are modulated by nitrenergic neurotransmission. The degree of this modulation varies among species: In the human corpus cavernosum, noradrenergic responses are under nitrenergic control, such that even very high concentrations of noradrenaline fail to show an effect when nitrenergic neurotransmission is operating. This situation is similar in the monkey and rabbit, where nitrenergic neurotransmission does not merely modulate but actually controls the sympathetic responses; however it differs in the rat, mouse and dog where the sympathetic system is predominant [169]. In intracavernosal arteries from experimental animals, prejunctional regulation of NANC nerves by α2-adrenergic receptors has been demonstrated. The activation of these adrenergic receptors inhibits vasodilation induced by NANC nerves in penile arteries and corpus cavernosum [210,211]. Several studies demonstrated that the interaction between the two systems occurs in the smooth muscle, suggesting a physiological antagonism [211-213]. NO-sGC-cGMP-cGKI pathway can lead to inhibition of several sites on the noradrenergic contractile pathway in the vascular smooth muscle such as production of IP3 by phospholipase C [214], inhibition of IP3 receptor [215-217] or inhibition of RhoA/Rho-kinase pathway [218]. The interaction site in penile smooth muscle has not yet been identified.

Nitricergic dominance over noradrenergic system in the penile corpus cavernosum also suggests a key role for this interaction in the pathophysiology of erectile dysfunction. Indeed, a nitrenergic-noradrenergic imbalance in favour of the noradrenergic system due to defective nitrenergic neurotransmission has been implicated in penile tissues from patients and from animal models with erectile dysfunction [219-221].
2. Interaction between NO and Endothelin

Similar to the interaction between nitricergic and noradrenergic pathways, vasoconstrictive actions of endothelin have been shown to be inhibited by NO during erection [222]. Since endothelin and noradrenaline share many intracellular contractile pathways, it would be interesting to study the interaction point of NO and endothelin in the smooth muscle cell.

3. Cholinergic Interaction with Nitricergic and Adrenergic Nerves

Erection is initiated by a sacral parasympathetic nerve input, the preganglionic neurotransmitter of which is acetylcholine. Because of this fact, it was initially assumed that post-ganglionic cholinergic nerves were the direct mediators of the penile smooth muscle relaxation. As it has already been explained above, it is now known that the relaxation of the smooth muscle is mediated by NO. Acetylcholine could be causing the release of NO from endothelium by activating the muscarinic receptors as mentioned above. The direct effect of acetylcholine on the smooth muscle is, interestingly, contraction. Nevertheless, cholinergic nerves are present in the corpus cavernosum and seem to have a modulator role on the other neuroeffector systems. Acetylcholine inhibits neurogenic relaxation mediated by NO in dog cerebral arteries [223,224]. In contrast, physostigmine (an inhibitor of acetylcholinesterase that potentiates acetylcholine-mediated effects) significantly potentiates neurogenic relaxation of human corpus cavernosum smooth muscle [128], suggesting the possibility that acetylcholine, via muscarinic receptors on nitricergic nerves, potentiates NO release in human penile tissue. In other parts of urogenital tract, NO has been shown to inhibit the release of acetylcholine [225]; whether or not a similar interaction occurs in the penile smooth muscle needs to be investigated.

Adrenergic nerves receive inhibitory interneuronal cholinergic modulation. The interaction of acetylcholine with muscarinic receptors in the adrenergic nerves reduces their release of noradrenaline [73,128]. This prejunctional regulation, therefore, would favor erection through the decrease of constrictor adrenergic tone.

In summary, cholinergic activity in the corpus cavernosum would have a modulatory role facilitating erection, on one hand reducing constrictor tone (adrenergic) and on the other facilitating NO-mediated relaxation (figure 17). In fact, the blockade of muscarinic receptors reduces the erectile responses to cavernous nerve stimulation [226,227].

4. Interaction between Prostanoids and the Adrenergic and Nitricergic Activities

In addition to their role as relaxants of trabecular smooth muscle as previously mentioned, and that of regulators of the collagen synthesis [228], also, PGE1 modulates adrenergic nerves through a prejunctional mechanism. It has been demonstrated in human cavernous tissue that PGE1 inhibits the release of noradrenaline by adrenergic nerves [229].

![Figure 17: Regulation of penile smooth muscle tone by adrenergic, cholinergic and nitricergic mechanisms. ACh, acetylcholine; DP, type D prostanoid receptor; EP, type E prostanoid receptor; M, muscarinic receptor; NE, norepinephrine; NO, nitric oxide; α1, type 1 α-adrenoceptor; α2, type 2 α-adrenoceptor; M, muscarinic receptor; NE, norepinephrine; NO, nitric oxide; α1, type 1 α-adrenoceptor; α2, type 2 α-adrenoceptor.](image-url)
PGE1, therefore, may promote erection by their direct relaxing effect on the muscle and by its indirect effect of reduction of adrenergic tone. Certain prostanoids, such as PGD2, have the opposite effect, since they facilitate the release of noradrenaline by adrenergic nerves [229].

On the other hand, an interaction of PGE1 with the NO pathway has been suggested. Repeated treatment with PGE1 upregulates eNOS and nNOS, leading to increased NO generation and improved erectile responses in rats [230]. In addition, a synergistic interaction of PGE1 and NO to relax human corpus cavernosum has been observed [231].

C. PATHOPHYSIOLOGY OF ERECTILE DYSFUNCTION

Normal erectile function requires the involvement and coordination of multiple regulatory systems and is thus subject to the influence of psychological, hormonal, neurological, vascular and cavernosal factors. An alteration in any of these factors may be sufficient to cause ED, but in many cases a combination of several factors is involved.

I. NEUROGENIC ERECTILE DYSFUNCTION

Erection can be initiated in the brain (central erection) and/or follow genital stimulation (reflex erection). The combination of both is probably involved in sexual activity.

Events that disrupt central neural networks or the peripheral nerves involved in sexual function can cause ED. This form of ED has been termed “neurogenic impotence”. It has been estimated that 10 to 19% of ED is of neurogenic origin [232,233]. If one includes iatrogenic causes and mixed ED, the prevalence of neurogenic ED is probably much higher. While the presence of a neurologic disorder or neuropathy does not exclude other causes, confirming that ED is neurogenic in origin can be challenging.

1. THE ETIOLOGIES OF NEUROGENIC ED CAN BE CLASSIFIED AS:

- Peripheral (peripheral ED)
- Spinal (sacral-peripheral ED, suprasacral-central ED)
- Supraspinal (suprasacral ED)

Peripheral ED can be secondary to the disruption of sensory nerves that bring local information to the brain and contribute the afferent arm of reflex erection, or to the disruption of autonomic nerves which mediate arterial dilation and trabecular smooth muscle relaxation. (Tables 1, 2, 3)

ED from central origin can occur from lack of excitation or increase inhibition of central autonomic pathways.

2. ERECTILE DYSFUNCTION IN SPINAL CORD INJURY

Men with spinal cord injury have several associated sexual dysfunctions including alterations in ejaculation, orgasm and erectile function. Patients are frequently young and face a life long perspective of difficulties in their sexual and reproductive capacities. The degree of completeness and the level of the lesion determines the erectile function of the patient [245]. In general patients with lesions above the sacral parasympathetic center maintain reflexogenic erection. In these patients minimal tactile stimulation can trigger erection, albeit of short duration, requiring continuous stimulation to maintain erection [245]. If the lesion is incomplete patients can receive...
input from psychogenic erection and maintain erectile function. Patients with significant lesions affecting the sacral parasympathetic center do not have reflex erections and have severe erectile dysfunction [245].

3. ERECTILE DYSFUNCTION AFTER RADICAL PELVIC SURGERY

The mechanism of erectile dysfunction after radical prostatectomy or cystoprostatectomy is usually neurologic but can also be vascular (due to disruption of anomalous pudendal arteries that course the anterior aspect of the prostate) [248]. The neurologic lesion occurs in the pelvic plexus or in the cavernosal nerves located in the postero-lateral aspect of the prostate. The incidence of erectile dysfunction after radical bladder or prostate surgery, was in the past in the vicinity of 100%, but has improved with the introduction of nerve-sparing procedures. Maintenance of erectile capacity with these techniques varies between 35% and 68% depending on the surgical technique, the clinical and pathological staging of the tumor and the age of the patient [249,250]. Recovery of erectile function after radical pelvic surgery can be slow over the course of 12- to 18 months. Early treatment (with self intracavernosmal administration of vasoactive agents) of these patients has been shown to improve the probability of recovering erectile function. It is believed that the pharmacologically-induced erections prevent the structural tissue changes associated with the prolonged ischemia associated in turn with infrequent or no erections during the nerve recovery process.

II. VASCULAR ERECTILE DYSFUNCTION

Arterial lesions in the pudendal arteries are much more common in impotent men than in general population of similar age [251]. Moreover, erectile dysfunction is more frequent in patients with other signs of atherosclerotic disease such as ischaemic heart disease and arterial leg disease [252-254], and erectile dysfunction and cardiovascular disease share the same risk factors such as hypertension, diabetes mellitus, hypercholesterolemia and smoking [105,253] (figure 18). This led to the suggestion that erectile dysfunction is another manifestation of vascular disease [255]. Morley and colleagues [256] also observed that a low penile brachial pressure index did seem to predict major vascular events like myocardial infarction and cerebrovascular events.

Table 2. Spinal ED
- Multiple sclerosis
- Spinal cord injury
- Tumor
- Syringomyelia
- Transverse myelitis
- Arachnoiditis
- Disk disease
- Myelodysplasia

References [238-245]

Table 3. Brain ED
- Tumor
- Stroke
- Encephalitis
- Parkinson’s disease
- Various dementias
- Olivopontocerebellar degeneration (Shy-Drager syndrome)
- Epilepsy (temporal lobe)

References [232,246,247]

1. ERECTILE DYSFUNCTION AND ATHEROSCLEROSIS / HYPERCHOLESTEROLEMIA

Originally arterial disease and impotence were linked together by the French surgeon Leriche, who in 1940 noted that a majority of patients with occlusive arterial disorders at the bifurcation of the aorta into the two major arterial trunks of the common iliac
arteries suffered from failure of erectile capacity [257]. 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.

In a rabbit model where proximal atherosclerotic lesions were induced by balloon-deendothelization of the iliac arteries and feeding a cholesterol-rich diet, it was followed by vasculogenic erectile dysfunction [258]. 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 [259,260]. 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 [261,262]. NO inhibits endothelial eicosanoid and superoxide production [263]. 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 [261,262]. In the latter studies the reduced NOS activity in these rabbits can probably be explained either by decreased NOS expression or a defect in the enzyme. The abovementioned 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. Moreover, in cholesterol-fed rabbit model the plasma cholesterol is extremely high (925 mg/dl or 20-25 mmol/l, [262]), and there is also an increase in liver weight [264] probably leading to altered metabolization of steroid hormones and hence expression of NOS in erectile tissue. In contrast to the changes induced in the penile vascular bed by atherosclerotic lesions in the large or conductive arteries, 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 [265], but this does not appear to be the case in small systemic arteries [264] or the trabecular smooth muscle [266]. In the latter study the lipoproteins did not interfere with the NO/cGMP-pathway, but ox-LDL induced contractions [266], and these contractions are probably mediated through increases in intracellular inositol phosphate and calcium [267]. In contrast, chronic hypercholesterolemia reduces endothelium-dependent relaxations, but not the endothelium-independent relaxations in the corpus cavernosum [268-270]. It has earlier been found that endothelium-dependent relaxation was impaired only in systemic arteries with atherosclerotic lesions [271,272]. In the rabbit corpus cavernosum ultrastructural studies have also revealed an early atherosclerotic process in the cavernosal sinusoids [269]. In contrast to the endothelial NO/cGMP-pathway, the neuronal vasodilation does not appear affected in hypercholesterolemic rabbits [262]. The selective affection of the endothelial NO/cGMP-pathway in hypercholesterolemia could be ascribed to an increased superoxide production [270] or the presence of an increased endogenous production of NOS inhibitors such as L-NMMA and ADMA. L-arginine supplementation reverses the impairment of the endothelium-dependent relaxations [262], and this observation supports that endothelial dysfunction is due to an increased endogenous production of NOS inhibitors. Further studies must clarify whether hypercholesterolemia has induced structural and functional changes in the distal part of the penile vascular bed in patients with erectile dysfunction.

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 erectile dysfunction was reported [273]. Moreover, five patients with coronary artery disease developed erectile dysfunction one week after starting treatment with simvastatin, and sexual function was restored after stopping the treatment, furthermore, erectile dysfunction recurred when two of the patients were rechallenged [274]. 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 6 weeks, although the increase was not significant after 6 weeks treatment [275]. Evaluation of the frequency of erectile dysfunction reported in the Scandinavian simvastin survival study, where 4444 patients with coronary heart disease were randomized to treatment with simvastatin or placebo for up to 6 years, erectile dysfunction was found in 28 placebo-treated patients with 8 resolved cases, while erectile dysfunction was present in 37 simvastatin-treated patients with 14 resolved cases [276]. Therefore,
in patients treated with statins an underlying diseased vasculature rather than the drug appears the cause of erectile dysfunction.

Lipid-lowering therapy in hypercholesterolemic patients improve endothelium-dependent vasodilation measured in the forearm of hypercholesterolemic patients probably due to an increased bioavailability of NO [277]. This suggests that the dysfunction of the endothelial NO/cGMP-pathway in hypercholesterolemia is reversible. However, it remains to be elucidated whether this is also the case for the penile vasculature.

2. ERECTILE DYSFUNCTION AND HYPERTENSION

Hypertension is an independent risk factor for development of erectile dysfunction [253,278,279]. Cardiovascular complications following hypertension such as ischaemic heart disease and renal failure are associated with an even higher prevalence of erectile dysfunction [253,279,280]. However, so far there are only a few studies which have investigated the potential determinants for erectile dysfunction in hypertension. Erectile dysfunction is also more frequent in treated hypertensive patients.

The erectile dysfunction seen in hypertensive men is probably the result of alterations in a number of the processes involved in normal sexual function such as psychogenic factors, neurogenic factors, hormones, and hemodynamic factors. A number of potential determinants for erectile dysfunction were examined in 32 consecutive hypertensive and 78 normotensive impotent men. 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 [281]. 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 [281]. These studies would suggest that the determinants in hypertensive and normotensive with erectile dysfunctions do not appear to be different.

There are several studies of erectile function in animal models. Thus, erectile function is decreased in diabetic rats, and rabbits with atherosclerotic lesions in the iliac arteries [258,282]. Erectile function, evaluated by measuring intracavernosal pressure expressed as percentage of mean arterial pressure, was also reported to be decreased in spontaneously hypertensive rats (SHR) [101,283,284]. However, the absolute increases in intracavernosal pressure did not appear different in these studies. Using apomorphine to elicit erection in young and old SHR suggested erectile function was improved after 2 weeks treatment with the angiotensin converting enzyme inhibitor, enalapril, but erectile function in normotensive rats were not reported for comparison [285]. Therefore, additional studies and/or other approaches seem necessary to confirm the presence of erectile dysfunction in these animals.

III. PATHOPHYSIOLOGICAL MECHANISMS IN VASCULAR ERECTILE DYSFUNCTION

1. ARTERIAL REMODELING AND ERECTILE DYSFUNCTION

Erectile dysfunction can be thought of as a three-fold process where arterial insufficiency is followed by inability to obtain tumesence due to defective filling of corpus cavernosum, and faulty veno-occlusion, although initial alterations in corpus cavernosum and primary venous leak can also be the cause of erectile dysfunction [286].

Arterial insufficiency is probably preceding corporal dysfunction and defect venoocclusion (figure 19). Thus, in a rabbit model where proximal atherosclerotic lesions were induced by ballon-deendothelization of the iliac arteries and by feeding a cholesterol-rich diet, this was followed by vasculogenic erectile function probably due to ischaemia of the corpora cavernosa [260]. In organic erectile dysfunction due to arterial insufficiency, there is lower oxygen tension in corporeal blood compared to that measured in patients with psychogenic erectile dysfunction [287]. 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-ß1-induced fibrillar collagen synthesis in the rabbit and human corpus cavernosum and vice versa [160,228,288]. Finally, a decrease in cavernous trabecular smooth muscle and an increase in connective tissue is correlated with diffuse venous leakage and a failure of the venoocclusive mechanism, hence resulting in erectile dysfunction [75,260]. Therefore, arterial insufficiency followed by diminished oxygenation of corpus cavernosum, decreased PGE2 production, and increased fibrosis play a role in erectile dysfunction.
In addition to proximal stenosis limiting flow, impaired penile vasodilation could also be a consequence of structural alterations in the penile vasculature. A narrowed lumen or increased wall to lumen ratio in the arteries contributes to increased peripheral vascular resistance in hypertension [289]. An increased resistance was also found in the penile vasculature of spontaneously hypertensive rats (SHR), and these alterations were ascribed to structural changes of the arterial and erectile tissue [290-292]. Thus, in erectile tissue from SHR and normotensive WKY rats stained with Masson trichrome and anti-alpha smooth muscle actin suggested increased proliferation score of both cavernous and vascular smooth muscle and a higher fibrosis score in SHR. The increase in extracellular matrix expansion did seem to affect not only interstitium but, interestingly, also neural structures of the penis [291]. Thus, there is definitely a need for additional morphological studies to elucidate the changes taking place in erectile tissue both from patients and experimental animal models with hypertension.

2. INCREASED VASOCONSTRICTION AND ERECTILE DYSFUNCTION

Enhanced basal and myogenic tone has been observed in arteries from hypertensive rats [293]. It is unclear whether enhanced myogenic constriction reflects a primary pathological defect contributing to the hypertensive state or a secondary adaptive process protecting the exchange vessels from elevated pressures [294]. Although, the role of myogenic tone in the penile vasculature for erection remains to be clarified [295], the increased vasoconstriction could contribute to decreased arterial inflow and erectile response in renal hypertensive rats. Studies of the microcirculation of the gracilis and cremaster muscle in renal hypertensive rats suggested vasoconstriction of the arterioles is important initially in renal hypertension, while structural changes such as thickened wall to lumen ratio and rarefaction become more important later [296]. Further studies must address whether enhanced myogenic tone is followed by structural changes in the penile vasculature at late stages of renal hypertension.

Activity of adrenergic nerves causes detumescence of the erect penis, and such activity probably also maintains the penis in the flaccid state, as indicated by the erection induced after injection of $\alpha$-adrenoceptor antagonists [297]. Therefore, enhanced adrenergic activity keeping the penile smooth muscle contracted is expected to result in erectile dysfunction. Sympathetic nerve activity accompanies hypertension in man and hypertensive animals [298,299]. However, in corpus cavernosum from SHR the content of sympathetic neurotransmitters was found to be unchanged [300]. Moreover, the enhanced vasoconstriction of the penile vasculature in SHR rats induced by infusion of phenylephrine was attributed to hypertrophy of the vascular wall [290]. Neither the contractions evoked by the $\alpha_1$-adrenoceptor agonist, phenylephrine, nor the contractions induced by electrical field stimulation were enhanced in arteries or erectile tissue from renal hypertensive compared to normotensive rats. In view of these findings

Figure 19: Pathophysiology of erectile dysfunction in vascular disease.
it is unlikely that changes in the peripheral sympathetic neuroeffector junction or responsiveness to α-adrenoceptor agonists play a role for the decreased erectile function observed in hypertensive rats.

3. IMPAIRED NEUROGENIC VASODILATATION AND ERECTILE DYSFUNCTION

Arterial vasodilatation and relaxation of the corpora cavernosa play a pivotal role for penile erection [3,295], and therefore impaired neurogenic relaxation of erectile smooth muscle will be expected to result in erectile dysfunction. In non-plasma renin-dependent hypertension neurogenic vasodilatation in the mesenteric vascular bed was reported either unchanged [301] or decreased in renal hypertensive (one-kidney one-clip) rats [302]. 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 [173, 303, 304]. Preliminary data point toward reduced neurogenic relaxations altered function of the non-adrenergic non-cholinergic vasodilator nerves in penile arteries from renal hypertensive rats [305].

4. IMPAIRED ENDOTHELIUM-DEPENDENT VASODILATATION AND ERECTILE DYSFUNCTION

In patients with essential hypertension, endothelium-dependent vasodilatation elicited by infusion of agonists such as acetylcholine, bradykinin, or flow, is diminished [306-308]. Impaired endothelium-dependent vasodilatation is thought to contribute to the increased peripheral resistance and vascular complications observed in hypertension. Recent evidence indicates that profound endothelial dysfunction in the coronary circulation can predict major coronary events [309,310]. Studies of endothelial cell function in small arteries from patients with essential hypertension are controversial, since endothelium-dependent vasorelaxation induced by acetylcholine was reported to be either unaltered [311,312] or impaired [313,314]. Endothelium-dependent relaxation of subcutaneous arteries correlates closely with flow-mediated dilation of the brachial artery [314]. Endothelial cell dysfunction measured as blunted acetylcholine vasorelaxation is evident in small arteries from patients with renovascular hypertension [315,316]. There is an obvious lack for studies addressing whether endothelium-dependent vasodilatation in the penile circulation is altered in hypertensive men.

Numerous studies have demonstrated impaired endothelium-dependent vasodilatation in experimental hypertension, but there are differences both with respect to type of hypertension, size of arteries studied, and protocol, which have been applied in the study of endothelium-dependent vasorelaxation. In the SHR, the relaxing effect of acetylcholine is blunted both in large and in small arteries [317], and endothelial dysfunction appears to develop with the appearance of hypertension. However, the blunted endothelium-dependent relaxation does seem to depend on agonist used to increase tension, since acetylcholine relaxation was abolished in noradrenaline, but not in vasopressin-activated arteries [318]. In noradrenaline-activated small vessel and aorta from SHR, the high doses of acetylcholine (> 3 µM) cause no further relaxation but rather an increase in tension [317,319]. In the presence of indomethacin, the differences between acetylcholine responses in arteries from WKY and SHR disappears [319], and more recent studies have demonstrated that there is an enhanced release of thromboxane and superoxide in arteries from SHR as described below [320,321]. Endothelium-dependent relaxation evoked by acetylcholine is also impaired in corporal strips from SHR rats and these relaxations are also restored in the presence of indomethacin [284]. Therefore, the pathophysiological mechanisms affecting endothelium-dependent relaxation in erectile tissue from SHR appear similar to those in systemic arteries. Impairment of endothelium-dependent relaxation could be ascribed to angiotensin II, since angiotensin infusion enhances NADPH oxidase and superoxide production which inactivates NO by promoting its breakdown and shortening of its half-life [322,323].
Thus, in SHR, renin-dependent renovascular hypertension (two-kidney one-clip) and hypertension evoked by angiotensin II infusion, enhanced superoxide production was found to lead to reduced endothelium-dependent relaxation [323,324] and enhanced vasoconstriction. However, in man endothelial cell dysfunction was suggested to be linked to hemodynamic load, and pressure per se impairs endothelium-dependent relaxation in human small arteries [325]. In non-renin dependent hypertension induced by feeding rats with deoxycorticosterone acetate-salt, endothelium-dependent relaxation was also impaired [326]. These changes suggest that endothelial dysfunction is a consequence of high blood pressure.

5. PELVIC/PERINEAL TRAUMA

Blunt trauma to the pelvic or perineal region of the corpora cavernosa has been considered a risk factor for the subsequent development of persistent ED. The pathophysiology of traumatic erectile impairment is multifactorial. Both psychogenic and hemodynamic factors have been reported with incidence of 4% and up to 80%, respectively. A retrospective nine-year review revealed CVOD prevalence in 62% and cavernosal arterial insufficiency in 70%. Another study reported 52% incidence of ED in patients who self-reported potency prior to the trauma. It has been proposed that the traumatic CVOD occurs as a consequence of focal trauma-induced changes in corporeal tissue compliance [11].

IV. DIABETES

1. DIABETES

Diabetes mellitus (DM) is a common chronic disease throughout the world with a prevalence of 0.5-2%. It is characterized by hyperglycaemia secondary to lack of insulin (Type I, insulin dependent DM), or overproduction of glucose with insulin insensitivity (Type II, non-insulin dependent DM) which leads to pathological changes in a number of cellular and organ systems. There is good epidemiological evidence of a causal link between diabetes and erectile dysfunction (ED) [327]. The prevalence of ED is three times higher in diabetic men (28% versus 9.6%) [253], occurs at an earlier age and increases with disease duration, being approximately 15% at age 30 rising to 55% at 60 years [328,329]. Erectile dysfunction amongst men with diabetes is more frequent in those with co-existing neuropathy but the relationship with vascular disease is less clear. The prevalence of coronary arterial disease (20%) and peripheral vascular disease (5%) amongst men with diabetes is far higher than in the general population; both common associated physical health risk factors for ED. Impotence however appears to be equally common amongst diabetics with and without evidence of atheromatous vascular disease.

Diabetes mellitus may cause ED through a number of pathophysiological changes affecting psychological function, CNS function, androgen secretion, peripheral nerve activity, endothelial cell function and smooth muscle contractility [330]. In a particular individual the problem may be due to one or a combination of these possible factors. This section will examine the evidence for a relationship between diabetes and penile haemodynamic, endothelial and smooth muscle dysfunction.

a) Experimental materials

Due to the multifactorial aetiology of ED in DM it is difficult to isolate haemodynamic factors from other changes, particularly peripheral neuropathy. Data have been obtained from results of vascular investigation of penile blood flow in impotent men with diabetes, responses of isolated human cavernosal tissue and histological studies. Indirect evidence is provided from isolated forearm blood flow studies and experiments using other endothelial tissue or cellular preparations.

The use of animal models such as streptozotocin-induced diabetic rats and alloxan-induced diabetic rabbits help the design of experiments focused on particular aspects of the problem, but extrapolation to the human condition is problematic. In addition these animal models tend not to develop long term atheromatous damage, commonly seen in the human disease, because of their limited life span.

A substantial body of work looking at the cause of vascular disease in diabetics is focused on changes in endothelial cell function, in particular the nitric oxide (NO)-cyclic GMP (cGMP) signal transduction pathway. Although not primarily concerned with penile erection, it seems reasonable to assume that results obtained from other vascular smooth muscle preparations will be applicable to endothelial cell - smooth muscle interaction within the corpora cavernosa.

b) Haemodynamic changes

Penile erection depends upon a greatly increased blood flow into the corpora cavernosa, which is in turn dependent upon perfusion pressure, relaxation of the supplying arterial tree and relaxation of caver-
nasal smooth muscle. Disturbances of these mechanisms can be clinically detected by anatomical studies such as angiography or functional studies such as duplex ultrasonography.

1. **ANATOMICAL IMAGING:** Large vessel atheromatous disease is 40 times more prevalent amongst men with diabetes compared to non-diabetics and is more commonly associated with ED. The only angiographic study primarily concerned with diabetic patients found that stenoses of the internal pudendal and, to a lesser extent, internal iliac vessels were more severe in men with ED in both diabetics and non-diabetics [331]. Other less well characterized studies suggest a greater degree of atheroma occurring at a younger age in men with diabetes.

2. **FUNCTIONAL STUDIES:** Men with diabetes show a reduction in the number and rigidity of nocturnal erections experienced during sleep [332]. Although this suggests an organic aetiology the test has many pitfalls; it has low predictive value and will not discriminate between vascular and neurological causes. Early diagnostic studies prior to the use of vasoactive agents relied upon the ratio of penile (measured by Doppler probe) over brachial blood pressure as an index of penile arterial insufficiency. Significantly lower values were found in diabetics compared with both potent and impotent men without diabetes suggesting penile arterial insufficiency [251]. However results showed considerable overlap as the method measured dorsal penile arterial pressure only and were conducted in the flaccid state, making the results of limited value. Reported use of artificial pharmacological erection as a test of intact penile vasculature is limited to several uncontrolled case series. In one study 40% of diabetic men with ED achieved full rigidity following intracavernosal papaverine (25 mg) compared to 70% in an unselected group of non-diabetic men with ED [333]. Studies using duplex ultrasonography following intracavernosal injection of vasoactive agents have found a high prevalence of penile arterial insufficiency amongst diabetics with ED ranging from 75 – 100% [334]. None of these studies found any differences between men with Type I or Type II DM. In general it can be said that atheromatous disease is more common in diabetic men and such disease within the penile arterial tree is associated with ED.

2. **THE EFFECT OF DIABETES ON CAVERNOSAL TISSUE**

   a) **Structural changes:** One study using electron microscopy has shown ultrastructural changes in cavernosal tissue from diabetic men compared with controls [335]. These include reduction in smooth muscle content, increased collagen deposition, thickening of the basal lamina and loss of endothelial cells. Although these changes were most marked in tissue from men with diabetes they were also seen in those with other non-diabetic causes. Several studies in animal models of diabetes have confirmed loss of smooth muscle and endothelial cells, increased collagen deposition in the corpus cavernosum, increased thickness of tunica albuginea and neurodegenerative changes in the erectile parasympathetic nerve fibers [336-338].

   b) **Functional changes:** A number of studies testing the response of isolated preparations of human cavernosal tissue to contractile and relaxant agents have found differences in tissue responses from diabetic and non-diabetic men. These experiments generally measure relaxant responses in tissue strips pre-contracted with α-adrenergic agonists. The studies have consistently found a reduction in the relaxation responses mediated by endothelial and neuronal NO in corpus cavernosum from diabetic impotent men and diabetic animals [339-341]. In comparison to control tissue from potent men, specimens from diabetic men showed a similar impairment in relaxant responses to non-diabetics with severe arterial disease or veno-occlusive dysfunction, suggesting a common aetiology [340]. Relaxation evoked by nitravasodilators such as sodium nitroprusside were similar in tissue from diabetic men with impotence, to those with non-diabetic impotence and controls, suggesting that the cellular events following NO release are not impaired [339-340]. Relaxation following PGE1, which is mediated through cAMP was significantly impaired compared to control tissue in one reported study [342]. One study has looked directly at NO formation following relaxant nerve stimulation in tissue from impotent men with and without diabetes compared to controls [341]. Neurogenic NO formation was significantly impaired amongst men with diabetes and vascular impotence compared to those with non-vascular impotence and controls. This was mirrored by reduced magnitude of the relaxant response. Subsequent cGMP formation was also reduced, although differences were less clear. These studies suggest a specific impairment in NO synthesis or release which appears common to diabetic and non-diabetic men with clinical evidence of vasculogenic impotence. Direct smooth muscle relaxation with various phar-
The contractile responses to II NOS (iNOS) which in turn down-regulates eNOS. The researchers went on to speculate that compared to a non-diabetic impotent control group cavernosal tissue of impotent men with diabetes revealed no change in smooth muscle responsiveness to endothelin-1, an endogenous contractile agent, revealed no change in smooth muscle responsiveness between potent men and those with ED irrespective of whether diabetes was present, suggesting that endothelin is unlikely to have a role in diabetic impotence [84]. A closer examination of the kinetics of cavernosal smooth muscle contraction suggested that tissue responsiveness to α-adrenergic agonist was higher in men with Type I diabetes, but unchanged in Type II, this however remains to be confirmed by other studies [344]. Overall there is limited equivocal evidence suggesting that smooth muscle contractility to adrenergic stimulation may be impaired in cavernosal tissue from men with diabetes.

All such studies using human tissue report a heterogeneous group of impotent men, generally with severe erectile dysfunction. In addition sample size, particularly in potent control groups, is small, hampering firm conclusions on the data presented.

It does appear that physiological pathways of relaxation of corpus cavernosum are impaired in impotent men with diabetes and that the main area of dysfunction appears to be at the level of NO synthesis and release rather than the transduction pathway within the smooth muscle cell.

3. ANIMAL MODELS

In the streptozocin-induced diabetic rat incubation of cavernosal tissue with low concentrations of sodium nitroprusside (a NO donor) resulted in higher levels of cGMP than healthy controls. Similarly, incubation with PGE1 produced higher levels of cAMP in the diabetic group [345]. In diabetic rabbits, three months of diabetes yielded neither alteration in cGMP generation in response to an NO-donor nor in cAMP generation in response to PGE1 or forskolin an adenylyl cyclase activator. Production of cAMP in the presence of PGE1 or forskolin was significantly reduced after six months of diabetes [346].

Endothelial and neurogenic relaxant responses mediated by NO are impaired in diabetes [347-349]. The decrease in availability of NO in diabetic penis has been suggested by several groups to be due to a decrease in nNOS and/or eNOS protein content [221,350-355] although some has found either no change [356] or an increase in nNOS [357]. The decrease in nNOS has been attributed to nitrergic nerve degeneration [221,351] or diabetes-induced alteration in nNOS expression which is reversible by insulin [352]. Further studies are required in order to understand the molecular mechanisms involved in changes in nNOS expression during diabetes. An alternative pathway of relaxation involving the release of the prostanoid, prostacyclin was also found to be impaired amongst diabetic rabbits and rats [346,358].

Increased smooth muscle tone may result from the alteration of the expression of endothelin receptors. ETB receptors [359] and, more recently, ET receptors [360] have been found to be upregulated in cavernosal tissue from diabetic rabbits. This latter study reported an increased sensitivity to endothelin in diabetic corpus cavernosum, resulting in increased tone. The presence of high bathing sugar solutions, mimicking the hyperglycaemic state, responses of rabbit corpus cavernosus to acetylcholine were impaired. This effect was reversed by both indomethacin and superoxide dismutase suggesting the involvement of prostaglandins and free oxygen radicals [361]. There was no change to the response evoked by nitrovasodilators in this study, suggesting a mechanism through reduced activity of eNOS. In another study using alloxan-induced diabetic rabbits the relaxant response to SNP was again unaffected but neurogenic relaxation was impaired and remained so despite insulin treatment [362]. In contrast the impairment in acetylcholine-induced relaxation via eNOS was reversed by treatment with either insulin or L-arginine.

Data from animal studies is far from complete, but despite conflicting results, some tentative conclusions can be drawn which can then be fitted into the prevailing view of the aetiology of generalized diabetic vascular pathophysiology. There appears to be a consistent finding of impaired endogenous NO-evoked relaxation from both neural and endothelial sources. The contractility of cavernosal smooth
muscle itself appears unaffected. This is in agreement with the findings in human tissue described above and suggests a defect in the formation or release of NO rather than in the signal transduction pathway within the smooth muscle cell. A possible pathological mechanism for these events is the NO-quenching action of elevated levels of AGEs.

a) Generalized endothelial dysfunction in diabetes

Introduction: Endothelial cells form a permissive layer that regulates the flow of nutrients and the action of bioactive molecules circulating in the blood upon the underlying tissue, particularly vascular smooth muscle. This is achieved by a wide range of membrane-bound receptors and junctional proteins. The endothelium also secretes vasoactive molecules that regulate blood flow in a paracrine fashion through induction of changes in vascular smooth muscle tone. Knowledge of endothelial physiology and pathophysiology in diabetes is chiefly derived from experimental data from in vivo measurements of blood flow in human subjects and laboratory animals together with cell biological studies using endothelial cell cultures from a variety of animal and human tissues. The main clinical marker for endothelial dysfunction in diabetes is the presence of renal microalbuminuria indicating the presence of renal epithelial dysfunction in diabetics is the presence of human tissues. The main clinical marker for endothelial cell cultures from a variety of animal and mammals together with cell biological studies using endothelial cells through the action of type III NO synthase (eNOS) located within the cellular membrane. The enzyme is activated by the binding of various agonists such as thrombin, adenosine 5’-diphosphate, bradykinin, substance P and acetylcholine to specific membrane receptors and also by gene amplification stimulated by shear stress. The released NO relaxes underlying vascular smooth muscle and may also be involved in enhancing endothelial repair following injury. The endothelium also secretes endothelium-derived hyperpolarising factor (EDHF) which enhances muscarinic receptor-mediated smooth muscle relaxation. The other major vasoactive molecule expressed by the endothelium is the potent vasoconstrictive agent, endothelin-1. This is formed by gene transcription stimulated by hypoxia, shear stress and ischaemia. Endothelin acts through G-protein coupled ET-A receptor activation which elevates plasma calcium and hence causes contraction. The eicosanoid, prostacyclin (PGI2) is also produced by the endothelium and acts as a paracrine signalling molecule, inducing vascular smooth muscle relaxation through the IP receptor. It is mainly implicated in the regulation of vascular tone in areas of injury or disease.

The following section describing our present knowledge of the effects of diabetes on endothelial cell physiology uses a number of recent specialist reviews to which the reader is referred for more information [363-369].

2. Effect of diabetes on endothelial cell turnover: Exposure to hyperglycaemia induces increased expression of collagen, decreased proliferation and increased programmed cell death (apoptosis). This has an adverse effect on repair mechanisms, enhancing the progressive damage associated with atherosclerotic injury. Expression of the cytokine TNF-α is also increased resulting in further endothelial cell destruction.

3. Effect of diabetes on nitric oxide synthase: Insulin is thought to enhance NOS activity by increasing transport of L-arginine into the cell and furnishing greater quantities of the essential co-factor NADPH. These effects are reversed in the insulin lack or insulin resistance of diabetes. Plasmatic concentration and vascular content of L-arginine are reduced in diabetic rats [370]. Arginase is an enzyme that competes with NOS for the substrate, L-arginine. The inducible form of the enzyme, arginase II, is overexpressed in corpus cavernosum from diabetic patients, where inhibition of arginase restores NOS activity [371]. Intracellular availability of L-arginine in diabetic cavernosal tissue could be reduced not only by transport impairment but also by excessive metabolism through arginase pathway.

Enhancement of NOS activity also occurs following exposure to adenosine, a potent circulating vasodilator. Some work has suggested a decreased responsiveness of endothelial cells to adenosine in gestational diabetes. The ratio of reductase co-factors NADH/NAD+ is increased in diabetes. This reduces the levels of NADPH, an essential co-factor for NOS and increases the levels of calcium-elevating second messengers such as diacylglycerol (DAG) and protein kinase C (PKC) thus increasing smooth muscle contractility. Interestingly, glucose-induced elevation of PKC seems to be mediated by oxidative stress in rabbit corpus cavernosum smooth muscle cells [372].

4. Effect of diabetes on nitric oxide-mediated endothelium-dependent vasodilatation: A number of human studies using arm vein plethysmography have demonstrated fairly consistent findings. Basal
levels of NO-mediated endothelium-dependent vasodilation appear similar to normal controls. The response to exogenous nitrovasodilators and some physiological agonists is blunted, whilst infusion of muscarinic agonists produces similar degrees of increased blood flow to control. One study has suggested that in well controlled diabetics vasoactivity appears normal. In experimental animals blood flow responses appear to be enhanced in the early stages of the disease with decreased responses becoming prevalent with increasing disease duration. Isolated reports also suggest increased endothelin levels in patients with NIDDM which may act to indirectly reduce dilator response.

5. EFFECT OF DIABETES ON EDHF-MEDIATED ENDOTHELIAL-DEPENDENT VASODILATION: In human penile arteries, EDHF plays a significant role in endothelium-dependent relaxation [108]. Responses attributable to EDHF have been found impaired in the vasculature of diabetic animals and, interestingly, EDHF-mediated endothelium-dependent relaxation is significantly reduced in penile resistance arteries from diabetic patients [373]. Defective EDHF-mediated responses could then contribute to endothelial dysfunction in diabetic penile tissue.

6. ENHANCEMENT OF OXYGEN FREE RADICAL PRODUCTION IN DIABETES: A body of evidence exists detailing various mechanisms by which levels of oxygen free radicals may be elevated in diabetes which quench released NO thereby reducing the vasodilator response. The most important appears to be the formation of products of protein non-enzymatic glycosylation (glycation). Glucose reacts non-enzymatically with the amino groups (lysine, arginine or N-terminal) of proteins forming Schiff bases and Amadori products to finally produce advanced glycosylation end products (AGEs). This process, the Maillard reaction, is known to generate reactive oxygen species (ROS). In fact, glycated proteins are a source of ROS [374]. Glycated hemoglobin, an Amadori product which is increased in diabetes, impairs endothelium-dependent relaxation in aorta [375] and corpus cavernosum [376] from diabetic rats, an effect which is reversed by superoxide dismutase (SOD), the scavenger of superoxide anions. In human penile tissue, diabetes is associated with increased content of AGEs [343].

In animal models, inhibition of AGE formation improves endothelium-dependent relaxation [377] and restores erectile function [378] in diabetic rats. These evidences suggest a role for intermediate and advanced glycation products in the diabetic impairment of penile endothelial function. In human diabetic vascular tissue, the increased activity of NAD(P)H oxidase has been proposed as an important source of ROS impairing NO bioactivity [379], but the relevance of this mechanism in diabetic penile tissue needs confirmation. However, irrespective to the source of ROS, oxidative stress interferes with endothelial function in diabetic erectile tissue. This is supported by the potentiating effect of SOD or the natural antioxidant, vitamin E, on endothelium-dependent relaxation of corpus cavernosum from rabbits and mice respectively [380,381]. In diabetic rats, preventive treatment with another antioxidant, α-lipoic acid, precluded the appearance of endothelial dysfunction in cavernosal tissue, while restorative treatment with this antioxidant only partially reversed the impairment of endothelium-dependent relaxations [348]. This observation indicates that, once established, a part of the damage induced by ROS in endothelial cells remains despite the subsequent treatment with antioxidant.

They may also have a further role in endothelial cell dysfunction by increasing inflammatory cell activity. Elevated PKC levels may also induce the formation of excess free oxidative radicals. Increased sorbitol production in the diabetic state encourages hydrogen peroxide formation which again enhances quenching of NO causing oxidative stress injury.

7. SUMMARY: Diabetes causes generalised endothelial cell dysfunction which results in increased prevalence of vascular disease in both type I and type II diabetics. Particular important effects are reduced activity of eNOS, diminished effect of released NO and the presence of oxidative free radicals including AGEs.

V. PRIMARY ERECTILE DYSFUNCTION

1. INTRODUCTION

The basic anatomical units subserving penile erection are the paired corpora cavernosa which begin to differentiate from the genital tubercle in the third month of embryological life. As part of this differentiation, growth of a vasculature and nerve supply appropriate to their ultimate erectile function is induced. It is therefore apparent that physical causes of primary ED are likely to relate to maldevelopment of the corpora or their blood and nerve supply. In addition vascular or neurological damage may occur during foetal life or childhood.
Primary psychological dysfunction can also occur and is usually related to anxiety about sexual performance stemming from adverse childhood events or traumatic early sexual experience. Endocrine abnormalities, particularly low testosterone levels, may also be implicated in primary ED although lowered sex drive is likely to be the main symptom. Evidence to support these concepts is confined to observation studies with varying numbers of cases. The largest study described 67 patients of whom 10 (15%) had a predominant psychological cause [382]. Those with physical abnormalities had a variety of neurological, arterial and veno-occlusive dysfunction.

2. M I C R O P E N I S

Symmetrical hypoplasia of the phallus, micropenis, is often related to urethral developmental abnormalities such as hypospadias and epispadias [383] or can have an endocrine or idiopathic aetiology. The erectile tissue in such cases often functions normally; sexual dysfunction usually relates to lack of penile length or the degree of chordee rather than ED [384].

3. V A S C U L A R A N O M A L I E S

Primary erectile dysfunction in the presence of an externally normal phallus is unusual and our knowledge of possible causes is derived from isolated case reports. Authors have described structural abnormalities of the cavernosal tissue such as absence [385] or replacement by fibrous tissue [386]. Others have found vascular abnormalities including hypoplasia of the cavernous arteries [387] or veno-occlusive dysfunction due to aberrant cavernosal venous drainage [388]. The underlying cause of these congenital abnormalities is unknown but may be the result of genomic mutations or local growth factor deficiency. Treatment in most described cases was by implantation of penile prosthesis.

4. G E N E T I C C A U S E S

Developments in cell biology and genomic research have stimulated the search for genetic factors in the causation of ED. Possible examples include the stubby gene mutation in mice [389] and genetic polymorphism in humans [390]. Such evidence suggests that a sub group of men may be made more susceptible to cavernous damage in later life by the presence of particular genetic environment.

5. S U M M A R Y

Pure congenital causes of ED are unusual since most abnormalities result in a functional micropenis. The presence of genetic polymorphism that predispose to the development of ED in the ageing male is an interesting possibility that is likely to be the subject of further research as rapid sequencing genomic technology continues to be refined.
tional NO may result from oxidative stress leading to inactivation of NO by oxygen radicals. Interestingly this effect was reversed by treatment with Vitamin E, an antioxidant [398]. Evidence from animal models of chronic uraemia therefore suggests that a decrease in functional NO may be responsible for vascular side effects including ED. Several putative mechanisms may be lead to such a deficiency such as reduced bioavailability of the NO substrate (L-arginine), reduced expression of nitric oxide synthase (NOS) isoforms in the relevant organs, rapid quenching of NO by reactive oxygen species that are known to be increased in CRF, and the accumulation of uraemic inhibitors of NOS [399].

3. HUMAN STUDIES

There are few experimental studies concerning the pathophysiology of ED in men with chronic renal failure in the literature. Those available include small numbers of subjects and lack control data making it impossible to reach firm conclusions. Evidence of autonomic neuropathy as a factor contributing to ED in such men comes from 3 studies which all found a high rate of abnormalities in vascular and bulbocavernous reflexes suggesting cavernosal nerve dysfunction [400-402]. The putative role of hyperprolactinaemia and zinc deficiency as factors reducing sexual and reproductive function in men and women on dialysis prompted researchers to establish a mechanism. The results were conflicting with one controlled trial finding no benefit of treatment with either a prolactin inhibitor or zinc [403], whilst others found that reduction in prolactin by treatment with erythropoietin [404] or treatment with zinc supplements [405] improved sexual and reproductive function in patients with uraemia. The significance of non-specific factors related to chronic disease state such as depression and fatigue was suggested by a case control study that found similar rates of ED in age-matched men on renal replacement therapy compared to those with rheumatoid arthritis and normal renal function [406].

Investigation of cavernosal vascular function in 20 men undergoing renal replacement therapy showed that 80% had both arterial insufficiency and veno-occlusive dysfunction [280]. Current knowledge would suggest that this combination represents failure of sinusoidal relaxation due to functional or structural alterations of cavernosal smooth muscle. A link with possible impairment of the NO-cyclic GMP pathway relating to failure of cavernosal relaxation is provided by the finding of increased serum levels of endogenous inhibitors of NO synthesis in uraemic patients [407].

4. SUMMARY

The cause of the high prevalence of ED amongst men receiving renal replacement therapy is likely to be multifactorial. Evidence from animal studies suggest that deficiency of bioavailable NO may be a factor caused by reduced synthesis or rapid removal by free radicals (figure 21). This mechanism is similar to that proposed for the aetiology of hypertension in renal failure, a link supported by lower rates of ED in uraemic men treated with ACE inhibitors.

![Figure 21: Pathophysiology of erectile dysfunction in chronic renal failure](Image)

VII. DRUGS CAUSING ERECTILE DYSFUNCTION

1. 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 [253]. 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 (figure 22). 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. 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. 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 [3]. 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 [408]. 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.

2. ANTIHYPERTENSIVE AGENTS

Current recommendations for treatment of hypertension suggest thiazide diuretics and beta adrenergic antagonists as first line agents with calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors and alpha adrenergic antagonists as second line agents [409]. All drugs have ED listed as a potential side effect but well designed controlled clinical trials give conflicting results concerning causative relationships [410]. Animal studies do suggest possible mechanisms using in vitro and in vivo methodology [3].

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. Older treatment regimens using higher doses of a thiazide showed a significant increase in ED compared to placebo [411]. 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 [412]. 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 [413]. 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 [414]. 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 dropouts. It may be that thiazide therapy unmasks latent ED at an earlier stage rather than 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 [415]. 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 [408] 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 pathophysiological mechanism is unknown.

b) β-adrenergic Antagonists

Receptor studies show that only 10% of adrenoceptors are of the β type and their stimulation is thought to mediate a relaxant response [3]. This response is attenuated in vitro by non-selective drugs such as propanolol, possibly via a pre-junctional β2 receptor effect [416], but not by cardiac selective agents such as practolol. Direct cavernosal injection of propanolol in the intact animal had no effect however. β antagonists may also exert an inhibitory effect within the central nervous system, perhaps leading to lowered sex hormone levels [417]. 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. Non-selective drugs such as propanolol were associated with higher prevalence of ED compared to placebo or ACE inhibitor groups in the previously quoted early trials [412,413]. Later trials using newer 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 [414]. This also applies to the use of selective β-blockers in the prophylaxis of angina [418]. The clinical evidence therefore suggests that older non-selective drugs such as propanolol were associated with higher prevalence of ED but this effect is not seen with newer β1 selective agents.

c) α-adrenoceptor agents

Animal studies have demonstrated a positive effect on erection for α-antagonists, particularly those acting on the α1-receptor, by increasing or prolonging the relaxant response of cavernosal smooth muscle [3]. In addition, pre-junctional α2-receptor activation modulates the release of noradrenaline, suggesting a putative relaxant role for α2-blockers. Direct cavernosal injection of α1-antagonists has been shown to cause erection in both experimental animals and humans, although this effect is not seen by α2 selective drugs [3]. These experimental findings have been borne out in clinical studies where drugs such as doxazosin used to treat hypertension [414] or lower urinary tract symptoms [419] were not associated with complaints of ED and indeed had lower rates than placebo groups. Unsurprisingly drugs stimulatory to the α2-receptor such as clonidine do result in diminished erectile function both clinically and experimentally by peripheral and central mechanisms [3,416,420]. The centrally acting drug, methyldopa, has also been associated with ED in controlled trials compared with placebo and other antihypertensive agents [412] and may act by antagonising hypothalamic α2-adrenoceptors.

d) Angiotensin Converting Enzyme (ACE) Inhibitors

These drugs lack any easily appreciated peripheral or central effect that would potentially interfere with sexual function. This is supported by an in vivo series of experiment in normotensive rats which suggested that the ACE inhibitor, captopril, did not cause any significant adverse effect on sexual function in awake rats [416]. 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 agents [412,414,417]. According to an early report, the newest antihypertensive agents, angiotensin-II receptor antagonists, have a beneficial effect on existing sexual dysfunction at baseline and have no adverse sexual effects during 12 months of treatment [421].

e) Calcium Channel Antagonists

Smooth muscle contraction requires increased cytosolic calcium derived from internal stores and extracellular fluid. It would therefore be anticipated that calcium channel antagonists 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 [3]. Clinical studies have demonstrated no adverse effect on erection and ejaculatory complaints seem short-lived [417]. In the TOMHS study there was no significant excess risk of ED in the amlodipine group compared to placebo [414]. 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 [422]. A comparative study of two calcium channel antagonists showed that neither had any significant effect on sexual function although two patients withdrew from the nifedipine arm because of reduced libido [423].
**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 antagonists and the novel angiotensin-II antagonists both tend to improve sexual functioning during treatment and may therefore be useful when commencing antihypertensive therapy in men with pre-existing ED [424] (figure 23).

![Antihypertensives](image)

**Figure 23**: Antihypertensive therapies associated or not with erectile dysfunction.

3. **Psychotropic Medication**

In common with drug treatment for hypertension, 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 interrelational of pathways within the CNS make it inevitable that neurones 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 [425]. 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.

**a) 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 β adrenergic blockade and anticholinergic properties together with antidopaminergic actions within the basal ganglia causing extrapyramidal side effects which commonly produce sexual symptoms [426]. 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 [427] or avidity for particular areas of the cerebral cortex [428]. An additional effect of dopamine blockade, hyperprolactinaemia, which will also alter sexual function by reducing dopamine release in permissive cerebral centres, is more common with older 'typical' agents [429].

The results of animal experiments, chiefly in the rat, examining the role of CNS dopaminergic pathways in penile erection and copulatory behaviours have recently been reviewed by one of the main researchers in this field [430]. 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 [431]. 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 [3]. In addition systemic administration of antipsychotic agents in the rabbit produced erection by a local non-dopaminergic action, possible involving antagonism of α1 adrenoceptors [432]. 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 [433].
In a non-randomised comparative study the prevalence of sexual dysfunction ranged from 40-70% [434]. 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 thio-ridazine, an 'atypical' agent caused ejaculatory problems rather than ED [435]. In summary, these agents have a credible mechanism of action but their clinical effect is variable due to differing overall CNS effect.

b) Antidepressants

Sexual side effects of these commonly prescribed medications in both men and women are varied but are important factors governing compliance since such drugs are commonly prescribed to younger and middle aged adults. Clinical evidence of causal relationship is limited by lack of controlled data [436] and animal studies but has lately improved, particularly for the newer agents. This evidence was summarised in a recent systematic review [437] and is also to be the subject of a forthcoming Cochrane review [438].

1. Tricyclics

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 [439,440]. Against this a case-control study showed no excess sexual dysfunction amongst patients taking a tricyclic [441]. In summary, these drugs most frequently cause orgasmic dysfunction for which the underlying mechanism is unclear.

2. Monoamine Oxidase Inhibitors

These drugs are now rarely used. In common with the tricyclics, they are associated with higher rates of orgasmic dysfunction in controlled trials [439], the nature of the central or peripheral mechanisms involved is uncertain.

3. 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 [442,443]. Possible mechanisms include stimulation of 5-HT2 and 5-HT3 receptors which may inhibit erectogenic pathways within the spinal cord [444], decreased dopamine release in the medial preoptic area [445] and inhibition of 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 [446]. Another placebo controlled randomised study however did reveal increased sexual dysfunction, mainly anorgasmia, in the SSRI treated group [447], a finding also reported by Labatte [448]. Further studies have suggested that these adverse effects can be modified by co-treatment with other drugs such as sildenafil [449] or mianserin [450].

SSRIs differ in their ability to cause ED. A high incidence of ED has been observed in patients under treatment with the SSRI, paroxetine [451], while a lesser impact on sexual function has been reported in patients treated with the SSRI, citalopram [452]. 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 [453]. Indeed, the inhibitory effects induced by acute paroxetine on erectile function in the rat can be prevented by inhibition of PDE5 with vardenafil [454] or by co-administration of the NOS substrate, L-arginine [455]. On the other hand, venlafaxine, a mixed inhibitor of serotonin and norepinephrine reuptake, produced ED in rats by increasing NE levels, since its inhibitory effects on erectile responses were prevented by phentolamine [455]. Thus, the ability to produce ED and the mechanism by which SSRIs cause ED may differ depending on the specific SSRI compound.

c) Newer 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 [456], although
they may also antagonise at the 5-HT2c receptor [457]. The isolated reports of priapism seen with a prototype agent, trazodone, which has been shown to increase nocturnal erectile activity despite reducing REM sleep [458] may be related to the 5-HT1c erectile effect seen with its primary metabolite, m-chlorophenylpiperazine, in experimental animals [3].

4. 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 [408]. 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 GABAergic drugs inhibit erection induced by apomorphine, a dopamine agonist [459]. Clinical correlates are scarce but a controlled study did demonstrate that a combination of lithium and benzodiazepine was associated with significantly higher rate of sexual dysfunction than treatment with lithium alone [460]. More recent anxiolytic agents such as bupropion, acting mainly by inhibiting dopamine re-uptake, and buspirone which acts on 5-HT1a receptors are not associated with sexual side effects in placebo controlled trials [461] and can be used to alleviate sexual symptoms caused by other antidepressant medication [462].

5. ANTIANDROGENS

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 [3]. 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 [463].

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 [464]. At the lower dose of 1 mg daily used to treat male pattern alopecia no excess sexual dysfunction was seen compared to placebo [465]. 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 antiandrogen, 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 antiandrogens 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 [466]. 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 [467]. 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 [468]. 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 [469].
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 [470]. This was objectively confirmed by nocturnal penile tumescence monitoring (NPT) before and after initiation of therapy in a small study [471]. These more recent findings make initial hopes that such drugs could be used to treat ED appear suspect [472].

In summary, antiandrogen drugs produce the expected effects of sexual desire and erection commensurate with the degree of androgen ablation achieved.

### 6. 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) Digoxin**

In an experimental *in vitro* study using isolated human corpus cavernosum, it was found that digoxin attenuated the relaxant response to acetylcholine and intrinsic nerve stimulation, this was linked to findings of reduced penile rigidity compared to placebo in men following visual sexual stimulation [473]. A randomised clinical study confirmed a negative effect on general sexual functioning linked to a decrease in plasma testosterone [474].

**b) Statins**

This class of drug is increasing used to lower lipid levels for the prophylaxis of cardiovascular disease. Statins are thus mainly used in the population at risk of these events who are likely to have established risk factors for sexual dysfunction, particularly ED [475]. The MMAS revealed that low levels of HDL cholesterol were an independent risk factor for ED [253]. In animal models of hyperlipidaemic states, supraphysiological total cholesterol concentrations resulted in reduced neuronal and endothelial dependent relaxant cavernosal smooth muscle responses. The responses were partly restored by the NO substrate L-arginine and lowering of cholesterol levels by dietary change [262,269]. In contrast to these experimental studies, a single placebo controlled trial found that the rate of ED was twice as high (12% versus 6%) in men taking a statin despite improvement in other parameters of hyperlipidaemic endothelial pathophysiology [273]. Not surprisingly, this unexpected association has been questioned [276]. The controversy concerning the balance of risk and benefit of statins and ED has recently been reviewed [476].

**c) 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 [477]. A single *in vitro* animal study suggested that H2 receptor stimulation did cause cavernosal relaxation possibly via endothelial release of nitric oxide [3]. These reports have not been confirmed by well designed trials.

**d) Opiates**

Long term intrathecal administration of opiates results in hypogonadotropic hypogonadism and associated sexual dysfunction that can be restored with appropriate supplementation [478]. Administration of opioid antagonists to older men with ED however did not improve erectile function measured objectively by NPT monitoring [479]. 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 [3].

**e) Retroviral Drugs**

A single recent retrospective cohort study suggested that the prevalence of ED in men taking protease inhibitors was approximately twice that of matched controls, the highest rate being observed with rotonavir [480].

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Committee 12 A

Endocrine Aspects of Men Sexual Dysfunction

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The First International Consultation on Erectile Dysfunction included a comprehensive report on the endocrine and metabolic aspects of male sexual function. In some areas of this field progress has been made during the last four years. In other aspects very little, if any, has changed. It was the collective decision of the Committee to provide an update to the chapter of the earlier publication without extensively reiterating previously accepted concepts but emphasizing some aspects on the pathophysiology, diagnostic process, treatment modalities and their efficacy as well as the monitoring needs of patients under medical supervision. The mandate for this chapter is to deal with those aspects in general but focusing on the relationships between hormonal alterations and sexual function in men.

The development of a remarkably sustained interest in hormone replacement therapy (HRT) has occurred since the 1st Consultation took place. This interest has not been limited to health care professionals and the pharmaceutical industry but has extensively spilled out to the lay press and the general public. Established concepts of female hormone replacement therapy have been vigorously challenged and some of the new findings were, erroneously and baselessly, extrapolated to androgen replacement therapy in men. The Committee has addressed those concerns and a separate committee attended to the issues of hormone replacement therapy (HRT) in women.

A great deal of the information included in this chapter is based on solid research and represents the most robust evidence on the topic. Publications marked in the References section with *** indicate well designed studies that, in the judgment of the Committee most closely fulfill the requirements for evidence based criteria. Those marked with ** are important credible studies, meta-analyses or review papers that provide reliable information. The remaining give supportive evidence in areas where medical science has not reached sufficient understanding, either because of the complexity of the issues, the rarity of the situation or, simply because a specific topic is new and unexplored to a level that provides confidence to make a definitive judgment. In other areas the Committee felt that there is too much controversy to grade a reference.

1. RATIONALE FOR DEFINITIONS

Definitions into sexual functions and dysfunctions are not pertinent to this chapter except in the areas concerning endocrinological aspects. The concepts detailed below, therefore, are limited to those aspects pertaining to endocrine alterations related to interference with the normal sexual response in the adult man.

In men, gonadal function is affected in a slow progressive way as part of the normal aging process [1]. Although the alteration in androgen production in aging men has been scientifically recognized for over 70 years [2], only recently, significant and sustained interest has developed on the importance of this condition which is variously known as male climacteric, andropause or, more appropriately, androgen decline in the aging male (ADAM) or late onset hypogonadism. The term andropause is biologically wrong and clinically inappropriate but it adequately conveys the concept of emotional and physical changes that, although related to aging in general, are
also associated with significant hormonal alterations. The inappropriateness of the term is based on the fact that in women, the reproductive cycle invariably ends with ovarian failure. In men this process is not universal and, when it occurs, it is normally subtle in its clinical manifestations.

The International Society for the Study of the Aging Male (ISSAM) has recommended a definition for the condition resulting from the decline in androgen production in the adult [3]. It has been adapted for this chapter to reflect the effect of hormones primarily on sexual functioning (see Recommendation 1). It is important to dispel the concept that endocrinopathies resulting from the normal process of aging in men are narrowly focused on sex hormones. Although hypotestosteronemia is the most widely recognized and investigated hormonal alteration associated with the aging process, the production of several other hormones is also profoundly affected by age and may have implications in sexual function. The Committee, therefore, felt that the ISSAM recommendation, although appropriate, should indicate that other hormones besides testosterone (T) can contribute not only to sexual dysfunction but to a myriad of other manifestations largely attributed solely to hypogonadism.

2. AN INTEGRAL VIEW OF THE EFFECT OF AGING ON SEX HORMONES AND SEXUAL FUNCTION

Several epidemiological studies have found age to be the most important factor associated with erectile dysfunction (ED) [4, 5]. Traditionally, it has been thought that vascular problems frequently associated with advancing age are the most prominent cause of this association. Undoubtedly, there exists an immediate relationship between them as well as with neurological alterations. But, other reasons may also play a prominent causal role in the relationship between age and ED.

a) Evidence of a direct connection from high neuronal centers to the corpus cavernosus of the penis

Some of the central and peripheral neurological mechanisms of sexuality are considered in other chapters. For the purposes of this chapter, it would suffice to indicate that an important contribution to our understanding of neurological control of a major portion of the sexual response arose from the ability to map central nervous system circuits by transneuronal tracing studies that allow delineation of circuits innervating specific organs. Thus, through a number of elegant animal experiments using a pseudorabies virus (PRV) capable of trans-synaptic transport and amplification, Marson et al. [6], among others, have documented consistent labeling of the following portions of the forebrain within a day of injection of PRV into the penis: the paraventricular nucleus (PVN), medial pre-optic area (MPOA) and supra-optic nucleus (SON). Such findings clearly support the view that these high locations of the central nervous system have a direct genital connection and are of fundamental importance in the control of sexual behavior and function. In addition to the anatomical links, further evidence has been provided, for a direct functional relationship by the induction of penile erections with either electric stimulation or the injection of the dopaminergic agonist apomorphine directly into the MPOA and PVN [7].

b) Endocrinology of aging

As indicated previously and discussed in detail later, there is incontrovertible evidence that aging is associated with a progressive decline in the production of several hormones including testosterone, dehydroepiandrosterone, thyroxine, melatonin and growth hormone [8] (anti-diuretic hormone production also declines and may have a role in the nocturia more commonly associated with bladder outlet obstruction; but this is a matter for another place and time). To what extent the changes in the hormonal milieu contribute to the development and persistence of ED remains speculative. It is known, however, that hypogonadism is associated with a decrease in sexual interest and deterioration in the quality of erectile function. Both of these situations can be improved with androgen supplementation therapy. The therapeutic response has been explained as the result of the central and peripheral activity of androgens. They appear to be fundamental in the signaling leading to the adequate production of nitric oxide (NO) concentrations in the smooth muscle of the penile corpora through the activity of NO synthase.

c) Could these fields join in an explanation of neuro-endocrine mechanisms?

To integrate the concepts of decreased sexual function and hormonal alterations in the aging male, basic animal research is providing important information. Until relatively recently, it was believed that testicular function would deteriorate on the basis of decreased gonadal perfusion leading to a loss in the population of Leydig cells. The causes may be more fundamental and complex than that. Chen and Zirkin [9] postulated as a cause a deterioration of Leydig
cells function due to accumulation of free radical damage that could be prevented by placing the Leydig cells in a state of steroidogenesis “hibernation”. Wang and her co-workers [10] have shown, in a series of investigations in rodents, that hypothalamic-pituitary functional alterations may not be the only or even the major cause of male gonadal dysfunction. They found evidence of a significant increase in apoptosis in both the hypothalamus and the gonads, a dual alteration that may explain the development of hypogonadism in aging. The areas of the forebrain closely linked to the decrease in gonadotropin-releasing hormone (GnRH) due to this apoptotic process are the same (MPOA and arcuate nucleus) or intimately related to the areas controlling the penile erection process (MPOA and PVN) and the synthesis and release of oxytocin (PVN and supraoptic nucleus) (Figure 1). Similarly, peptides normally characterized by their ability to release growth hormone (GH) were found capable of inducing penile erections when injected into the PVN of experimental animals. GH production also declines in relation to advancing age. These integrated views remain speculative but are worth additional research.

II. EPIDEMIOLOGICAL ASPECTS

Accurate information on global prevalence of hypogonadism in mature men is largely unknown. However, it can be predicted from population projections that diseases and conditions, such as ED, commonly and specifically associated with aging will increase significantly in the first half of this century. Data from the United Nations estimates and projections of world population trends over a 75-year period [11] tell the full story: In the last decade of the 20th century the number of humans increased by 1 billion and will do so by close to 2 billion over the next 25 years [12]. A man born in 1920 had to share this planet with 1860 million other humans; the same man now shares the planet with 6000 million (Figure 2) [13]. Much more revealing are the figures for life expectancy that, over this period, will increase by several years. In other words, in our life time there will be a large and rapid increase in the number of elderly (+65 years) and in the old-old (>85 years) human population (Figure 3). Over that period the number of elderly persons will triple, while the proportion of children will diminish from 35 to 20% [14]. Although the development of hypogonadism in association with advancing age is unquestionable, discrepancies on its prevalence among studies varies. On the other hand the estimates for ED fall within a relatively narrow margin (Figure 4). The reasons for this discrepancy are not readily apparent. In North America several cross-sectional and longitudinal studies [15-17] have confirmed the decline in androgen production associated with age (Table 1). It has been estimated that in the United States there are 5 million hypogonadal men but only about 5% receive treatment (Figure 5) [18].

The decline in serum testosterone (T) in the aging male population is, however, a universal phenomenon [5, 19]. Unfortunately, the information on hypogonadism and ED is still largely derived from limited, region-specific longitudinal surveys or larger but still limited cross-sectional, population based studies. A comprehensive review on studies aimed at the prevalence of ED has been recently published [20].

III. PHYSIOLOGICAL ASPECTS OF HORMONES INVOLVED IN SEXUAL FUNCTION

1. Gonadotropins and Androgens

The hypothalamic-pituitary gonadal system is a closed loop feedback control mechanism directed at maintaining normal reproductive function [21]. The gonadal hormones have inhibitory effects on the secretion of LH and FSH. Although testosterone, the major secretory product of the testes, is a primary inhibitor of LH secretion in men, other testicular products, including estrogens and other androgens, also inhibit LH secretion. The inhibitory effects of testosterone are both produced by testosterone itself and indirectly through aromatization to estradiol. Dihydrotestosterone (DHT), a non-aromatizable androgen, also inhibits LH secretion.

a) Luteinizing hormone (LH)

Both androgens and estrogens independently appear to moderate LH secretion. The fact that the magnitude of the LH rise after exogenous GnRH administration is lessened by estradiol administration but remains normal during testosterone infusion suggests that estradiol acts at the pituitary level, while testosterone acts at the hypothalamic level. Estradiol is produced both by the testes and from peripheral conversion of androgenic precursors. Although the blood level of estradiol is low compared to that of
Figure 1: Representation of the hypothalamic-pituitary area where integration of neuroendocrine processes controlling both production of gonadotropins and erectile function takes place. The figure illustrates both, the pathways of endocrinological control and the pulsatile nature of GnRH production. (Courtesy of Mechanisms in Medicine, 2003)

Figure 2: United Nations estimates of population growth over a 75 year period.

Figure 3: World Health Organization estimates of increase in the over 65 and 85 year old population.
Figure 4: Estimated global and regional increment in prevalence of erectile dysfunction in the first quarter of this Century.

Figure 5: Estimated prevalence of hypogonadism in the United States.

Table 1. Prevalence of hypogonadism in older males (%)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Baltimore Longitudinal Study*</th>
<th>Mayo Clinic^</th>
<th>Canadian MDs^</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>50-59</td>
<td>9</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>60-69</td>
<td>34</td>
<td>20</td>
<td>45</td>
</tr>
<tr>
<td>70-79</td>
<td>68</td>
<td>34</td>
<td>70</td>
</tr>
<tr>
<td>80+</td>
<td>91</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Based on a free androgen index
^Based on bioavailable testosterone
Adapted from Morley J. [17]
testosterone, it is a more potent inhibitor of LH and FSH secretion. Several studies have demonstrated suppression of LH levels by physiological concentration of both testosterone and estradiol [22]. Both these sex-steroid hormones influence the frequency and/or amplitude of LH secretory pulses in men by acting at the level of the GnRH pulse generator in the hypothalamus and in part at the level of GnRH-stimulated LH secretion [23].

### b) Follicle stimulating hormone (FSH)

The mechanism for the feedback control of FSH secretion is more controversial than that of LH. After castration, FSH increases, indicating a negative feedback from the testes. Like LH, both testosterone and estradiol are capable of suppressing FSH serum levels.

A nonsteroidal tubular factor may also be important in the feedback regulation of FSH. "Inhibin" has been isolated and characterized in follicular fluid and is produced by the Sertoli cells of the testes. Inhibin has two subunits, alpha and beta. Two forms of inhibin have been isolated, inhibin A (alpha, beta A subunits) and inhibin B (alpha, beta B subunits). Form B is the major negative feedback regulator of FSH secretion [24].

### c) Testosterone

The major functions of androgen include regulation of gonadotropin secretion, initiation and maintenance of spermatogenesis, formation of male phenotype during sexual differentiation, promotion of sexual maturation at puberty and controlling sexual drive and potency.

Testosterone is synthesized from pregnenolone within the Leydig cells (Figure 6). Testosterone production in men approximates 5 milligrams per day and the secretion occurs in an irregular, pulsatile manner. There is a diurnal pattern, with the peak level in the early morning and the nadir in the evening. Inside androgen target cells, testosterone can be converted to dihydrotestosterone (DHT) by 5α-reductase. Both these androgens bind to the same high-affinity-androgen receptor protein and subsequently the hormone receptor complex is attached to acceptor sites in the nuclei to effect the biologic response. Testosterone (but not DHT) can be converted into estrogens by the action of aromatase.

Androgens and estrogens, like other steroid hormones, initiate their effect at the cellular level by interacting with high-affinity receptor proteins. Androgen receptors are present in the highest concentration in androgen target tissues such as the accessory organs of male reproduction. In the testes androgen receptors are present both in Sertoli cells and Leydig cells (Figure 7).

In normal males, 2% of testosterone is free (unbound) and 30% is bound to sex-hormone-binding globulin (SHBG) with high affinity [25]. The remainder is bound with much lower avidity to albumin and other proteins. The fraction of T not bound to SHBG makes up the measure known as bioavailable T. These binding proteins regulate androgen function.

It was formerly believed that the physiologic active androgen moiety was the non-protein-bound “free” testosterone. It now appears that the transport of steroid hormones in a cell is more complicated and that enhanced rates of hormone dissociation from the binding proteins may occur in the microcirculation. It is now known that albumin-bound testosterone is also available to transfer into target tissue in the brain and liver. SHBG has a higher affinity for testosterone than for estradiol, and changes in SHBG reduce or amplify the hormonal milieu. Elevated estrogens, thyroid hormone and healthy aging will increase plasma SHBG and therefore decrease the “free” testosterone fraction as it is the case in the elderly (Figure 8).

### d) Androgen target organs

In males, androgens are known to have many important physiological actions, including effects on muscle, bone, central nervous system, prostate, bone marrow, and sexual function. The biological effects of testosterone and its metabolites have been classified according to their sites of action. Effects related to growth of the male reproductive tract or development of secondary sexual characteristics are called androgenic. The growth-promoting or trophic effects on somatic tissue are termed anabolic. Although early studies suggested that these might be two independent biological actions, more recent information indicates that these are organ specific responses and that the mechanisms that initiate androgenic responses are the same as those that stimulate anabolic activity.

Androgens are responsible for the prenatal differentiation and for the development of the male reproductive tract. Androgens have a key role in both stimulating and maintaining sexual function in men. It appears that testosterone is necessary for normal libido, ejaculation and spontaneous erections. There is a threshold with individual variation, below which
Figure 6: Synthesis of testosterone

Figure 7: Schematic representation of androgen physiology.

Figure 8: The effect of age on the various fractions of plasma testosterone.
sexual function is impaired[26]. It has been reported that androgens are important in the expression of neuronal NOS and in the expression of the phosphodiesterase-5 (PDE-5) gene expression [27]. Recently these views have been further confirmed by the conclusive demonstration, in animal model, that normal androgen levels are a prerequisite for a PDE-5 inhibitor (vardenafil) to work appropriately. The same study showed that androgen deprivation (by either surgical or medical means) leads to fundamental structural alterations in the corpus cavernosus resulting in failure of the veno-occlusive mechanisms [28].

Androgens also play an activating role in cognitive function throughout life. The relationship between androgens and mood is still unclear.

Androgens increase nitrogen retention, lean body mass and body weight. In the skeletal system, androgens have an impact both on bone formation and bone resorption. The amount of androgens required to maintain bone mass in men is not known, nor is it known whether the beneficial effect of androgen is due to androgen itself or to the estrogen produced from it. It is beyond doubt, however, that hypogonadism is a major cause of osteoporosis in men [29].

The stimulatory effect of testosterone on erythropoiesis is well documented. Androgens also have an effect on serum lipids. Men generally have a lower plasma concentration of high-density lipoprotein (HDL) cholesterol and higher concentration of triglycerides, low-density lipoprotein (LDL) cholesterol, and very low-density lipoprotein cholesterol than do premenopausal women. It also appears that hypogonadism is associated with coronary artery disease [30]. A definitive answer on the effect of androgens in lipid profile in men is not yet available but the early evidence is reassuring [31-33]. Hyperlipidemia, on the other hand, is a recognized risk factor for ED [34]. A lipid profile is a recommended part of the work-up of men with ED.

Safety issues demand special consideration regarding androgens and the prostate gland. Although the pathogenesis of BPH is still poorly understood, there is evidence that androgens and, more specifically, dihydrotestosterone are necessary for benign prostatic growth. The risks of androgen therapy, listed later on in this chapter, are widely accepted. Undoubtedly, the most prominent concern about androgen use relates to prostate safety and several publications have addressed this topic recently. It is well established that hypogonadal men receiving supplemental testosterone experience an increase in prostate growth that corresponds to their eugonadal age-match counterparts [35], but more recent evidence indicates that the volume and growth of the gland in those hypogonadal men are modulated by CAG polymorphism of the androgen receptor gene [36]. There is a majority consensus that testosterone administration does not cause prostate cancer. It is also commonly agreed that sub-clinical (not detectable by digital rectal examination and determination of prostatic specific antigen) prostatic adenocarcinoma may become manifest rapidly after androgen therapy. The recommendations on prostate safety are based on a number of publications [37, 38] which include extensive literature reviews. None of the published studies have included sufficient number of men or have adequate follow-up, therefore definitive answers are not yet available.

The Sexual Medicine Society of North America, adopted the following Position Statement at its annual meeting in April 2003: “Testosterone supplementation is indicated for men who have signs and symptoms of hypogonadism accompanied by subnormal serum testosterone measurements. Testosterone supplementation can provide important health benefits to these hypogonadal men. Testosterone supplementation should be administered only under competent and careful medical surveillance in order to identify early signs of possible adverse effects. Although the benefits and risks of long-term testosterone supplementation have not yet been definitively established, the weight of current evidence does not suggest an increased risk of heart disease or prostate cancer with long-term use of testosterone. Testosterone is not medically indicated in men who do not have hypogonadism”.

It is a reasonable position on the relevant issues of cardiovascular and prostate health, pending definitive studies.

e) Adrenal androgens

The adrenal androgens are dehydroepiandrosterone (DHEA), its sulphate (DHEAS) and androstenedione. Their androgenic action is much weaker than that of testosterone which in turn is weaker than DHT (Table 2). The adrenal androgens undergo conversions to other sex steroids such as testosterone, estrone and estradiol, mainly locally in tissues (Figure 9). Their contribution to circulating levels of testosterone in adult men and to estrogens in women is, however, insufficient to prevent hypogonadism in cases of gonadal failure. The relative potency of DHEA in relation to other sex steroids is illustrated in Table 2.

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Adrenal androgens are produced in abundant quantities, in the order of 20-30 mg per day, which is 10 times the daily production of cortisol but the production declines steadily in an age related fashion (Figure 10). This pattern of production is rather unique to primates and humans. Most laboratory animals have a much lower production and the origin is the gonad rather than the adrenal gland. In spite of the high levels observed in humans, it has been difficult to establish a well-defined biological function of the adrenal androgens DHEA and DHEAS.

f) DHEA and DHEA-S: hormones or pro-hormones?

Until recently it was thought that both DHEA and DHEA-S are capable of interacting with different classes of hormone receptors [39] and that they do not exert true hormonal effect on their own. Especially no DHEA-specific receptor had been identified, which is a prerequisite for production of hormonal effects. Therefore, DHEA was considered only as a pre-hormone exerting indirect androgenic and estrogenic effects following its peripheral conversion into small amounts of testosterone and estradiol. This physiological conversion indicates that DHEA administration may carry the same risks as testosterone or estradiol. Since DHEA and its sulphated form are freely interconverted by extra-adrenal sulphotransferase and sulphatase activities, DHEA-S constitutes a large plasma reservoir of DHEA.

Our understanding of DHEA is rapidly changing due to the identification of a putative specific DHEA-receptor on the plasma membrane of bovine aortic endothelial cells [40]. This receptor is functionally coupled to the G protein family, primarily to Ga12 and Ga13 subtypes. Activation of these G proteins promotes the production of endothelial nitric oxide synthase (eNOS). The putative DHEA receptor resembles the plasma membrane estrogen receptor but estrogens and anti-estrogens do not alter either the binding of DHEA to this new receptor nor its effects on eNOS production. This discovery opened the way to the concept of an intracellular receptor since all major steroid hormones in which plasma membranes receptors have been reported also have well characterized intracellular receptors. A further recent study by Williams et al [41] brought up evidence supporting the existence of a DHEA-specific receptor in human vascular smooth muscle cells (VSMC), involving ERK 1 signaling pathways: VSMC proliferation contributes to remodelling of blood vessels, and may be implicated in the pathogenesis of atherosclerosis. This proliferative process, that is inhibited by estradiol and stimulated by testosterone, is inhibited in vitro by DHEA. The activity of DHEA in it is altered by anti-estrogens or anti-androgens. Binding studies confirmed the presence of estrogen- and androgen-receptors in VSMC. In this study DHEA showed minimal affinity with either receptor, but bound specifically and with high affinity to putative receptors in intact cells. Although not negating the mechanism of action through conversion into testosterone and estradiol, these findings will have a fundamental impact on our interpretation of the biological actions of DHEA. This may be especially relevant in regards to sexual function which involves many vascular mechanisms in both men and women.

DHEA is also a neurosteroid, suggesting the possibility of specific effects on the nervous system exerted by non genomic mechanisms [42]. Neurosteroids are steroids persisting in the brain or nerves after castration and adrenalectomy, therefore produced by neural synthesis from cholesterol. In vitro and in vivo

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Table 2. Potency of various sex steroids, taking testosterone at a relative value of 100 (see text).

<table>
<thead>
<tr>
<th>Relative Activity of Androgens</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydrotestosterone</td>
<td>300</td>
</tr>
<tr>
<td>Testosterone</td>
<td>100</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>10</td>
</tr>
<tr>
<td>DHEA, DHEAS</td>
<td>5</td>
</tr>
</tbody>
</table>

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Figure 9: Adrenal androgen metabolism

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Figure 10: Pattern of DHEAS decline in production as a function of age in men and women.

Figure 11: Decision tree for the management of hypogonadal men with ED
effects on brain neurotransmission have been documented in animals for DHEA and, in rats, it has been shown that hypothalamic and cortical astrocytes convert DHEA into testosterone and estradiol [43].

g) Role of DHEA in physiology and diseases of humans

Studies in humans have found associations between the serum levels of DHEA or DHEA-S and many physiological functions and diseases. Thus, several recent reviews [44-48] have described a large array of situations where DHEA may be of benefit. However, as discussed earlier, with the notable exception of psychological and sexual symptoms associated with adrenal insufficiency, utility and safety of long-term DHEA supplementation has not been fully established.

2. OTHER HORMONES

a) Growth hormone

It is known that the production of growth hormone (GH), after puberty, also decreases with age, about 14% per decade [49]. Since the production of circulating insulin-like growth factor-I (IGF-I) is controlled by GH levels, both decline together [50]. This reduction is associated with changes in lean muscle mass, bone density, hair distribution and the pattern of obesity also described in hypogonadal states [51, 52]. Administration of GH reverses these alterations [53] and does it more efficiently in eugonadal men than in their hypogonadal counterparts [54]. GH has been identified as an anti-apoptotic agent in neuronal model systems [55], a finding that would have major implications, for instance, in the prevention of degradation of neurofibrils proteins seen in Alzheimer's disease. In spite of earlier studies supporting the concept that administration of GH to adults with growth hormone deficiency improved mood and sense of well being, such observations have not been confirmed by controlled investigations [56]. Although the body of evidence favors the use of androgens in the treatment of some of the manifestations of ADAM, more recent studies clearly indicate that elderly patients respond to GH administration alone. These individuals exhibit an improvement in body composition, including and increase in lean body mass [57], and a definitive positive response by bone parameters [58, 59]. It appears that GH deficient males are more responsive to GH supplementation than females [60]. It is evident, therefore, that many of the signs of androgen deficiency are shared by a deficiency in GH. Also some of the concerns about androgen supplementation in adult males (e.g. prostate health) may be shared by GH administration [61]. Although no changes in PSA were found in a group of men older than 50 years receiving injectable growth hormone [62], when GH is combined with testosterone, there is a synergistic effect in relation to prostate growth [63]. Finally, GH deficiency may have profound implications in the alteration of sleep patterns observed in the elderly [64]. Although the literature is silent on a possible role of GH in sexual functioning, its administration improves peripheral circulation and emotional status [65].

b) Melatonin

The circadian rhythm of melatonin secretion by the pineal gland is regulated by the suprachiasmatic nucleus and in response to hypoglycemia and darkness. The production of this hormone also decreases with age regardless of these stimuli [66]. The physiological role of the pineal is not completely understood but it is involved in gonadal function and regulation of bio-rhythms [67]. Other physiological effects ranging from analgesic and antioxidative [68] to immunomodulating [69] properties have been attributed to melatonin. However, the large popular enthusiasm around the hormone has precarious scientific basis. It is likely that administration of melatonin may improve the significant sleep disorders frequently seen in the elderly [70], although other factors, such as interleukin-6 production may be operational too [71]. As mentioned earlier, profound hypotestosteronemia is associated with alterations in melatonin production, therefore hindering the attribution of some symptoms (sleep disturbances) exclusively to deficits of one or the other hormone. Evidence continues to emerge about a wide range of direct and indirect activities of melatonin on many human organ systems [72].

c) Thyroxin

There are well established changes occurring with aging in the hypothalamic-pituitary-thyroid axis. These include decrease in pituitary thyrotropin (TSH) to thyrotropin releasing hormone, diminished response to the thyroid to TSH and decreased serum concentration of total or free T3 and T4. These changes and the increasing prevalence, with age, of auto-immune thyroid diseases may result in the development of hypothyroidism which may reach an incidence of close to 20% in the elderly, depending on the dietary supply of iodine [73]. Erectile function is usually not affected. Hyperthyroidism, on the other hand, increases the levels of SHBG and increa-
se the aromatization of testosterone into estrogen. These two events may have detrimental effect on sexual functioning.

**d) Prolactin**

Prolactin has no known definitive role in the physiological control of human sexual behaviour, with the possible exception of a contribution to the orgasm-induced prolactin secretion usually observed in normal men and women. This may also bear a relationship to the sexual-satiation mechanisms since this burst in prolactin secretion was not observed in a multi-orgasmic male [74]. On the other hand, all types of hyperprolactinemia (idiopathic, tumoral or drug induced) can inhibit most of the aspects of male sexual behaviour.

1) **Sexual dysfunction and hyperprolactinemia**

In a literature review encompassing more than 300 men with hyperprolactinemia, Buvat et al [75] found sexual disturbances in 88%. The most common manifestation was a decrease in erectile function associated with a marked reduction in sexual interest. Delayed or absent orgasm was also found but virtually never as an isolated symptom. Some cases of retrograde ejaculation were also reported. Other manifestations of hyperprolactinemia were less frequent: reduced body hair in 40% of the cases, gynecomastia 21%, galactorrhea in 13%. Erectile dysfunction is thus the leading revealing symptom of hyperprolactinemia in men, a rather uncommon condition which should not be missed since many cases result from pituitary adenomas likely to result in serious endocrinological, visual and neurological complications, the last two due to an expanding prolactinoma.

2) **Mechanisms of the sexual problems of the hyperprolactinemic men**

Hyperprolactenemia impairs the pulsatile LH secretion, which, in turn, produces a decline in serum testosterone production by the gonads. The resulting hypogonadism is generally thought to be the main cause of erectile dysfunction. This simplistic view, however, may not explain the whole picture. Serum testosterone is indeed in the (low) normal range in nearly half of the males with marked hyperprolactinemia and erectile dysfunction. In addition plasma sex hormone-binding globulin is lowered in hyperprolactinemic males, which attenuates the effects of low serum total testosterone by increasing the proportion of unbound testosterone. Moreover, during treatment of hyperprolactinemic men [76] with the dopamine-agonist bromocriptine, sexual improvement correlates better with the decrease of serum prolactin than with the increase of the testosterone level. It is not uncommon that these men report a return of their erections prior to any increase in serum testosterone. Other studies, including that of Bancroft et al [77], who compared bromocriptine with a placebo a double blind design in a single man, tend to support the hypothesis of a direct, testosterone independent, effect of prolactin on sexual behaviour of men.

The mechanisms independent of the circulating level of testosterone may be related to a decrease in the 5-alpha reduction of testosterone to dihydrotestosterone which was reported by Lobo and Kletzky [78] in hyperprolactinemic men; this factor may be relevant since dihydrotestosterone appears to be the main metabolite accountable for the effects of testosterone upon the brain centers in primates. In addition, the main testosterone-independent mechanisms may be related to the interactions between the high prolactin levels within the central and peripheral neurological circuitry involved in the human sexual response. Prolactin increases the synthesis, turn-over and release of central dopamine from neurons of the hypothalamus, which could explain the biphasic effect of hyperprolactinemia in rats [79].

3) **Prevalence of hyperprolactinemia in men with erectile function**

Systematic determinations of serum prolactin in men referred for erectile dysfunction found very low prevalences of hyperprolactinemia (1 to 5%). The compilation of the largest series showed a prevalence of marked hyperprolactinemia (serum prolactin greater than 35 ng/ml) at 0.76% (25/3265 patients with individual values available) and of pituitary adenomas at 0.4% (18 of 4363 men) [80-85]. The prevalence of hyperprolactenemia remains low even in men with ED, including those with only mild hyperprolactinemia (serum prolactin 20 to 35 ng/ml); the prevalence was 1.5% in a series of 1370 consecutive ED patients having undergone systematic prolactin determination [86]. It is unlikely that such modest hyperprolactinemias are the real cause of the ED. Occasionally, however, even marginal elevations are associated with a pituitary tumor or a low serum testosterone level. Of interest, is that the improvement in erectile function following the administration of the dopaminergic agonist bromocriptine was about 40%. This is a similar result to the one reported in normoprolactinemic men treated with bromocriptine for ED [87]. Conversely the efficacy of bromocriptin alone in
cases of ED with serum prolactin greater than 35 ng/ml suggests a causative effect. Current experience is in line with the Masters and Johnson' group [88], uncontrolled study reporting that the sexual function of markedly hyperprolactinemic men responds better to bromocriptine than psycho- or sex therapy.

When evaluating the association between hyperprolactinemia and sexual dysfunction, it must be considered that biologically inactive, or only marginally active, variants of prolactin may be detected by immunological assays. It is especially the case of the “big” and “big-big” molecular variants of prolactin which have molecular weights of respectively 50-60 and 150 kilo Daltons (kDa) compared with the 22 kDa of the biologically active prolactin [89]. When secreted in excess, these “macroprolactins”, generally, do not carry clinical significance. They account for 10% of hyperprolactinemia [90] and are typically observed in normal individuals (mostly women with normal reproductive function despite high serum prolactin levels) but are also coincidentally found in some men with ED [91, 92]. In such cases the serum T level is usually normal, as are CT scans and MRI of the hypothalamic-pituitary area. Hypoprolactinemic agents such as bromocriptin or cabergolin are ineffective in improving sexual function. In this situation, the hyperprolactinemia is not the cause of ED. Chromatographic analysis of the prolactin in a specialized laboratory, allows identification of the macroprolactin molecule. However a diagnosis of macroprolactinemia in a man with ED should preclude neither MRI testing, since some cases are associated with pituitary adenomas, nor a trial of an hyperprolactinemic agent, since a biological activity of the macroprolactin has been demonstrated in some women. Some of the cases included in the review by Vallette-Kasic [90] may have been instances of undiagnosed macroprolactinemia. The finding by Buvat et al [91], of a tendency to a decrease in the incidence of hyperprolactinemia over time, could be explained by the simultaneous improvement of the specificity of the assays, leading to less confusion with macroprolactinemas. Another explanation could be the relatively large number of “old” cases waiting for a proper diagnosis because of the unavailability of methods for prolactin assay 25 years ago.

4) Prevalence of hyperprolactinemia in the other sexual dysfunctions of men

Buvat et al [86], in a limited study, systematically determined serum prolactin in consecutive patients investigated for low sexual desire without ED (n=53), anorgasmia (n=74), and premature ejaculation (n=124). They found no case of hyperprolactinemia in the 2 former sexual dysfunctions. Schwartz et al. [88] reported cases of hyperprolactinemia in men consulting for isolated low sexual desire or anorgasmia. Serum prolactin was mildly elevated (less than 35 ng/ml) in 13 men with premature ejaculation (10%). This mild hyperprolactinemia was not the cause of the sexual dysfunction since bromocriptine failed to prolong the time to ejaculation in every case. In addition serum testosterone was normal in all these 13 and no pituitary adenoma was detected in any of them.

5) Diagnosis of hyperprolactinemia in men with sexual dysfunction

Many believe that the very low prevalence of significant hyperprolactinemas can hardly justify the routine determination of prolactin in males with ED, considering the frequency of ED and the cost of the determination [81-83]. It has often been recommended to determine it only in cases of low serum testosterone level, or of low sexual desire. However testosterone level was subnormal (< 3 ng/ml) in only 10 of the 17 hyperprolactinemic men of Buvat et al [85], including only 5 of the 10 who had been referred for ED. It was in the low normal range (3 to 4 ng/ml) in 4 of the 7 others. Many other cases with normal serum testosterone level, in spite of marked hyperprolactinemia have been reported, including some with pituitary tumors, thus unlikely to be macroprolactinemas. Determining serum prolactin only in cases of low testosterone levels would miss 50% of the 12 marked hyperprolactinemas and 3 of the 7 pituitary tumors detected by Buvat et Lemaire in ED patients [85].

Likewise sexual desire may be normal or may be perceived as normal by men with hyperprolactinemia. Johri et al [93] found no difference in the mean serum prolactin level according to the level of sexual desire reported during clinical assessment, or according to the score of the Sexual Desire Domain of the International Index of Erectile Function (IIEF). By determining serum prolactin only in case of a score <3 in the Sexual Desire Domain of the IIEF, they would have missed 50% of the hyperprolactinemas detected in their ED patients. It then appears that the IIEF may be potentially useful for screening for hyperprolactinemia, since Johri et al [90] found that, among the 136 ED patients they screened, every one with marked or mild hyperprolactinemia had severe ED according the IIEF criteria (score < 10 at the Erectile Function Domain). This report, however,
needs confirmation since others have found an only slightly disturbed pattern of erections in their hyperprolactinemic men (normal nocturnal erections and normal erectile responses to audio-visual sexual stimulation). Buvat et al [94] reported that by restricting the serum prolactin determination to those men with low sexual desire, gynecomastia, or serum testosterone < 4 ng/ml (low + low normal values) they would have avoided more than half of the laboratory determinations while missing only 1 of the 10 marked hyperprolactinemic men and none of the 6 pituitary tumors.

Precautions should be taken to avoid false diagnosis of hyperprolactinemia resulting from stress, meals, or the intake of certain types of drugs. Blood sampling ideally should be carried out fasting, following a 20 minutes rest in a quiet place. Elevated serum prolactin levels should be confirmed. In case of discrepancy between high serum prolactin and a pattern of non-endocrine sexual dysfunction the patient should be investigated to rule out macroprolactinemia.

Finally, any man with (non drug-induced) confirmed diagnosis of hyperprolactinemia should undergo investigation of the hypothalamic-pituitary area (if possible Magnetic Resonance Imaging) to rule out the presence of a tumor responsible for the hyperprolactinemia.

6) Treatment of the men wit sexual dysfunction and hyperprolactinemia

The sexual dysfunction of the hyperprolactinemic men may be improved by non specific treatments such as psycho- or sex-therapy or, in cases associated with ED, the use of sildenafil has been reported to be effective [95]. However dopamine-agonists (bromocriptine, lisuride, quinagolide, and cabergolide), most often normalize all aspects of sexual function, and shrink the size of the possible pituitary adenoma, or at least prevent its growth. In addition, they allow the return of sexual desire, and in cases of ED, of spontaneous erections avoiding the necessity of planning sexual intercourse as is the case with sildenafil. Therefore they must be the first choice treatment. However, in the case of a pituitary tumor exceeding 10 mm diameter (macroadenoma) the patient should undergo a thorough investigation of its pituitary function. It must also be known that in cases of low T level, T administration may stimulate the growth of an eventual pituitary tumor through its aromatization into estradiol if the hyperprolactinemia is not totally controlled by dopamine-agonist therapy.

Surgical treatment of prolactinomas is reserved for large tumors that failed to respond to medical therapy.

e) Corticosteroids, estrogens and leptin

The production of corticosteroids and estradiol, in males, remains fairly constant throughout life. On the contrary, leptin is altered in hypotestosteronemia which explains, in part, some the changes in fat distribution observed in these men [96]. Levels of leptin can be brought down by androgen supplementation resulting in an improvement in obesity [97]. No specific, direct role has been attributed to corticosteroids or leptin in sexual function. The role of estrogens is further discussed later on in this chapter.

f) Insulin and Diabetes Mellitus

Among the endocrine causes of sexual dysfunction, diabetes mellitus (DM) occupies the most prominent position and it should be ruled in men with erectile insufficiency. The American Diabetes Association considers a fasting blood sugar as diagnostic of DM and this test is recommended in men with ED. Not uncommonly determination of glycosalated hemoglobin is used for the same purpose. The documentation of DM does not imply that that other co-morbidities are absent in the etiology of ED in diabetics. This correlation between DM and ED has been recognized for many years. Buvat et al. [99] in a case controlled study of diabetic and non-diabetic men, found that the psychological factors were additive to the arterial and neuropathic factors in diabetic ED. A study of 110 consecutive diabetic men reported that 11% of them had psychogenic factors for ED as the only cause found, while they were the main cause in 24%, and contributory in an additional 17% [100].

Organic factors, however, are prominently causal in diabetic ED, and appear quite early in the course of the disease, just as neuropathic changes may begin before clinical symptoms are noted.

The primary organic, pathophysiological factors causing diabetic ED can be categorized as neuropathic and vascular. The vascular changes are quite prominent as Wang found, in an observational study of 78 diabetic males with ED. These men had complete medical evaluations, including duplex ultrasound examinations after an intracorporeal injection of PGE1, and 87.2% were found to have moderate or severe cavernous arterial insufficiency. This increased to 100% if hypertension or alcohol abuse were added risk factors to the diabetes [101]. DeAngelis studied 30 type 2 diabetic men with ED versus 30 similar but potent diabetic men in a case-controlled
study. Factors in the group with ED correlated with endothelial dysfunction. Indices of coagulation activation and reduced fibrinolysis were higher in the ED patients, as were concentrations of thrombomodulin, P-selection and ICAM-1, while the decrease of blood pressure to L-arginine was lower [102]. Additional factors, found in diabetic women but easily applicable to men include an enhanced expression of endothelin-1, decreased nitric oxide activity, decreased prostacyclin release, increased adhesion molecule expression, increased platelet adhesion and procoagulant activity, along with increased advanced glycosylated end products [103]. The Atherosclerosis Risk in Communities (ARIC) Study monitored 1,675 middle-aged persons who had diabetes but no history of coronary artery disease found that endothelial dysfunction factors were predictive of future cardiovascular disease [104].

A major consequence of endothelial dysfunction is decreased production and/or action of nitric oxide, the main penile microcirculation vasodilation factor. It has been documented that diabetic rats exhibit a marked decrease of penile nitric oxide synthase activity, and a reduced nNOS content in penile tissue [105]. This and other experimental studies have shown that diabetes impairs neurogenic and endothelium-mediated relaxation of rabbit corpus cavernosum smooth muscle with possible mechanisms involving cholesterol or advanced glycation end products [106].

1) Diabetes and vascular disease

Inherent to the definition of type 2, or adult onset DM, is insulin resistance. Insulin is the body's most potent anabolic hormone, as it is the main mediator of storage of metabolic fuel. Insulin is also a vasodilator and acts via a NO-dependent mechanism as well as endothelial function [107]. These mechanisms are active in the penile vasculature to produce ED: Corpus cavernosus duplex US was studied after an injection of PGE1 and it was found that vascular ED was the most common etiological factor, as it was the prime factor in 64% of the diabetic men, thus supporting the theory that microangiopathy is the most important cause of diabetic erectile dysfunction [108]. Hyperglycemia in diabetes causes other metabolic changes that can affect penile physiology. Sobrevia, in an extensive review of the literature, noted that elevated blood sugar causes regional hemodynamic changes and endothelial-dependent relaxation is impaired. PKC is activated and oxygen radicals are generated, which inactivate NO and cause endothelial injury [109]. Christ studied the mechanism of the known association between hyperglycemia and endothelial dysfunction using porcine coronary arteries in tissue culture and controlling for normal or high glucose levels, as well as using sucrose as a different sugar. Hyperglycemia induced significant levels of free oxygen radicals, but not sucrose or normal glucose levels. This was completely blocked by removal of the endothelium, proving that the source of the free radicals was from abnormal endothelial function. Further studies showed that one of the mechanisms was through NAD(P)H oxidase activation [110].

2) Diabetes, peripheral and autonomic neuropathy and ED

An early observational study of 25 patients with IDDM found that 60% had cardiac autonomic neuropathy, 68% had diabetic cystopathy, while 80% had signs of peripheral neuropathy. Surprisingly, the most common symptom was ED (44%), rather than postural hypotension (28%) [111]. Bemelmans, in a case-controlled study, looked at 27 impotent and 30 potent diabetic IDDM men, as well as 102 impotent non-diabetic men. Somatic and autonomic neurological testing were carried out. Intracavernosal pharmacological testing again showed a preponderance of vascular abnormalities in the diabetic subjects. Hormonal values did not differ between groups. Neurological testing revealed that 85% of the impotent diabetic men had some form of neuropathy versus 40% of the potent diabetic men and 44% of the impotent non-diabetic men. They also found that poor diabetic regulation, as measured by A1C levels, correlated with increased sexual dysfunction [112]. It should be indicated, however, that a case-controlled study failed to find a significant difference in the bulbocavernosus reflex latencies between the diabetic and non-diabetic men. This may reflect, in part, inherent deficiencies of the test. He felt that this specific test was not useful in evaluating neuropathy as an etiological cause of ED in diabetic men.

3) Diabetes and hypogonadism

Diabetes lowers testosterone, and hypogonadism may be yet another factor contributing to ED in this population. The sum of co-morbidities has more of an effect than a single risk factor. Low testosterone levels and elevated gonadotropins were found in a large observational study of 100 IDDM men and 314 NIDDM men, but only in the population of diabetic men with neuropathy. Abnormal seminal volume and abnormal sperm parameters in this population suggested an effect of neuropathy on testicular function.
and/or anatomy [114]. The MMAS longitudinal epidemiological study of 1,709 men, aged 40 to 70 years of age, looked at 1,156 men 7-10 years later. They found that testosterone and SHBG levels were predictive of new cases of diabetes. The odds ratio for future diabetes was 1.58 for a decrease of 1 SD in free testosterone (4 ng/dL), and 1.89 for 1 SD decrease in SHBG (16 nmol/L), both having p < 0.02). This was consistent with prior cross-sectional data from this study [115].

4) Diabetes and the vascular endothelium

The vascular endothelium produces endothelin, a powerful vasoconstrictor, as well as vasodilating substances. If there is an enhanced production or an enhanced effect of endothelin, vasoconstriction can occur. Francavilla et al [116] reported that plasma concentration of endothelin-1 was increased in both the nondiabetic and diabetic men with ED versus the control non-diabetic men (p<0.0005 and p<0.0001, respectively, and was significantly higher in the diabetic versus the non-diabetic men with ED (p<0.002); elevated levels of endothelin-1 in the corpora cavernosa correlated with the blood levels in all of the men with ED. These findings suggested that endothelial dysfunction might contribute to erectile failure but, others found no difference in the response of endothelin on contraction of smooth muscle in the diabetic versus the non-diabetic corporeal tissue, in vitro [117]. More research is needed in this area, in order to see if alterations in endothelin level and/or action in diabetic men has any clinical significance in the pathophysiology in diabetic ED.

### IV. DIAGNOSIS OF HYPOGONADISM

1. **Clinical**

A diagnosis of hypogonadism in men should always be based on both a suggestive clinical picture and the biochemical demonstration of hypoadrogenism. The combined presence of clinical and biochemical features of decreased androgens is particularly important in aging men where the clinical picture alone loses much specificity. In contrast to the menopause, the process of the andropause is, most commonly, characterized by an insidious onset and a very slow progression. The clinical picture can be easily attributed to the natural and unavoidable consequences of aging. True andropause is seen in the hormonal ablative treatment of advanced prostate cancer and in this situation the manifestations are defined more clearly. However, a similar but subtler picture develops in adult men affected by hypoadrogenism [118]. It also need to be emphasized that whenever this diagnosis of has been confirmed, it is important to exclude reversible causes. The syndrome of late onset hypogonadism in men is characterized by:

1. the easily recognized features of diminished sexual desire and erectile quality, particularly nocturnal erections;
2. changes in mood with concomitant decreases in intellectual activity, spatial orientation ability, fatigue, depression and anger;
3. decrease in lean body mass with associated diminution in muscle volume and strength;
4. decrease in body hair and skin alterations;
5. decreased bone mineral density resulting in osteoporosis;
6. increase in visceral fat. These manifestations need not all be present to identify the syndrome.

In addition, the severity of one or more of them does not necessarily matches the severity of the others, nor do we yet understand the uneven appearance of these manifestations [119]. In practice, the clinical diagnosis may be facilitated with the use of screening questionnaires. Validated ones are currently available for screening men suspected of hypogonadism [120, 121]. The ADAM questionnaire is a simple and sensitive questionnaire but performs marginally on specificity, particularly in the elderly. It is, however, useful for its purpose of initial screening, leading to a biochemical assessment (Tables 3 and 4). A more extensive, validated instrument, the Aging Male Scale (AMS), is also available (Table 5). Neither of these questionnaires replaces a proper history and physical examination [122].

2. **Biochemical**

It is helpful to review some facts that constitute the background for the biochemical diagnosis of hypogonadism in men. We lack a clinically useful biological marker of tissular androgen activity. This has two consequences. First, we are presently not able to precisely assess possible differences in androgen sensitivity that may exist between individuals or in different physiological and pathological situations. Secondly, for estimation of the androgen status of individuals we can only rely upon determination of serum concentrations of testosterone and/or its meta-
Table 3. The ADAM questionnaire. A suggested self-administered screening instrument for adult hypogonadism

![ADAM Screening Questionnaire](image)

Table 4. Scoring of the ADAM screening questionnaire.

![How to Evaluate ADAM Questionnaire](image)

Further investigation should include a laboratory assay for:
- Bioavailable testosterone
- or, alternatively
- a 'non age-adjusted' free testosterone

363
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Intensity of symptom (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>1. Deterioration of general well being (health status, and perceived general situation)</td>
<td></td>
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<tr>
<td>2. Complaints in joints or muscles (pain in lower back, joints or legs)</td>
<td></td>
</tr>
<tr>
<td>3. Sweating (eruptions of sweat, hot flushes)</td>
<td></td>
</tr>
<tr>
<td>4. Sleep disturbances (falling asleep, continuing to sleep, waking too early or tired, sleepiness)</td>
<td></td>
</tr>
<tr>
<td>5. Increased need for sleep (often tired)</td>
<td></td>
</tr>
<tr>
<td>6. Irritability (ill-humored, irritated by minor causes, become angry or cross easily)</td>
<td></td>
</tr>
<tr>
<td>7. Nervousness (inner tension, unrest, unable to stay calm and relaxed)</td>
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<tr>
<td>8. Anxiety (panic)</td>
<td></td>
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<tr>
<td>9. Exhaustion/decreased energy (general limitation of performance, reduced activity, less interest to do something, perceived low achievement, need for unusual stimulation to be active)</td>
<td></td>
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<tr>
<td>10. Decrease in muscular strength (weakness)</td>
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<tr>
<td>11. Depressed mood (discouraged, sad, tearful, less drive, frequent changes of mood, feeling of senselessness)</td>
<td></td>
</tr>
<tr>
<td>12. Feeling to have passed zenith of life</td>
<td></td>
</tr>
<tr>
<td>13. Wish to be dead, arrived at dead point, totally discouraged</td>
<td></td>
</tr>
<tr>
<td>14. Decrease in beard growth</td>
<td></td>
</tr>
<tr>
<td>15. Decrease in potency</td>
<td></td>
</tr>
<tr>
<td>16. Decrease in frequency of morning erections</td>
<td></td>
</tr>
<tr>
<td>17. Decrease in libido and sexual activity (desire for sex, interest in sex)</td>
<td></td>
</tr>
</tbody>
</table>

Date: ___________________  Patient Initials: ___________  Patient Number: ___________
bolites and other sex steroids. It is important to realize that even the most sophisticated measure of serum androgens can be at best an approximation of the androgen status. Such a measure does not take into account the role of intra-tissular metabolism of androgens into bioactive metabolites (“intracrinology”), or inter-individual differences in androgen sensitivity, the so called “endocrine disruptors”.

Measurement of serum testosterone and, in particular, of those fractions that are readily available for biological action (free and bioavailable), has been successfully applied to the diagnosis of hypogonadism in young and middle aged men. In fact, the diagnosis of hypogonadism in young men poses little diagnostic challenges as the clinic is often straightforward, the serum testosterone levels are often markedly low, and there is often an evident clinical context and/or corroborating biochemical evidence supporting the diagnosis and pointing towards a particular pathophysiological mechanism. In the absence of a reliable marker (vide supra) of androgen activity, we have no answer to the basic question of whether androgen sensitivity and androgen requirements change with age.

There is significant inter-individual variability on the inception, speed and depth of the androgen decline observed in adult males and no factors have emerged that predict the onset or severity of the condition [123]. It has been argued, therefore, that only a minority of individuals develops hypogonadism. This may not be the case. As shown earlier (Figure 8) associated with advancing age, there is also an increase in the levels of sex hormone binding globulin (SHBG), which translates in a further decrease in bio-available (free and albumin-bound fractions) testosterone [124]. An additional phenomenon associated with aging is the flattening of the circadian rhythm leading to steady low levels of androgens throughout the 24 hour cycle [125]. To compound the difficulties in establishing biochemical and clinical correlates, there are 3 important areas that require further elucidation:

a) it is not yet known what level of serum T defines deficiency in men over the age of 50 (when ED becomes most prevalent), although it is generally accepted that 2 standard deviations below the normal values for young men is conclusively abnormal;
b) there may be variable responses by the target organs (brain, bone, prostate, muscle, etc) to the levels of androgens and,
c) the response by target organs may be influenced by a variety of endocrine disruptors, the nature of which is only beginning to be explored in men.

The combination of these 3 uncertainties is important: Androgen deficiency may become clinically apparent at different points within an individual or a population, depending on the marker used.

Establishing the presence of hypogonadism on purely clinical basis is, in most cases, extremely difficult. Only the most severe cases bring up clinical suspicion. Despite this, there is considerable controversy as to the need for hormonal evaluation in a man complaining of sexual dysfunction. Its usefulness has been questioned on the basis that it is not cost-effective [126]. This skepticism is not shared by most [127, 128]. There are several reasons to justify, at least, basic hormonal assessment of men with sexual dysfunction. It is commonly accepted that the combination of low sexual desire and erectile difficulties may be the result of serious hormonal abnormalities.

The reality is not as simple or clear cut as that. Not only may hypogonadal men be capable of adequate sexual erections but also hormonal supplementation resulting in normal T values does not always result in restoration of libido and quality of erectile function [129]. It is important in this context to point out that there are indications that the threshold for testosterone levels required for normal sexual function may be clearly below the physiological range. It is highly recommended therefore, that in patients with sexual difficulties and at risk or suspected of hypogonadism the following biochemical investigations be done:

a. serum T between 8:00 and 11:00 AM. The best parameter to determine hypogonadism might be the

**Table 6. Relative merits of the various methodologies for measurement of circulating levels of testosterone. The more + the better the test performs in each category.**

<table>
<thead>
<tr>
<th>Method</th>
<th>Availability</th>
<th>Reliability</th>
<th>Cost</th>
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<tbody>
<tr>
<td>Total T</td>
<td>+++</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>FTd</td>
<td>+</td>
<td>++++</td>
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<td>FTm</td>
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<td>BT</td>
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<td>FAI</td>
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<tr>
<td>cFT</td>
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measurement of bio-available T (it includes the free and albumin-bound fractions). In men beyond middle age levels of total T may be misleading due to alterations in SHBG levels and flattening of the circadian rhythm mentioned previously.

b. If T levels are below or at the lower limit of the accepted normal values, it is prudent to confirm the results with a second determination together with assessment of luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin.

c. In the younger (<40 years) male low levels of T (<12 nmol/L or <350 ng/dl) with chronically elevated gonadotropins makes a clear diagnosis of primary hypogonadism or testicular failure.

d. In an older man the diagnostic lines are not as clearly defined and additional information may be needed. Thus in these men as well as the obese an SHBG determination may be useful in establishing the true clinical significance of T measurements.

e. It is prudent to confirm abnormal results (after a weeks interval) prior to onset of therapy.

a) Is an age corrected value for T necessary? This complex area was reviewed authoritatively by Vermeulen [130]. In this review it is emphasized that there is no generally accepted cut off value of plasma testosterone to unambiguously define androgen deficiency. In the absence of convincing evidence for an altered androgen requirement in men at different ages, he considers the normal range of free T levels in young males is also valid for elderly men. This view is backed by fairly strong research: in his healthy male, non-obese, population age 20-40 yrs (N = 150), the mean of log transformed early morning T levels was 21.8 nMol/l (627 ng/dl); the mean minus 2 S.D. was 12.5 nMol/l (365 ng/dl) and mean minus 2.5 S.D. was 11 nMol/l (319 ng/dl). For free T, measured by equilibrium dialysis or calculated from T and SHBG levels the mean was 0.5 nMol/l (14 ng/dl), minus 2 S.D. was 0.26 nMol/l (7.4 ng/dl) and minus 2.5 S.D. was 0.225 nMol/l or 6.5 ng/dl [131]. If one takes as lower normal limit and threshold of partial androgen deficiency, a conservative value of 11 nMol/l for T and 0.225 nMol/l for FT, which represent the lower 1 % value of healthy young males, then it appears that more than 30 % of men over 75 yrs old have subnormal (F)T levels. Most authors report rather similar values [132-135]. Again it should be pointed out that these values are only indicative and may vary according to the assays used in different laboratories. This is particularly true for free and bioavailable testosterone as the methodology used for estimation or calculation of these testosterone fractions may not be the same in different laboratories.

b) Assays for measuring testosterone

Although measuring total T is a fairly standardized test in most laboratories, it measure amounts of hormone not available at tissue level and may, therefore, be misleading. It is generally agreed that assessment of free T FT provides a reliable index of androgenicity. The confusion arises on the methodologies used to measure FT [129]. It should be mentioned that direct FT assays using a testosterone analogue (FTra), do not yield a reliable estimate of FT129. Reliable assays for FT include equilibrium dialysis (FTd) and ultracentrifugation (FTu). These two are more difficult to perform and not widely available. Bio-available T by ammonium sulphate precipitation is more commonly accessible, reliable and less expensive. The free androgen index (FAI) is easy to perform, widely available but unreliable. The calculated FT (cFT) is widely available, reliable and inexpensive. The cFT can be calculated using the formula described by Vermeulen et al [136] and readily available from the web page of the International Society for the Study of the Aging Male [137]. Table 6. provides a guide to the relative value of current methods for biochemical assessment of hypogonadism. Plasma levels of T exhibit significant variability within a single individual and within a short period of time [138]. Therefore, it is prudent to confirm abnormal results.

The age associated decline in T levels has both a testicular (decreased Leydig cell number) and central origin, the latter being characterized by a decrease in the amplitude of LH pulses in elderly men. Hence, older men frequently have normal LH levels. An increase in LH levels is not required for the diagnosis of hypogonadism in elderly men [139].

V. TREATMENT OF HORMONAL (NON-DIABETIC) ABNORMALITIES

The issues related to the treatment of sexual function in diabetics are competently presented in a separate chapter of this volume. This section deals with (long-term) androgen treatment. In addition, it focuses on the adult male -the common victim of both ED and hypogonadism- eligible for androgen supplementation in whom androgen deficiency has been diagno-
A decision tree is shown on Figure 10. It summarizes in a practical way the views in the text. In general terms hormone replacement therapy aims to substitute the deficient hormone with a perfect copy of the natural hormone, with a dose schedule that generates physiological hormone levels over 24 hours of the day. Currently, it is not known whether the treatment schedule should ideally mimic the circadian rhythm of production of the deficient hormones.

Unlike thyroid hormone and corticosteroid hormone substitution, androgen supplementation modalities are still not completely satisfactory. Though subcutaneous testosterone implants [140], transdermal patches [141], and more recently the transdermal gel constitute veritable improvements, the pharmacokinetics and pharmacodynamics of the more traditional forms of androgen replacement fail to mimic the serum androgen profiles produced by the testes. This situation is reflected in the reported side effects of androgen administration. Such side effects might be the result of the modes of testosterone replacement leading to un-physiologically high/low levels of testosterone/5α-dihydrotestosterone (DHT) or the aromatization product estrogen, and their ratios. Further, the route of administration matters; transdermal administration of testosterone is associated with high DHT levels. This is also the case with the oral testosterone undecanoate. This oral androgen circumvents a first pass through the liver through its absorption from the gut along with the fats via the thoracic duct. Probably a fair amount of testosterone still arrives via the portal vein in the liver and causes a significant decline in the production of sex hormone binding globulin (SHBG) [142]. While it is documented much clearer for estrogens, it seems likely that androgens exert different metabolic effects depending on their route of administration, oral or parenteral.

In contrast to replacement with thyroid hormone or corticosteroids, suitable valid clinical and biochemical indices of optimal testosterone supplementation have not been established in the scientific literature. This make studies that aim to define beneficial and deleterious effects of androgen supplementation still a difficult undertaking. Therefore, the studies and reports currently available need to be considered cautiously. Basic knowledge and good clinical judgment are mandatory in applying that knowledge to clinical situations.

1. **Suitable Testosterone Preparations**

Due to the feedback mechanisms hormone replacement therapy in both young and old men normally would require full substitution [143]. These findings have challenged the view that the natural (as opposed to the iatrogenic) androgen deficiency of the aging male is, in most cases, only partial and consequently only partial substitution will be required. Most commonly available testosterone commercial formulations are listed in Table 7.

### a) Injectables

The most widely used pharmaceutical forms are the intramuscularly administered hydrophobic long chain T-esters in oily depot, T-enanthate and T-cypionate, at a dose of 200-250 mg/2 weeks. They yield transient supraphysiological levels the first 2-3 days after injection, followed by a steady exponential decline to subphysiological levels, 10-12 days following administration. Plasma testosterone levels in the days remaining before the next injection are subnormal. When the instructions of the manufacturer to administer T-esters every 3-4 weeks are followed, this period of actual testosterone deficiency can be as long as 10-18 days [144]. These fluctuations in T levels are experienced by some of the patients as unpleasant and accompanied by changes in energy, libido and mood. The transient supraphysiological levels might, in fact, increase the frequency of side-effects. Preliminary studies with intramuscular injection of testosterone undecanoate 1000 mg indicate that this treatment might yield physiological T levels during 6-8 weeks [145]. Longer acting T esters (4-6 months), such as the buciclate are probably not suited for use in elderly males. In cases of serious side effects, a rapid withdrawal of T should be possible. Oral or transdermal testosterone may be better candidates, though both preparations are associated with high plasma DHT levels.
b) Orally administered T is almost completely inactivated by its first pass through the liver. The only orally active and safe form is T-undecanoate in oleic acid (TU) which, due its lipophilic side chain, is partly taken up by the lymph and partly escapes hepatic inactivation.

The maximal plasma concentration of T is generally observed within 2-3 hrs, but after 6-8 hrs, levels have returned to pre-treatment levels. Hence, TU should be administered 2-3 times daily, always with a meal, to improve absorption [147]. A dosage of 2-3 x 40 mg, generally provides adequate androgen replacement, yielding T levels within the (low) normal range, whereas DHT levels are moderately increased (2-4 nMol/l) [148]. The absorption is, however, rather variable (dependent on food consumption) and the dose required should be determined on the basis of plasma levels and clinical effects. Other orally active, synthetic androgen/anabolic steroids are either only weakly active (mesterolone; fluoxymesterone) or hepatotoxic due to the presence of an alkylgroup in position 17 of the molecule [149].

c) Transdermal

Transdermal scrotal or permeation enhanced non scrotal patches, delivering 4-6 mg of T per day, provide physiological T levels both in young and elderly hypogonadal men [150]. Peak levels are obtained 2-4 hrs after application; subsequently levels decrease to two thirds of peak levels after 22-24 hrs, mimicking the normal circadian variation of T levels in young adults. The non-scrotal patches often cause local irritation. With a second generation torso patch (Testoderm R) this, irritation is reportedly seen less frequently. Besides providing physiological levels in young and elderly hypogonadal men, the patches have the advantage that the therapy can be immediately stopped, when necessary [151]. Whether the increased DHT levels have deleterious effects is unknown. But this might not be so (see below).

More recently various hydro-alcoholic T gels have become available in many countries [152, 153]. When administered to young or elderly hypogonadal men, a variable percentage of the T applied becomes bioavailable and with daily application, plasma T levels in the upper normal quartile can be reached and maintained. The gels permit an easy adaptation of the dose to the individual needs. It is not known whether the elevation of plasma DHT with oral or transdermal administration is a cause for concern. The target organs of testosterone, in as far as they convert testosterone to DHT, have high local concentrations of DHT, and plasma levels of DHT might be a reflection of these conversions in target organs, the products of which leak into the circulation. It is currently unknown as to whether elevated plasma levels of DHT are of pathophysiological significance. In any case they are far below local concentrations in target organs.

d) Other T formulations, such as bio-degradable testosterone microspheres or cyclodextrin complexed sublingual formulations are in the process of clinical evaluation and have not yet reached wide commercial availability. As such, they are not further discussed in this chapter.

e) Dihydrotestosterone

The effects of testosterone are mediated directly as testosterone or after conversion to either dihydrotestosterone (DHT) or estradiol locally in target tissues. DHT binds to the same receptor as testosterone but its receptor binding is stronger, resulting in a considerable higher biopotency than testosterone itself. The reduction of testosterone to DHT is an amplification mechanism of the androgenizing effects of testosterone. DHT, as opposed to testosterone, cannot be aromatized to estradiol and therefore acts as a pure androgen. As a result, in certain clinical conditions a pure androgen might have advantages over aromatizable testosterone, such as in hypogonadal men with a propensity to gynecomastia or constitutionally delayed puberty in boys since estrogens are pivotal in closure of the epiphyses.

The potential benefits of aromatizable androgens have been highlighted in regard to the effects of estrogens on bones, brain and the cardiovascular system in men. In contrast, estrogen's effects on the prostate might be deleterious and in this regard DHT might be the preferred androgen for the androgen-deficient aging male. Since DHT is such a potent prostate stimulating androgen, it is paradoxical to recommend DHT for androgen replacement of aging men. But the available evidence suggests that administration of DHT is relatively prostate sparing.

The available studies in hypogonadal men show that DHT maintains sex characteristics, increases muscle mass and improves sexual functions without significant increases in prostate size [154]. In elderly men DHT administration resulted in a 15% decrease in prostate size [155]. This effect was ascribed to the lack of aromatization of DHT to estradiol, therewith reducing the hypothesized synergism between androgens and estrogens on the prostate. An alternative explanation is that DHT is less well transported from
the circulation to the prostate. In a more recent study of three month DHT administration to aging men [156], no effect on circulating estradiol levels was noted. Prostate disease markers such as serum PSA, the prostate symptom score and central and peripheral volume of the prostate measured with sonography showed no changes following DHT replacement. In another recent study [157] DHT was administered for six months. In this study a reduction of plasma estradiol was noted but again, effects on the prostate were not observed. Neither were detrimental effects on lipid profiles noted. On the basis of the above findings DHT cannot be dismissed as a potentially useful androgen for the aging male but a number of issues raised above have to be addressed in future studies.

DHT gel is available at a dose of 125-250 mg /d which yields plasma DHT levels comparable to physiological T levels ; more recently it has been shown that in healthy elderly males, a lower dose of 32 - 64 mg /day yields comparable levels. DHT cannot be aromatized and, therefore, it will not induce gynecomastia, but it is probably less active at the bone level [158-160]. It has been hypothesize that the decrease in E2 levels by DHT gel treatment may be favorable at the level of the prostate, where estrogens stimulate the proliferation of the stroma.

f) 7α-methyl-19-nortestosterone (MENT)

Much Interest exists on the use of androgens that will spare the most prominent adverse effects of testosterone supplementation. Among the drugs better recognized and most promising, although not yet commercially available is 7α-methyl-nortestosterone (MENT) [161]. It is undergoing clinical trials. It has a high biopotency per molecule, (approximately 10 times more potent than testosterone), and it does not undergo 5α-reduction which may or may not be an advantage for its effects on the prostate. However, It retains its capacity to be aromatized to estradiol. It has anti-gonadotropic properties and anabolic effects on muscles. It maintains sexual function in hypogonadotropic men. Its effects on the prostate are less pronounced [162-166].

g) Estrogens in men

Traditionally conceptualized as “female hormones”, estrogens have been considered detrimental to male sexual function. This may turned out to be a simplistic view. Estrogen receptor knockout mice show abnormalities of the testis and accessory sex organs [167]. Impaired estrogen action in men leads to dyslipidaemia and to impaired flow-dependent vasodilation in peripheral arteries, in response to an ischemic stimulus probably resulting from endothelial dysfunction [168]. Evidence suggests that the effects of estrogen on the vascular system are not entirely receptor-mediated [169]. Estrogen effects on the brain are also becoming increasingly recognized [170]. In view of the effects of estrogen on many important organ systems in the male, further research into the role of estrogens is necessary. A better understanding of estrogen receptor physiology and its two subtypes may allow for improved therapeutic possibilities in terms of selective effects of estrogens in men. It may also be significant in clarifying the potentially negative effect of estrogens on prostate.

Since androgens are the precursors of estrogens and the main production of estrogens in men is in peripheral organs, part of exogenously administered testosterone is aromatized to estradiol. The rise in plasma estradiol levels following administration of testosterone lies somewhere between 50 and 150%. In other words, supplementing testosterone implies also supplementing estradiol.

2. SELECTIVE ANDROGEN/ESTROGEN RECEPTOR MODULATORS (SARMs AND SERMs)

In cases of hormone deficiencies traditional endocrinology aims to replace the missing hormone with a substitute. To afford the full biological action of the hormone, this substitute ideally mimics the natural hormone in molecular structure as closely as possible ; and plasma levels to be achieved over the day must come close to average levels, and ideally follow the normal diurnal pattern. Increasing insight how hormones exert their biological effects, has paved the way for rethinking this traditional aim. Concerns have recently been heightened with the report of the Women's Health Initiative (WHI) [171]. Whether or not the findings of the WHI will withstand the passage of time, further experience and additional statistical review remain to be seen. The therapeutical potential of SERMs in women may set the stage for the development of selective androgen receptor modulators (SARMs). The availability of these molecules with their diversity of ligands provide the opportunity to explore the utility and activities of SARMs [172].

3. DHEA REPLACEMENT THERAPY

The public infatuation with DHEA supplementation in old age, often presented by the lay press as a “fountain of youth”, began following a paper by
Morales et al [173]. In a randomized, placebo-controlled, crossover trial, 13 men and 17 women 40-70 yr of age received nightly oral administration of 50 mg DHEA or a placebo for 3 months. In the DHEA group the serum levels of DHEA and testosterone were restored to the young adult range. IGF 1 increased while Insulin Growth Factor Binding Protein 1 decreased, suggesting a further increase in free IGF 1. HDL cholesterol also decreased. An improved sense of well-being was reported by the majority of women (82%) as well as men (67%) after 12 weeks of DHEA administration whereas less than 10% reported any change after placebo. No difference was noted in libido assessed with a visual analog scale. A placebo-controlled study of 39 men receiving 100 mg DHEA daily for 3 months resulted in no effect on well-being and sexual function [174] in a study of 60 peri-menopausal women 50 mg DHA daily for 3 months was not superior to placebo on mood, cognition, well being and sexual desire [175]. Lastly, in a study on 22 men 50 to 69 years old, Arlt et al [176] observed no significant effect of 50 mg DHEA for 4 months on well being and sexual function with respect to the placebo, although none of their patients had sexual dysfunction, a remarkable situation, indeed.

The most comprehensive, long term study on DHEA supplementation in aging men and women was reported by Beaulieu et al [177]. 140 men and 140 women (70 aged 60 to 69 years and 70 aged 70 to 79 in each group) received for 12 months either 50 mg of DHEA daily or a placebo according to a double blind design. No significant difference between the DHEA and placebo groups was found in the men (including in sexual function, bone mineral density - BMD- and the cardio-vascular system). Conversely several significant differences were found in women: in the DHEA group, at any age, there was an increase in the sebum production, an androgen-like effect, and skin hydration, as well as increase in BMD, an estrogen-like effect. Only in the subgroup 70-79 years old, was an increase in sexual interest found from the 6th month of supplementation, and in sexual arousal, sexual activity, and sexual satisfaction at 12 months of treatment. These different effects probably resulted from the increase in the serum levels of testosterone and estradiol which were observed on DHEA supplementation. In men serum estradiol, but not serum testosterone, significantly increased on DHEA. No effect on different measures of well being was observed in any gender. No important clinical or biological deleterious effect was observed during the course of this study.

More recently Hackbert and Heiman [178] tested in a placebo controlled study the acute effects DHEA effects on sexual arousal in 16 postmenopausal women with an average age of 60 years. 300 mg DHEA or placebo were administered 60 mn before they watch erotic and a neutral videos. A modest but significant increase in subjective mental and physical sexual arousal was observed on DHEA. The rapid occurrence of these effects suggests the possibility of a direct and central rather than peripheral action. Interestingly, when the same study was conducted in premenopausal women, no effect on arousal was observed [179]. The possible positive effects of DHEA in female sexuality is discussed thoroughly in other section of this chapter.

**a) DHEA and Erectile Dysfunction**

It has also been speculated that DHEA plays a role in erectile function. Indeed DHEA-S was the only one among 17 hormones, that strongly and inversely, correlated with the prevalence of ED in the Massachussetts Male Aging Study (MMAS) [4]. These data were partly confirmed in a study by Reiter et al [180] found DHEA-S levels to be significantly lower in otherwise healthy men with ED with respect to age-matched normal controls, but only under the age of 50. The same authors evaluated the effects of DHEA replacement (50 mg daily) in 40 men with ED in a double blind placebo-controlled study [181]. DHEA treatment was associated with higher mean scores for all five domains of the IIEF but it is unclear in this paper whether the difference was reached statistical significance. Regardless, it is obvious that these results need to be confirmed and presently there is no convincing evidence for the involvement of DHEA in ED, although the recent data supporting the probability of DHEA-specific receptors on vascular endothelial and smooth muscle cells, cited above, allow the speculation of a possible involvement of DHEA in the vascular mechanisms of erection.

It is evident that the interpretation of the biological effects of adrenal androgens is hampered by the fact that DHEA administered orally undergoes extensive conversion to other sex steroids. The conversion is mainly into D4-derivatives which, in turn, are strongly metabolized into 5α-3 keto-reduced steroids with a pronounced increase of testosterone, estrone and estradiol [182]. In adult men with normal adrenal function, serum testosterone levels do not rise significantly in relation to the extant circulating testosterone levels. However, estrogen levels do rise [183].
It has been argued that the effects of the adrenal androgens cannot be reliably assessed from their levels or the levels of their conversion products in the circulation, the more “classical” sex steroids, Their biological effects may be exerted locally in tissues with potential conversion to hormones like androgens and estrogens, for which the term intracrinology has been coined [184].

b) Side effects

A consequence of the conversion of DHEA to androgens and estrogens is that the effects of DHEA administration are not necessarily harmless. They may influence hormone-sensitive diseases such as breast or prostate cancer. So far there are no reports in the literature of any side effects from self-administration of DHEA, which occurs on a massive scale with DHEA sold over-the-counter as a health product. This may appear comforting, however it should be taken into account that physicians are unlikely to relate the occurrence of cancers and other diseases to the use of a non-medical drug such as DHEA. Patients, on their part, might be secretive about the use of DHEA, or simply not perceive this ‘health product’ to be a hormonal agent. Well-designed studies, with specific endpoints aimed at investigating the effects of deficiency of adrenal androgens and the results of replacement therapy in humans are required to resolve the long-term effect of DHEA therapy [185].

4. HUMAN CHORIONIC GONADOTROPIN

Only one study has monitored the effects of three months administration of human chorionic gonadotropin to aging men with plasma testosterone levels in the lower range of normal [186]. Plasma levels of total and free testosterone and estradiol increased 50% above baseline. The effects were very similar to those of androgen administration to aging men: a decrease in fat mass, an increase in lean body mass but no effect on muscle strength. No adverse effect on hemoglobin or on the prostate were noted.

5. ADEQUACY OF ANDROGEN REPLACEMENT AND CLINICAL END-POINTS

It is common clinical practice to judge the adequacy of androgen replacement by the effects on general well-being, mood, sexual interest and sexual activity. Hemoglobin and hematocrit levels might provide another index in the sense that anemia, for which no other explanation can be found, might point to undersubstitution. Bone mineral density, though determined by multiple factors, can be regarded as an indicator of adequacy of sex steroid replacement but changes in bone mineral density are slow and a higher frequency of measurement of bone mineral density than every two years is usually not informative. These parameters do not provide quick reference whether androgen is adequate.

On the specific activity of androgens in ED, recent reports suggest a marginal synergistic effect when testosterone is added to phosphodiesterase inhibitors in hypogonadal men who had failed the latter as a single therapy [187, 188], apparently mediated by an increase inflow in the cavernosal arteries [189]. These and other studies are preliminary and involve only small groups of patients who have been followed for limited periods. The results must be interpreted with much caution.

A general principle in hormone replacement therapy is that plasma levels to be achieved over the 24 hours of the day must come close to normal reference values, and ideally follow the normal diurnal pattern. So, an impression of adequate levels might be gained by determining plasma testosterone before administration of the next dose of the androgen preparation; but this measurement does not reveal deviations from reference values between two administrations. Fluctuations of plasma testosterone levels are strong with injectable testosterone esters but much less so with oral or transdermal testosterone preparations.

VI. ABUSE OF ANDROGENS

1. “Rationale” for abuse

Androgens have both androgenic (masculinizing) and anabolic (muscle-building) effects. Anabolic androgenic steroids (AAS) are modified forms of testosterone and in general they have more anabolic than androgenic effects. No pure anabolic steroid exists. Androgens are essential in the development and maintenance of the secondary sexual characteristics in men and their role, for instance in sexual desire, sexual thoughts and feelings, male phenotype and in spontaneous nocturnal erections is well recognized.

The anabolic action is secondary to an increased retention of nitrogen, and this positive balance in the cells promote the entrance of amino acids and protein synthesis. Testosterone acts through the androgen receptors and it increases the size of the muscle cells with few effects on their number. In 1954, Russian researchers described the properties of anabolic
steroids in enhancing the effectiveness of athletes in sport competitions [190]. After this the use of steroids was widespread among athletes, with the purpose of increasing muscle mass, specially in sports in which muscle mass and strength are important like weightlifting, bodybuilding, football, etc. For this reason they were banned for use in international sport competitions for the first time in 1974 [191].

Controversy has existed for many years whether there is really a positive athletic performance-enhancing effect with the use of steroids. Some studies suggest only a limited evidence for it [192]. While others indicate that previously trained athletes have moderately better results in muscle strength following androgen use, than untrained persons [193]. Bhasin et al [194] demonstrated a significant increase in body weight when testosterone enanthate was administered in supraphysiological dosage but the largest increase was obtained when testosterone administration was combined with exercises. There was no significant increase in the placebo and in the no exercise group, reinforcing the idea that muscle training is important in increasing muscle growth. Two other studies [195, 196] further supported this view. Difficulties in determining the real efficacy of AAS include:

1) All the studies used fixed dosage, contrary to the AAS users that usually take flexible and frequently increasing doses;
2) The doses in most studies were much lower than the normally employed by AAS users;
3) Most studies employed a single drug while AAS users frequently take a variety of agents;
4) Frequently there has been a lack of adequate tools to measure the real increase in strength due to the medication.

Testosterone has a four-ring chemical structure containing 19 carbon atoms. Most synthetic derivatives of testosterone are produced by one or more of the following modifications:

1) alkylation of the molecule at the 17-alpha-hidroxy position - this is the process of synthesis of most of the oral AAS presentations;
2) forming an ester at the 17-beta-hidroxyl group - represented by the parenteral presentations;
3) altering the structure at a different carbone site.

2. COMMON PREPARATIONS

The use of androgens outside medical indications is widespread. The most commonly employed AAS are:

a) Oral
   - Ethylesterol
   - Fluoxymesterone
   - Methyltestosterone
   - Methandienone
   - Oxymetholone
   - Oxandrolone
   - Stanozolol
   - Mesterolone
   - Mibolerone (veterinary compound)
   - Testosterone undecanoate

b) Parenteral
   - Testosterone salts:
     - Cypionate,
     - Ecanoate,
     - Enanthate,
     - Propionate
     - Phenpropionate,
     - Isocaproate
   - Nortestosterone
   - Nandrolone
   - Boldenone (veterinary compound)
   - Methenolone
   - Stanozolol (veterinary compound)
   - Trenbolone (veterinary compound)

3. EPIDEMIOLOGY

Most of the prevalence studies on AAS use come from the United States and most of them are limited to surveys of students and athletes. The secrecy surrounding androgens use to enhance performance is a barrier for objective and controlled studies and most of the published data are flawed because of many variables, like small number of subjects, lack of control groups, wide variations in the baseline characteristics of the subjects, variations in the training regimens and differences in the measures used to assess the outcome [197].

After Olympic athletes the second most prevalent group believed to misuse AAS is the bodybuilding and/or weight lifting population [198]. Korkia and
Stimson [199] reported that 9.1% of 1667 gym attendees had used AAS and 5% were current users. Evans [200] reported that 15% of 100 athletes attending gyms had been using AAS regularly for more than 6-12 years. Buckley et al [201] (12) estimated that 7% of male high school seniors in US have used AAS and the majority of them initiated at age of 16. Some studies [202, 203] show that from 1 to 3 million American people are former or current users of AAS. Yates et al [204] reported that 4 to 12% of US high school boys have used AAS sometime in their lives and Durant et al reported that among 1000 American secondary school students, 6.5% of men and 1.9% of women had tried AAS [205]. A survey conducted by the Blue Shield Association [206] reported that AAS were the second most commonly used drugs for enhancing athletic performance among 12 to 17 year old people! All these figures clearly show that the misuse of androgens is currently, a significant health issue.

The dissatisfaction with one’s body image and the tendency in the modern societies to yearn towards a leaner and more muscular body are some of the cultural and social factors that could explain this misuse/abuse of AAS. A multicentric study in Boston, Paris and Vienna [207] showed 2 groups at risk of AAS abuse: weightlifters (aesthetic) and competitive sports athletes. In general men are more likely to take AAS than women and athletes are more likely than non-athletes. The muscle dysmorphia - a form of body dysmorphic disorder in which the individual feels that he is not sufficiently muscular and lean - is also a risk factor to AAS abuse since these people perceive themselves to be much smaller and weaker than they really are [208].

4. VARIANTS OF USE

Therapeutic regimens of treatment in the presence of clinical indications are based on a fixed adequate dose of an androgen taken at regular intervals and on a continuous basis. Contrary to this orthodox approach, regimens that are popular among AAS users, consist of a mix of several drugs taken orally, parenterally or in a combination of both, taken intermittently and in progressively higher doses. The dosage is from 10 to 100 times the therapeutic doses for testosterone deficiency. This is known as “stacking”. Mixing 2 or more compounds in the same syringe is called “blending”. They are taken in cycles between 4 to 12 weeks followed by a drug-free period of 4-12 weeks (“cycling”). A cycle may start at low doses (one or two AAS), then taking different AAS at higher doses, then tailing them off (“pyramiding”). If the user finds that the effect lessens with time with one preparation they change to a different combination (“plateauing”) [209]. The regimens may include androgens with very limited clinical indications (including veterinary compounds).

Polypharmacy is also widespread among AAS users in order to minimize the side effects or to maximize the action of these drugs. Many compounds are used but their description is not germane to this consultation.

5. SIDE EFFECTS ASSOCIATED WITH USE OF ANDROGENS FOR NON-MEDICAL REASONS

The risks and side effects essentially reflect and exaggeration of complications well recognized when androgens are used for a clear indication and under proper medical supervision. AAS abuse is correlated to a variety of complications. Perry et al [210] reported that 85% of the users had more than 1 side effect including testicular atrophy (50%) and hypertension (34%) together with a variety of behavioral alterations [211]. Many of these changes have direct implications in sexual functioning.

a) Dependence

The mechanism of AAS dependence is not firmly established but the effects produced by their use are quite similar to those produced by cocaine and crack [212]. Steroids do bind to specific receptors in the brain and may cause disorders in neurotransmitters and they also appear to sensitize the brain to the rewarding properties of amphetamine. Tennant et al showed that AAS dependence may be correlated with brain monoaminergic and endogenous opioid systems as the AAS withdrawal symptoms are the same as some of the hyperadrenergic symptoms seen with opioids and alcohol withdrawal [213] (22). Pathological narcissism and lower empathy could also be involved. Whether dosage or duration of use are dependence correlated is not yet well established. Treatment first includes of all discontinuation of the drugs, control of the withdrawal symptoms (hospitalization may be necessary), counseling about psychosocial problems and treating psychiatric disorders associated.
1. **Definition**  
**Grade B**  
Adult onset hypogonadism is a clinical and biochemical syndrome frequently associated with advancing age and characterized by a deficiency in serum androgen levels, with or without changes in receptor sensitivity to androgens. It may affect the function of multiple organ systems and result in significant detriment in the quality of life, including major alterations in sexual function.

2. **Clinical Diagnosis**  
**Grade A**  
The clinical manifestations of adult hypogonadism are not specific. Sexual dysfunction (decrease in sexual interest and quality of erections) is prominent and, often the presenting symptom. Depression, irritability, cognition and sleep, as well as diminished strength and endurance may also be present. The physical examination is frequently unhelpful. But, alterations in testicular size and consistency, hair distribution, muscle mass, body shape and sequelae of osteoporosis can be detected. Not all the manifestations need to be evident simultaneously and their intensity shows marked inter-individual variability.

3. **Biochemical Diagnosis**  
**Grade A**  
In patients with sexual dysfunction and at risk of or suspected of hypogonadism the following biochemical investigations are recommended: a blood sample for testosterone (T) determination between 8:00 and 11:00 AM. The most accessible and reliable assays to establish the presence of hypogonadism are the measurement of bio-available T or the calculated free T (cFT). Assays for total testosterone, particularly in the elderly, may not reflect the man’s true androgenic status. If T levels are below or at the lower limit of the accepted normal values, it is prudent to confirm the results with a second determination together with assessment of luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin.

4. **Prolactin**  
**Grade A**  
Hyperprolactinemia is an uncommon cause of ED. However, determination of serum prolactin is recommended in cases associated with diminished sexual interest and when biochemical hypogonadism has been documented.

5. **Other Hormonal Alterations Besides Sex Hormones**  
**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. In general terms, determinations of estradiol, DHEA, DHEAS, melatonin, GH and IGF-1 are not indicated in the uncomplicated evaluation of hypogonadism. Under special circumstances or for well defined clinical research, assessment of these and other hormones may be warranted.

6. **Diabetes**  
**Grade A**  
Diabetes mellitus is a frequent endocrinological cause of erectile dysfunction. It should be ruled out in men complaining of sexual inadequacy. Appropriate glycemic control is fundamental before consideration of any other hormonal treatment in men with ED.

7. **Lipids**  
**Grade A**  
A lipid profile should be considered as a relevant option in the initial assessment of men with erectile dysfunction.

8. **Indications for Therapy**  
**Grade A**  
A clear indication (a clinical picture together with biochemical evidence of hypogonadism) should exist prior to initiation of androgen therapy.

9. **Age**  
**Grade C**  
In the absence of defined contraindications, age is not a limiting factor to initiate ART in aged men with hypoandrogenism.

10. **Sexual Function**  
**Grade A**  
Hypogonadal men with specific sexual dysfunctions (e.g.: ED and/or diminished interest) are candidates for androgen therapy. Absence of an adequate response after appropriate testosterone treatment calls for further investigation to rule out associated co-morbidities.
11. Combined treatment for erectile dysfunction  
GRADE C
Evidence is emerging suggesting therapeutic synergism with combined use of testosterone and phosphodiesterase-5 inhibitors in hypogonadal or borderline eugonadal men. These observations are very preliminary and require additional study. However, the combination treatment can be considered in patients failing adequate treatment with phosphodiesterase inhibitors alone. No credible evidence for or against exists with other drugs in combination with androgens.

12. Testosterone commercial formulations  
GRADE B
Currently commercially available preparations of testosterone (with the exception of the alkylated ones) are safe and effective. 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 androgen formulation.

13. Serum levels  
GRADE B
The purpose of ART is to bring and maintain serum T levels within the physiological range. Supraphysiological levels are to be avoided. Although it may appear desirable, no evidence exists for or against the need to maintain a circadian rhythm of serum T levels.

14. Other androgens  
GRADE B
The use of DHEA has not been proven to be effective specifically in male sexual dysfunction. Current evidence on DHT efficacy is also insufficient. There is a need for additional studies aimed expressly at investigating the effects of these hormones on sexual function.

15. Androgen abuse  
GRADE A
Androgens should be used only when specific indications exist. Their (ab)use for performance enhancement, in the absence of hypogonadism, is to be condemned.

16. Monitoring - liver  
GRADE A
Currently available T preparations are largely free of hepatic toxicity (methylated forms are an exception). Liver function studies are advisable prior to onset of therapy. Periodic assessment during treatment may be considered. Despite the lack of evidence, commercial manufacturers (for regulatory purposes) include warnings about hepatic risks in their product insert.

17. Monitoring - lipids  
GRADE A
A fasting lipid profile prior to initiation of treatment, if not done as part of the initial evaluation - Recommendation 7) and re-assessment at 3 or 6 months after onset of testosterone administration is also recommended.

18. Monitoring - prostate  
GRADE A
In men over the age of 40 years, digital rectal examination (DRE) and determination of serum prostatic specific antigen (PSA) are mandatory as baseline measurements of prostate health prior to therapy with androgens, every three (3) to six (6) months for the first 12 months, and yearly thereafter. Transrectal ultrasound guided biopsies of the prostate are indicated only if the DRE or the PSA are abnormal.

19. Prostate and breast safety - I  
GRADE A
Androgen administration is absolutely contraindicated in men suspected of harboring carcinoma of the prostate or breast.

20. Prostate safety - II  
GRADE D
Men successfully treated for prostate cancer and suffering from symptomatic hypogonadism may become candidates for androgen therapy, after a prudent interval, if there is no evidence of residual cancer. The risk and benefits must be clearly understood by the patient and the follow-up must be particularly careful. No reliable evidence exists in favor or against this recommendation. The clinician must exercise good clinical judgment together with adequate knowledge of the advantages and drawbacks of androgen therapy in this situation.
19. TAN HM.: Erectile dysfunction, men's health and the aging


40. LIU D, DILLON JS : Dehydroepiandrosterone activates endo- thelial cell nitric-oxide synthase by a specific plasma membrane receptor couplet to Ga2,A. Biological Chemistry 277 : 21379, 2002.


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151. MEIKLE AW, MAZER NA, MOELLERMER JD, STRINGHAM JD, TOLMAN KG, SANDERS SW, ODELL WD.: Enhanced transdermal delivery across non scrotal skin produces physiological concentrations of testosterone and its metabolites in hypo- gonadal men J Clin Endocrinol Metab.74:623,1992


Committee 8

Priapism, Peyronie’s Disease, Penile Reconstructive Surgery

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### IV. Summary and Recommendations

**REFERENCES**
Priapism and Peyronie's disease were considered by committees 12 and 15 in the first consultation on erectile dysfunction [1, 2] and there have been few advances in the subjects since that time. The committee will attempt to provide an “evidence based” review of the conditions with the emphasis very much on the practical management of patients.

The literature has been reviewed but most of it consists of observational studies and greater reliance has been placed upon the views of the expert panel than one would have wished. The committee has debated contentious issues and modified some of the views of the earlier committee.

I. PRIAPISM

1. CLASSIFICATION

A priapism is a persistent unwanted erection that is not associated with sexual desire or sexual stimulation. It is uncommon in men and rare in women.

It is important to distinguish between the 3 different types of priapism (Table 1) but remember that they are not necessarily separate entities:

1. Low flow, ischaemic or anoxic priapism. This is the most common and if untreated results in necrosis of the cavernous muscle and subsequent fibrosis and impotence. It is an example of the compartment syndrome and requires urgent treatment.

2. High flow well oxygenated priapism. Classically this condition occurred following penile revascularisation procedures but it has subsequently been recognised as occurring after penile and perineal injuries when the cavernosal artery is damaged. It may also be idiopathic and this form may be related to the recurrent, or stuttering, priapism.

3. Recurrent or stuttering priapism commonly occurs in men with sickle cell disease but is not confined to them. Such a priapism is usually high flow but may become low flow and anoxic.

2. INITIAL MANAGEMENT OF PRIAPISM

Little has changed with regard to priapism during the past 3 years and the modern management stems from the recognition of the difference between low flow and high flow priapisms [3, 4], the damaging effect of ischaemia, and the importance of muscle contraction to maintain flaccidity. The initial management is summarised in Table 2. It is usually possible to distinguish between the two main types of priapism from the clinical history and examination and first aid measures may be tried whilst awaiting the arrival of an urologist. Aspiration is not necessary if the diagnosis of a high flow priapism is probable as judged by the history and examination.

---

Table 1. Priapism: Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Flow, Ischaemic or Anoxic Priapism</td>
<td>Most common</td>
</tr>
<tr>
<td></td>
<td>A compartment syndrome</td>
</tr>
<tr>
<td></td>
<td>Requires urgent treatment</td>
</tr>
<tr>
<td>High Flow, Non Ischaemic Priapism</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Well oxygenated</td>
</tr>
<tr>
<td></td>
<td>No urgency to treat</td>
</tr>
<tr>
<td>Recurrent or Stuttering Priapism</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Ill understood</td>
</tr>
<tr>
<td></td>
<td>Not just in sickle cell disease</td>
</tr>
</tbody>
</table>

Table 2. Initial Management of Priapism

1. Priapism is a persistent unwanted erection that is not associated with sexual desire or sexual stimulation. It is uncommon in men and rare in women.
2. It is important to distinguish between the 3 different types of priapism (Table 1) but remember that they are not necessarily separate entities:
   1. Low flow, ischaemic or anoxic priapism. This is the most common and if untreated results in necrosis of the cavernous muscle and subsequent fibrosis and impotence. It is an example of the compartment syndrome and requires urgent treatment.
   2. High flow well oxygenated priapism. Classically this condition occurred following penile revascularisation procedures but it has subsequently been recognised as occurring after penile and perineal injuries when the cavernosal artery is damaged. It may also be idiopathic and this form may be related to the recurrent, or stuttering, priapism.
   3. Recurrent or stuttering priapism commonly occurs in men with sickle cell disease but is not confined to them. Such a priapism is usually high flow but may become low flow and anoxic.
3. Initial management of priapism during the past 3 years and the modern management stems from the recognition of the difference between low flow and high flow priapisms [3, 4], the damaging effect of ischaemia, and the importance of muscle contraction to maintain flaccidity. The initial management is summarised in Table 2. It is usually possible to distinguish between the two main types of priapism from the clinical history and examination and first aid measures may be tried whilst awaiting the arrival of an urologist. Aspiration is not necessary if the diagnosis of a high flow priapism is probable as judged by the history and examination.
3. ISCHAEMIC PRIAPISM

a) Pathophysiology

This may be regarded as a prolongation of a normal erection and in the idiopathic form is frequently present on waking. Table 3 shows some of the factors associated with a low flow ischaemic priapism.

Intracavernous drug therapy was infrequently associated with this type of priapism and this has greatly increased our understanding of the condition. During erection there is a relaxation of the smooth muscle in the cavernous arteries and tissue, this is associated with the increased arterial inflow and the decreased outflow of blood. The intracorporeal pressure may rise above mean arterial pressure and the inflow of arterial blood is limited. The persistence of erection and failure of detumescence, the contraction of cavernous smooth muscle, is associated with increasing anoxia, a rising pCO2 and acidosis. These changes have been well documented [5]. The prolonged erection is not painful initially but becomes painful after a variable length of time. It has become customary to warn patients that any erection lasting more than 4 hours requires urgent medical attention.

Pain increases the longer the erection persists and this is associated with increasing tissue anoxia until muscle necrosis (Figure 1) eventually occurs. It follows that in order to reverse the process it is necessary to lower the intracavernous pressure, reoxygenate the tissues, and contract the cavernous muscle to restore flaccidity of the penis. Ultrastructural changes in the corporal smooth muscle were seen after a priapism of 12 hours duration and these changes became marked after 24 hours [4].

The tissue necrosis is patchy at first, possibly related to the proximity of arterial blood entering the corpus, but it is a useful concept to consider an anoxic, low flow priapism as an example of a compartment syndrome. Early relief will be associated with the return of normal flaccidity, but more prolonged ischaemia is associated with tissue oedema - clinically a brawny penis, and necrosis with a failure to obtain detumescence.

The end result of muscle necrosis after a priapism is fibrosis (Figure 2) which may be patchy in distribution and it is thought that TGF-beta has an important role in this process [6].

b) Assessment Of Ischaemic Priapism

A history and examination are more than sufficient to make the diagnosis. In truth, the history only serves to assess whether there are any causative factors and the possible duration of ischaemia. The examination serves to assess the severity of pain, the rigidity of the penis, and the lack of involvment of the glans penis and corpus spongiosus. It will also identify the man in whom the priapism is secondary to a secondary tumour in the penis.

A blood sample should be analysed to exclude sickle cell disease, thalassaemia major, and leukaemia. These conditions require appropriate management at an early stage. Prolonged erections and priapism are not uncommon in sickle cell patients and will be discussed in a separate section.

c) First Aid Management Of Priapism (Table 4)

This may be initiated by the man himself or by the staff before a doctor makes an assessment. The traditional remedy of ice-packs or a cold shower may be successful in the early stages and are probably act by inducing reflex vasoconstriction. The act of micturition may occasionally releave a priapism.

The original description of using an exercise bicycle [7] has been replaced by the more readily available exercise of mounting stairs - taking care not to over-stress the coronary arteries. It is likely that the exercise acts by introducing a gluteal steal type of action.

Analgesics should be given as appropriate and, as the pain may be severe and the man distressed, this may need to be an opiate. Oral treatment may be considered according to availability and choice:

Terbutaline [8, 9] : A placebo controlled study was performed on 65 men who had received an intracavernosal injection of prostaglandin E1 and if the erection had persisted 2.5 hours they were randomised to receive either pseudoephrine 60 mg [10], terbutaline 5mg, or sodium bicarbonate 648 mg (as placebo). The terbutaline treated men received an additional 5mg dose if detumescence had not occurred within 15 minutes. Any patient with an erection per-

---

Table 2 : Initial Management of Priapism.

<table>
<thead>
<tr>
<th>ASSESSMENT</th>
<th>FIRST AID MEASURES</th>
<th>ASPIRATE CORPUS CAVERNOSUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>History, Examination, Haematology</td>
<td>Analgesia, Physical, Pharmacological</td>
<td>Dark blood = Low flow priapism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Red blood = High flow priapism</td>
</tr>
</tbody>
</table>
Table 3. Factors Associated with Ischaemic Priapism.

<table>
<thead>
<tr>
<th>Haematological Disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell disease</td>
<td></td>
</tr>
<tr>
<td>Thalassaemia</td>
<td></td>
</tr>
<tr>
<td>Leukaemia</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs</th>
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</thead>
<tbody>
<tr>
<td>Erectogenic</td>
</tr>
<tr>
<td>Antidepressant</td>
</tr>
<tr>
<td>Antihypertensive</td>
</tr>
<tr>
<td>Recreational</td>
</tr>
</tbody>
</table>

| Malignancy                |

Table 4. First Aid Measures in Priapism.

<table>
<thead>
<tr>
<th>Physical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micturate</td>
</tr>
<tr>
<td>Ice pack : cold shower</td>
</tr>
<tr>
<td>Exercise</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analgesics</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Pharmacological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procyclidine</td>
</tr>
<tr>
<td>Terbutaline</td>
</tr>
<tr>
<td>Pseudoephrine</td>
</tr>
<tr>
<td>Etilephrine</td>
</tr>
</tbody>
</table>

Figure 1: Muscle necrosis in priapism.

Figure 2: Muscle fibrosis post priapism.
sisting more than 3 hours after the initial prostaglandin injection received 2-4 mg of intracorporeal phentolamine (0.1 mg/ml). Oral treatment was successful in only 19 of the 75 men with prolonged erections and occurred in 3 (12%) with placebo, 7 (28%) with pseudoephedrine, and 9 (36%) of the 25 men treated with terbutaline. Three of the 9 men responding to terbutaline received 10 mg of that drug. The authors [9] concluded that it was worth trying terbutaline in a pharmacologically prolonged erection. Oral therapy has now largely replaced intracavernous treatment of erectile dysfunction and terbutaline is no more than a first aid measure.

Pseudoephedrine: This was almost as effective as terbutaline in the above trial and may also be considered as a first aid measure.

Etilephrine [10, 11]: this is an alpha adrenoreceptor agonist that is only available in some countries. It is a useful drug in that it is active when used orally or by intracavernosal injection.

The intravenous injection of procyclidine [12] or clonidine [13] were sometimes successful in terminating an idiopathic priapism in the pre-intracavernous therapy era. It is likely that they act by blocking the parasympathetic pathway as both drugs have the side effect of causing a dryness of the mouth and difficulties of eye accommodation.

d) Urological Assessment And Management (Table 5)

The history and examination are directed towards finding aetiological factors. Haematological abnormalities require proper assessment and management as are indicated. Once a low flow priapism has been confirmed on clinical grounds it is essential to decompress the corpora as soon as possible. The withdrawal of 5 ml of blood may be associated with immediate pain relief and detumescence. This is particularly likely in the early stages of a prolonged pharmacologically induced erection.

Consideration should be given to local penile anaesthesia. This is unnecessary in the early stages, particularly when pain is severe and an opioid analgesic has been given. The introduction of a 19 gauge butterfly needle is all that is required and if further analgesia is required, then a penile ring block may be performed.

The colour of the blood aspirated in a low flow priapism is almost black and the blood gases will confirm the hypoxic conditions [14]. It is necessary to slowly aspirate until oxygenated red blood is obtained before injecting an alpha-adrenoreceptor agonist in an attempt to cause contraction of the smooth muscle. This process may take 1 hour to occur and the pulse and blood pressure should be monitored. Escape of the vasoconstrictor into the systemic circulation is indicative of the restoration of venous outflow from the penis and may be accompanied by retching and a reflex bradycardia. Detumescence soon occurs and may be accompanied by a tachycardia and hypertension. It is doubtful whether irrigation of the corpora is of any benefit.

It is preferable to use an adrenergic agent with a pure alpha receptor action as possible to minimise harmful effects on the heart [15, 16]. It is for this reason that phenylephrine is the agent of choice (10 mg/ml diluted with 9 ml of saline and injected 2 ml at a time).

Failure to bring about detumescence by repeated aspiration over the course of at least an hour is suggestive of permanent injury of the smooth muscle and the role of surgery should be considered. There must be doubts about its effectiveness in these circumstances [17] although for medico-legal reasons shunt operations may still be performed. It is recommended that the corporal muscle should be biopsied at such operations.

e) Surgery

Winter [18] in his classic review of 105 patients with priapism made many important observations. He emphasised that the man should sign a well formulated consent form that is witnessed by a friend or family member, that a priapism was followed by impotence in half of the patients and that this was due to the disease and not the treatment. He described the glans shunt in the first instance, repeated after 12 hours if unsuccessful, and then by a spongioscavernous shunt. Should this prove to be unsuccessful-

<table>
<thead>
<tr>
<th>Table 5. Urological Management of Anoxic Priapism.</th>
</tr>
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<tbody>
<tr>
<td><strong>Aspiration</strong></td>
</tr>
<tr>
<td>20 ml: confirm diagnosis</td>
</tr>
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<td></td>
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<tr>
<td>Surgery:</td>
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</table>
ful, then he would perform a corporeal-saphenous shunt. We now know that failure of the shunt to bring about detumescence is not due to the shunt clotting but to the inability of the smooth muscle to contract due to muscle necrosis.

The major problem is knowing when irreversible muscle necrosis has occurred as it is not after a fixed period of time. Some recovery of function is likely in the first 24 hours but this then becomes increasingly unlikely (vide section on post priapism erectile dysfunction). The reason that surgery may be successful is probably because there is a revascularisation of the muscle when the shunt is being fashioned in addition to blood being able to escape from the closed compartment.

Some authors [19, 20] have suggested that in the man who presents a long time after the onset of a priapism and if it fails to respond to conservative measures, it is reasonable to biopsy the cavernous muscle and implant a penile prosthesis as part of the initial management.

The initial outcome of “successful” priapism treatment is often difficult to assess as the penis remains somewhat painful and turgid. The cessation of the severe pain associated with the compartment syndrome is probably the most useful sign, particularly when associated with the aspiration of oxygenated blood.

The surgical techniques of shunt surgery are well known, described and illustrated in the 1st consultation, and are no longer performed by some of the committee.

f) Prognosis

The end result of an untreated, or many a late treated, priapism is muscle fibrosis and subsequent fibrosis. The timescale may vary but interstitial oedema was found to occur after 12 hours, destruction of endothelial lining after 12 to 24 hours and muscle necrosis after 24 to 48 hours. The onset of pain in a prolonged erection is an indication for urgent intervention. The relationship of post priapism impotence to the duration of priapism is shown in Table 6. This shows that 90% of men with a priapism lasting 24 hours do not regain the ability to have intercourse [21].

g) Post Priapism Erectile Dysfunction

Reassurance and/or psychological counselling are invaluable in the early phase and men should be warned not to expect a rapid return of function. The return of orgasm suggests that major psychological sequellae have passed and further investigation and/or treatment indicated. Post priapism erectile dysfunction is rarely due to a patent shunt and closure of these shunts or fistulae rarely restores potency.

The failure of oral or intracavernous therapy to improve potency following a priapism is not uncommon, and a vacuum device may be tried but is often unsatisfactory. In these circumstances a penile prosthesis should be implanted, but the operation may be very difficult and is best performed by an experienced surgeon.

4. HIGH FLOW PRIAPISM

The prognosis is good in this type of priapism, intervention is not urgent and often unnecessary. Unfortunately, it is much less common than the ischaemic low flow priapism.

a) Classification

1. Congenital : arterial malformations may be associated on rare occasions with a priapic condition of the penis.
2. Traumatic :
   a : external trauma to the perineum,
   b : Internal trauma, usually needle injury of the cavernosal artery.
3. Neoplastic
4. Iatrogenic : post revascularisation procedures.
5. Idiopathic.

b) Diagnosis

Awareness is the key to diagnosis. Pain is less of a feature than in the ischaemic priapism and it is never as severe. The onset of a post traumatic priapism is usually delayed and may occur up to 72 hours after the injury. It is thought that the clot that forms initially becomes dislodged when the blood flow increases during erection. The penile erection is not rigid and arterial pulsation may be visible in the penis. Such a situation may resolve spontaneously after days or, even months, and erectile capacity is preserved.

<table>
<thead>
<tr>
<th>Duration</th>
<th>Potent</th>
<th>Impotent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 24 hr</td>
<td>18 (56%)</td>
<td>14</td>
</tr>
<tr>
<td>&gt; 24 hr</td>
<td>4 (11%)</td>
<td>34</td>
</tr>
</tbody>
</table>

_p>0.001_ Pryor 1998
Idiopathic high flow priapism is more difficult to diagnose clinically and typically, but not exclusively, occurs in men with sickle cell disease.

A high flow priapism is confirmed by aspirating bright red arterialised blood from the corpora and the diagnosis is then confirmed by Doppler examination. Examination with a simple Doppler probe may enable the site of a fistula to be identified, digital compression may assist in identifying the site of injury. The more sophisticated Doppler probes are often too large to permit accurate identification but may show the area of increased blood flow. Selective pudendal arteriography should demonstrate the site of arterial injury. There is no urgency in carrying this out as erectile function is unlikely to be lost by delay. The reason for this is that the corporal smooth muscle is not relaxed, except during concurrent erections, and the outflow mechanism is intact.

c) Treatment

There is no urgency to treat a non ischaemic priapism as many resolve spontaneously; presumably as the fistula clots and is sealed off. In other patients, even after months’ of delay, treatment of the high flow state is associated with a return of normal erectile function.

The definitive management of a traumatic high flow priapism is by selective embolisation with autologous blood clot. This is usually successful and may be repeated. Surgical ligation of the fistula may be successful but it is more difficult and more invasive.

The management of the idiopathic high flow priapism will be discussed under recurrent priapism.

d) Prognosis

This is good and nothing should be done to harm this. It should be remembered that an idiopathic high flow priapism may convert to a low flow one and urgent intervention is then required.

5. Recurrent or Stuttering Priapism

This condition is uncommon, not confined to men with sickle cell disease, and poorly understood. The onset of the prolonged erection is usually during sleep and detumescence does not occur immediately upon waking. Many men establish an exercise routine in order to bring about detumescence. These erections are usually painfree at first but become painful after an hour or so. These painful erections interfere with the patient’s lifestyle and encourage him to seek medical help.

Eleven of 18 men with sickle cell disease who presented with an ischaemic priapism gave a history of preceding prolonged erections whereas such a history was only present in 11 of 33 men with non sickle cell ischaemic priapism [21]. In a recent study [22] it was found that in a group of 130 men with sickle cell disease, 46 (35%) men reported a history of priapism and of these 33 had a history of stuttering priapism.

The mechanism for recurrent priapism is obscure. The men may have abnormal patterns of nocturnal penile tumescence [12] but does this reflect a central mechanism or an abnormality of the corpus cavernosus [23].

The management of recurrent priapism is difficult as the episodes may be ischaemic or non ischaemic in the same patient. Sickle cell disease, if present, requires haematological management (Table 7) and this may help in reducing the frequency of attacks. Table 8 summarises the pharmacological attempts to control the problem but none of them are entirely successful [24-30]. Androgen suppression is the most effective but has the undesirable effect of causing testicular atrophy. An acute ischaemic episode requires urgent management in the usual way and ephedrine (1:1000000) was found to be effective in 37 of 39 episodes of ischaemic priapism in young men with sickle cell disease [31].

Recurrent priapism is often a nuisance rather than dangerous as it is usually high flow and non ischaemic. However a full blown ischaemic episode may occur and that requires urgent intervention.

<table>
<thead>
<tr>
<th>Table 7. Sickle Cell Disease Management.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 8. Pharmacological Control of Recurrent Priapism.</th>
</tr>
</thead>
</table>
6. SUMMARY
A priapism is a persistent unwanted erection that is not associated with sexual desire or sexual stimulation and its management is summarised in Figure 3 and Table 9.

II. PEYRONIE’S DISEASE
Peyronie's disease is named after the French physician Francois Lapeyronie (1678 - 1747) and is an acquired disorder of the tunica albuginea. It is characterised by the formation of a plaque of fibrous tissue which may be associated with erectile dysfunction and pain on erection. There may be difficulty of penetration as a result of the curvature and the condition may be accompanied by some impairment of erectile capacity.

The early stage of Peyronie's disease is characterised by an inflammatory response beneath the tunica albuginea with fibroblast proliferation to form a thickened plaque of fibrous tissue in the tunica albuginea. Calcification and/or ossification may occur.

Classical Peyronie's disease may be differentiated from localised cavernous fibrosis which may be due to direct external trauma to the corpus, injury from a fractured penis, or damage to the cavernous tissue intracavernous injections. Atypical areas in the crura are probably due to external trauma.

Peyronie's disease is usually easy to diagnose by clinical history and examination and it should be differentiated from congenital abnormalities (vide infra) and extremely rare secondary tumours in the penis.

Committee 12 considered Peyronie's disease in the first consultative document [1] and no purpose will be served by repeating all the information contained in that chapter. This chapter will concentrate on the existing evidence base for management. There are few clinical trials and the task is made more difficult by the natural history of the disease which shows some improvement with pain almost always disappearing. A Medline seach was performed in March 2003 and the 930 articles published since 1998 reviewed. Members were asked to notify of other relevant papers and the recent journals were also reviewed.

1. PATHOPHYSIOLOGY OF PEYRONIE’S DISEASE
The incidence is estimated to be between 0.4-3.2% [32-38] and depends upon upon the definition of Peyronie's disease (curvature vs plaque) and the means of detection (questionnaire vs examination).

The literature is devoid of robust epidemiologic studies conducted in a multinational, multi-ethnic fashion using rigorous data collection and statistical analysis. The data available suggest that the incidence of Peyronie's disease (as defined by a plaque) is higher than previously thought.
Current basic science research on Peyronie's disease is focused on one of two models, the Lue animal model or in vitro fibroblast culture model. Each has their specific advantages and disadvantages. Cell culture models are hampered by the fact that they probably do not fully represent the in vivo condition, however, they are useful to define the pathobiology of the constituent cells and may allow the exploration of agents that can manipulate the biology and behavior of these cells.

The pathophysiology of Peyronie's disease remains poorly understood and is considered to be multifactorial with the interplay of a genetic predisposition, trauma and tissue ischaemia. There is an abnormality of wound healing with the implication of TGF-beta, cell cycleregulators, inducible nitric oxide synthase, and gene abnormalities [39-46]. It is likely that the final common pathway involves fibrogenic cytokine indecued fibrosis in the tunica albuginea. Research is hampered by the absence of a universally accepted animal model and concern over the applicability of the cell culture models employed.

2. ASSESSMENT OF PEYRONIE’S DISEASE

A history and examination are usually sufficient to make the diagnosis and further investigation is only necessary in selected patients. The committee discussed the question of a standardised assessment and there is certainly merit in adopting a unified symptom score as suggested in the first consultative document (Table 10).

Plaque size is measured in the flaccid penis but the committee discussed the cost benefit of greater accuracy with the measurement of plaque size from ultrasound, CT or MRI in the flaccid or erect penis. We concluded the the additional cost was only justified in the context of a clinical trial, but even here we preferred to increase the size of the trial rather than have the greater accuracy.

Clinical estimation of the deformity compared well with the operative findings [47]. Photographic documentation of a natural, pharmacologically induced or vacuum induced erection may be considered and would be of benefit in the context of a clinical trial.

Assessment of the quality of erection by a simple scoring system should be replaced by the IIEF-5 or an agreed successor.

Penile scintigraphy using human IgG labelled with 99mTc [48] might be useful to distinguish between stable and unstable Peyronie's disease but at the present time this is only of value with regard to surgical correction of the deformity.

a) Non Operative Management

This review will look at the evidence and small observational studies will only be mentioned in order to clarify the “story”. This is because there is a high chance of spontaneous improvement in the condition even in untreated men with Peyronie's disease. A recent review of the literature [49] found that there was a 35-100% improvement in pain, 11-100% improvement in plaque size, and a 10-82% improvement in angulation. The overall quality of evidence is limited and there have been few clinical trials.

3. ORAL THERAPY

a) Procarbazine

The initial studies with this drug had shown that 9 (53%) of 17 patients were cured [50] and a separate study [51] showed that 11 men were cured and a further 3 improved from a group of 21 men. In the same year a third study reported that only one of 10 men improved with procarbazine treatment [52].

In an open label study [53], 34 men were randomly allocated to receive procarbazine (20 mg twice daily) or vitamin E (200 mg three times daily) for the first 3 months and they would then crossover to receive the opposite drug. The symptoms of pain, deformity, lump, ease of penetration and whether intercourse was possible were graded 0, 1, or 2. The men were seen monthly and assessed at the end of each 3 months.
The results are shown in Table 11 where it can be seen that vitamin E was superior to procarbazine. Side effects were common with procarbazine and 6 men discontinued treatment for this reason.

The background to this study has been reported in detail as it emphasises the need for some form of control group. The study is rated 2- as it was not blinded and only 67% completed it and shows that procarbazine is not useful in Peyronie's disease (C).

b) Vitamin E

This antioxidant has been widely used since it was first recommended in 1948 [54]. In 1978 it was shown to be more effective than procarbazine and on that basis a double blind, randomly allocated clinical trial was performed [55].

Sixty men were randomly allocated to receive vitamin E (200 mg) or matching placebo 3 times daily for 3 months each. The severity of symptoms were scored on each of the monthly visits and only 40 (67%) of the men completed the study.

The results are shown in table 12 but showed no difference between vitamin E and the matching placebo with the possible exception for the improvement of pain - particularly as 2 patients commencing with vitamin E had a marked improvement in pain and stopped attending. (Evidence level 2-).

In summary, there is no evidence as to the effectiveness of vitamin E but the drug has been widely used, is free of side effects, and cheap (Grade C).

c) Paraaminobezoate (Potaba)

The first clinical trial of this drug was a multicentre study with the random allocation of 60 men to receive 12 months treatment with 12 gram daily of paraaminobezoate or matching placebo. A preliminary report [56] of the outcome when 41 men had completed the study was published but a final report has never appeared.

The results are shown in table 13 and show little benefit for the active treatment with the possible exception of improvement in pain (75% v 43%). The drug was unpleasant to take with frequent side effects (Evidence level 2).

An abstract [57] has been published of a randomised, placebo controlled, double blind prospective multicentre trial of paraaminobezoate which showed no difference in the improvement of pain but less worsening of symptoms in the treated group. However, only 75 of the 103 men completed the study. It would seem that paraaminobezoate has little benefit in the treatment of Peyronie's disease (Grade C).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Commenced</th>
<th>Completed</th>
<th>Cured</th>
<th>Improved</th>
<th>No Change</th>
<th>Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procarbazine 50mg b.d. x 3m</td>
<td>31</td>
<td>22</td>
<td>0</td>
<td>2 (9%)</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Vitamin E 200mg t.d.s. x 3m</td>
<td>33</td>
<td>31</td>
<td>2</td>
<td>10 (37%)</td>
<td>19</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 12. Vitamin E Trial in Peyronie's Disease [55].
Double blind : Placebo controlled : Crossover : Random allocation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number</th>
<th>Vitamin E Improved</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>14</td>
<td>5*</td>
<td>1</td>
</tr>
<tr>
<td>Deformity</td>
<td>38</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Erection Q.</td>
<td>39</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Penetration</td>
<td>35</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Coitus</td>
<td>35</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

*2 additional patients had improvement but did not crossover
d) Tamoxifen

Tamoxifen is thought to act by inhibiting the inflammatory response that occurs in Peyronie's disease by modulating the TGF-beta secretion from fibroblasts. In the initial report [58] of 36 men treated with 20 mg twice daily there was some improvement in 20 (55%) patients and there was no deterioration in any man. There was a better response in the early stages of the disease (< 4 months). A small biopsy was taken from the tunica albuginea in 12 men and an excellent response was observed in 6 of the 8 men in whom an inflammatory response was observed. No improvement occurred in any of the 4 men in whom no inflammatory response was seen. The authors concluded that tamoxifen was only of benefit in early stage disease (level 3 evidence).

A placebo controlled study [59] of tamoxifen (20 mg twice daily) or placebo in 25 men with later stage disease (mean duration from onset of 20 months, range 4 - 72) showed no difference between the tamoxifen and placebo (level 2 evidence). Table 14 gives the results of this study and shows that there is no evidence for the benefit of tamoxifen in late stage Peyronie's disease (Grade C).

e) Colchicine

Colchicine has anti-inflammatory activity that may reduce collagen synthesis and stimulate collagenase activity. In a study of 60 men, receiving 500mg three times daily, with early disease it was found that pain improved in 95% and the deformity was better in 30% [60] (Level 4 evidence).

f) Colchicine and Vitamin E

A recent study [61] of a combination of colchicine (2 mg) and vitamin E (600 mg) daily was compared with the effectiveness of the anti-inflammatory analgesic ibuprofen (400 mg daily). The results after 6 months of treatment in the 45 men are shown in table 15 and show benefit with regard to curvature and plaque size for treatment with the combination.

g) Acetyl Esters of Carnitine

Two placebo controlled randomised clinical trials have been reported showing the benefit of these esters. In the first study [62], 48 men with acute (15) or early chronic (33) Peyronie's disease received either acetyl-L carnitine (1 gm twice daily) or tamoxifen (20 mg twice daily) for 3 months and the assessment was made after 6 months. The results are shown in table 16 and show that the acetyl carnitine was superior to the tamoxifen and with fewer side effects.
Interpretation of this study is a little difficult as the patients categorised as suffering with acute Peyronie’s disease are atypical. The duration of the disease was a mean of 5 weeks (range 0.5 - 8) and it is exceedingly uncommon for there to be spontaneous pain in the flaccid penis or “penile paraesthesia”. Furthermore the mean curvature of all patients in the study was less than 15 degrees, remained unchanged in the tamoxifen group, and improved by 7 degrees in the treated group. Most patients would not normally seek help with such symptoms nor would such a small change be of functional benefit (Evidence level 2).

The same group conducted a further study using a different carnitine ester - propionyl-L carnitine [63] as the acetyl carnitine was no longer available. In this study, 75 men were randomly allocated to receive on a double blind basis verapamil injections into the plaque (10 mg once weekly) and propionyl-L carnitine (1gm twice daily) or tamoxifen (20 mg twice daily) for 3 months. The outcome was assessed after 6 months in the 60 (80%) of men who completed the study (Table 17). There was an improvement of pain in 97% of men but although there was a statistically significant improvement in plaque size and deformity in the treated group, this only amounted to 11.8 degrees and 7.6 mm$^2$ (Evidence level 2). The authors conclude that the benefits were probably the result of the mechanical effect of injection rather than of the drug itself (Level 2).

### 4. INTRAPLAQUE INJECTION THERAPY

#### a) Steroids

Plaque injection with steroids has been used for the past 50 years with variable results. In a study [64] of 30 men with Peyronies disease who were randomly allocated to receive intraluesional betamethasone or placebo (saline) for 24 weeks and were followed up after 12 months. The results are shown in Table 18 and the authors conclude that the benefits were probably the result of the mechanical effect of injection rather than of the drug itself (Level 2).

#### b) Collaginase

The injection of chlostridium collagenase into a plaque was reported in 1985 and a clinical trial was subsequently carried out in 49 men with Peyronie’s disease for 3 months [65]. They were stratified into 3 groups - essentially on the angle of erectile deformity and plaque size - and randomly received collagenase or sodium chloride in a dosage that varied with plaque size. The outcome after 3 months was assessed and the results are summarised in Table 19. The authors concluded that an acceptable clinical improvement occurred only in category 1 patients (that is the deformity was < 30 degrees) and that the maximal improvement was only 15 -20 degrees. They did not consider this to be of clinical benefit (Level 2 evidence).

#### c) Verapamil

Verapamil has been used in the treatment of Peyronies disease since 1994 and the authors [66] have

### Tables

#### Table 16. Acetyl L Carnitine in Peyronie’s Disease [62].

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Carnitine</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain improved</td>
<td>22 (92%)</td>
<td>12 (50%)</td>
</tr>
<tr>
<td>Curvature</td>
<td>before 15.9º</td>
<td>13.7º</td>
</tr>
<tr>
<td></td>
<td>after 8.4º</td>
<td>13.2º</td>
</tr>
<tr>
<td>Plaque size</td>
<td>before 109.8</td>
<td>116.5</td>
</tr>
<tr>
<td>(mm$^2$)</td>
<td>after 61.0</td>
<td>89.6</td>
</tr>
</tbody>
</table>

#### Table 17. Proprioyl L Carnitine and intraplaque Verapamil in advanced and resistant Peyronie’s Disease [63].

<table>
<thead>
<tr>
<th>Symptom</th>
<th>PLC + V</th>
<th>T + V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain improved</td>
<td>29 (97%)</td>
<td>29 (97%)</td>
</tr>
<tr>
<td>Penile Deformity</td>
<td>before 39.4</td>
<td>38.5</td>
</tr>
<tr>
<td></td>
<td>after 27.6</td>
<td>36.6</td>
</tr>
<tr>
<td>Plaque size</td>
<td>before 31.8</td>
<td>33.2</td>
</tr>
<tr>
<td>(mm$^2$)</td>
<td>after 24.2</td>
<td>31.9</td>
</tr>
<tr>
<td>I.E.F.</td>
<td>before 19.0</td>
<td>18.2</td>
</tr>
<tr>
<td></td>
<td>after 27.0</td>
<td>18.6</td>
</tr>
</tbody>
</table>

#### Table 18. Intraplaque Betamethasone in Peyronie’s Disease [64].

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number Improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>10 (66%)</td>
</tr>
<tr>
<td>Plaque volume</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Reduction in curvature</td>
<td>3 (20%)</td>
</tr>
</tbody>
</table>
reported the results of injecting 10 mg verapamil into the plaque twice weekly for 6 weeks with an improvement of curvature in 60% of patients (Evidence level 4).

In a single blind controlled study [67], verapamil injection or saline injection into the plaque was performed weekly in a group of 18 men but 4 men dropped out. A decreased plaque volume was measured in 57% of the verapamil treated men (28% in the control group) and there was also an improvement in deformity (Table 20). The authors concluded that verapamil injection was a reasonable option in men with a deformity < 30 degrees (Evidence level 2).

In an observation study [68] the result of verapamil injection was compared to the outcome with verapamil injection combined with electro shock wave therapy. The outcome is shown in table 21 and shows the benefit of the combination therapy (evidence level 3).

The above studies suggest that there is some benefit from verapamil injection but there is no evidence to suggest that it is superior to other forms of treatment for the majority of patients (Grade C).

5. OTHER NON INVASIVE THERAPIES

a) Transdermal Electromotive Therapy

“Electromotive drug administration” (EMDA) is a method reported to give enhanced dermal passage of a drug. The technique has been tried in Peyronie’s disease using a combination of drugs. In the first study [69] the men received 3 applications of 20 minutes duration each week for 3 weeks of orgotein 8 mg, dexamethasone 8 mg and lidocaine 120 mg or placebo. Those receiving placebo, then received the combination treatment. The results (Table 22) showed a marked treatment benefit. Orgotein, which had been used in Peyronie's disease intermittently for many years, was withdrawn from sale and a further study was performed using the combination of dexamethasone 8 mg and verapamil 10 mg in 25 men [69]. The same combination of drugs, but in a different dosage has also been reported [70]. In both studies colour Doppler studies were carried out and the penile deformity and plaque size measured before and after treatment. The favourable outcome is shown in table 23 and the fact that many of the men had received previous treatment, and the well documented objective measures of outcome, means that the technique merits further study.

b) Extracorporeal Shock Wave Therapy (ESWT)

ESWT has been used in Peyronies disease since 1989 and the results have been reviewed recently [71]. Unfortunately the dosage and machines used have varied although the results are usually favourable (Table 24) [71-75]. There have been no controlled trials but one case controlled study [76] was favourable (Table 25).

c) Radiotherapy

This has been used for many years but in a retrospective study [77] it was not considered to be superior to no treatment (Table 26). Radiotherapy should probably be avoided because of the the possible risk of malignancy (low in the dosage involved) and increasing the risk of erectile dysfunction in an aging man.

6. SUMMARY OF NON SURGICAL TREATMENT OF PEYRONIE’S DISEASE

There is an improvement in the symptoms of many
Table 22. Transdermal Electromotive Drug Therapy [69].
Placebo controlled : Double blind : Partial crossover
40 men Orgotein 8mg, dexamethasone 8mg, lidocaine 120mg 20min x 3 x weekly x 3 Assessed at 3m

<table>
<thead>
<tr>
<th>Pain during flaccidity</th>
<th>Treated</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>disappeared</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Pain during erection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>disappeared</td>
<td>30 (100%)</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>improved</td>
<td>-</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>Penile deformity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>disappeared</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>improved</td>
<td>20 (62%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>unchanged</td>
<td>12 (38%)</td>
<td>19 (95%)</td>
</tr>
</tbody>
</table>

Table 23. Outcome of Dexamethasone / Verapamil Combination by EMDA [69, 70].

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain during erection</td>
<td>disappeared 16 (100%)</td>
<td>43 (88%)</td>
</tr>
<tr>
<td></td>
<td>improved - 4 (8%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Deformity</td>
<td>disappeared 2 (12%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td></td>
<td>improved 13 (76%)</td>
<td>36 (74%)</td>
</tr>
<tr>
<td>Lump</td>
<td>disappeared 2 (12%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td></td>
<td>improved 13 (76%)</td>
<td>36 (74%)</td>
</tr>
</tbody>
</table>

Table 24. ESWL for Peyronie's.
Machine and dosage varies
Often abstracts only

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Pain improved</th>
<th>Deformity improved</th>
<th>Positive result</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>52</td>
<td>15 (83%)</td>
<td>21 (42%)</td>
<td>28 (54%)</td>
</tr>
<tr>
<td>73</td>
<td>90</td>
<td>32 (94%)</td>
<td>31 (43%)</td>
<td>62 (72%)</td>
</tr>
<tr>
<td>74</td>
<td>153</td>
<td>48 (96%)</td>
<td>102 (68%)</td>
<td>103 (67%)</td>
</tr>
<tr>
<td>71</td>
<td>54</td>
<td>31 (91%)</td>
<td>29 (54%)</td>
<td>33 (61%)</td>
</tr>
<tr>
<td>75</td>
<td>42</td>
<td>21 (84%)</td>
<td>22 (58%)</td>
<td>27 (64%)</td>
</tr>
</tbody>
</table>

Table 25. ESWT in Peyronie's: A Case Controlled Study [76].
22 men with failed oral therapy received ESWT
23 untreated men received oral placebo for 6m

<table>
<thead>
<tr>
<th>ESWT</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain during flaccidity</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Pain during erection</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Pain improved (N.S.)</td>
<td>58%</td>
<td>33%</td>
</tr>
<tr>
<td>Deviation</td>
<td>42°</td>
<td>31°</td>
</tr>
<tr>
<td>Deviation improved &gt; 30°</td>
<td>50%</td>
<td>21%</td>
</tr>
<tr>
<td>Plaque size mm²</td>
<td>183</td>
<td>206</td>
</tr>
<tr>
<td>Overall improvement</td>
<td>13 (65%)</td>
<td>12 (52%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Control</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain during flaccidity</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Pain during erection</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Pain improved (N.S.)</td>
<td>58%</td>
<td>33%</td>
</tr>
<tr>
<td>Deviation</td>
<td>46°</td>
<td>45°</td>
</tr>
<tr>
<td>Deviation improved &gt; 30°</td>
<td>50%</td>
<td>21%</td>
</tr>
<tr>
<td>Plaque size mm²</td>
<td>244</td>
<td>206</td>
</tr>
<tr>
<td>Overall improvement</td>
<td>13 (65%)</td>
<td>12 (52%)</td>
</tr>
</tbody>
</table>
patients without treatment and it is therefore important that all studies should include a control group (grade D).

In those studies that have included a control group, the results often show no difference between the treated and control groups, and when there is a difference, it is often small and not clinically significant.

The absence of a best buy in treatment is evident from the observation that members of the panel utilise different treatment options. The combination of vitamin E and colchicine would appear to be a simple, well tolerated, evidence based option.

7. SURGICAL MANAGEMENT OF PEYRONIE'S DISEASE

a) Indications For Surgery

Many different operations have been described but most authors are agreed as to the indications for surgery (Table 27).

The quality of erection is important in the choice of operation and may be categorised as good, impaired but satisfactory with a phosphodiesterase inhibitor, or poor even with treatment. In this latter group of men, the implantation of a penile prosthesis should be considered as the results are excellent. In such men, particularly in the older age group and when there is other evidence of vascular disease, it is not necessary to have the same time constraints.

There are few controlled studies of any surgical treatments and this is certainly the case in Peyronie's disease. The method of reporting varies greatly and many authors combine the results of treatment of Peyronie's disease with congenital curvature. We would have liked to have limited ourselves to those reports consisting of at least 50 men, having the same operation for the same condition, and with a follow up of at least a year. Few studies meet these simple criteria and we have therefore had to be a little more flexible. The way in which the outcome is measured is also variable and this adds to the difficulties in assessment.

b) Plaque Excision and Dermal Graft

This operation was simultaneously described in Sweden [78] and the United States [79] and in some centres it was the standard treatment until recently. There were no long term studies of outcome until 1995 and in a group of 418 men it was found that 17% required further surgery for curvature and that 20% had troublesome post operative erectile dysfunction [80]. This operation may now be regarded as outmoded.

c) Nesbit Procedure

This operation was introduced [81] for the treatment of congenital penile curvature but was adapted for Peyronie's disease [82]. It has given consistently good results (Table 28) and may be regarded as the standard operation for the condition [82-87]. It has few complications but some surgeons feel that penile shortening is a problem. This has not proved to be the case in most series but in this respect, as in most surgery, patient expectation is the key to a happy outcome. An explanation that the disease process and scarring have shortened the penis and that the tuck will be taken from the opposite side to straighten the penis is essential.

It is perhaps useful to concentrate on the poor results which may range from 4 - 26% (Table 28) and a review of poor results [88]. Erectile dysfunction immediately after a Nesbit procedure is uncommon and usually improves. This is because the erectile tissue is not disturbed. Poor preoperative erectile dysfunction may improve when it is due to anxiety but
pharmacotesting/colour Doppler examination should diagnose any underlying vasculogenic deficit. Such patients are better treated by the implantation of a penile prosthesis. It should be noted that there is an increasing incidence of erectile dysfunction with time after operation due to the underlying vascular problems.

Shortening of the penis of more than 2 cm was reported in 4.7% of 359 men in one series [85] and of more than 1.5 cm in 14% of men in another series [87]. It should be noted that intercourse was reported to be impossible in only 6 of these 39 men. Severe shortening does occur in some men and may be the result of scarring from infection or from a failure to reattach the subcutaneous tissue distally.

An immediate recurrence of the deformity after a Nesbit procedure is usually due to the sutures cutting out. Recurrence after 2 -3 months is the result of suture failure whereas recurrence after one year is usually due to progression of the disease [88]. Recurrent deformity after a Nesbit procedure occurred in 1.3 - 10.6% of men depending upon definition used and the length of follow up.

d) Plication Techniques

Nesbit [81] also reported the technique of penile plication for congenital erectile deformities and two new plication techniques were described in 1985 [89-90]. The operation is simpler and there have been subsequent reports (Table 29) although many of these are of small mixed series of both congenital and acquired curvatures [91-96]. In general terms the outcome is inferior to the standard Nesbit technique and some authors have abandoned plication for the standard Nesbit procedure.

e) Corporoplasty

This technique was described by Lemberger [97] in 1984. Instead of excising an ellipse of tunica, he made a longitudinal incision in the tunica and sutured it up transversely to shorten the longer side. This technique has more recently been popularised by Yahia [98] and the overall results are satisfactory. In a study of 30 patients in each group having a Nesbit operation, a Lemberger/Yahia procedure or a modification of it, the authors [99] preferred their own modification although there was little to choose between them.

### Table 28. Nesbit Excision Procedure for Peyronie’s Disease.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number</th>
<th>F.Up(m)</th>
<th>Excellent/ Satisfactory</th>
<th>Poor</th>
<th>Recurrent Bend</th>
<th>Post-op E.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>83*</td>
<td>78</td>
<td>50 (6-132)</td>
<td>62 (79%)</td>
<td>16 (21%)</td>
<td>4%</td>
<td>18%</td>
</tr>
<tr>
<td>84</td>
<td>78</td>
<td>18(3-48)</td>
<td>62 (79%)</td>
<td>2 (4%)</td>
<td>4%</td>
<td>23%</td>
</tr>
<tr>
<td>85 A</td>
<td>174</td>
<td>21 (2-108)</td>
<td>138 (74%)</td>
<td>46 (26%)</td>
<td>38 (11%)</td>
<td>25%</td>
</tr>
<tr>
<td>47</td>
<td>185</td>
<td>167 (90%)</td>
<td>18 (10%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>86 C</td>
<td>53</td>
<td>(77%)</td>
<td>(23%)</td>
<td>(5%)</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>86 D</td>
<td>65</td>
<td>(94%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>87</td>
<td>157</td>
<td>72 (16-156)</td>
<td>88%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Includes 12 congenital

### Table 29. Plication Operations for Peyronie’s Disease.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number</th>
<th>Follow-up</th>
<th>Satisfactory</th>
<th>Recurrent bend</th>
</tr>
</thead>
<tbody>
<tr>
<td>91*</td>
<td>33</td>
<td>42m</td>
<td>64%</td>
<td>5%</td>
</tr>
<tr>
<td>92</td>
<td>51</td>
<td>20m</td>
<td>82%</td>
<td>5%</td>
</tr>
<tr>
<td>93</td>
<td>54</td>
<td>36m</td>
<td>89%</td>
<td>10%</td>
</tr>
<tr>
<td>94*</td>
<td>31</td>
<td>6m</td>
<td>58%</td>
<td>47%</td>
</tr>
<tr>
<td>95</td>
<td>116</td>
<td>6m</td>
<td>93%</td>
<td>15%</td>
</tr>
<tr>
<td>96</td>
<td>41</td>
<td>48m</td>
<td>52%</td>
<td></td>
</tr>
</tbody>
</table>

* Same centre
f) Plaque Incision And Grafting

This technique was introduced in 1991 using a temporalis fascial graft [100]. Lue [101] suggested the use of the dorsal penile vein or a segment of the long saphenous vein and this form of grafting would seem to give the best results (Table 30) [102-106]. However the technique fails to lengthen the penis in many men and has the drawback of being associated with an appreciable incidence of post operative erectile dysfunction. It should be noted that in many of the of incision and grafting operations it was often necessary to perform an additional plicating procedure. It would seem advisable to limit this operation to a highly selected group of men with marked foreshortening of the penis, obesity and with good erectile function.

Various other grafts have been used [107-110] but the numbers are generally small, the follow up short, and the outcome generally satisfactory.

g) Penile Prosthesis

This has already been mentioned and is covered by committee 13. This is a reliable option for the older man with vascular impairement, erectile dysfunction and an erectile deformity.

8. SUMMARY

The management of Peyronie's disease is summarised in figure 4. The man with this benign condition often requires reassurance and no active treatment. The natural history is one of improvement in many men and this is fortunate as ther is no good evidence for any effective conservative treatment. In those men with an impaired erection due to a vascular defect , the implantation of a penile prosthesis gives good results. The Nesbit technique would seem to give better results than plication, and it is too early to make a final decision with regard to the plaque incision and grafting procedures.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number</th>
<th>Satisfied</th>
<th>Penile straight</th>
<th>Decreased potency</th>
<th>Penile shortening</th>
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<tbody>
<tr>
<td>102</td>
<td>113</td>
<td>92%</td>
<td>96%</td>
<td>12%</td>
<td>17%</td>
</tr>
<tr>
<td>103</td>
<td>20</td>
<td>100%</td>
<td>75%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>104</td>
<td>50</td>
<td>88%</td>
<td>80%</td>
<td>6%</td>
<td>40%</td>
</tr>
<tr>
<td>105</td>
<td>58</td>
<td>86%</td>
<td>82%</td>
<td>7%</td>
<td>22%</td>
</tr>
<tr>
<td>106</td>
<td>51</td>
<td>92%</td>
<td>82%</td>
<td>8%</td>
<td>35%</td>
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Figure 4 : Peyronie's Disease Management.
mity that interferes with sexual function. When the urinary tract function is satisfactory, it is reasonable to treat any deformity with a Nesbit procedure.

In men with chordee without hypospadias the corpus spongiosus is deficient and the skin is adherent to the urethral mucosa. Attempts to separate the two layers usually results in a fistula and fails to correct the erectile deformity. The Nesbit excisional procedure is recommended as it is for the curvature without chordee. This condition is due to disproportion in the shape of the cavernous bodies and tunica albuginea. Penile shortening is not a problem in these men as penile length tends to be long.

It should be noted that these men are young and sexually inexperienced. Many of them are afraid to become involved with a partner because of embarrassment, and occasionally they are teased because of the bend. It is often advisable to correct minor curvatures even though older men with an acquired deformity could easily manage without surgery.

The results of surgical correction by plication (Table 31) and the Nesbit technique (Table 32) tend to be better than those for Peyronie's disease and show an advantage for the Nesbit operation. [111-118].

**Table 31. Plication Correction of Congenital Curvature of Erection.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number</th>
<th>Straight</th>
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<tr>
<td>112</td>
<td>39</td>
<td>95%</td>
<td>5%</td>
</tr>
<tr>
<td>111</td>
<td>140</td>
<td>94%</td>
<td>4%</td>
</tr>
<tr>
<td>92</td>
<td>48</td>
<td>81%</td>
<td>5%</td>
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<tr>
<td>113</td>
<td>30</td>
<td>77%</td>
<td>23%</td>
</tr>
<tr>
<td>114</td>
<td>40</td>
<td>77%</td>
<td>23%</td>
</tr>
</tbody>
</table>

**Table 32. Correction of Congenital Erectile Curvature. Nesbit Corporoplasty.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number</th>
<th>Straight</th>
<th>Recurrent deformity</th>
</tr>
</thead>
<tbody>
<tr>
<td>116</td>
<td>100</td>
<td>96%</td>
<td>4%</td>
</tr>
<tr>
<td>84*</td>
<td>95</td>
<td>91%</td>
<td>9%</td>
</tr>
<tr>
<td>86</td>
<td>110</td>
<td>99%</td>
<td>5%</td>
</tr>
<tr>
<td>117</td>
<td>55</td>
<td>95%</td>
<td>9%</td>
</tr>
<tr>
<td>118</td>
<td>106</td>
<td>96%</td>
<td>4%</td>
</tr>
</tbody>
</table>

* Only 22% of 23 patients had good result with plication

Suspensory ligament problems are easy to diagnose once the condition is considered. The penis, often long and sometimes with a congenital erectile curvature, engorges but fails to assume the normal erect position - hence the term of non erecting penis used by Yachia. Clinical examination reveals the gap between the symphysis pubis and the erectile tissue and the problem may be rectified by placing non absorbable sutures between the symphysis and the tunica albuginea [119].

2. **HIDDEN PENIS**

   a) **Classification**

   1. Concealed penis: In this condition the penis is essentially normal but is hidden in the underlying abdominal fat. The penis may be exposed by pressing back on the surrounding skin. No specific treatment is usually necessary for this condition as the corporal bodies are normal and sexual function is not disturbed.

   2. Congenital hidden penis: In this rare congenital abnormality there are dense dysgenetic fascial bands that tether the penis and retract it backwards. It is also associated with an abnormally large suprapubic fat pad.

   3. Acquired hidden penis: This is usually the result of the inadvertent removal of too much penile shaft skin during circumcision.

   b) **Surgical Management [120-122]**

   This may be necessary in the partially or completely hidden penis for both psychological and physical reasons. Inability to urinate whilst standing due to spraying, chronic bathing of the skin during micturition may cause balanitis xerotica obliterans, or there may be an interference with sexual function.

   A wide range of surgical techniques are available and the surgeon should have the ability to perform them all as the precise technique required in any man may not be clear until the defect is exposed. Circumcision often makes the situation worse.

3. **PENILE ENLARGEMENT**

   There was a remarkable uniformity of opinion amongst the committee on this contentious topic. Men with a true micropenis - stretched penile length of less than 9.5 cm - adapt surprisingly well to the problem [123] although vaginal penetration is rarely possible with a length of less than 7 cm. In these circumstances a penile lengthening procedure [124] is
indicated although it is recognised that the length of the erectile tissue remains unchanged. Division of the suspensory ligament and separation of the crura from the symphysis allows the penis to hang lower with an apparent increase in the length of the penile shaft. This gain of 1-3 cm may be enough to give vaginal penetration.

Most men presenting for penile lengthening procedures have a normal sized penis [125-126] although it may appear small in the flaccid state. This may give rise to anxiety, or it may cause more severe distress, and in rare instances be sufficient to cause suicide. No patient seeking enlargement of a normal penis should be operated upon without a psychiatric assessment. The committee felt that most patients, when properly informed for consent, declined to proceed with operation and those who chose to proceed required psychiatric advice. Unlike in many other forms of cosmetic surgery, penile lengthening does not increase the overall length of the erectile tissue. The men usually have poor self esteem and feelings of sexual inadequacy. Many of those who proceed to surgery are still unhappy - either their feelings persist, their goal is not achieved, or the normal penis has become abnormal as a result of post operative complications [127].

Penile lengthening techniques are based upon division of the suspensory ligament and mobilisation of the crura [124, 128, 129]. Post operative fibrosis often mitigates against any increase in length and additional techniques have been introduced to try and prevent this. Penile stretching is popular and may be of benefit without the need for surgery.

Girth enhancement procedures using fat injection, dermal fat grafts, alloderm implantation or incision of the tunica albuginea with grafting have all been tried with generally disappointing results.

In brief, those men with a normal penis who are eager to undergo surgery to improve their perception of their penile appearance are rarely satisfied and not infrequently litigious.

4. PENILE INJURIES

The unique anatomy of the penis often dictates the management. Simple injuries are straightforward but those injuries involving the urinary tract require temporary urinary diversion. The risk of a rapidly spreading infection is ever present.

Nonpenetrating injuries to the penis requiring surgical intervention are usually true or subclinical fractures of the penis. The term subclinical fracture of the penis implies a fracture of one or more of the layers of the corpora cavernosa, but without the usual symptoms of a true fracture of the penis, those being a buckling injury with immediate detumescence and hematoma. The older literature favoured the conservative management of penile fractures but nowadays early intervention and closure of the defect in the tunica albuginea is recommended, except in men presenting late. The urethra is at risk for injury with a fracture of the penis and must be evaluated. A recent study of fracture of the penis patients has shown that if the patient has voided asymptomatically and his urine is clear both grossly and microscopically, that a retrograde urethrogram is not required. The use of cavernosograms for the diagnosis of fracture of the penis remains controversial but is probably useful.

Penetrating injuries of the penis often involve the urethra; and when they do, are termed complex injury of the penis. Simple injuries to the penis are defined as those injury that do not involve either the corpora cavernosa, corpus spongiosum, or the urethra. The management of penetrating injuries of the penis depends on the ballistic properties of the missile, if a gunshot wound is involved with the injury (shotgun injuries behave as high velocity when close to the gun, and low velocity when shot at a distance). Laceration injuries of the penis are best managed with immediate repair. Bullet wounds from relatively low velocity firearms can be managed with immediate reconstruction. Bullet injuries from high velocity firearms are often best managed in delayed fashion, as the blast effect renders viability of the tissues unreliable.

Penile amputation, there is agreement in the literature that microreplantation is the state of the art management. Microreplantation involves reanastomosis of the dorsal arteries and dorsal vein, with coaptation of the dorsal nerves. The erectile bodies are repaired in anatomic fashion. The urethra should be repaired with a spatulated two-layer anastomosis. The patient should be diverted with a suprapubic tube and a small urethral stenting catheter is also suggested.

There will be some cases where microreplantation cannot be accomplished, either because of lack of expertise, or because of the general condition of the patient. In those cases a macroreplantation technique may be used with an anatomic closure of all structures, a dorsal vein can be reanastomosed, but with no attempt to reanastomosis of the dorsal arteries or
coaptation of the dorsal nerves. The skin should be debrided and discarded in late presenting injuries and the penis is placed in a scrotal pouch and may be liberated in delayed fashion.

**Avulsion injuries** of the penis rarely involve the deep structures. The skin is avulsed in the layer between the superficial lamina of Buck's fascia and the deep lamina of the dartos fascia. That said, these injuries are very effectively managed with primary graft techniques. If there is avulsion injury of the deep structures, then replantation is very difficult because of the tissue damage involved with the avulsion. These cases must be managed in individual fashion with no blanket recommendations possible. While not classically trauma, necrotizing fasciitis involving the penis rarely penetrates to the layers deep to Buck's fascia. The debridement is usually adequate with the skin and dartos fascia removed. As the wounds clean, primary grafting of the penis is usually possible with very acceptable functional and cosmetic results. It is controversial as to whether mesh graft or sheet grafts are optimal.

### 5. LYMPHOEDEMA

**a) Classification**

**Primary**

1. Congenital (Milroy's disease) and would be expected to be part of the constellation of lower body lymphoedema;
2. Lymphoedema precox (presenting at puberty);
3. Lymphoedema tarda (presenting later onset).

**Secondary (acquired)**

The congenital varieties of lymphoedema are familial with an autosomal dominant transmission. Primary lymphoedema is associated with hypoplasia or aplasia of the lymphatics and in many cases, only the lower extremities are involved with genital skin sparing. Secondary causes are frequently associated with radiotherapy. Rare causes are filariasis, tuberculosis, hydradenitis supurativa, verrucus lymphoedema, and as a consequence of sarcoidosis.

Much has been written regarding the management of lymphoedema but there is no overwhelming agreement on the best management. With regards to penile lymphoedema, it is generally agreed, that the use of local flaps or of thinned penile skin flaps yield unacceptable results with unacceptable recurrence rates. Thus most series have resorted to complete excision of the lymphoedematous skin and subcutaneous tissues, and grafting with a split-thickness skin graft, either sheet or mesh, directly applied to the Buck's fascia. There is not agreement as to whether the suture line should be dorsal, ventral or with a Z-plasty closure of the ventral graft suture line.

There is even less agreement about the management of scrotal lymphoedema. Many series emphasize the relative sparing of the dorsal wall of the scrotum and advocate complete excision of the lymphoedematous anterior wall and complete excision of the lymphoedematous subcutaneous tissues down to the level of the external spermatic fascia, with scrotal reconstruction using the uninvolved posterior scrotal skin if possible. Genital lymphoedema is often associated with a hydrocele and a complete excision of the parietal tunic vagina lis with orchidopexy advocated by most authors. In many cases the posterior scrotal wall is involved, and in these the best management is split-thickness skin grafting, again either as a sheet or mesh graft to cover the defect.

### 6. PHALIC CONSTRUCTION

Modern day phallic construction was first accomplished in Russia by Borgoras [130]. Gillies [131] went to Russia to learn the technique, brought it back to England, and accumulated a large series associated with the war injured. The technique has been popularly referred to as the abdominal tube within a tube technique. The technique suffers from the fact that in days prior to epilation, the urethra was hair bearing, often plaguing the patient with infections. The method creates two tubes from abdominal wall skin which are then transferred to the area of the penis by classic delay techniques.

A variety of other flaps have been described but the state of the art was revolutionized by the description of the radial forearm flap for phallic construction [132]. The medial location of the urethral paddle caused problems and was modified to centralise the urethral paddle over the vessel, ostensibly making that paddle more reliable, and diminishing urethral complications [133].

The team at the Eastern Virginia Medical School [134] has used a Biemer modified forearm flap, with a Puckett extension, using the ulnar vessels. Fifty-one of 113 patients preceded the switch to the ulnar forearm flap, while 62 were based on the ulnar forearm fascia with the modified Biemer design. Analysis of the results showed no overall difference in successful flap construction, with a 94% success rate. There was however a significant reduction in
urethral complications with the ulnar based modified Biemer design. This was primarily due to a reduction in the rate of urethrocutaneous fistula from 23% to 11% (p=0.05). The incidence of urethral strictures was unaffected by these modifications (18% and 22%; p=0.64). Moreover, flap sensibility was achieved in 90% of all patients achieved by coapting the lateral and medial antebrachial cutaneous nerves of the flap to the recipient dorsal genital nerves or ilioinguinal nerves. Prosthetic implantation is generally required for sexual activity [135].

IV. SUMMARY AND RECOMMENDATIONS

1. PRIAPISM

A persistent unwanted erection that is not associated with sexual sexual desire or sexual stimulation. Its management is summarised in table 9 and figure 4.

2. RECOMMENDATION 1

A low flow ischaemic priapism requires urgent treatment in order to prevent muscle necrosis. Haematological management should not delay treatment of this condition which may be regarded as a compartment syndrome. First aid measures may be carried out whilst awaiting the start of definitive treatment. Terbutaline was of some benefit in pharmacologically induced priapism (grade C).

3. RECOMMENDATION 2

The aspiration of cavernous blood through a 19G butterfly needle confirms the diagnosis of a low flow ischaemic priapism, relieves pain, and reduces intracavernous pressure to permit reoxygenation of the cavernous muscle. If the priapism does not resolve after 10 minutes of detumescence, an alpha adreno-receptor agonist should be injected. This should be repeated and detumesence maintained for 1 hour before proceeding to surgery. (Grade D)

4. RECOMMENDATION 3

A cavernous muscle biopsy should be taken at the time of shunt surgery in order to better document the onset of irreversible muscle damage and future severe erectile dysfunction (Grade D).

5. RECOMMENDATION 4

In men with the late presentation of a low flow ischaemic priapism - perhaps more than 72 hours - consideration should be given to the implantation of a penile prosthesis (Grade D).

6. RECOMMENDATION 5

A high flow non-ischaemic priapism has a good prognosis and may resolve spontaneously. Expectant observation is a reasonable option before definitive treatment by embolisation with autologous clot. (Grade D)

7. RECOMMENDATION 6

Recurrent or stuttering priapism is not confined to men with sickle cell disease, may be ischaemic or non ischaemic -even at different times in the same patient. It may be controlled by first aid measures but this is often unsuccessful and anti-androgen therapy has proved useful although long term use in young men will cause hypogonadism and infertility. Further research is required in this condition (Grade D).

8. PEYRONIE’S DISEASE

An acquired disorder of the tunica albuginea characterised by the formation of a plaque of fibrous tissue and often accompanied by penile pain and deformity on erection.

9. RECOMMENDATION 7

The management of Peyronie’s disease often requires no more than reassurance of the patient. Many treatments have been described but only 11 prospective controlled trials have been carried out and 7 of these showed little benefit from treatment, in 2 the drugs used are no longer available. A combination of vitamin E and colchicines was the simplest but there is clearly a need for further research to find effective treatment for this common condition (Grade D).

10. RECOMMENDATION 8

Surgical correction of the penile deformity in Peyronie’s disease should not be corrected until at least 12 months after the onset and after the symptoms have been stable for 3, and preferably, 6 months. The deformity should make intercourse difficult and the quality of erection should be adequate. It is essential for the man to have a correct expectation of the outcome and give a proper informed consent (Grade D).

11. RECOMMENDATION 9

The Nesbit excision technique has given the best
results and is the method of choice for most men as there have been more failures with the plication operations. **Plaque incision and vein grafting** gives good straightening but with an increased risk of postoperative erectile dysfunction and should only be used in selected patients. It is too soon to comment on vein substitutes (Grade C).

12. **RECOMMENDATION 10**

*Outcome reports of surgical procedures* should contain an adequate number of patients (50), having the same operation, and followed up for at least 1 year (Grade D).

13. **RECOMMENDATION 11**

A **penile prosthesis** is a good option for men with severe erectile dysfunction that does not improve sufficiently with other forms of treatment. It is not necessary to wait for the disease to stabilise in these men (Grade C).

14. **RECOMMENDATION 12**

Men with a **congenital erectile deformity** of erection associated with chordee without hypospasias, or without chordee (sometimes called congenital shot urethra when the curvature is ventral) should have a Nesbit excisional procedure to correct the deformity. This gives a better outcome than plication (Grade C).

15. **RECOMMENDATION 13**

Men seeking **elongation of the normal sized penis** have a dysmorphic condition and require psychological advice. **Penile stretching** may be useful and most men will not wish to proceed to surgery when properly informed of the likely outcome and risks of complications (Grade D).

**REFERENCES**


34. RHODEN EL., TELOKEN C., TING HY ., LUCAS ML., TEO-....


Committee 9 A

Disorders of Orgasm and Ejaculation in Men

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M. Perelman (USA),

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M. Sipski (USA),

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Z. Cheng Xin (China)
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Disorders of Orgasm and Ejaculation in Men

C. G McMAHON, C. ABDO, L. INCROCCI, M. PERELMAN, D. ROWLAND, B. STUCKEY, M. WALDINGER, Z. CHENG XIN

INTRODUCTION

Ejaculatory dysfunction or male orgasmic disorder (MOD) is one of the most common male sexual disorders. The spectrum of MOD extends from early ejaculation, through delayed ejaculation to a complete inability to ejaculate, anejaculation, and includes retrograde ejaculation. The sexual response cycle can usefully be conceptualized as having four interactive, non-linear stages: desire, arousal, orgasm, and resolution. The sexual dysfunctions are disruptions of any of these phases [1]. The fourth stage of orgasm is usually coincident with ejaculation, but represents a distinct cortical event, experienced phenomena logically both cognitively and emotionally. 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].

THE EJACULATORY RESPONSE

Orgasm and ejaculation constitute the final phase of the sexual response cycle. Ejaculation is a reflex comprising sensory receptors and areas, afferent pathways, cerebral sensory areas, cerebral motor centres, spinal motor centres and efferent pathways. The ejaculatory reflex is predominantly controlled by a complex interplay between central serotonergic and dopaminergic neurons with secondary involvement of cholinergic, adrenergic, oxytocinergic and GABAergic neurons.

A. PHYSIOLOGY OF EJACULATION

There are 3 basic mechanisms involved in normal ante-grade ejaculation - emission, ejection and orgasm (Table 1) [3]. Ejaculatory dysfunction can result from disruption at any point in this cascade of events. Emission is the result of a sympathetic spinal cord reflex initiated by genital and/or cerebral erotic stimuli. Emission involves the sequential contraction of accessory sexual organs and the sensation of emission is due to distension of the posterior urethra. There is considerable voluntary control of emission. As the sensation of ejaculatory inevitability increases, voluntary control progressively decreases until a point at which ejaculation cannot be stopped is reached. Ejection also involves a sympathetic spinal cord reflex upon which there is limited voluntary control. Ejection involves bladder neck closure to prevent retrograde flow, rhythmic contractions of bulbocavernous, bulbospongious and other pelvic floor muscles, and relaxation of the external urinary sphincter. Intermittent contraction of the urethral sphincter prevents retrograde flow into the proximal urethra [4]. 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.

The ejaculate can be divided into several fractions by serial biochemical analysis [5]. It comprises secretions from the seminal vesicles, prostate and bulbourethral (Cowper’s) glands, and spermatozoa. It is produced when the combining the 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 [6]. 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 contribution is derived from the bulbo-urethral (Cowper's) glands which is rich in enzymes and plasminogen activator [7]. Spermatzoa 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.

1. NERVOUS CONTROL OF EJACULATION AND ORGASM

The ejaculatory reflex comprises sensory receptors and areas, afferent pathways, cerebral sensory areas, cerebral motor centres, spinal motor centres and efferent pathways (Figure 1) [8].

1. SENSORY RECEPTORS AND AREAS

The mucosa of the glans penis contains specialised sensory receptors, Krause-Finger corpuscles. They 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 from variable extra-genital erogenous organs e.g. nipples, anal sphincter, modulates, usually enhancing, afferent information from the Krause-Finger corpuscles.

2. AFFERENT PATHWAYS

Sensory information from the glans penis travels in afferent pathways to the spinal cord. Sensory fibres of the pudendal nerve, contained within the dorsal nerve of penis extend to the S4 level and autonomic fibres within the hypogastric plexus transmit information to the sympathetic ganglia located along the spinal cord.

3. CEREBRAL CONTROL OF EJACULATION AND ORGASM

Seminal emission and ejaculation are controlled by the paraventricular nucleus of the anterior hypothalamus (PVN) and the medial preoptic area (MPOA) (Figure 2) [9]. The medial pre-optic area (MPOA) is located rostral to the anterior hypothalamus and appears to have a pivotal role in augmenting copulatory behaviour. Electrical stimulation of the MPOA can elicit seminal emission or ejaculation in monkeys and rats [10, 11]. Electrical stimulation of the MPOA, also elicits the urethrogenital reflex in rats, which may mimic orgasm in humans [12]. This occurs in the absence of genital stimulation. This reflex is usually elicited in anesthetized, spinally transected rats by distending the urethra with saline and then suddenly releasing the pressure. This 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.

Table 1. The three stages of normal antegrade ejaculation

<table>
<thead>
<tr>
<th>Emission</th>
<th>Sympathetic spinal cord reflex (T10–L2)</th>
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<tr>
<td></td>
<td>Genital and/or cerebral erotic stimuli with considerable voluntary control</td>
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<tr>
<td></td>
<td>Peristaltic contraction of epididymis and vas deferens</td>
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<td></td>
<td>Contraction of seminal vesicles and prostate</td>
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<tr>
<td></td>
<td>Expulsion of spermatozoa/seminal/prostatic fluid into posterior urethra</td>
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<td></td>
<td>Ejaculatory inevitability sensation resulting from distension of posterior urethra</td>
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<table>
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<tr>
<th>Ejection</th>
<th>Parasympathetic spinal cord reflex (S2–S4)</th>
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<tr>
<td></td>
<td>Limited voluntary control</td>
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<tr>
<td></td>
<td>Rhythmic contractions of bulbocavernous/pelvic floor muscles</td>
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<td></td>
<td>Bladder neck closure</td>
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<td>Relaxation of external urinary sphincter</td>
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<table>
<thead>
<tr>
<th>Orgasm</th>
<th>Build-up and release of pressure in posterior urethra</th>
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<tr>
<td></td>
<td>Smooth muscle contraction of accessory sexual organs and urethral bulb</td>
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<tr>
<td></td>
<td>Sensation due cerebral processing of pudendal nerve sensory stimuli</td>
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</table>
Figure 1: Nerves involved with emission and ejection. Sympathetic nerves from T10-L2 innervate the vas deferens, prostate and bladder neck, and contraction results in emission and bladder neck closure. Somatic nerve fibers in the pudendal nerve arise from S2-S4 and innervate the pelvic floor musculature, the contraction of which causes forceful ejection.

Figure 2: The ejaculatory reflex comprises sensory receptors and areas, afferent pathways, cerebral sensory areas, cerebral motor centres, spinal motor centres and efferent pathways.
Microinjection of moderate doses of a mixed D1/D2 dopamine agonist (apomorphine) or of a pure D1 agonist (thienopyridine), into the MPOA, promotes erections and copulation of male rats, apparently by increasing parasympathetic tone [13,14]. Higher doses of a mixed D1/D2 agonist, or of a selective D2 agonist, favour seminal emission and ejaculation [12]. 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 [15]. Dopamine is released in the MPOA of male rats in the presence of an estrous female, and increases more during copulation [16]. The levels of extracellular dopamine in the MPOA may regulate the phases of copulation, with high levels triggering ejaculation.

In a series of elegant rat experiments involving selective pharmacologic and/or radiofrequency lesions, Liu et al. demonstrated that the parvocellular neurons of the hypothalamic paraventricular nucleus (PVN) mediates erectile function in rats, whereas the magnocellular PVN neurons mediate ejaculation [17]. Oxytocinergic PVN neurons possibly modulate the male sexual response as evidenced by increased cerebrospinal fluid concentrations of oxytocin after ejaculation, augmented male sexual behaviour following intraventricular administration of oxytocin and decreased seminal emission in rats with lesions of the parvocellular PVN neurons [18].

The MPOA is also of importance to the cholinergic influence on sexual behaviour. Injections of the cholinergic agonists oxotremorine and carbachol cause a stimulation of sexual behaviour in male rats seen as 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]. 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 released the urethrogenital reflex from this 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 stimulating an excitatory site.

4. Spinal motor centers

A spinal centre, located at the Th12-L1-L2 spinal level, is controlled by the sympathetic nervous system and is responsible for emission. A second centre, is located at the S2-S4 level, is controlled by the somatic nervous system and is responsible for expulsion.

5. Efferent pathways

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 3).

The nerves proceed via the thoracic sympathetic chain to the caudal (inferior) enteric plexus, the major/minor splanchnic nerves, the celic/cranial mesenteric plexuses, and the intermesenteric nerves. Descending nerves from these ganglia 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 former plexus mainly innervates the colon via the colonic nerve and from the latter arise paired hypogastric nerves. 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 4) [23].

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 1-adrenergic receptors causing a rise in intracellular calcium, actin-myosin interaction, vas deferens smooth muscle contraction, a marked elevation of intraluminal pressure in the cauda 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 demonstrate that the majority of post-ganglionic neurons distributed in the vas deferens originate from the pelvic plexus [24]. The pelvic plexus receives neural input from both the hypogastric and pelvic nerves. Electrical stimulation of the hypogastric nerve elicited contraction of the vas deferens, while stimulation of the pelvic nerve caused no detectable motor responses [25-27]. Histochemical studies of the vas deferens have also shown that the adrenergic fibers mainly innervate the smooth muscle layers, whereas cholinergic fibers chiefly innervate the subepithelial layer [3].

Almost all the lumbar splanchnic nerves originate from L2 and/or L3 lumbar sympathetic ganglia (corresponding to L1-2 spinal levels) [23]. Preservation of the L2 and/or L3 lumbar splanchnic nerve in retroperitoneal lymph node dissection of testicular cancer allows preservation of ejaculatory function [28]. Partial interruption of the pathway from the spinal cord to the seminal tract would be expected to cause insufficient closure of bladder neck and retrograde ejaculation. Complete interruption of the pathway is likely to cause failure of emission.

The anatomical architecture of the peripheral sympathetic nervous system suggests probable cross-innervation and has been confirmed in the dog and rat [29]. 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 probably provide a bilateral innervation to postganglionic neurons in the pelvic plexuses, which also exhibit crossing to the bilateral vasa deferentia [29].

The pudendal nerve arises from the S2-4 segments of the sacral spinal cord and does not enter the pelvic plexus, but exits the pelvis through the greater sciatic foramen, re-enters it through the lesser sciatic foramen, and innervates the perineal striated muscles (Fig. 1). Rhythmic contractions of these perineal striated musculature including the bulbocavernous and ishiocavernous muscles, propels the seminal fluid. Sacral spinal cord injury patients usually show dribbling ejaculation due to the lack of contribution of the musculature.

Ejection is controlled by the parasympathetic nervous system. Efferent somatic fibres emerge from the anterior horn of the S2-S4 spinal segments
(Onuf’s nucleus), and travel in the motor branch of the pudendal nerve to innervate the pelvic floor striated muscles including the bulbospongiosus and bulbocavernous muscles. Rhythmic contractions of the bulbocavernous, ischiocavernous and other pelvic floor striated muscles propel seminal fluid into the urethra. These muscles are innervated by the pudendal nerve and show excitement during ejaculation. Shafik 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 distinct reflexes.[30] The glans-vasal reflex is responsible for the emission phase and the urethromuscular reflex is responsible for the ejection phases of ejaculation. In a further study in dogs, Shafik reported increased electrical activity of the pelvic floor muscles and external anal (EAS) and urethral sphincters (EUS) during electroejaculation [31]. He suggested that the increased puborectalis muscle activity might express the prostatic secretions into the posterior urethra, that levator ani contraction elevates the prostate and partially straightens the prostatic-membranous urethral kink that might occur during erection and that the EAS and EUS contractions are believed to abort the urge to defecate or urinate and prevent leak of faeces, flatus, or urine during coitus. The rhythmic EUS contraction at ejaculation might act as a «suction ejection pump,» sucking the genital fluid into the posterior urethra while being relaxed and ejecting it into the bulbous urethra upon contraction.

The marked elevation of blood pressure, tachycardia, tachypnoea and perspiration that accompanies ejaculation are probably elicited by catecholamines secreted from the adrenal medulla. The adrenal medulla receives sympathetic nerves via the thoracic sympathetic plexuses of the gut and as an autocrine hormone when secreted by the enterochromaffin cells in the gastrointestinal tract [37]. Peripheral 5-hydroxytryptamine acts as a vasoconstrictor, platelet aggregator when released from platelets, a neurotransmitter in the enteric plexuses of the gut and as an autocrine hormone when secreted by the enterochromaffin cells in the gastrointestinal tract, pancreas and elsewhere [38]. Circulating 5-HT is unable to enter the brain as it cannot cross the blood-brain barrier.

Eighty percent of the total body serotonin is found in the enterochromaffin cells of the gut by Erspamer in 1940 [34]. This factor was subsequently structurally identified as 5-hydroxytryptamine (5-HT), found to be identical to the serum vasoconstrictor and called serotonin [35, 36].

II. NEUROCHEMICAL CONTROL OF EJACULATION

Dopamine and serotonin are important neurotransmitters in the brain. Many studies have been conducted to investigate the role of the brain in the development and mediation of sexuality, and dopamine and serotonin have been identified as essential neurochemical factors.

1. DOPAMINERGIC CONTROL

It has been known for a long time that treatment with dopaminergic drugs has a significant effect on the sexual behaviour of rodents. Kimura et al. attributed the dopaminergic system, particularly that in the anterior hypothalamus, with a sexual facilitatory role [32]. Gessa & Tagliamonte proposed the «dopamine positive-serotonin negative» hypothesis [33]. However, dopamine-serotonin balance is more complex as evidenced by the paradoxical hypersexuality of spontaneous involuntary orgasm reported with some members of the selective serotonin re-uptake inhibitor (SSRI) class of anti-depressant drugs.

Five types of dopaminergic receptors have been identified. On a pharmacological basis, these subtypes have been divided into two families: the D1- and D2- family. The D2 family has the most important therapeutic role and the D1- family might have an important modulating effect on the D2-receptors. 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 oestrous female, and progressively increases during copulation eventually triggering ejaculation [15]. In addition, electrical stimulation of the MPOA, even in the absence of genital stimulation, also elicits the urethrogenital reflex in rats, resulting in sequential firing of the hypogastric, pelvic, and motor pudendal nerves and rhythmic contractions of the perineal muscles, similar to those seen during orgasm in humans.

2. SEROTONERGIC CONTROL

Whereas dopamine, via D2 receptors, promotes seminal emission/ejaculation, serotonin is inhibitory. A potent vasoconstrictor, subsequently identified as serotonin, was first identified in the blood more than 100 years ago. An endogenous factor, enteramine was found in the enterochromaffin cells of the gut by Erspamer in 1940 [34]. This factor was subsequently identified as 5-hydroxytryptamine (5-HT), found to be identical to the serum vasoconstrictor and called serotonin [35, 36].
mical techniques. More recently, the development of antibodies against 5-HT and autoradiographic techniques have permitted identification of detailed 5-HT receptor locations [39]. In 1979, Peroutka and Snyder first identified different 5-HT receptors using radioligand binding technology. Currently, at least 16 different receptors have been characterised, e.g. 5-HT1a, 5-HT1b, 5-HT2a, 5-HT2b, etc [40]. Although the function and localization of many of these receptors is becoming increasingly clear, much remains unknown.

Serotonergic neurons are widely distributed in brain and spinal cord and are predominantly found in the brainstem, raphe nuclei and the reticular formation. There are two different groups of serotonergic neurons. A rostral group with cell bodies located in the midbrain and rostral pons project their axons into the forebrain. A second caudal group of serotonergic neurons with cell bodies in medulla project their axons into spinal cord [124]. The rostral part of the 5-HT system comprises the caudal linear nucleus, the dorsal and median raphe nuclei and the reticular formation of the pons and midbrain. The caudal system contains the nuclei raphe magnus, pallidus and obscurus, the adjacent reticular formation, solitary nucleus and the nucleus subcoeruleus [41].

The ascending projections from the rostral 5-HT neurons comprises two parallel but functionally and morphologically distinct pathways [41]. Projections that arise from the median raphe nucleus and are called the «basket-axon» system, comprise thick fibres (M-fibres) that branch into short, thin fibres and form multiple, large, round boutons (varicosities) and extensive synapses. The second system arises from the dorsal raphe nucleus and has thin fibres (D-fibres) which branch extensively and are characterised by multiple fusiform-like boutons (varicosities) which do not seem to contain any synaptic structures. Both systems are extensively distributed throughout the brain. In the cerebral cortex, both M- and D-fibres co-exist whereas the striatum receives only fine D-fibres and the gyrus dentatus primarily receives the thick M-fibres. The caudal raphe nuclei project to the caudal brain stem and spinal cord. The raphe magnus nucleus predominantly projects to the dorsal horn of the spinal cord. The nuclei pallidus and obscurus project to the ventral horn, intermediate zone and the intermediolateral cell column of the thoracolumbar and sacral spinal cord. Most of the afferent projections to the caudal raphe nuclei arise from the mesencephalic periaqueductal grey area and the medial cell groups of the hypothalamus and pre-optic area, the so called «limbic system» [42].

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 5). Each of these mechanisms is a negative feedback system which reduces synaptic cleft 5-HT and prevents over-stimulation of the postsynaptic receptors. Somatodendritic 5-HT1A autoreceptors are found in high concentrations on the cell bodies and dendrites of serotonergic neurons in raphe nuclei. They are activated by endogenous 5-HT and cause a reduction in firing rate of 5-HT neuron and reduced 5-HT neurotransmission. This endogenous 5-HT probably originates from somatodendritic release as opposed from synaptic release. Administration of the selective 5-HT1A receptor agonist, 8-OH-DPAT, to rats lowers central 5-HT levels and causes male rats to ejaculate at the first or second intromission. Activation of 5-HT1A receptors is attenuated or blocked by activation of 5-HT2C receptors. Presynaptic 5-HT1B 1D autoreceptors also inhibit 5-HT release into synaptic cleft. This receptor is linked to an inhibitory (GI protein) transaction mechanism which blocks the release of 5-HT and blocks the release of 5-HT from axonal vesicles, the exact mechanism of which has yet to be identified.

Large numbers of 5-HT transporters (5-HTT) are located predominantly on axonal terminals but also
reported that activation of 5-HT1A receptors in male rats with a selective agonist shortens the ejaculatory latency time [46]. Hillegaart et al. recently confirmed this but also reported that activation of 5-HT1B receptors inhibited male rat ejaculatory behaviour [47]. Berendsen demonstrated that activation of 5-HT1A receptors is attenuated or blocked by activation of 5-HT2C receptors [48]. More recently, Rehman et al. suggested that 5-HT1A receptors at different locations (brain, raphe nuclei, spinal cord and autonomic ganglia) may modulate rat sexual behaviour in opposing ways [49].

3. GABAergic Control

Several studies have identified an inhibitory and regulatory role in sexual functioning in rats of gamma-amino-butyric acid (GABA). Administration of GABA or compounds that induce elevated levels of GABA in the cerebrospinal fluid inhibits sexual behaviour. Elevated CSF GABA levels have been demonstrated during the post ejaculatory interval in male rats and during weaning in female rats also suggesting an inhibitory role. Benzodizepines, used in the treatment of anxiety, are believed to exert their effect through enhancement of GABAergic neurotransmission. Diazepam inhibits sexual behaviour in male rats, suggesting a possible mechanism for anxiety induced psychogenic sexual dysfunction [19].

It is estimated that 30-40% of neurons in the CNS use GABA as their primary neurotransmitter. GABA-receptors are divided into two classes on a pharmacological basis: GABA⁰ and GABA⁰. GABA-receptors are distributed throughout the CNS, and it is estimated that 30-40% of neurons in the CNS use GABA as their primary neurotransmitter. GABA⁰ receptors are probably tonically (and constantly) activated, while GABA⁰ receptors are activated only under certain physiological situations. Activation of a GABA receptor has an inhibitory effect on the target neuron, such that a higher concentration of other neurotransmitters (e.g. dopamine, serotonin) is required to achieve a neurotransmission of the same intensity.

GABA⁰ agonists inhibit sexual behaviour as evidence by a reduced number of mounts and intromissions when these drugs are administered systemically or locally in to the medial pre-optic area [50]. GABA⁰ antagonists, on the contrary, have no effect on sexual behaviour when administered systemically but when administered by micro-injection direct in to the medial pre-optic area have a positive sexual

on the serotonergic cell bodies and its dendrites and glial cells. As 5-HT is released into the synaptic cleft from pre-synaptic axonal vesicles, 5-HT transporters re-uptake and remove 5-HT from the synaptic cleft, preventing over-stimulation of the postsynaptic receptors. After blockage of 5-HT transporters by selective serotonin re-uptake inhibitor class drugs (SSRIs), synaptic cleft 5-HT increases but is counteracted by activation of 5-HT1A autoreceptors which inhibit further 5-HT release.

The cerebral serotonergic (5-HT) system exerts an inhibitory role on ejaculation and male sexual activity in the rat model. Serotonin is released in the anterior lateral hypothalamus (LHA) of male rats at the time of ejaculation [43]. In 1969, Tagliomonte and Gessa reported that the serotonin depletor, P-chlorophenylamine (PCPA) promoted aggression, insomnia and aberrant, often compulsive hypersexual behaviour in rats suggesting that the cerebral serotonergic (5-HT) system exerts an inhibitory role on male sexual activity in the rat model [44]. Micro injection of a selective serotonin reuptake inhibitor (SSRI) into the LHA delayed both the onset of copulation and also delayed ejaculation after copulation had begun [43]. This parallels the reported adverse effects of the SSRI class of antidepressant drugs, which include decreased libido and delayed ejaculation/orgasm. Kondo and Yamanouch localised this inhibitory action to serotonergic neurons in the median raphe nucleus [45]. Lorrain et al. suggested that the observed increase in extracellular 5-HT in both the anterior lateral hypothalamus and MPOA of male rats following ejaculation, may inhibit subsequent ejaculation and is responsible for the ejaculatory refractory period [43]. The post ejaculatory decrease in libido may result in part from decreased dopamine release in the nucleus accumbens, a major terminal of the mesolimbic dopamine tract [16]. Dopamine in the nucleus accumbens has been related to motivation and/or reward related to numerous behaviors, including eating, drinking, copulation, and drug addiction. Therefore, one site at which SSRIs may inhibit both libido and ejaculation is the LHA. While the N. accumbens probably mediates the SSRI-induced decrease in libido, it probably does not influence ejaculation directly. The structure mediating that effect is not known; however, neurons from the LHA do descend to the lumbar spinal cord, where the neurons controlling genital reflexes reside.

Different 5-HT receptor subtypes may have opposing effects on sexual function. In 1981, Ahlenius

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Peripheral or central neurotransmission is essential in ejaculation, it is difficult to conclude whether peripheral or central neurotransmission is essential in determining the direction of the effect. It is reasonable to conclude that a cholinergic-adrenergic balance is essential to keeping sexual functions in balance. As such priapism has been reported as an adverse effect of alpha-adrenergic blockade with the alpha-1 antagonists prazosin especially if cholinergic activity is reduced or eliminated at the same time [51]. Prazosin has also been shown to increase the ejaculatory latency time and the post ejaculatory interval in both rats and humans.

4. Cholinergic control

Cholinergic receptors are divided into two classes: muscarinic and nicotinic receptors. Although both are found in almost all parts of the human body, the nicotinic receptor is seen in particularly high concentrations at the neuromuscular junction, autonomic ganglia and in the brain. Through its effect on cognition and blood flow via its action on the cholinergic system of the forebrain, nicotine regulates and/or coordinates a large array of central nervous system functions.

Administration of nicotinic receptor agonists such as nicotine or carbachol or phystostigmine, anti-cholinesterase inhibitor, potentiates cholinergic neurotransmission and results in a reduction of sexual behaviour in rats. Low doses of nicotine have been reported to cause elevated levels of serotonin in the brain. As previously described, enhanced serotonergic neurotransmission most often results in an inhibition of sexual behaviour. Cholinergic antagonists such as atropine or scopolamine, exert an inhibitory effect on sexual behaviour. Micro-injection of scopolamine into the ventricles of the brain, prolongs initiation of copulation and reduces the number of intromissions and ejaculation in rats [50]. Micro-injection of the cholinergic agonists oxotremorine or carbachol into the MPOA causes a stimulation of sexual behaviour in male seen as reduced ejaculatory latency time.

5. Adrenergic control

The wide distribution of adrenergic receptors throughout the peripheral and central nervous system makes the adrenergic nervous system an essential part of the mechanism that controls many different physiological functions including sexual function. In the CNS, alpha-adrenergic receptors are present throughout the brain, while beta-1 and -2 receptors are found only in the cortex and cerebellum. Although noradrenaline effects both erection and ejaculation, it is difficult to conclude whether peripheral or central neurotransmission is essential in determining the direction of the effect. It is reasonable to conclude that a cholinergic-adrenergic balance is essential to keeping sexual functions in balance. As such priapism has been reported as an adverse effect of alpha-adrenergic blockade with the alpha-1 antagonists prazosin especially if cholinergic activity is reduced or eliminated at the same time [51]. Prazosin has also been shown to increase the ejaculatory latency time and the post ejaculatory interval in both rats and humans.

6. Nitric oxide

Nitric oxide (NO) is becoming recognized as one of the important intracellular messengers in the brain [52,53]. Several authors have reported that NO might be involved in the regulation of emotional and behaviour [54-56]. There is a possibility that brain NO is involved in regulating male rat sexual behaviour. Mellis reported the role of NO in a specific brain area on male copulatory behaviour, especially penile erection [57, 58]. Sato et al. investigated the influence of the extracellular nitric oxide (NO) level on male rat copulatory behaviour [59]. Micro-injection of the NO precursor, L-arginine into the MPOA, induced significant elevations of extracellular NO and a increased male copulatory behaviour with significant increase in mount rates. Microinjection of the NO synthase inhibitor N-monomethyl-L-arginine (L-NMMA) significantly reduced NO levels and inhibited copulatory behaviour. These findings suggested that the elevation of extracellular NO in the MPOA facilitates male copulatory behaviour of rats, whereas the decrease of NO reduces their copulatory behaviour.

There is a possibility that NO facilitates male copulatory behaviour through acceleration of dopamine release, Lorrain and Hull reported that micro-injection of the NO precursor, L-arginine, into the MPOA, increased the extracellular dopamine level[60] Moreover, they showed the possible role of CGMP/NO pathway in the control of dopamine release during copulation [61]. They suggested that NO may play a role in control of male copulatory behaviour and temperature regulation through the modulation of monoamine release. L-Glutamate elicits an intracavernous pressure increase in the MPOA [62]. It increases NO production by activation of NMDA receptors. This suggest that NO in the MPOA directly promotes penile erection, and supports a biological role of NO in the MPOA for positive mediation of male sexual behaviour.

Hull et al. demonstrated that microinjection of the
NO synthase inhibitor, N-nitro-L-arginine methyl ester (NAME) decreased the number of erections, but also increased the number of seminal emissions and decreased the latency to the first seminal emission [63]. The results indicate that not only does nitric oxide promotes erection in intact male rats, but may also inhibit seminal emission, probably by decreasing sympathetic nervous system activity. Kriegsfeld reported that mice homozygous for eNOS gene deletion have striking ejaculatory anomalies [64]. A significantly higher percentage of eNOS gene deletion mice than normal controls ejaculated during the testing period, requiring less stimulation and few mounts and intromissions.

Intraperitoneal injection of pilocarpine caused a dose-related seminal emission adult male rats [65]. The seminal emission response to pilocarpine was greatly reduced in atropinized animals, suggesting a cholinergic effect. N-nitro-L-arginine methyl ester (NAME), a nitric oxide synthesis inhibitor, inhibited the pilocarpine-induced seminal emission, which was reversed by L-arginine or by coinjection of sodium nitroprusside. These results suggest that nitric oxide mediates the inhibitory neurotransmission responsible for seminal emission in pilocarpine stimulated rats.

Consistent with this, Ferrari et al. have demonstrated that the specific type V isoenzyme phosphodiesterase inhibitor, sildenafil, modifies central DA-mediated behaviour in rats [66]. They also reported that sildenafil diminished both the ejaculation latency and the inter-intromission interval in normal rats [67]. Following castration, the effect of sildenafil on copulatory function was not observed but as restored following testosterone replacement.

It is also known that testosterone is fundamental for a normal mating pattern, which is totally disrupted by castration and can be restored by the replacement of the hormone. It has been suggested that testosterone-induced activation is linked to increased synthesis and/or release of DA in the brain and NO could be the bridge between testosterone and DA for copulatory behaviour [68].

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**B. THE EFFECTS OF DRUGS ON ORGASM AND EJACULATION**

**I. ANIMAL STUDIES**

Male rat studies (Table 2) 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 and 5-HT1A 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 [255].

However, 2,5-dimethoxy-4-iodophenyl-2-aminopropane, which equally stimulates 5-HT2A and 5-HT2C receptors, also increases ejaculation latency [256], whereas the selective 5-HT2A receptor agonist 2,5-dimethoxy-4-methylamphetamine does not have this effect [255]. 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 resulted in shorter ejaculation latency [255].

Administration of selective serotonine 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 [124]. Initially, the 5-HT level is only mildly increased, but due to desensitisation of the 5-HT1A and 5-HT1B/1D autoreceptors, 5-HT levels in the synaps increase highly. The higher levels of 5-HT consequently activate the postsynaptic 5-HT2C and 5-HT1A receptors [124,257]. Acute administration of clomipramine and SSRIs does not lead to a significant change in sexual behavior of male rats [258]. However, chronic administration with fluoxetine [259] and paroxetine [260] significantly delays ejaculation latency time 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 Waldinger et al. [124, 126, 261] formulated the hypothesis that in men with early ejaculation there is a hyposensitivity of the 5-HT2C and/or hypersensitivity of the 5-HT1A receptor. 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 find an answer 2 human studies with the 5-HT2C blocking antidepressants nefazodone [181] and mirtazapine [182] 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 a significant delay after 20 mg paroxetine daily and 50 mg sertraline daily. In a similar study the 5-HT2C/5-HT3 receptor antagonist and noradrenergic and specific serotonergic antidepressant mirtazapine did not induce ejaculation delay compared with the significant delay resulting from 20 mg paroxetine daily and 50 mg sertraline daily. In both studies nefazodone and mirtazapine did not delay ejaculation. Further studies with selective 5-HT2C and 5-HT1A agonist and antagonists are encouraged to elucidate still undiscovered pharmacological mechanisms underlying the ejaculatory process.

### II. HUMAN STUDIES (Table 3)

<table>
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<tr>
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<td>Waldinger MD, Berendsen HHG, Blok BFM et al</td>
<td>Animal</td>
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</tr>
<tr>
<td>126</td>
<td>Waldinger MD, Olivier B</td>
<td>Animal</td>
<td>1A</td>
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<td>Mos J, Mollet I, Tolboom JT, Waldinger MD, Olivier B</td>
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<td>Waldinger, M. D., Zwinderman, A. H., Olivier, B</td>
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</tbody>
</table>

### III. SIDE EFFECTS OF SPECIFIC DRUGS ON EJACULATION

#### 1. 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” on 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 [262].

#### 2. 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 [263]. 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
<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>DRUG</th>
<th>MECHANISM OF ACTION</th>
<th>EFFECT ON EJACULATION: ORGASM</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Decrease Latency</td>
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<tr>
<td>ANALGESICS</td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>N.S.A.I.D’S</td>
<td>Naproxen</td>
<td>Inhibition of cyclooxygenase (inhibition of prostaglandine synthesis)</td>
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<tr>
<td>Opioids</td>
<td>Meclizine</td>
<td>Agonistic activity (inhibition of activity in locus coeruleus - nucleus related with anxiety and fear)</td>
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<td>ANTIHYPERTENSIVES</td>
<td>Phenoxymethamine</td>
<td>Agonistic activation 1 adrenergic receptors</td>
<td>X</td>
</tr>
<tr>
<td>Alpha blockers</td>
<td>Labetolol</td>
<td>1 adrenergic blockade</td>
<td>X</td>
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<tr>
<td></td>
<td>Bynonol</td>
<td>1 adrenergic blockade</td>
<td>X</td>
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<tr>
<td></td>
<td>Captopril</td>
<td>1 adrenergic blockade</td>
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<td></td>
<td>Guanethidine</td>
<td>Sympathetic blockade (by noradrenaline depletion)</td>
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<tr>
<td></td>
<td>Methylsene</td>
<td>Central 1 adrenergic agonistic action</td>
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<td></td>
<td>Reserpine</td>
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<td>ANTI-PARKINSONISM</td>
<td>Levodopa</td>
<td>Agonistic action in dopaminergic receptors and residual agonist in α and β adrenergic receptors</td>
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<td>DRUGS</td>
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<tr>
<td>APPETITE</td>
<td>Levodopa</td>
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<td>SUPPRESSANTS</td>
<td>Pergolide</td>
<td>Potent agonistic D2 agonist</td>
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<td>CYTOTOXICS</td>
<td>Methotrexate</td>
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<td>X</td>
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<td></td>
<td>Vincristine</td>
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Table 3 Effects of drugs on ejaculation (CTD)

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<th>MECHANISM OF ACTION</th>
<th>EFFECT ON EJACULATION/ORGASM</th>
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<tr>
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<td>Cyproterone acetate</td>
<td>Antagonism of prostatic androgenic receptors</td>
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<td>Barbiturates (all)</td>
<td>Increase of parasympathetic tone</td>
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<tr>
<td>LITHIUM</td>
<td></td>
<td>Reduction of noradrenergic tone to coorticosteroid stimulation (blockage of IP₁ production)</td>
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<tr>
<td>PSYCHOPHARMACEUTICALS</td>
<td>SSRI's</td>
<td>Increase of serotonergic tone, especially by agonistic action in 5HT₂ and 5 HT₃ receptors</td>
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<td></td>
<td>Tramadol</td>
<td>Blockage α₁ adrenergic</td>
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<td></td>
<td>MAOIs</td>
<td>Increase of serotonergic and noradrenergic tone</td>
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<td>Isosorbosid</td>
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<td>Phenelzine</td>
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<td>Triazolmepine</td>
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<td>Pipodazine</td>
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<td>MECHANISM OF ACTION</td>
<td>EFFECT ON EJACULATION/Orgasm</td>
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<td>Thiosanthenes</td>
<td>Chlorprothixene</td>
<td>Blockage of dopaminergic receptors and residual blockage of α₁ adrenergic receptors</td>
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<td>Chlorpromazine</td>
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<td>Thioperidol</td>
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<td>Tamsulosin</td>
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<tr>
<td>Alpha reductase inhibitors</td>
<td>Finasteride</td>
<td>5 Alpha reductase-2 inhibition leads to decrease of prosthetic DHT (dihydrotestosteron)</td>
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<td>RECREATIONAL DRUGS</td>
<td>Alcohol</td>
<td>Increase of glibergic tone and blockade of NMDA receptors</td>
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<td>Amphetamine</td>
<td>Increase of noradrenaline and dopamine activity</td>
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<td>Anilintrite</td>
<td>Reduction of adrenergic tension in contractility of human seminal vesicle by NO-cGMP pathway</td>
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<td>MECHANISM OF ACTION</td>
<td>EFFECT ON EJACULATION/ORGASM</td>
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<tr>
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<td>Cocaine</td>
<td>Increase of catecholamines activity by noradrenaline and dopamine receptors</td>
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<td>Heroin</td>
<td>$\mu$ Agonistic activity (inhibition of activity in locus coeruleus – nucleus related with anxiety and fear)</td>
<td>Increase Latency X Absent Ejaculation X Retrograde Ejaculation X Spont. Ejaculation X Other X</td>
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<td>Marijuana</td>
<td>Activation of LBI receptors cannabinoidians</td>
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<td>Methadone</td>
<td>$\mu$ Agonistic activity (inhibition of activity in locus coeruleus – nucleus related with anxiety and fear)</td>
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<tr>
<td></td>
<td>Tobacco</td>
<td>Activity in cholinergic and noradrenergic transmission</td>
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ejaculation [263]. 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 seem to be important for sexual incentive motivation [264]. These conflicting results indicate that at least there is a role for the enkephalines in the modulation of sexual behavior in the male rat.

3. 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 less rats to display mounting behavior, and an increase in ejaculation latency in the responders [265]. 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.

4. GABA

The neurotransmitter gamma-aminobutyric acid (GABA) occurs in the brain tissue. Two distinct types of GABA receptors are recognized: GABA_A and GABA_B. 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 GABA_A receptor agonist) when given into the paraventricular nucleus of the hypothalamus reduce dose-dependently male rats sexual behavior [266].

5. 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 [267].

6. 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.

7. CYPROHEPADINE

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.

8. 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, lorazepam, temazepam, flunitrazepam, flurazepam, nitrazepam, chloridiazepoxide, 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 ansiolitic drugs [268].

9. 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 the intromitting and ejaculating behavior [269]. 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.

10. DOPAMINE ANTAGONISTS

Dopamine antagonists block central dopamine receptors and clinically used as antipsychotics or neuroleptics. Ejaculation may be prevented by centrally acting
dopamine receptor blockers such as pimozide, sulpiride and haloperidol [262,270]. Thoridazine, chlorpromazine delay ejaculation but also block adrenergic receptors [271]. Atypical neuroleptics such as risperidone and clozapine, that block dopamine and serotonin receptors, have been reported to delay ejaculation.

11. 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 [272-274].

12. 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 of these agents in the treatment of early ejaculation exists [275].

13. 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.[276] Tricyclic class antidepressants inhibit ejaculation in a dose dependent manner due to their anticholinergic and alpha-adrenergic antagonistic properties [89]. The influences of different drugs on ejaculation are delineated in Table 3.

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### C. PREMATURE EJACULATION (PE)

#### 1. DEFINING CRITERIA

Both DSM-IV-R and ICD-10 provide definitions of premature (early) ejaculation. Specifically, DSM-IV-R [69] defines premature (early) ejaculation as “the persistent or recurrent ejaculation with minimal stimulation 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. PE is not due exclusively to the direct effects of a substance (e.g., withdrawal from opioids).”

ICD-10 [70] 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 PE. Included in both is reference to three general criteria: short ejaculatory latency, 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.

#### 2. OPERATIONALIZING THE CRITERIA

Each of the three criteria above has been operationalized, although not always with consistency [71]. The first criterion—short ejaculatory latency—is typically operationalized by intravaginal ejaculatory latency time (IELT), defined by the number of seconds/minutes between vaginal intromission and
ejaculation, averaged over a number of attempts. ICD-10 indicates that latencies of 15 sec or less are consistent with a PE diagnosis. Other sources suggest latencies up to 60 sec—90% of ejaculations of men with this disorder occur within this timeframe [72] — or even up to two minutes [73] (Figure 6). IELT’s of 2 minutes or less show minor overlap with those of men without PE, which typically range from about 2 to 10 min. Accordingly, any latency under 2 min suggests a possible PE diagnosis.

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 criterion is yet undecided. The former strategy offers greater precision and less bias [72], perhaps with the downside of being intrusive and/or overemphasizing the weight of objectively quantified measures relative to patient’s subjective assessment of the problem. Interestingly, recent data indicate that estimations of IELT tend to over- rather than under-estimate ejaculatory latencies, suggesting a bias toward “misses” rather than “false positives.” Whatever method is used, IELT should be considered only one of several conditions important for a PE diagnosis.

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-R). 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 [74].

The second criterion—self-efficacy or the patient’s ability to control the dysfunctional response—distinguishes men who ejaculate rapidly because they are incapable of any other response 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 [75-77]. 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 mere 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 address 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

Figure 6 : Intravaginal ejaculation latency time (IELT) measured with stopwatch in 110 men with lifelong premature ejaculation, of whom 90% ejaculated within 1 minute after vaginal penetration, including 80% within 30 seconds. [72]
measures of general anxiety (e.g., BSI [78]), sexual functioning (e.g., GRISS [79]) or dyadic distress (Dyadic Adjustment Scale [80]) might also be included to further assist in operationalizing this criterion.

• Exclusionary factors

Both DSM-IV and ICD-10 definitions prescribe conditions that exclude an individual from a PE diagnosis. These include early ejaculation mediated by alcohol, substance use, or medication; a context that leads to very high levels of arousal because of novelty of partner or situation; and a low frequency of sexual activity.

3. Diagnostic subgroups

Given the lack of consensus (and supporting data) regarding possible etiologies of PE, it is not surprising that identification of clear subtypes of PE based upon cause has not been successful. Nevertheless, classification of PE into various subtypes based on developmental histories and response characteristics has sometimes proved useful. For example, most clinicians and researchers distinguish between lifelong and acquired PE, and between PE that is limited to specific situations or partners and that which is more global. Knowing that the patient has had a lifelong history of PE not specific to one partner may argue toward a biological and/or cognitive etiology. As such, the need to address interpersonal and relationship issues may be less important in these men. In contrast, knowing that the PE developed recently in specific situations and in conjunction with erectile dysfunction may suggest the need to address relationship issues and attend less to a biological etiology.

a) Relevant covariate conditions of men with PE

Men with high risk for PE often report other symptoms that characterize their condition, and these might be used to assist in identifying individuals with PE, particularly when they are not familiar with the nosological terminology employed in clinical settings. Such men may present their problem using language that reflects various other aspects of their dysfunctional experiences.

b) Penile sensitivity

Many PE men report a high level of penile sensitivity, although empirical data supporting such hypersensitivity is mixed [81-83]. Perceived hypersensitivity may reflect strong responsivity or low thresholds of the ejaculatory reflex as much as hyperresponsivity of sensory receptors in the penis.

4. Ejaculatory latency during masturbation

PE is defined primarily by ejaculatory latency and control during coital activity. Nevertheless, many PE men report short latencies during masturbation as well. Others, on the other hand, experience short latencies during intercourse but not masturbation [73]. Presumably men in this latter category are better able to control the timing of ejaculation during masturbation because they are less aroused and/or can exert more control over the intensity of penile stimulation. Alternatively, the absence of anxiety that emanates from the evaluative nature of psychosocial interactions surrounding intercourse may diminish or eliminate the conditions typically leading to early ejaculation.

5. Desynchronization of arousal and ejaculation

Ejaculation and orgasm typically define the high point of arousal within the sexual response cycle. Yet some PE men characterize their ejaculation as being unexpected, that is, occurring prior to their anticipated peak of arousal. Furthermore, there is evidence from psychophysiological analysis suggesting that in response to psychosocial stimulation, PE men report lower sexual arousal but closer proximity to ejaculation when compared to sexually-functional counterparts [73]. PE men may underestimate their level of arousal, or alternatively, may reach orgasm at submaximal arousal levels and prior to their anticipated peak arousal.

6. Dissociation of semen expulsion and somatic contractions

Ejaculation involves the dual responses of sympathetically-controlled emission of semen mediated through prostate function and bladder neck closure and somatically-controlled expulsion of semen through rhythmic contractions of the bulbocavernosal and anal sphincter musculature. The former response, which is associated with ejaculatory inevitability, typically acts as the stimulus for the second reflex response, which is primarily associated with the experience of orgasm. A limited subset of PE men not only report short latencies to ejaculation, but also fail to experience the full complement of somatic contractions, with the resulting consequence of semen dribbling from the penis. Although this condition is sometimes associated with acetylcholine inhibitors, it has been know to occur in the absence of medications as well.
7. CO-EXISTING ERECTILE DYSFUNCTION

A significant number of men with PE also report having problems achieving and/or maintaining an erection, estimated as high as 30% [77]. Typically, these men ejaculate without a full erection, with penile tumescence reaching a maximum—although less than complete erection—at the moment of ejaculation. The extent to which these co-existing dysfunctions are either independent or interrelated is unknown, although careful analysis of the developmental histories of each problem may assist in devising an appropriate treatment strategy.

8. FREQUENCY OF EJACULATION

Self-reported frequency of ejaculation/orgasm has been related to short ejaculatory latencies, with PE men exhibiting lower frequencies of sexual activity and orgasm relative to sexually functional counterparts [84-86]. Both ICD-10 and DSM-IV-R exclude men from the diagnosis who ejaculate rapidly due to infrequent sexual activity. Presumably, lower frequencies in PE men lead to shorter IELT’s because arousal levels may be unusually high and the normal inhibition of ejaculation caused by the male refractory period plays a diminished role.

II. THE ETIOLOGY OF PREMATURE EJACULATION

Historically, attempts to explain the etiology of early ejaculation has included a diverse range of biogenic and psychological theories (Table 4). Most of these proposed aetiologies are not evidence based and are speculative at best. Psychological theories include the effect of early experience and sexual conditioning, anxiety, sexual technique, the frequency of sexual activity and psychodynamic 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 inadequate definitions used, is a common flaw in the majority of these studies.

1. ANXIETY

Anxiety has been reported as a cause of PE by multiple authors and is entrenched in the folklore of sexual medicine as the most likely cause of PE despite scant empirical research evidence to support any causal role [86-90]. Several authors have suggested that anxiety activates the sympathetic nervous system and reduces the ejaculatory threshold as a result of an earlier emission phase of ejaculation [87, 89]. Strassberg et al. (1990) used a multivariate definition of PE incorporating both latency and control dimensions and failed to demonstrate any difference in sexual anxiety between a control group of men with normal ejaculatory control and men with PE [91]. Kockott reported that men with PE and low levels of sexual anxiety ejaculated rapidly during both intercourse and solitary masturbation [92]. Men with PE and high levels of sexual anxiety, however, ejaculated rapidly only during sexual intercourse and had superior ejaculatory control during solitary masturbation. This study contained several methodological flaws which make interpretation of results difficult. Anxiety was only measured during sexual intercourse and not during solitary masturbation and was subjectively self evaluated by the patient and not by an objective validated inventory. Furthermore, anxiety levels in a control group of men with normal ejaculatory control were not examined.

Isolated anecdotal reports suggest a potential role for anxiolytic medication in the treatment of PE. Segraves (1987) reported the successful treatment of a 71-year-old man with primary PE with the benzodiazepine, lorazepam whereas Cooper and Magnus (1984) failed to distinguish any difference in ejaculatory latency times of men with PE at baseline or following treatment with beta-blocking drug, propranolol or placebo [93, 94].

The possibility that high levels of anxiety and exces-
sive concerns about sexual performance and potential sexual failure might distract a man from monitoring his level of arousal and recognising the prodromal sensations that precede ejaculatory inevitability has been suggested as a possible cause of PE by several authors [88,90,95]. The causal link between anxiety and PE is speculative, is not supported by any empirical evidence and is in fact contrary to empirical evidence from other researchers. No difference in either subjectively or objectively measured sexual arousal or sexual sensory awareness was found between men with PE and men without PE in a laboratory setting [85,91,96]. In direct contradiction to this theory, Kockott et al. found that men with severe PE demonstrated higher objective and subjective measures of arousal than men with erectile dysfunctions or normal control subjects [92, 97]. This study was limited, however, to solitary stimulation without ejaculation making extrapolation of results to ejaculation during sexual intercourse difficult. All published studies ignore the possibility that the presence of anxiety in men with PE may just as likely be the result of PE as the cause and fail to establish the direction of the presumed causal relationship.

2. EARLY SEXUAL EXPERIENCE
Masters and Johnson were the first of several researchers to suggest that early sexual experiences characterized by anxiety and rush might condition men to develop a subsequent pattern of early ejaculation [86,98]. However, no empirical evidence was offered to support this hypothesis and no distinction was made between men with lifelong PE and men with acquired PE. All researchers failed to recognise that anxiety and rush define the early sexual experiences of most men. Furthermore, the early sexual histories of a control group of men with subsequent normal ejaculatory control were not examined to determine whether early conditioning experiences are unique to men with PE. Williams reported a small cases series of four men with acquired PE and suggested that some men might initially condition themselves to ejaculate quickly due to their perception that their partner was sexually disinterested, and remain subsequently unable to control ejaculation when the initial negative circumstances were no longer present [89]. The resultant sexual anxiety and concern about the legitimacy of the partner’s renewed sexual interest might serve to maintain the PE.

3. FREQUENCY OF SEXUAL INTERCOURSE
The evidence to support a link between ejaculatory control and frequency of sexual activity is conflicting. Speiss reported that the frequency of sexual activity in men with PE is lower than age-matched controls with normal ejaculatory control whereas Strassberg failed to demonstrate any relationship [85,96]. The mechanism of this relationship is yet to be characterised but may include reduced performance anxiety, a higher ejaculatory threshold or superior ejaculatory control due to earlier and superior recognition of prodromal ejaculatory sensations. Consistent with these observations, McMahon and Touma in a placebo controlled cross-over study of the efficacy of paroxetine in treating PE, reported that the pre-treatment frequency of sexual intercourse increased from 0.5 to 3.2 times per week with paroxetine but fell to pre-treatment levels with placebo [99]. The observation that men with PE may develop a pattern of sexual avoidance may also explain this reduced frequency of sexual intercourse indicating that the polarity of the relationship between PE and frequency of sexual activity remains undetermined [97].

4. EJACULATORY CONTROL TECHNIQUES
Zilbergeld suggested that some men with adequate ejaculatory control might consciously learn a variety of effective sexual techniques for deferring ejaculation during their early sexual experiences and unconsciously continue to use those techniques subsequently [88]. These techniques may include thought distraction, pelvic floor muscle contraction or alteration of the speed and /or depth of penile vaginal thrusting. Data to support this hypothesis is weak and studies to evaluate the use and effectiveness of control techniques in men with PE is lacking.

• Evolutionary
Hong suggested that PE was the result of evolutionary natural selection, arguing that rapid intercourse allowed insemination of more females with transmission of a possible genetic basis for PE to more offspring [100]. The observation that primate courtship and sexual contact are often extended is inconsistent with this hypothesis [101].

5. PSYCHODYNAMIC THEORIES
Abraham was the first to suggest a psychodynamic basis of PE. He theorised that PE was the adult manifestation of unresolved and excessive narcissism during infancy which resulted in exaggerated importance being placed on the penis and the associated pleasure of urination [102]. He offered no empirical
basis for this theory and subsequent studies by other authors have failed to demonstrate any evidence for his narcissism hypothesis [103]. Kaplan initially theorised but later recanted a link between male anger and hostility towards women and PE, suggesting that the man both symbolically «soils» the woman and denies her sexual pleasure as a result of an unconscious, deep-seated hatred of women [87, 95].

6. PENILE HYPERSENSITIVITY

Multiple authors have proposed that men with PE have hypersensitive penis’ and either reach ejaculatory threshold more rapidly or have a lower ejaculatory threshold than men with normal ejaculatory control [91,102-104]. A limitation of the universal applicability of this theory is its inability to explain acquired PE.

Xin et al. demonstrated that men with early ejaculation have lower biothesiometric vibration perception thresholds and significantly shorter mean somatosensory evoked potential latency times of the glans and penile shaft than controls [82, 105]. Paick et al. and Rowland, however, were unable to reproduce these findings, reporting no significant statistical differences between normal controls and patients with primary early ejaculation [81,106]. Several authors have reported that penile sensitivity reduces with ageing [104,107,108]. This is probably due to loss of the fastest conducting peripheral sensory axons from the third decade, dermal atrophy, myelin collagen infiltration and pacinian corpuscle degeneration [106]. Some researchers have suggested this observation as the reason why PE is reported more often in younger men [90]. However, a more attractive explanation of this observation is the presence of greater anxiety and less frequent sexual activity in the absence of a long-term relationship resulting in fewer sexual opportunities to learn ejaculatory control. Fanciullacci et al. measured significantly higher amplitude cortical somatosensory evoked potentials following penile electrical stimulation in men with severe lifelong PE compared to control subjects [109]. They hypothesized that men with PE have a greater representation of the penile sensory nerve supply in the cerebral cortex than controls, and suggested this as an indication of an organic basis for PE. Consistent with this is the report by Bradley that the cortical distribution of the dorsal nerve of the penis is larger in men with lifelong PE [110]. Brain imaging with functional MRI and positron emission tomography is required in humans to identify the central control of the ejaculatory process in man.

Research in to the relationship between PE and penile hypersensitivity has effectively excluded the impact of other factors which may affect the level of arousal achieved and the time required to reach and the level of the ejaculatory threshold. These factors include the extent of use of fantasy and other forms of non-contact stimulation. If penile sensitivity were, in fact, a cause of PE, men with PE would be expected to ejaculate more quickly than controls only in situations where there was direct stimulation of the penis.

7. HYPER-EXCITABLE EJACULATORY REFLEX

Several authors have suggested that PE is due to a defective and early ejaculatory reflex with a faster emission and/or expulsion phase. Several authors have reported a link between PE and a malfunctioning bulbocavernosal reflex (BCR). The bulbocavernosus muscle (BCM) surrounds the urethral bulb and is one of several muscles responsible for the expulsive phase. This hypothesis lacks a firm physiological basis as the emission phase of the ejaculatory process has already started by the time the BCM contracts. Gospodinoff (1989) suggested that a faster bulbocavernosus reflex (BCR) might impede the process of learning to control ejaculation [111]. One of the most common treatments for PE, the squeeze technique, is based on the assumption that PE is due to a defective ejaculatory reflex [112]. Colpi et al. demonstrated that men with lifelong PE, defined as ejaculating within 15 thrusts of penetration, have higher amplitude sacral evoked potentials measured through perineal and perineal surface electrodes compared to age-matched controls [113]. He concluded that men with PE have a hyper-excitable BCR. However, the sacral evoked potential latency in men with lifelong PE did not differ from age-matched controls which is inconsistent with this conclusion. Similar results were reported by Fanciullacci et al [109]. A shorter BCR latency time in men with lifelong PE compared to men with acquired PE and normal controls was, however, reported by Gospodinoff [111]. Unlike Colpi et al., Gospodinoff’s study groups were not age matched and the cohort of men with acquired PE were 13 years younger than men with lifelong PE, suggesting that the difference in these two groups could be due to age-related degeneration of the afferent and efferent nerves of the BCR. In addition, men with acquired PE had a longer BCR latency time than controls which is at odds with the suggestion that PE is due to a hyper excitable ejaculatory reflex.
8. AROUSABILITY

Laboratory studies using solitary stimulation during audiovisual stimulation have failed to demonstrate greater, more frequent or more rapid arousal in men with PE compared to a control group of sexually non-dysfunctional men [85].

9. ABNORMAL LEVELS OF SEX HORMONES

Although there are several reports of a possible link between PE and levels of sexual hormones, a careful review of the published literature fails to confirm any causal link. Pirke failed to demonstrate any difference in the levels of free and total testosterone and luteinizing hormone (LH) during serial sampling between men with PE, ED or normal controls [114]. Cohen, however, reported that levels of free and total testosterone, LH and Follicle Stimulating Hormone (FSH) were reduced in men with PE. He also reported that 4 of 12 men with PE had elevated prolactin levels and suggested that PE may be the result of a hypothalamic-pituitary disorder [115]. He subsequently reported that pharmacological treatment of PE with a selective serotonin reuptake inhibitor (SSRI) class drug improved ejaculatory latency and elevated androgen and LH levels [116].

10. GENETIC PREDISPOSITION

A familial predisposition to early ejaculation was first reported by Schapiro in 1943 [103]. Waldinger reported that 10 of 14 first-degree male relatives of men with lifelong PE also suffered from PE with an IVELT of less than 1 minute [117]. Based on this small study, the odds ratio of a familial occurrence of PE far exceeds the incidence in the general community and supports Schapiro’s contention that PE may have a genetic basis.

11. 5-HT RECEPTOR SENSITIVITY

The current understanding of the functional neuroanatomy and the role of central serotonin and dopamine neurotransmission in ejaculation are based on male rat studies. The hypothalamic medial preoptic area (MPOA) and the medullary nucleus paragigantocellularis (nPGI) in the ventral medulla have pivotal roles in the central control of ejaculation [118,119]. Electrical stimulation of or microinjection of dopamine agonists into the medial preoptic area promotes ejaculation [120]. It has been suggested descending serotonergic pathways from the nPGI to the lumbosacral motor nuclei tonically inhibit ejaculation and that disinhibition of the nucleus paragigantocellularis results in ejaculation [20]. The prevalence of serotonergic neurons in the nPGI and the observation that selective serotonin re-uptake inhibitor class drugs inhibit ejaculation, suggests that the nPGI is a possible site of action of these drugs [22]. Coolen et al identified ejaculation initiated neural activation in several brain regions after ejaculation, including the posterodorsal medial amygdala, the posteromedial bed nucleus of the stria terminalis, and the medial parvicellular subparafascicular nucleus of the thalamus [121-123]. It is likely that afferent neurons ascend in the spinal cord to the medullary parvicellular subparafascicular nucleus and the other brain areas mentioned and activate ejaculation. These areas are extensively and reciprocally interconnected and probably form the basis of an ejaculation «brain circuit» [123].

Multiple dopamine and 5-HT receptor types have been identified. Studies using highly selective 5-HT receptor agonists and antagonists have identified a pivotal role of 5-HT2C and 5-HT1A receptors in the central control of ejaculation. Stimulation of the 5-HT2C receptors in male rats with non-selective 5-HT2C agonists such as d-lysergic acid diethylamide and quipazine, delays ejaculation [124]. Contrary to this, activation of postsynaptic 5-HT1A receptors by the selective 5-HT1A receptor agonist 8-hydroxy-2-(di-n-propylaminotetralin) in male rats facilitates ejaculation [125]. 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 [124]. They suggested that men with low 5-HT neurotransmission and probable 5-HT2C receptor hyposensitivity may have their ejaculatory threshold genetically «set» at a lower point and ejaculate quickly and with minimal stimulation and often prior to reaching their erectile threshold. Men with a genetically determined higher set point men can sustain more prolonged and higher levels of sexual stimulation and can 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 [126]. Treatment with an SSRI class drug will activate the 5-HT2C receptor, adjust the ejaculatory threshold set point and delay ejaculation. The extent of ejaculatory delay may vary widely in different men according to the dosage and frequency of administration of 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
III. PSYCHOLOGICAL TREATMENT OF PREMATURE EJACULATION

1. THE RATIONALE FOR PSYCHOLOGICAL/BEHAVIORAL STRATEGIES

Even though a physiological basis for some types of PE has been suspected for years [130,131], 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 [1,132] 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 five 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 [133].

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 [134,135], 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 [136, 137].

2. EPIRICALLY SUPPORTED PSYCHOLOGICAL APPROACHES

In addition to countering the current trend toward pharmacotherapeutic 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 falls 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 no 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 [138]. 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 [139,140].

Two 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 stop-squeeze method, developed by Semans [141] and later adopted by Masters & Johnson [86] in their sex therapy clinic. The second method, advocated by Kaplan [1], is the stop-pause method. Both methods suppress the urge to ejaculate by stopping sexual stimulation, but the former substitutes a squeeze of the glans penis for a pause in stimulation at the point of impending ejaculation.

- Details of successful psychological-behavioral methods of treatment for PE

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 [142]. 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% [143-145]. 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.

The start-stop behavioral approach to the treatment of PE men was developed by Kaplan [132] 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 stop-start method with marital therapy for couples who showed “resistance” (discussed below) during the treatment process was also quite successful in men with secondary early ejaculation [1,132]. Although Kaplan’s high success rates have been challenged, the differential procedures for patients with primary versus secondary appears to be a robust finding [145].

Detailed descriptions of both the stop-squeeze and start-stop behavioral methods have been provided in the literature [139,142,144], with different therapists emphasizing their own variations. Some therapists advocate using techniques such as slowing down, breathing deeply, or moving [144] in a circular fashion, techniques that many men without PE develop without conscious awareness [144]. 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 [142]. Still others emphasize the importance of providing the couple with accurate information about the sexual response cycle and its physiological underpinnings [146,147]. 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 [144,148].

3. PARAMETERS AFFECTING 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/stop methods and more to a lack of attention to the parameters and context surrounding the treatment. In addition, long-term compliance 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.

Beyond these broad factors described above, other parameters appear to maximize treatment efficacy with psychological-behavioral strategies.

4. 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 it unrealistic for most couples [142]. 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 symptomology [144]. In fact, such relapses are common in PE men. Yet, if the couple is not adequately prepared, the resulting setback can lead to sexual avoidance, the development of erectile dysfunction, and other adverse secondary effects. Strategies from the relapse prevention model [149], 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 [144,146]. 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.

5. 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 [142]. 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 format.

Data on group (vs. individual) treatment for early ejaculation are mixed. Some investigations have found the two formats equivalent whereas others have not [144]. 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 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 stop-pause techniques may be adapted to masturbation, especially when intensity of arousal is enhanced by adding a lubricant and using erotic literature or fantasy [139]. 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.


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 partner deceit is present; and where PE is the consequence of a major health problem [133]. 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 [135], that is, the attempted solutions contribute to rather than ameliorate the problem [150]. 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 counteracts 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 early 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 [135].

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].

7. 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 [91,132,151], 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 [152,153]. 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.

Recent research actually supports both possibilities [154]. For example, positive emotions such as pleasant/enjoyable increase in PE men 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 PE men, 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 [155].

8. 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[76,156]. 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 early ejaculation» than with one that specifically assesses «ability to control ejaculation (or its timing).»

IV. PHARMACOLOGICAL TREATMENT OF PREMATURE EJACULATION

1. Selective serotonin reuptake inhibitors (SSRIs) (Table 5)

In 1943 Bernard Schapiro [103] 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 form to treat early ejaculation. In 1973 the first report of successful ejaculation delay by clomipramine was published [157]. However, in the seventies and eighties of last century, drug treatment of early ejaculation was not very popular. The introduction of the selective serotonin reuptake inhibitors (SSRIs) meant a revolutionary change in the approach to and treatment of early ejaculation. Selective serotonin reuptake inhibitors encompass 5 compounds (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) with a similar pharmacological mechanism of action. In 1994 the first double-blind study was reported on the ejaculation delaying effect of paroxetine [158]. In the last decade all other SSRIs and clomipramine have repeatedly been investigated in their propensity to delay ejaculation [159-179]. There is some evidence that fluvoxamine and citalopram have less effect in delaying ejaculation than paroxetine, sertraline and fluoxetine [166,169,177].

Although the methodology of the initial drug treatment studies was rather poor, later double-blind and placebo-controlled studies replicated the genuine effect of clomipramine and SSRIs to delay ejaculation. In spite of a development towards more eviden-
For the interpretation of drug treatment studies it is important to bear in mind that the outcome values of the ejaculation time are dependent on both gender (e.g. assessment by the male or his female partner) and method (e.g. assessment by subjective reporting, questionnaire, or stopwatch) [72]. A recent systematic review and meta-analysis of all drug treatment studies [180], clearly demonstrated that single-blind and open design studies and studies using subjective reporting or questionnaires showed a higher variability in ejaculation delay than double-blind studies in which the ejaculation delay was prospectively assessed with a stopwatch. Of all 76 studies only 11 studies (14.4%) [94,164,169,177-179],[181-185] have been performed according to the established criteria of evidence based medicine [180].

Nevertheless, in spite of the inaccuracy of most drug treatment studies to assess the delay accurately, there are 3 drug treatment strategies to treat early ejaculation: 1) daily treatment with serotonergic antidepressants 2) as-needed treatment with antidepressants and 3) anaesthetic topical ointments

<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Author/s</th>
<th>Drug</th>
<th>Level Of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>76</td>
<td>Strassberg DS, de Gouveia Brazao CA, Rowland DL, et al.</td>
<td>Clomipramine</td>
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</tr>
<tr>
<td>94</td>
<td>Cooper AJ, Magnus RV</td>
<td>Propranolol</td>
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<td>99</td>
<td>McMahon CG, Touma K</td>
<td>Paroxetine</td>
<td>1B</td>
</tr>
<tr>
<td>156</td>
<td>Haensel SM, Rowland DL, Kallan KTHK, Slok AK</td>
<td>Clomipramine</td>
<td>1B</td>
</tr>
<tr>
<td>157</td>
<td>Eaton H.</td>
<td>Clomipramine</td>
<td>3B</td>
</tr>
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<td>158</td>
<td>Waldinger MD, Hengeveld MW, Zwinderman AH.</td>
<td>Paroxetine</td>
<td>1B</td>
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<td>Goodman RE</td>
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<td>Assalian P</td>
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<td>164</td>
<td>Althof SE, Levine SB, Corty EW et al</td>
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<td>165</td>
<td>Mendels J, Camera A, Sikes C.</td>
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<td>166</td>
<td>Kery S, Kozma A</td>
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<td>167</td>
<td>Kara H, Aydin S, Agargun Y</td>
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<td>168</td>
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<td>171</td>
<td>Biri H, Isen K, Sinik Z, Onaran M, Kupeli B, Bozkirli I</td>
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<td>172</td>
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<td>Kim SC, Seo KK</td>
<td>Fluoxetine, Sertraline, Clomipramine</td>
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<tr>
<td>175</td>
<td>Yilmaz Ugur, Tatlisem A, Turan H et al</td>
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<td>176</td>
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<td>Waldinger MD, Zwinderman AH, Olivier B</td>
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<td>178</td>
<td>Novaretti JPT, Pompeo ACL, Arap S</td>
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<td>179</td>
<td>Atmaca M, Kuloglu M, Tezcan E, Semercioz A</td>
<td>Citalopram</td>
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<tr>
<td>180</td>
<td>Waldinger MD</td>
<td>Meta-analysis</td>
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<td>183</td>
<td>Kara, H., Aydin, S., Yucel, M. et al</td>
<td>Fluoxetine</td>
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<td>185</td>
<td>Greco E, Polonia-Balbi P, Speranza JC</td>
<td>Levosulpiride</td>
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<td>186</td>
<td>Segraves RT, Saran A, Segraves K, Maguire E</td>
<td>Clomipramine</td>
<td>1B</td>
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<tr>
<td>187</td>
<td>Kim SW, Paick J-S</td>
<td>Sertraline</td>
<td>1B</td>
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</tbody>
</table>
a) Daily treatment with serotonergic antidepressants

Daily treatment can be performed with paroxetine (20-40 mg), clomipramine (10-50 mg), sertraline (50-100 mg) and fluoxetine (20-40 mg). Meta-analysis of all drug treatment studies has demonstrated that paroxetine exerts the strongest ejaculation delay. Paroxetine, sertraline and fluoxetine may give rise to side effects like fatigue, yawning, mild nausea, loose stools or perspiration. These side effects often start in the first week after intake and gradually disappear within 2-3 weeks. Ejaculation delay with daily treatment usually manifests itself at the end of the first or second week and sometimes even earlier. With the exception of fluoxetine, it is advised not to stop the SSRIs acutely but gradually within 3-4 weeks, in order to avoid withdrawal symptoms. Side effects of clomipramine may consist of nausea, dry mouth and fatigue. Sometimes clomipramine and the SSRIs may give rise to reversible feelings of diminished libido or moderate decreased rigidity of the penis. It is advised to inform patients about all aforementioned side effects when starting treatment.

b) On-demand treatment with antidepressants

Since 1993 only 8 studies [76,99,156,186-190] on as-needed (on-demand) treatment have been published. Due to this limited number of studies and to inadequate designs, a meta-analysis is insufficiently powered to provide final conclusions with regard to difference in efficacy and dose-relationships. In spite of these scientific limitations it has been found that clomipramine (10-50 mg) taken minimally 4-6 hours prior to intercourse may be efficacious lasting for at least 15 hours. Another strategy is the daily use of paroxetine, sertraline and fluoxetine in a low dose combined with as-needed higher doses shortly before intercourse.

Based on the rating of the Level of Evidence of the studies reviewed, treatment of early ejaculation with the SSRI class drugs, paroxetine, sertraline, fluoxetine and citalopram, and the serotonergic tricyclic antidepressant, clomipramine, has a Grade A recommendation.

2. Topical local anaesthetics (Table 6)

Application of the topical anaesthetics to the penis virtually abolishes the display of penile reflexes in rats [191]. Sachs and Liu demonstrated that division of the sensory branches of the pudendal nerves severely impaired the ability of male rats to achieve intromission, and hence ejaculation [192]. Weidner reported that ejaculatory response to penile vibrotactile stimulation in spinal cord injured men requires the presence of intact dorsal penile nerves [193].

The use of topical local anaesthetics such as lignocaine and/or prilocaine as a cream, gel or spray is well established and they appear moderately effective in retarding ejaculation, but do so at the price of possibly causing significant penile hypo-anaesthesia, and possible transvaginal absorption, resulting in vaginal numbness and resultant female anorgasmia unless a condom is used [194-198]. Atan et al. reported the combined use of fluoxetine and topical lidocaine in 43 men with PE. Seventy two percent of the fluoxetine treated improved as opposed to 83.3 % of the fluoxetine/lidocaine group [199].

Xin et al. reported significantly improved ejaculatory control in 89.2% of patients treated with SS-cream [200,201]. SS-cream is made with extracts from nine natural herbs - Ginseng radix alba, Angelicae gigantichis, Cistanchis herba, Zanthoxyl fructus, Torlidis semen, Asiasari radix, Caryophylli flos, Cinnamom cortex and Bufonis veneum. Some of these herbs have local anaesthetic properties. It is applied

Table 6. Level of Evidence - Drug Treatment for Premature Ejaculation – Topical Local Anaesthetics

<table>
<thead>
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<th>Reference No.</th>
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<td>184</td>
<td>Choi HK, Jung GW, Moon KH. et al</td>
<td>SS-Cream</td>
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<td>195</td>
<td>Atikeler, M. K., Gecit, I., Senol, F. A</td>
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<td>Damru, F</td>
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<td>Berkovitch, M., Keresteci, A. G., Koren, G</td>
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<td>208</td>
<td>Sahin et al</td>
<td>Prilocaine-lidocaine</td>
<td>3B</td>
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<td>209</td>
<td>Atan, A., Basar, M. M., Aydoganli, L</td>
<td>Fluoxetine, lidocaine</td>
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<tr>
<td>200</td>
<td>Xin, Z. C., Choi, Y. D., Choi, H. K</td>
<td>SS Cream</td>
<td>3B</td>
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<tr>
<td>201</td>
<td>Xin, Z. C., Choi, Y. D., Lee, S. H. et al</td>
<td>SS Cream</td>
<td>1B</td>
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<td>202</td>
<td>Xin, Z. C., Choi, Y. D., Seong, D. H. et al</td>
<td>SS Cream</td>
<td>1B</td>
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</tbody>
</table>
to glans penis 1 hour before and washed off immediately prior to coitus. Adverse effects were noted in 5.9% of patients which included mild local irritation and delayed ejaculation. Both the latency and amplitude of somatosensory evoked potentials measured at the glans penis were increased over baseline after the application of SS-cream [202].

Based on the rating of the Level of Evidence of the studies reviewed, treatment of early ejaculation with topical anaesthetics has a Grade A recommendation.

3. PHOSPHODIESTERASE INHIBITORS (TABLE 7)

Several authors have reported their experience with sildenafil citrate as a treatment for PE [188, 190, 203]. Abdel-Hamid et al. compared the efficacy and safety of the “on demand” clomipramine, sertraline, paroxetine, sildenafil and the pause/squeeze technique in the treatment of lifelong early ejaculation in a prospective randomised double blind crossover study of 31 potent men [188]. Treatment with sildenafil was associated with a significantly higher IVELT (15 minutes) and sexual satisfaction score than all other treatments and sexual satisfaction scores positively correlated with the IVELT for each treatment. The lack of a placebo group, the estimation of baseline IVELT by patient recall only and the use of the EDITS treatment response inventory which is validated for ED and not PE are major limitations of this study. Many men with entirely normal ejaculatory control will, as a result of inadequate sexual education and/or unrealistic patient/partner expectations incorrectly perceive themselves as “early ejaculators”.

In an open label study of 80 potent men, Salonia et al. compared treatment with paroxetine alone using initial chronic and then “on demand” dosing, with a combination paroxetine and sildenafil, using the same dosing regime for paroxetine and sildenafil administered one hour prior to intercourse [190]. Both treatments significantly improved the ejaculatory latency time and intercourse satisfaction domain of the IIEF. The combination of paroxetine and sildenafil produced superior results in both end points at 6 months treatment and the authors suggested a possible role of sildenafil in the treatment of early ejaculation.

Using a validated scoring inventory for the severity of PE, Chen et al. studied 58 men with PE who were previously refractory to psychosexual counselling and pharmacological treatment [203]. Treatment with sildenafil administered one hour prior to sexual intercourse significantly improved the baseline inventory score for the severity of PE. The authors suggest improved erectile function as the possible mechanism and a potential role of sildenafil in the treatment of early ejaculation. The proposed mechanisms for the effect of sildenafil of ejaculatory latencies include a central effect involving increased NO and reduced sympathetic tone, smooth muscle dilatation of the vas deferens and seminal vesicles which may oppose sympathetic vasoconstriction and delay ejaculation, reduced performance anxiety due to better erections and down regulation of the erectile threshold to a lower level of arousal allowing so that increased levels of arousal are required to achieve the ejaculation threshold. None of these studies are placebo controlled and the results are confusing and difficult to interpret. It is unlikely that phosphodiesterase inhibitors have a significant role in the treatment of PE with the exception of men with acquired PE secondary to co-morbid ED.

The results of a manufacturer sponsored double blind placebo controlled multicentre study have yet to be fully reported. Preliminary results show no significant difference in the IVELT of sildenafil compared to placebo but do demonstrate significant improvements in the ejaculatory control domain and the ejaculatory function global efficacy question. The latter is possibly consistent with the erectile response of sildenafil.

Based on the rating of the Level of Evidence of the studies reviewed, treatment of early ejaculation with Phosphodiesterase inhibitors has a Grade C recommendation.

<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Author/s</th>
<th>Drug</th>
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<tr>
<td>189</td>
<td>Chia SJ</td>
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<td>2B</td>
</tr>
<tr>
<td>190</td>
<td>Salonia, A., Maga, T., Colombo, R. et al.</td>
<td>Sildenafil</td>
<td>1B</td>
</tr>
</tbody>
</table>
Men with early 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 7)

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 rapid 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

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 [71,127]. Several paper and pencil instruments that enable the health provider to tap into some or most of the specific domains above are also available [128,129].

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 [73, 75]. 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 [109, 111, 113]. 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 rapid ejaculation secondary to erectile dysfunction, other sexual dysfunction or genitourinary infection should receive appropriate etiology specific treatment. Men with lifelong rapid ejaculation should be managed with pharmacotherapy. Men with significant contributing psychogenic or relationship factors may benefit from concomitant behavioural therapy. Recurrence of rapid ejaculation is highly likely to occur following withdrawal of treatment. Men with acquired rapid ejaculation can be treated with pharmacotherapy and/or behavioural therapy according to patient/partner preference. Restoration of ejaculatory control in men with acquired rapid ejaculation is likely to occur following completion of treatment but is the exception in men with lifelong rapid ejaculation. Behavioural therapy may augment pharmacotherapy to enhance relapse prevention.

**D. DELAYED EJACULATION, ANEJACULATION AND ANORGASMIA**

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 8). 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 anaesthesia.
PATIENT COMPLAINING OF PREMATURE EJACULATION (PE)

PATIENT/PARTNER HISTORY
- Establish presenting complaint
- Intravaginal Ejaculatory Latency Time
- Perceived degree of ejaculatory control
- Degree of patient/partner distress
- Onset and duration of PE
- Psychosocial history
- Medical history
- Physical Examination

MANAGE PRIMARY CAUSE

YES

PE SECONDARY TO ED OR OTHER SEXUAL DYSFUNCTION

NO

ACQUIRED PE

TREATMENT
First Line
BEHAVIOURAL THERAPY
- Stop/Start
- Squeeze Technique
- Sensate Focus
RELATIONSHIP COUNSELLING
Second Line
PHARMACOTHERAPY
- SSRI agents
- Topical anaesthetics
OR
Combination Treatment

PATIENT PREFERENCE

ATTEMPT GRADUATED WITHDRAWAL OF PHARMACOTHERAPY AFTER 6 TO 8 WEEKS

LIFELONG PE

TREATMENT
First Line
PHARMACOTHERAPY
- SSRI agents
- Topical anaesthetics
Second Line
BEHAVIOURAL THERAPY
- Stop/Start
- Squeeze Technique
- Sensate Focus
RELATIONSHIP COUNSELLING
OR
Combination Treatment

Figure 7: Management algorithm for premature ejaculation
and difficulty in achieving the ejaculatory threshold [65]. 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.

### I. PATHOPHYSIOLOGY

#### 1. CONGENITAL DISORDERS

**a) Mullerian duct obstruction**

As the male foetus 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 [204]. 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 (Figure 8). 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 [205].

**b) Wolffian duct abnormalities**

Congenital anomalies may be either sporadic, with a localized defect in the proximal part of the vas deferens or there may be a 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 trigo-
ne, which fails to close effectively producing retrograde ejaculation.

Bilateral abnormalities are often associated with carriage of the cystic fibrosis gene [206]. Unilateral absence of the vas deferens was observed in 5%, and bilateral absence in 18% of 370 azoospermic males with normal serum FSH levels investigated by the author [207].

c) 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 [208]. 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: 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

2. Traumatic Damage

a) 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 [209]. Investigation revealed that both vasa were blocked in 5 men and one vas in a further 8 patients, apparently as a result of the original operative procedure.

b) Operations on the prostate

Antegrade 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% [210] to 45% [211] 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 [212]. 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% [213] to 100% [214]. Although these men may have some antegrade ejaculation and usually experience orgasmic sensation, both 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 the rule 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 [215]. 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 [215]. 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 [216]. These drugs include pseudoephedrine andephedrine, and phenylpropanolomine. 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 pre-coital. The tricyclic antidepressant, Imipramine which blocks the reuptake of noradrenaline by the axon from the synaptic cleft is also occasionally useful [217]. The usual dose is 25mg twice daily. Current feeling is that long-term treatment with imipramine is likely to be more effective. Whilst medical treatment may not always produce normal ejaculation it may result in some prograde ejaculation. In patients who do not achieve antegrade ejaculation with either surgery or medication, sperm retrieval and artificial insemination is an alternative approach. The basic method of sperm retrieval involves reco-
very of urine by either catheter or voiding after masturba-
tion, and then centrifugation and isolation of the sperm.

3. INFEKTIVE DISORDERS

Genital infection such as gonorrhoea or non-specific
urethritis can produce cicatrisation and obstruction
anywhere in the male reproductive tract, especially if
treatment is delayed. Urinary infection, especially if
complicated by epididymitis, can also produce ob-
struction that may be situated at ejaculatory duct
level. Routine vasography in subfertile men with
azoospermia and normal serum FSH levels revealed
post-infective vasal blocks in 8% and acquired eja-
culatory duct obstruction in 4% [207]. Schistosomiasis
is endemic in large parts of Africa, and is seen
with increasing frequency in tourists returning from
Africa who have contracted the disease whilst
enjoying water sports. The disease may present with
haematospermia [218] and fibrosis and calcification
may lead to genital obstruction. Genito-urinary
tuberculosis can cause great damage to the male
reproductive tract, and since healing occurs with
calcification, the lesions may be irreparable. Plain
X-ray will often show the extent of the disease.

Haematospermia 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 [219].

It should be remembered, also, that schistosomiasis
and tuberculosis could present in this way. Routine
investigation of haematospermia by TRUS not uncom-
monly reveals the presence of small stones in the eja-
culatory ducts, which may be associated with ob-
struction and dilatation of the seminal vesicles. Such
stones usually pass spontaneously.

4. NEUROLOGICAL DISORDERS

a) Spinal cord Injury

The ability to ejaculate is severely impaired by spi-
nal 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 9) [220,221]. Unlike erectile capacity, the
ability to ejaculate increases with descending levels
of spinal injury. Less than 5% of patients with com-
plete upper motor neuron lesions retain the ability to
ejaculate. Ejaculation rates are higher (15%) in
patients with both a lower motor neuron lesions and
an intact thoracolumbar sympathetic outflow.
Approximately 22% of patients with an incomplete
upper motor neuron lesion and almost all men with
incomplete lower motor neuron lesions will retain
the ability to ejaculate. In those patients who are
able to ejaculate, 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 subcu-
taneous phystostigmine 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 [222,223]. Vibratory
stimulation is successful in obtaining semen in up to
70% of men with spinal cord injury [224]. This tech-
nique induces a reflexogenic ejaculation via the
sacral roots and the ejaculatory coordination centre
in the upper thoracolumbar spinal cord. The use of
electro-ejaculation to obtain semen by electrical sti-
mulation of efferent sympathetic fibres of the hypo-
gastric plexus is an effective and safe method of
obtaining semen. Brindley have reported that 71% of
men with spinal cord injury who underwent elec-
tro-ejaculation achieved ejaculation [225]. However,

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<th>Cord Lesion</th>
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<th>Psychogenic Erections (%)</th>
<th>Successful Coitus (%)</th>
<th>Ejaculation (%)</th>
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<td>0</td>
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<td>100</td>
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Table 9. Correlation of erection, ejaculation and intercourse with level and severity of spinal cord injury [87]
both are associated with a significantly higher risk of autonomic dysreflexia than electro-ejaculation. Pre-treatment with a fast acting vasodilator such as nifedipine will minimise the risk of severe hypertension should autonomic dysreflexia occur with either form of treatment [226]. If the spinal reflex arc is intact, a hypogastric plexus stimulator can provide ejaculation in the comfort and security of the patients’ home [227]. Percutaneous aspiration of semen from the vas deferens has also been reported as a means of harvesting semen for use with artificial reproductive techniques [228].

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 catheterisation, 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 [229]. In a recent collective analysis of 40 paraplegic patients, 22 successfully produced pregnancies by natural insemination or assisted reproductive techniques [230].

b) Para-aortic lymphadenectomy

This operation is usually done to clear lymph node metastases from testicular tumours, 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 tumour have residual masses in the para-aortic region [231]. Amongst 231 consecutive patients undergoing para-aortic lymphadenectomy after chemotherapy at the Royal Marsden Hospital, there was persistent undifferentiated tumour in 21% [232]. In our experience of 186 patients, a nerve sparing operative technique introduced in 1984 lead to a significant reduction in ejaculatory dysfunction from 37% to 19% [233]. 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 tumours 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 [234].

5. FUNCTIONAL DISORDERS

a) Seminal megavesicles

Adult polycystic kidney disease has been found in association with pathological dilatation of the seminal vesicles in 6 patients [235]. TRUS and percutaneous puncture of the seminal vesicles before and after resection of the ejaculatory ducts 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 aetiology remains obscure [236].

b) Radiotherapy for male pelvic cancer

Quality of Life (QoL) in general and sexual functioning in particular have become very important in cancer patients. Due to modern surgical techniques, improved quality of drugs for chemotherapy and very modern radiation techniques, more patients can be successfully treated without largely compromising sexual functioning (Table 10).

• 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 elicited 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 [237], only a few questionnaires included items related to ejaculation and orgasm.

Already in the 1980s ejaculatory disturbances following RT of PC were reported [238]. 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, a decreased frequency of orgasm by 57%; all men reported a decrease in ejaculate volume [239]. By using a validated questionnaire, Borgø and Sullivan [240] 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.

Also in early BT studies sexual functioning was assessed. Herr [241] reported already in 1979 on 51 patients treated with retropubic Iodium-125 seeds. Loss of ejaculate was experienced by 6% of the patients. In a later study dry ejaculation was reported by 16% of the patients after BT [242]. In both studies, all patients had previously undergone a transurethral resection of the prostate (TURP). For the first time a discomfort with ejaculation was mentioned in two studies (up to 25% of the patients) [243, 244]. This is quite common in clinical practice after BT; it is 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 [245]. Also decreased interest in sex and sexual desire, and libido was mentioned in up to 50% of the patients evaluated [240, 244-246].

There are a few data on the etiology of post-RT decreased libido and ejaculatory disorders. Daniell et al. [247] studied retrospectively levels of testosterone (TST) and other hormone after RT of PC. TST was found to be low 3 to 8 years after EBRT. Lower levels were 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 retro-

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<td>Scammell GE, White N, Stedronska J et al.</td>
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grade 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.

c) 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 [248]. Numbers were too small to draw final conclusion.

d) 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 [249]. Libido and orgasm seem to be normal in these patients.

Following RT a deterioration in sexual functioning has been reported between 1% and 25% of the patients [250-254]. Tinkler et al. reported on 237 patients after orchectomy and abdominal RT and compared these data to 402 age-matched controls [252]. 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 [252]. Caffo et al. evaluated toxicity and QoL of 143 patients treated for early-stage testicular cancer [253]. Twenty-three per cent reported a decreased libido, 27% problems with getting an orgasm and 38% ejaculation disturbances, including early ejaculation (PE).

A decrease in sexual desire, in orgasm and volume or semen was negatively correlated with age [250]. Jonker-Pool et al [251] 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 12% in the chemotherapy group. Decrease of absence of ejaculation was reported in 15%, 7% and 21% in the three groups, respectively; decreased orgasm in 15%, 12% and 30%, respectively. Although the differences are not statistically significant, in the RT group ejaculation and orgasm disturbances are higher than in the wait and see group. Similar results were reported by Arai et al.[237].

PE was reported in up to half of the patients [237,254], but it was the same as recalled before treatment [254]. The superior hypogastric plexus is responsible for ejaculation and it is mediated by the sympathetic system; it is a fenestrated network of fibres 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.

A 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 [234].

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E. INHIBITED EJACULATION (IE)

This section describes the definition, incidence, etiology, and treatments for inhibited ejaculation (IE), commonly known as delayed or retarded ejaculation. The literature contained few randomized clinical trials and despite the consensus conference’s strong preference for evidence based medicine, adequate summarizing of the etiological and treatment literature currently requires inclusion of expert opinion, anecdotal and case study information, at this time. Generally speaking, the information presented and the interventions described may produce beneficial results, but further evidence and evaluation is required. The specifics are delineated below and point the way toward the necessary future research, which is summarized at the conclusion of this sub-chapter.

I. NOSOLOGY, DEFINITION AND DESCRIPTION OF INHIBITED EJACULATION (IE)

There are multiple terms used to describe a delay or absence of male orgasmic response. Retarded ejaculation, delayed ejaculation and inhibited ejaculation as well as idiopathic anejaculation, primary impotency ejaculationis, and psychogenic anejaculation have all been used essentially synonymously to describe this problem in men. Like the term “early ejaculation,” the most commonly used term “retarded ejaculation” is often avoided because of its pejorative associations. This sub-chapter will use the initials IE, but the reader should understand that as of this moment all investigators agree on what is being named, but not the name itself.

The Diagnostic and Statistical Manual of Mental Disorders, 4th edition [69] defines inhibited ejaculation (IE) as the persistent or recurrent difficulty, delay in, or absence of attaining orgasm following sufficient sexual stimulation, which causes personal distress. Parenthetically, partially retarded ejaculation is sometimes observed in men who attempt to control a early ejaculation by suppressing the muscular contractions associated with ejaculation. They experience diminished pleasure and sensation as semen is released during emission, but the ejaculatory sensations are dulled through over control of striated muscle. Failure of ejaculation can be a lifelong primary event (e.g., congenital anorgasmia) or an acquired or secondary problem. It can happen in every sexual encounter or it may be intermittent. Some men with secondary IE can masturbate to orgasm; others, for a multiplicity of reasons, would or could not masturbate. Some men lose masturbatory capacity secondary to emotional or physical trauma. Some men have reported intermittent nocturnal emissions, and others were either unaware of or did not have - an orgasm nocturnally. Coital anorgasmia was usually an issue for the extremely religious (e.g., Ultra-Orthodox Jews) referred for fertility problems, although this was not the case for other men who were distressed by their inability to orgasm in response to manual or oral stimulation by their partner.

Incidence

Since the beginning of sex therapy, IE was seen as a clinical rarity and difficult symptom to treat.[277] Masters and Johnson [86] reported only 17 cases, while Apfelbaum [277] reported 34 cases, and Kaplan [278] fewer than 50 cases, in the history of their practices. Perelman [279] reported over 100 cases, including both primary and secondary RE. Simons & Carey [280] reviewed 52 studies showing “community samples indicate a current prevalence of “0-3% for male orgasmic disorder” versus 4%-5% for early ejaculation.” They indicate that clinic populations may be characteristically higher. The popularity of urologic-based treatments for erectile dysfunction has resulted in an anecdotally reported, clinically observed, unexpected increase in men suffering from IE [279]. IE, like other sexual dysfunctions, is also likely to become more prevalent with the aging of the world population [281].

II. ETIOLOGY

IE is not yet well understood and there are a number of etiological explanations, offering both psychological and somatic explanations.

1. DRUG INDUCED

It has been well known for years that adverse sexual side effects of many drugs and alcohol cause delayed or fully impaired orgasm in men and women (Table 5) [282-284]. This was especially true of psychotropic medications [283,285-289].

2. BIOLOGICAL VARIABILITY

In addition to psychodynamic and interpersonal
causes for IE, a biological etiology should also be considered. There is strong likelihood of biological variability in the threshold of arousal necessary before experiencing orgasm. Furthermore, it seems likely that the dispersal pattern of ejaculatory latency should resemble the same bell shaped distribution as do many other human characteristics. Extrapolating from Waldinger’s laboratory rat research, individuals experiencing either early ejaculation (PE) or IE are likely to be biologically predisposed to their symptom. The dysfunction becomes manifest given certain external factors: medications, sexual circumstances, and intra- and interpersonal dynamics, etc [279,290]. One could speculate that normal variation in the function of the nervous systems responsible for ejaculation could result in a somatically determined variation between men’s ejaculatory latency and capacity. Explanation of biologic predisposition is often helpful by itself in reducing patient and partner anxiety and mutual recriminations, while simultaneously assisting the formation of a therapeutic alliance with the health care professional [279].

3. CULTURAL AND PSYCHOLOGICAL ETIOLOGIES

a) Religious/culture.

Masters & Johnson [86] first indicated that IE was associated with orthodoxy of religious belief. Beliefs may limit sexual experience necessary for developing the knowledge necessary to learn to ejaculate or may result in an inhibition of normal function. Regardless of specific religion involved (Muslim, Hindu, Jewish, etc.), many devout 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” often resulted in idiosyncratic masturbatory patterns, which in turn resulted in IE. These men often had little contact with women prior to marriage (which may have been arranged after a few chaperoned dates). These very religious men may date, but 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.

b) Concurrent psychopathology

Multiple explanations for IE have been offered, with unconscious aggression and unexpressed anger recurring as themes in the IE literature [291-294]. Additionally, pregnancy fears received emphasis, since the reason for professional referral is often the female partner’s wish to conceive. Finally, Bancroft’s [295] model of psychogenic factors in erectile dysfunction depending on a delicate balance between central excitatory and inhibiting mechanisms would seem to have potential applicability to the understanding of IE as well.

c) Insufficient sexual arousal

An excellent critical review of the psychological etiology of IE was provided by Apfelbaum [277], who provocatively first noted the sexual politic surrounding IE and female anorgasmia: “Like the women who has inappropriately been castigated for willfully depriving her husband of the pleasure of bringing her to orgasm. The retarded ejaculator’s own belief that he is withholding is widely endorsed, understandably by his partners and less justifiably by most therapists”. Not only psychoanalysts, but sex therapists and behavior therapists as well, seemed to assume the IE patient’s orgasm is blocked, rather than the patient’s level of arousal being insufficient.

Apfelbaum [277] observed that some males appeared able to achieve erections sufficient for intercourse despite a relative absence of subjective arousal. He felt these “automatic erections” were taken as erroneous evidence by both the male and his partner that the man was ready for sex and capable of achieving orgasm. This same process is the likely cause of increased anecdotal clinical reports of IE for patients using popular urologic-based treatments for ED [2, 296]. Urologists received a few early complaints of IE, secondary to successful penile prosthesis surgery and ICI. However, Sildenafil brought huge numbers of patients to physician’s offices. Many of these patients experienced restored erections and coitus with ejaculation. While Sildenafil has been used with some success to facilitate reversal of the antidepressant sexual adverse effects [297], the effect of PDE 5 inhibitors may be bimodal [2,296]. The phenomena of erection without adequate psychoemotional arousal occurred in some men using sildenafil when 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, 296].

d) Masturbation

Apfelbaum [277] coined autosexual orientation to describe men with IE who prefer masturbation to partnered sex. Perelman [296] discussed the role of
fantasy, as well as masturbation frequency, motivation, and idiosyncratic technique in the etiology and maintenance of IE. Many men with IE engage in stimulation that was striking in the speed, pressure, duration, and intensity necessary to produce an orgasm, and dissimilar to what they experienced with a partner. In this manner, they have preconditioned themselves to likely difficulty with a partner and experience secondary IE. Disparity between the reality of sex with the partner and the sexual fantasy (whether unconventional or not) used during masturbation is another cause of IE. This disparity takes many forms: body type, orientation, sex activity performed, etc. Many men and women remain inhibited about using their masturbatory fantasies when with their partner. Yet like their female counterparts, when anorgasmic men integrate their masturbation fantasies into sex with their partner, orgasm is more likely [296].

e) Mixed etiology

It would seem that IE, like other sexual dysfunctions, is best understood as being caused by an interaction of both organic and psychogenic factors. A biological set point for ejaculatory latency is impacted upon 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 each of these factors determines the endpoint dysfunction for a particular individual, at a particular moment in time.

III. EVALUATION

Assessment begins by reviewing the conditions under which the man is able to ejaculate, e.g., 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 [298]. If orgasmic attainment had been possible previously, the life events/circumstances temporarily related to orgasmic cessation are reviewed. The events in question maybe pharmaceutical, illness, or a variety of life stressors and other psychological factors e.g. 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.

Haemospermia requires full investigation. Culture of expressed prostatic secretion and urine will define the nature of an infective process such as prostatitis [299] 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.

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. 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.

Patients with ejaculatory duct obstruction usually present with infertility. Seminal analysis may simply be reported a showing azoospermia or oligozoospermia, 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 vas deferens, the urinary system must also be checked by ultrasound scanning, as coexisting renal anomalies may be present [300]. 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 [206].
1. IMAGING IN EJACULATORY DUCT OBSTRUCTION

The lesion 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 (Figures 8, 9). 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 [301].

![Figure 8](image1.png)

Figure 8: Mullerian duct cyst shown by a. transrectal ultrasound scan, and b. percutaneous puncture (reproduced from the British Journal of Urology with permission).

2. 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.

a) 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 2 different levels, 3 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 obtai-
ned by subtracting the peripheral from the total transit time). The peripheral transit time is approximately 13.5 ms. The total transit time is approximately 34 msec (onset) and 43 msec (top of P1 deflection) [302, 303].

b) Pudendal motor evoked potentials (Pudendal MEPs)

Motor Evoked Potentials (MEPs) explore the efferent pathways (pyramidal tracts) from brain to target muscle (bulbocavernous muscles). The 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 bulbocavernous 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 deflection. 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).[304]

c) Sacral reflex arc testing: the somatic-somatic reflex arc

The 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 [303, 305].

d) 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. The dorsal nerve of the penis is stimulated using 2 ring electrodes wrapped around the penis 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 [306, 307].

IV. TREATMENT

Treatment should be etiology specific and address the issue of infertility in men of a reproductive age.

1. PSYCHOLOGICAL TREATMENT FOR INHIBITED EJACULATION

Heiman and Meston’s [138] summary of sex therapy treatments concluded that “inadequate data” on the topic of delayed orgasm in men prevented any conclusion regarding efficacy of treatment. However, many treatments for IE have been suggested in the psychotherapy literature, including early psychodynamic and sex therapy approaches [86,301,308-312]. Masters and Johnson [86] 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, 81% of men who were anorgasmic prior to fertility treatment were successful in reaching orgasm through vibrator stimulation.[313] Apfelbaum [277] treated almost all of his RE cases with «body work» using sexual surrogates. Perelman [296] reported retrospective chart review success rates of over 80% in treating IE using a cognitive-behavioral sex therapy. However, these were uncontrolled case reports with treatment ranging from a few brief sessions of sex education to the nearly two years of multiple-modality treatment in more complex multiple etiologic cases.

Numerous drugs, herbs and medication dosing strategies have been reported to offset an iatrogenic induced, antidepressant-related IE. Widespread use of selective serotonin reuptake inhibitors (SSRIs) in the last decade has triggered tremendous interest in
the effect of these antidepressants on sexual function [288,314]. Additionally, case reports indicated successful use of sildenafil to treat SSRI-induced orgasmic latency problems in men and women, with clinical trials currently investigating this phenomenon.[283,315,316] Recently, Nurnberg et al. [297] published a prospective, parallel-group, randomized, double-blind, placebo-controlled multi-center in order to assess the efficacy of sildenafil citrate in men with sexual dysfunction associated with the use of selective and nonselective serotonin reuptake inhibitor antidepressants. In this study, sildenafil effectively improved erectile function and other aspects of sexual function in men with sexual dysfunction associated with the use of SSRI antidepressants. While the endpoints used were very limited, regarding the question of ejaculatory latency, this is one of the few RCT studies to address this question and accordingly becomes important. It remains to be seen whether sildenafil will be shown to be an orgasmogenic agent, however, it is probable that multiple compounds will be developed to reduce orgasmic threshold and assist us in treating people who have difficulty reaching orgasm. Indeed, some speculate that a dopaminergic pathway might facilitate orgasm.

2. DRUG TREATMENT

Whilst retrograde ejaculation can be surgically treated with bladder neck reconstruction, no surgical procedure exists for the treatment of failed emission. As is the case with retrograde ejaculation, drug treatment is the most promising approach. Whilst 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.

There are multiple reports in the literature of the use of a variety of drugs in the treatment of delayed ejaculation or anejaculation (Table 11). The drugs facilitate ejaculation by either a central dopaminergic or anti-serotonergic mechanism of action. There are not published placebo controlled studies and most are anecdotal case reports/series that dealing with the treatment of SSRI induced ejaculatory dysfunction.

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 [317, 318]. The ejaculatory dysfunction commonly associated with the anti-hypertensive alpha-methyldopa which reduces cerebral monoamine levels by suppressing the cerebral dopaminergic system is consistent with these reports [176]. The occurrence of paradoxical hyper sexuality, e.g. spontaneous orgasm, with clomipramine and fluoxetine, however, suggest

Table 11 Level of Evidence - Drug Treatment for Delayed Ejaculation

<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Author/s</th>
<th>Drug</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>321</td>
<td>McCormick, S., Olin, J., Brottman, A. W</td>
<td>Cyproheptadine</td>
<td>4</td>
</tr>
<tr>
<td>322</td>
<td>Ashton, K., Hamer, R., Rosen, R</td>
<td>Cyproheptadine</td>
<td>2B</td>
</tr>
<tr>
<td>323</td>
<td>Feder, R</td>
<td>Cyproheptadine</td>
<td>4</td>
</tr>
<tr>
<td>324</td>
<td>Lauerma, H</td>
<td>Cyproheptadine</td>
<td>4</td>
</tr>
<tr>
<td>325</td>
<td>Lauerma, H</td>
<td>Cyproheptadine</td>
<td>4</td>
</tr>
<tr>
<td>326</td>
<td>Aizenberg, D., Zemishlany, Z., Weizman, A</td>
<td>Cyproheptadine</td>
<td>4</td>
</tr>
<tr>
<td>329</td>
<td>Balon, R</td>
<td>Amantadine</td>
<td>4</td>
</tr>
<tr>
<td>330</td>
<td>Shrivastava, R., Shrivastava, S., Overweg, N. et al.</td>
<td>Amantadine</td>
<td>4</td>
</tr>
<tr>
<td>331</td>
<td>Valevski, A., Modai, I., Zbarski, E. et al.:</td>
<td>Amantadine</td>
<td>4</td>
</tr>
<tr>
<td>332</td>
<td>Gitlin, M. J</td>
<td>Amantadine</td>
<td>4</td>
</tr>
<tr>
<td>333</td>
<td>Balogh, S., Hendricks, S., Kang, J</td>
<td>Amantadine</td>
<td>4</td>
</tr>
<tr>
<td>334</td>
<td>Price, J., Grunhaus, L. J</td>
<td>Yohimbine</td>
<td>4</td>
</tr>
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<td>335</td>
<td>Jacobsen, F. M.</td>
<td>Yohimbine</td>
<td>4</td>
</tr>
<tr>
<td>336</td>
<td>Hollander, E., McCarley, A.</td>
<td>Yohimbine</td>
<td>4</td>
</tr>
<tr>
<td>337</td>
<td>Witkin, J. M., Perez, L. A.</td>
<td>Buspirone</td>
<td>4</td>
</tr>
<tr>
<td>338</td>
<td>Othmer, E., Othmer, S. C</td>
<td>Buspirone</td>
<td>4</td>
</tr>
<tr>
<td>339</td>
<td>Cooper, B. R., Hester, T. J., Maxwell, R. A</td>
<td>Bupropion</td>
<td>4</td>
</tr>
<tr>
<td>340</td>
<td>Ashton, A., Rosen, R.:</td>
<td>Bupropion</td>
<td>4</td>
</tr>
<tr>
<td>342</td>
<td>Aizenberg, D., Gur, S., Zemishlany, Z. et al.:</td>
<td>Mianserin</td>
<td>4</td>
</tr>
</tbody>
</table>
that this balance is more complex and that different 5-HT receptor subtypes may have opposing effects on sexual function [297,319,320].

The antihistamine, cyproheptadine which increases cerebral serotonin levels, has been shown to increase male sexual activity in the rat [317]. 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 contains no controlled studies [321-326]. These studies suggest an effective dose range of 2-16mg., administration on a chronic or «on demand» basis. McCormick (1995) reported the use of cyproheptadine to reverse the anorgasmia induced by the SSRI fluoxetine has been reported in 2 patients [321]. Ashton et al. also reported improvement in 12 of 25 men with SSRI induced sexual dysfunction with a mean dose of 8.6mg with efficacy limited by sedation and potential reversal of antidepressant effect [322]. The author’s experience suggests a role for cyproheptadine in the treatment of both retarded ejaculation and anejaculation which is limited to a degree by its sedative effect.

Central dopamine activity can be increased by a variety of mechanisms ranging from the provision of dopamine synthesis precursors e.g. l-dopa, to use of substitute neurotransmitters to directly stimulate central dopamine receptors (Tables 12, 13). 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 [327,328]. Several authors have reported a place for amantadine in the reversal of SSRI antidepressant induced anorgasmia [322,329-333]. Ashton et al. reported improvement in SSRI induced sexual dysfunction in 8 of 19 men with mean dose of 200mg.[322] Balon reported some efficacy with «on demand» amantadine (100mg) administered 5-6hrs before coitus in a similar group of patients [329].

Several authors have reported their experience with Yohimbine, a derivative of the bark of the Yacon tree, in the management of SSRI induced sexual dysfunction [334-336]. Yohimbine is an alpha-2 antagonist, an alpha-1agonist, a calcium channel blocker and inhibits platelet aggregation. Price and Grunhaus reported reversal of clomipramine-induced anorgasmia with a dose of 10mg administered 90 minutes

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### Table 12: Adjunctive Drug Therapy for SSRI-Induced Sexual Dysfunction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Symptom</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>Anorgasmia, Decreased libido, Erectile dysfunction</td>
<td>As Needed: 100-400 mg (for two days prior to coitus) Daily: 75-100 mg bid or tid</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Anorgasmia</td>
<td>As Needed: 75-150 mg Daily: 75 mg bid or tid</td>
</tr>
<tr>
<td>Buspirone</td>
<td>Anorgasmia, Decreased libido, Erectile dysfunction</td>
<td>As Needed: 15-60 mg Daily: 5-15 mg bid</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>Anorgasmia, Decreased libido, Erectile dysfunction</td>
<td>As Needed: 4-12 mg Daily: On Demand</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>Anorgasmia, Decreased libido, Erectile dysfunction</td>
<td>As Needed: 5.4-10.8 mg Daily: 5.4 mg tid</td>
</tr>
</tbody>
</table>

### Table 13: Mechanism of Action of Drugs which increase Dopamine Neurotransmission

<table>
<thead>
<tr>
<th>Mechanism of Increasing Dopamine Neurotransmission</th>
<th>Drug</th>
</tr>
</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>
</tr>
</tbody>
</table>
prior to coitus [334]. In a placebo-controlled study of 15 patients with fluoxetine-induced anorgasmia, Jacobsen reported a 73% response rate to yohimbine [335]. Hollander reported that yohimbine reversal of anejaculation in 5 of 6 men with intercourse and/or masturbation [336]. 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.

Buspirone is a benzodiazepine class anxiolytic which possesses 5HT-1A receptor agonist activity [337]. 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 [338]. Bupropion is a novel antidepressant which prolongs the action of dopamine by reducing its uptake from the synaptic clef [339]. Ashton and Rosen described reversal of SSRI induced anorgasmia in 66% of patients studied. An improvement in sexual function was noted by Rowland in 14 non-depressed diabetic men with ED with «on demand» doses of 75-150 mg [340].

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 50mcg/kg. DA receptor antagonists block this effect [262,341]. 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) [342]. 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.

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 [343]. Prior administration of a dopamine antagonist eliminated these stimulatory effects confirming that these sexual effects were due to stimulation of DA receptors. They 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 appears 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 [344]. 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 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 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.

Based on the rating of the Level of Evidence of the studies reviewed, pharmacological treatment of delayed ejaculation or anejaculation has a Grade C recommendation (Table 11).

V. OFFICE MANAGEMENT OF DELAYED EJACULATION, ANEJACULATION AND ANORGASMIA

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 10)

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

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. Management involves identification of the etiology and disease specific treatment. 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. The former is managed with behavioural therapy and/or psychotherapy. Men with age related penile hypoanaesthesia should be educated, reassured and be instructed in revised sexual techniques which maximise arousal.

The majority of men who always achieve orgasm but never experience prograde ejaculation or have a greatly reduced prograde ejaculatory volume, have 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.

VI. THE FUTURE

The management of inhibited ejaculation is likely to evolve towards combination treatment using integrated pharmacotherapy and sex therapy approaches. It seems likely that the most effective treatments for IE will follow the pattern seen in the treatment of ED, where an integration of pharmacotherapy and sex therapy is becoming the treatment of choice [297,345-355]. 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 dysfunctions (including IE), but large controlled prospective studies are needed in order to define an appropriate treatment algorithm.[356] The development of new pharmaceuticals will only refine such an algorithm and improve our opportunity for enhancing orgasmic function.
Figure 10: Management algorithm for delayed ejaculation, anejaculation and anorgasmia

MANAGEMENT ALGORITHM FOR DELAYED EJACULATION, ANEJACULATION AND ANORGSAMIA

DELAYED EJACULATION ANEJACULATION ANORGASMIA

NEVER

INHIBITED MALE ORGASM
→ Psychosexual therapy

IS THERE ORGASM?

SOMETIME

INHIBITED MALE ORGASM
Nocturnal/Masturbation Emissions
→ Psychosexual Therapy
AGE RELATED DEGENE RATION
→ Reassure/alter sexual technique

ALWAYS

IS THERE EJACULATION?

YES

ARE SPERM PRESENT IN URINE AFTER ORGASM?

YES

ASPERMIA
→ Ejac.Duct Obstruction

NO

RETROGRADE EJACULATION
→ Reassure/Educate
→ Pharmacotherapy
→ Surgery

FAILRE OF EMISSION
• Neurogenic
• Metabolic
• Drug Adverse Effect
→ Disease Specific Management
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300. SCHLEGEL, P. N., SHIN, D., GOLSTEIN, M.: Urogenital


303. OPSOMER, R. J., CARAMIA, M. D., ZAROLA, F. et al.: Neuro-

304. OPSOMER, R. J., BOCCASENA, P., TRAVERS, R. et al.: Neu-

305. NORDLING, J., MEYHOFF, H. H.: Dissociation of urethral


309. FISHER, W.: Multimodal sex therapy with a blind man suffering from retarded ejaculation. Special issue: Social work prac-


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## A. PENILE IMPLANT

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## REFERENCES
Penile implants were introduced into the marketplace over 30 years ago with the marketing of the three piece inflatable and the semi rigid rod almost simultaneously [1,2]. Prior to that time, there was little interest in erectile dysfunction, little was known of the causes and epidemiology, and the treatments which were prescribed were in most cases unsuccessful. The rudimentary implants used prior to that time simply acted as inadequate splints, attempting to maintain the penis in a rigid state. The French surgeon Ambroise Paré suggested an “artificial penis” made of 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 replaced the whole organ or part of the body. On the other hand one should always confine to the term “penile implant” when referring to the modern devices discussed in this chapter.

The first real penile implant to facilitate an erection was used in a phalloplasty procedure performed by the Russian surgeon Nikolaj A. Bogaraz in 1936 [3]. He used the patient’s rib cartilage and in later years, he even performed this operation in patients with a morphologic intact penis, but suffering from erectile dysfunction.

The first alloplastic material for the treatment of erectile dysfunction was implanted in a single patient in 1949 using an unpaired acrylic subcutaneous implant by Goodwin and Associates. Robert A. Loeffler and R.O. Pearman both also implanted acrylic rods directly to the tunica albuginea in the 1960’s whereas the Egyptian plastic surgeon G.E. Beheri was the first to place the implants into the corpora cavernosa [5,6,7]. In addition to providing a treatment for erectile problems, the introduction of the semirigid rod and inflatable implants sparked interest in studying the mechanisms of an erection, the anatomy of the penile bodies and the interrelation between patient and partner in achieving satisfactory sexual compatibility. Tests were developed which could differentiate between physical and psychological causes for erectile dysfunction. Basic science advances attempting to elucidate cellular mechanisms including penile smooth muscle relaxation have occurred. Hand in hand with our understanding of these cellular mechanisms, medical treatments acting on muscles in the penis soon became very effective. Twenty years ago, intracorporal injections to relax penile smooth muscle became popular [8]. Over five years ago, sildenafil, an oral agent which is effective in improving erections in the majority of patients not only simplified the treatment for erectile dysfunction for many men, but brought numerous patients into the fold, who otherwise would not have opted for more aggressive therapies [9]. Two other oral medications in the class type-5 phosphodiesterase inhibitors, namely tadalafil [10] and vardenafil [11] are now also available. About 2/3rds of men will respond to these oral agents and another small percentage can be successfully treated with intraurethral [12] or intracorporally injected agents. Vacuum erection devices, which were popularized in the 1980s, [13] are also available and when medication has not been successful, these agents, as well as penile implants have been used by some patients.

In the current environment, penile implants have played a secondary role in the treatment of erectile difficulties. When medical therapy has been ineffective or contraindicated, and when vacuum devices have proven unsatisfactory or unacceptable, implants
have offered a predictable and reliable way of restoring erectile abilities. Patients who present for consideration of a penile implant, are those who have been unable to use medical therapy. Patients with diabetes mellitus and those who have had radical prostatectomy for prostate cancer respond less well to the oral medications. For patients taking organic nitrates, these medicines are contraindicated. For patients with scar tissue in the erectile bodies from trauma or following priapism, or after a previous prosthesis has been removed, penile implant placement is their only option for restoring erections. In patients with Peyronie’s Disease, where soft erections and curved erections make intercourse impossible, a penile implant will both straighten and strengthen the erection.

I. TYPES OF PENILE IMPLANTS

There are three classes of penile implants, hydraulic, semirigid, and soft silicone. The hydraulic consists of two types, the three piece inflatable and the two piece inflatable. In the three piece inflatable group, there are two vendors, Mentor Corporation and American Medical Systems (AMS). (Figure 1) Mentor promotes two types, the alpha I and the narrow based cylinders. Both cylinders expand in girth, but not in length. The narrow cylinder is more appropriate for the smaller penis and the penis with considerable scar tissue where dilation to a larger caliber corporal body is not easily accomplished. American Medical Systems sells the Ultrex, CX, and CXM cylinders. The Ultrex is composed of three layers. The inner layer is silicone, the middle layer is a bidirectional Dacron-lycra weave and the outer layer is silicone to prevent in-growth of tissue into the woven material. The bidirectional weave allows the cylinder to expand both in length and in girth. The CX cylinders and CMX are of similar construction, except that the middle woven layer has an unidirectional Dacron-Lycra weave allowing the cylinder to expand in girth only. The CMX is a narrower cylinder, more appropriate for the small penis or scared corporal bodies. (Figure 2) The only two piece implant available is the Ambicor of American Medical Systems, which has two cylinders, one to be placed in each corporal body connected to a resipump which is placed through a penoscrotal approach into the scrotum. (Figure 3) There are two types of semi-rigid rod prostheses, the malleable and the mechanical. The Accuform of Mentor Corporation is a malleable composed of braided silver wire surrounded by a silicone coat. (Figure 4) The AMS 650 and 600 M implants have a stainless steel woven core with a silicone jacket. The Jonas implant produced in Germany has a silver core and a silicone covering [14]. The mechanical prosthesis, termed the Dura II, has articulating segments of polyethylene held together by a central spring and is now sold by American Medical Systems. (Figure 5) These articulating segments are covered by a polytetrafluoroethylene sleeve surrounded by a silicone outer jacket to prevent ingrowth of tissue into the prosthesis parts. The soft silicone implant was introduced by Subrini. Currently these devices are manufactured in France and sold under the names “SSDA” and “Virilis” in a number of countries. [15] This implant is indicated in the presence of residual spongy erectile tissue which permits tumescence and complementary girth expansion around a central silicone support. (Figure 6) There are a few homemade rod implants present throughout the world, but none of these has been used for export to other countries.

The three piece inflatable penile implants are somewhat complex to insert, and they require a reservoir placed in the abdominal cavity. However, they do give the best rigidity and the best flaccidity since they will fill every part of the corporal bodies, just as an inner tube will fill a bicycle tire. They also give the best flaccidity, as all fluid can be drained out of the cylinder into the reservoir when the non-erect state is desired. The pumping mechanism of both the AMS and the Mentor prosthesis does require some manual dexterity, and patients who are lacking in this ability, may find it difficult to work these devices. For patients with previous complex abdominal procedures such as a kidney transplants or neobladder, the reservoir should be placed out of the pelvis in another part of the abdomen. A surgeon might consider a simpler prosthesis in these circumstances. These devices come in the largest and the smallest size cylinder and hence give the best flexibility in sizing. The two piece prosthesis, can give good rigidity and fair flaccidity, or fair rigidity and good flaccidity, but rarely good rigidity and flaccidity simultaneously. The device however, is advantageous if the hydraulic device is preferred, but the abdominal cavity needs to be avoided. 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 the extremely thin patient. The semi rigid rod implants are easy to insert and usually easy to manipulate. The tubes are espe-
Figure 1: Mentor Alpha I – Three-piece inflatable penile implant. One cylinder is placed in each corporal body, the pump in the scrotum and the reservoir in the prevesical space.

Figure 2: Top Ultrex Cylinder. Middle – CX Cylinder. Bottom – CXM cylinder in full inflation.

Figure 3: Ambicor 2-piece penile implant.

Figure 4: Accuform semirigid rod penile implant.

Figure 5: Dura II mechanical penile implant.

Figure 6: Virilis soft silicone penile implant.
cially bendable and with minimal exertion can easily be maneuvered in the upward or downward position. The wire devices will sometimes have spring-back and may not be perfectly positionable for erection or in a straight downward position. Cystoscopy in a patient with a rigid prosthesis may be difficult, but with flexible cystoscopes, this is less of a problem today. Patients with diminished sensation, such as those with spinal cord injury, have been more prone to have erosion of the semirigid rod cylinders to the exterior in the region of the glans because of the pressure of these cylinders in the face of absent sensation. The patient with sensation can feel pain or discomfort as these rods are rubbed against the undergarments; the patient without sensation may not appreciate that the rods are wearing through.

In the decade prior to the introduction of Sildenafil in 1998, sales of penile prostheses varied between 20,000 and 30,000 per year worldwide. In the latter part of 1998 and in 1999, sales plummeted to the range of 12,000 per year. More patients were now coming in to doctors’ offices for treatment of erectile dysfunction, and choosing medications. We are now seeing implant sales approaching the pre-Sildenafil era rising to the range of 18,000 per year. 75% of the sales of penile implants are in the United States. 70% of the market in the USA is the 3-piece inflatable, while 20% goes to the Ambicor with the remaining 10% semi-rigid rods. Outside the United States, the inflatable market is about 60%, the rod market is about 40%.

II. SELECTION OF PATIENTS – INFORMED CONSENT

A patient would be considered a good candidate for a penile prosthesis if he has failed medical therapy or if medical therapy was contraindicated. Patients are usually advised to try to at least consider a vacuum device before a penile implant. Patients who opt for the implant usually are highly motivated to continue with sexual activity. The patient is usually offered the choice of an inflatable, semi rigid or soft silicone implant, guided by the surgeon’s advice related to his body habitus and manual dexterity. Patients with a larger penis will be best served by a three-piece inflatable. These devices tend to give the best rigidity, especially in the longer phallus. Patients with limited manual dexterity or those who would have difficulty manipulating the hydraulic devices are best encouraged to choose a semi-rigid rod or soft silicone implant. The patient should be advised that the size of the penis will likely be shorter than the original erection was. When the penile implant is in place, a sheet of scar tissue forms around the cylinders as the body’s healing reaction. The scarred sheath does not stretch as the device is inflated as the natural tunica albuginea would stretch. Hence, elastic qualities of the tunica albuginea are negated by this inner sheath of scar tissue. Sensitivity of the penis, ejaculatory abilities, and sexual drive are usually unchanged following placement of the prosthesis. The patient should also be advised that the function of the implant is to make a firm and soft or bendable penis only. The devices do not restore any special sensitivity or sexual drive that may have been present years ago. When an implant is placed, the spongy tissue is pushed to the periphery to make room for the cylinders. If the cylinders are removed at a later date for whatever reason, the space will fill in with scar tissue, which will not respond adequately to other treatments such as medication or a vacuum erection device.

III. PRE-OPERATIVE PREPARATION

It is recommended that the patients bathe the genital area with a strong soap for a few days prior to the surgery. Shaving of the genital area is performed in the operating room to minimize the chance of nicks in the skin being colonized by bacteria with prior shaving. Open sores on the penis, or comedones should be treated or removed prior to the surgery to avoid these being a source of contamination during the procedure. Bishop and Associates found that patients with diabetes mellitus whose blood sugar was in better control for a period of time preoperatively as manifest by a normal hemoglobin A1C, were less prone to develop a penile implant infection than a group whose hemoglobin A1C was abnormal [16]. A larger series reported by Wilson and Associates found no difference in infection rates with penile prosthesis placement in those with a normal or an elevated level of hemoglobin A1C preoperatively [17]. The urine culture should be negative if possible. Patients who are prone to develop urinary tract infections such as those with a neurogenic bladder should be placed on antibiotics for a number of days prior to the surgery to maintain sterile urine. The urinary tract is usually not invaded during the placement of the penile prosthesis, although spilling of urine onto the operative field during the procedure is a possibility. Antibiotics are usually started prophylactically one hour prior to the procedure. The deci-
sion of which antibiotics to use is usually made by the surgeon, and are those antibacterials which are appropriate for treating infections due to skin contaminants. The antibiotics are usually continued for 48 hours postoperatively, at which time the wound is sealed. Some surgeons will prefer to maintain antibiotics for a week after surgery. A catheter is sometimes used to identify the corpus spongiosum during the procedure and may be removed at the conclusion of the operation or continued for up to 24 hours in the postoperative period. Some surgeons will opt to use drains at the conclusion of the procedure to reduce the edema and to provide an exit for any bleeding which may occur in the immediate postoperative period. These drains are usually removed a day or two following the surgery. Pain following placement of a penile prosthesis is variable depending upon the patient’s tolerance and the particular disease process. The pain is usually more prolonged than that associated with an operation of the same magnitude, i.e., inguinal herniorrhaphy or appendectomy. Patients relate that the pain usually improves each day and that by 3-4 weeks, most of the pain has subsided. Patients are taught to operate the hydraulic devices at about six weeks. Some surgeons prefer to begin cycling these devices at four weeks, but in many patients pain may still be present to the degree where it would make such a maneuver uncomfortable. At six months, most patients relate that they hardly notice any pain present. Especially in cases of neuropathy, pain may persist beyond six months. If prolonged pain does occur, especially if the pain is unchanging or worsening, then the suspicion of an infection associated with the prosthesis should be entertained. When the patients are taught to operate the hydraulic devices, they are advised to cycle them regularly. Every week, the patient should inflate the device completely to avoid cylinder cavity contracture. They are advised to completely deflate the device daily, to avoid scar formation over the reservoir which would limit its expansion. When the patient leaves the cylinders semi-inflated for prolonged periods of time, a capsule forms over the reservoir in the collapsed state which will restrict its expansion in the future.

**IV. INCISIONS**

The inflatable prostheses are usually placed through an infrapubic or a penoscrotal incision. The advantage of the infrapubic incision is the secure placement of the reservoir in the midline location. If the midline prepubic area is scarred or a renal transplant is present, the epigastric extraperitoneal or intraperitoneal placement of the reservoir can be accomplished. If a prosthesis is placed through an infrapubic incision on the dorsal surface of the corpora cavernosa, care should be taken to avoid damaging the neurovascular bundle which runs between 11 o’clock and 1 o’clock on the upper surface of the corporal bodies. Making corporotomies at about the 10 o’clock or 2 o’clock position will avoid damaging this structure. The sensory nerves to the end of the penis and the glans run through the neurovascular band, and it is important to avoid damaging these nerves. By doing so, good sensitivity to the distal penis should be maintained after the surgery. With the infrapubic approach, the pump tubing is placed around the side of the penis into the scrotum and the pump is not usually secured in position. Migration of the pump may occur and the patient is encouraged to push the pump inferiorly each day in the immediate post-op period to assure optimal positioning. During placement of a hydraulic implant through a penoscrotal or transverse scrotal approach, the reservoir is placed blindly through the inguinal canal. Care should be taken in this approach to place this part medially to avoid injury to the iliac vessels. Decompressing the bladder will minimize the chance of injuring this structure. The advantages to this approach are the secure placement of the pump in the scrotum and the fact that the skin is not violated in the prepubic area, for a more acceptable cosmetic result. The Ambicor prosthesis can only be placed through a penoscrotal approach. The tubing from the pump to the cylinders, which is preconnected will not reach into the scrotum if this device is placed through an infrapubic incision. The semi rigid rods and soft silicone implant are commonly placed through a subcoronal, penoscrotal or ventral penile incision. A ventral incision is used in the uncircumcised patient. If a subcoronal incision is used simultaneous circumcision is recommended. If the excess foreskin is left following the closure, maceration of the suture line or lymphedema may develop. Through the subcoronal approach, there is also less tissue to close over the suture line of the corporotomy. When the penoscrotal approach is used to place semi rigid rod implants, it may be difficult to bend the rods to fit under the distal edge of the corporotomy. Extending the corporotomy may be necessary under these circumstances. In the ventral penile approach, a proximal midline skin incision is made on the ventral surface of the penis [19]. This is
retracted distally using a vein retractor and relatively distal corporotomies are made (Figure 7). The distal end of the corporotomy can then be lifted over the end of the rod using a vein retractor, avoiding the need to bend the rod. The layered subcutaneous tissue and skin closure can then be performed without overlapping suture lines. The corporotomy closures are lateral and the skin closure is in the midline.

**VI. OPERATIVE TECHNIQUE**

The critical portion of the surgery is appropriate cylinder sizing. If a cylinder is larger than the corporal body can accommodate the patient may have persistent pain, protrusion of cylinders far into the glans, or curvature of the penis when it is erect. The rigid rods should be sized about 1/2 cm less than the measured length of the corporal body. This will allow comfortable bending and less springback phenomenon. With most inflatable cylinders, the cylinder of the same size as the measured corporal length should be implanted. The cylinders which expand distally (Ultrex) should be sized slightly shorter than the measured corporal length, perhaps 1/2 to 1 cm [20]. As the cylinder expands distally during inflation, it will easily make up the difference in length and fill out the distal aspects of the corporal body to give good support to the glans. In addition to length sizing, proper width fit is critical for optimal support for the erection. Models of the three-piece inflatable, the Mentor and the AMS CX come in two widths. The narrow-width cylinders with modest inflation are 9.5 mm in diameter. Upon full inflation, they will expand to at least 14 mm in girth. The wider versions, when expanded to modest inflation are 12 mm in diameter and when fully expanded are at least 18 mm in girth. The optimal width fit of an inflatable cylinder is that which fills the corporal body in a finger in glove like fashion. Hence when the corporal body is relatively narrow, a narrow cylinder will give equally good rigidity as a larger cylinder with less discomfort and less possibility of causing penile deformity. The technique to determine whether the wider or narrower cylinder would be more appropriate in a particular patient is to assess the ease with which the dilator passes during dilation of the corporal body. If the 12 mm dilator passes with some snugness, it would be more appropriate to use the narrower cylinder rather than the wider cylinder under the circumstance as it would give equally good support with less potential for problem. The semi-rigid rods, the soft silicone device and the Ambicor implant are sold in fixed-width sizes. Deciding which size of these devices to implant would be appropriate before opening the sterile package. The simple technique to determine which size would be more appropriate would give the better fit would be to place two dilators of the proposed size simultaneously, first distally, then proximally into the corporal bodies. One then apposes the thumb to the index finger between the two dilators (Figure 8). If there is wide separa-

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**Figures 7 and 8:**

**Figure 7:** Ventral penile approach to placing semirigid and soft silicone penile implants.

**Figure 8:** Schematic diagram showing the technique for determining the size of inflatable penile cylinders.
tion of the dilators i.e., if one is able to appose the thumb to the index finger between the two dilators, then that particular size would be too narrow and a larger size would be more appropriate. An ideal fit would be achieved if one were to obtain a slight separation of the dilators as the thumb is apposed to the index finger. If there is no separation of the dilators as this maneuver is performed, then a tight fit would be achieved with that particular size cylinder.

The inflatable cylinders have an input tube which exits from the cylinder at the proximal location. This tube may run intracorporally and exit at a convenient location from the corporotomy or may exit directly where the tube comes off the cylinder. In some previously constructed cylinders, if this tube rubbed against the cylinder, input tube wear would occur. However, the current model cylinders with the polyurethane of the Mentor and the triple layer of the AMS 700 and Ambicor have eliminated this wear feature. Either technique allowing the tubing to exit directly where it comes off the cylinder or allowing it to run intracorporally is appropriate and is the surgeon’s choice. Caution should be noted with either technique. If the cylinder is allowed to run intracorporally and extensive scar tissue is present in the corporal body, one should determine that inflation and deflation of the cylinder readily occur. The scar tissue may be so dense that once the cylinder is infla-

An adequate reservoir cavity should be created to minimize the chance of autoinflation. Auto-inflation occurs when the cylinders of a hydraulic penile prosthesis do not stay deflated. The implant patient has a chronic partial erection sometimes causing embarrassment and discomfort. This problem is caused by abdominal pressure or a tight reservoir cavity forcing fluid from the reservoir into the cylinders. If auto-inflation persists, the condition becomes generally irreversible and in need of surgical intervention to expand the reservoir cavity. The body reacts to any foreign body by surrounding the object with a fibrous capsule. All components of a penile prosthesis are surrounded by such a sheath. Earlier series reported the incidence of auto-inflation in 11% of patients with 2% requiring operative correction. \(^2^1\) Mentor Corporation has introduced the “lock-out valve” to prevent the occurrence of auto-inflation (Figure 9). The lock-out valve works by responding to fluid pressure changes in the tubing to the prosthesis and not to pressure from the reservoir. The apical location of this valve modification allows fluid to pass through the system.
flow bi-directionally. During cylinder deflation, the valve opens to positive pressure in the tubing. During cylinder inflation when the collapsed pump bulb recovers, negative pressure opens the valve. The fluid in the reservoir flows in and out due to prosthesis fluid pressure. There must be negative pressure from the pump side for the fluid to flow from the reservoir. Elevated reservoir pressure, such as that due to the Valsalva maneuver, does not result in fluid flow from the reservoir. Follow-up with this reservoir modification has been excellent. When placing the reservoir, care should be taken to avoid placing the lock-out valve against a firm structure such as hard scar or bone. This may indent the valve causing it to malfunction. The usual location for the reservoir is the prevesicle space, either placed through a midline incision or through the inguinal canal. If this area however is excessively scarred following pelvic surgery, then the reservoir can be placed in an alternative location, such as within the peritoneal cavity. If this is done however, the reservoir should be placed against the pelvic wall and not allowed to float freely within the abdominal cavity. The bowel can readily be intertwined around a reservoir floating freely in the peritoneal cavity which can result in bowel obstruction. In addition, there should be no pressure on the tubing pulling the reservoir against a viscus as erosion of the reservoir into bowel and bladder has been reported [22]. The circumstances in which this has happened have been those in which there has been pressure pushing the foreign body against the wall of the viscus. In addition to the peritoneal cavity an extrapelvic location of the reservoir is also an option. The epigastric placement of the reservoir is certainly appropriate and this can be accomplished by an upper abdominal incision, incision of the aponeurosis of the external oblique with separation of the internal oblique and transversalis muscle fibers. Preperitoneal placement is possible and the tubing can then be tunneled down to the prepubic or scrotal area for connection with the tubing leading to the pump. This location is also appropriate for placement of a three-piece prosthesis in renal transplant patients or those awaiting transplant. This will obviate the need for dealing with prosthetic parts or reservoir when operating on the transplanted kidney. Fluid placed in the reservoir should be slightly less than the reservoir capacity, but at least 10 ccs more than the volume of the inflated penile cylinders. This will permit some expansion of the cylinders which may occur as scar is stretched in the postoperative period.

With the infrapubic approach, the prosthesis pump is placed freely in the scrotum after an adequate subcutaneous pocket has been created. A large Hegar dilator, size 20, has proven helpful in achieving an adequate space for pump placement. The pump should be placed anterior to the testis and as far inferiorly in the scrotum as possible. Patients are encouraged to push down on the pump gently in the first few weeks in the postoperative period to maintain this dependent position. If it migrates to the location adjacent to the shaft of the penis, it becomes difficult to operate and inconvenient during intercourse. When the scrotal approach is used, the pump can be fixed in its location by bring one or more of the tubes exiting the pump through the scrotal septum to prevent the pump from twisting or migrating during the postoperative healing. During the placement of a penile prosthesis, copious irrigations with antibiotic fluid should be stressed. Every five minutes the field is flooded with these irrigations, instilled under force with an Asepto syringe. At the conclusion of the procedure, two layers of subcutaneous and a layer of skin closure are recommended over any prosthetic parts.

VII. RESULTS

Repairs of the early model of inflatable penile prosthesis introduced over 30 years ago were relatively common. One report cited 50% repairs in 5 years following implantation. [23] Manufacturers have eliminated or reinforced areas which have tended to wear, and the products we are seeing today have reliability rates equal to or greater than other mechanical products. In addition, surgeons have gained experience over the years in implantation techniques and proper sizing and placement of parts. A number of recent series have been published which attests to this fact. Milbank and his colleagues have reported a mechanical survival rate at 5 years of 78% using the Ultrex penile implant [24]. Levine, Estrada, and Morgentaler reported 93% survival at 31/2 years with the Ambicor prosthesis. [25] Choi reporting on the reliability of the AMS 700 CXM prosthesis in Asian men, related that 90% were working well at 5 years [26]. Carson, Mulcahy, and Govier reporting in a prospective study on the AMS 700 CX showed an 86% mechanical survival at 5 years [27]. Wilson and his colleagues related that 93% of the enhanced Mentor Alpha I prosthesis were still working well after 5
years following implantation [28]. Govier and co-workers reported that 91% of their prostheses were working well at 3 years. A number of different types of implants were reported in this series [29]. Debocq and colleagues related a series with a mean follow-up of 51/2 years, which showed that the Mentor Alpha had a 96% survival while the AMS 700 Ultrex and CX had an 84% survival [30]. In late 2000, American Medical Systems introduced parylene microcoating as a feature to enhance the 700 series’ cylinder durability and subsequent longevity. Parylene coating is applied via a vapor deposition process, to non-tissue-contacting surfaces only and increases lubricity to the silicone surface, hence reducing friction and wear. This micro-thin (60 millionths of an inch) parylene layer, has been demonstrated in bench testing to add millions of fold and tube wear stress cycles before detectable wear is measured on both sides of the inner tube cylinder component and the inside of the outer tube cylinder component. This feature is expected to further reduce the incidence of revisions with the 700 series inflatable implant. In addition to improving product longevity, this innovation maintains cylinder flaccidity and functionality. Repair rates in the range of 10-20% within the first 5 years are to be expected and when counseling patients, these figures may be quoted.

**VIII. IMPLANT REPAIR**

In the United States, all penile prosthesis sold now have a lifetime warranty. When approaching a patient who needs a repair, one should keep this in mind. A prosthesis which has been in place for a number of years, i.e., two years or more and certainly more than 5 years should be entirely replaced. This provides the extended wear time on all of the parts in place. If the prosthesis develops a malfunction within a few months of placement, consideration should be made to leave in parts which are not defective. This is particularly applicable to the penile cylinders. When the corporal bodies are opened to replace cylinders, scar tissue forms which in time will contract. Patients who have had a number of repairs relate that after each change of cylinders, the penis has become noticeably shorter. If the surgeon plans on leaving parts of the device behind, the first parts of the prosthesis inspected are the connections. These are usually in one location and the connection should then be disassembled and the volume of fluid in the reservoir determined. Each of the parts can then be tested using an ohmmeter. With this technique, the part to be tested is filled with saline. A blunt metal needle is then placed into the tubing leading to that particular part. One limb of the ohmmeter cable is placed on the metal needle, the other limb is placed on a retractor located in another part of the wound. A deflection of the ohmmeter needle would indicate that current is passing from that part to the retractor, i.e., there is a leak in that part and sodium chloride ions are passing through the defect to complete the circuit (Figure 10). That part should then be replaced. If no deflection of the ohmmeter needle occurs while testing a particular part, this would indicate that the wall of the part is intact and sodium chloride ions are unable to pass from the interior of that part to complete the circuit to the retractor in the wound. Filling parts of the implant with contrast material and then checking for extravasation with an x-ray has also been used to detect the site of leakage. When incising scar tissue over the tubing electrocautery is helpful. The setting should be less than 35 watts. Higher currents will not damage the silicone, but will be detrimental to the polyurethane coating of the Mentor device [31]. For repairs, it is important to check for the presence of infection. Recent reports have indicated that on revisions the infection rate is higher than it is with initial implants [32, 33]. The Incidence of positive cultures taken from the wound during repair is also significantly high, even in the absence of signs of infection. For this reason some surgeons are now copiously irrigating the wound of
revision cases with additional antiseptic solution such as hydrogen peroxide and Betadine in addition to the antibiotic irrigations used on all prosthesis cases [34, 35]. Upon placement of the cylinders in revision cases, one should re-measure the length of the corporal bodies. Longer or shorter cylinders may be more appropriate in the particular circumstance.

**IX. SCARRED CORPORAL BODIES**

Peyronie’s Disease is a common condition in which scar replaces the natural elastic covering of the corporal bodies. This is usually a focal scar which results in curvature of the penis towards the side of the scar as the tunica albuginea no longer expands in this area. If hydraulic penile implant cylinders are to be placed in scarred corporal bodies, the Ulnex type should not be used [36]. This tends to expand distally, completely filling the end to corporal bodies and not allowing the ends to shift over the body of the cylinder. If the AMS CX or the Mentor cylinders are used which do not expand distally, then the corporal bodies can shift over these cylinders and the intrinsic rigidity of the cylinders will usually straighten the penis very adequately [37]. If one has used Ulnex cylinders and finds that curvature of the erection when these cylinders are inflated occurs, they should be switched to the CX variety, which will usually straighten the penis very adequately. If hydraulic cylinders are placed and significant curvature of the penis persists, then a modeling technique described by Wilson and his colleagues can be tried [38]. With this technique cylinders are inflated to maximum. The tubing leading to the cylinders is then clamped and the cylinder is forcibly bent against the curve and held for 90 seconds. A feeling of the scar tearing can sometimes be appreciated during this maneuver. The cylinders are then reinflated to determine if straightening has been achieved. If significant curvature persists despite this initial modeling maneuver, then the modeling can be repeated. A high percentage of curved erections can be straightened using this technique. One should then maintain the penis in the semierect position for two months following this procedure to allow the scar to heal in the straight position. The corporotomy closures are checked for rupture and the urethra is inspected for injury as this has been reported during this modeling maneuver. If modeling has failed to straighten the penis, then a formal straightening procedure can be performed. The Nesbit technique has been used successfully in this regard [39]. Using this operation, elliptical wedges of tunica albuginea are removed from the convex surface of the curve. The cautery device is useful for this purpose and will avoid damaging the prosthesis with a sharp instrument. The edges of the tunica albuginea are then approximated using long term absorbable suture such as PDS. An alternative procedure would be to incise the concave or inner surface of the curvature. The cylinders are then inflated and the wedge-shaped defect is obvious. This defect can then be covered using graft material. A Gortex or Dacron graft was used for this purpose and permanent suture was employed to attach the graft to the tunica albuginea. Recently SIS (porcine small intestinal submucosa) and Tutoplast (cadaver pericardium) which are more natural materials have been used very satisfactorily [40, 41]. If the latter materials are used a long term absorbable suture can be used to attach the graft to the tunica albuginea. A 10% larger size graft than the gap should be used when these natural materials are employed due to contracture of the graft over the long term. Occasionally the circumstance is encountered where the wall of the tunica albuginea is inadequate to completely cover the prosthesis cylinders without excessive tension. This could follow resection of the tunica, or a situation where excessive scar tissue will not enable the surgeon to close the tunica over the prosthesis without severely narrowing the corporal cavity. In this case, these graft materials, either synthetic or natural may be used to reinforce the wall and replace the wall to give complete covering of the cylinder and adequate caliber to the corporal body (Figure 11). The technique of placing these grafts is similar to that described for straightening the erection with the cylinder in place. Austoni et al. used a variety of grafts as strips placed to fill longitudinal incisions in the tunica albuginea to broaden the caliber of the corporal bodies enhancing girth in association with hydraulic implant placement (Figure 12) [42]. A narrow caliber of the corporal body can be made larger using the Otis urethrotome to incise the scar sharply or various cavernotomes which shave slivers of scar as the instruments are maneuvered backward and forward. Deformities or malposition of implant cylinders can usually be detected by palpation of the penile shaft. However, if palpation does not give a definitive answer, MRI (Magnetic Resonance Imaging) of the corporal bodies will clearly delineate the location and shape of the cylinders (Figure 13) [43].
Protrusion or extrusion of penile prosthesis cylinders distally out of the corporal body is unusual (Figure 14). Circumstances which may dispose to this are aggressive distal dilation during placement, oversizing of cylinders, i.e., placing wider cylinders, where narrower cylinders may be more appropriate, or excessive pressure against the end of the penis during sexual activity. The protrusion can be repaired using a natural tissue method [44]. A hemi-circumcising tissue is created on the side of the extrusion. A longitudinal corporotomy is made over the cylinder and the cylinder removed from the cavity. The back wall of the sheath that contained the cylinders is then incised and a new plane developed behind this wall down to the distal end of the corporal body (Figures 15-16). This original back wall will now provide the outer covering of the penile prosthesis cylinder. The cylinder is then replaced into the newly created cavity and the outer wall reinforced, closing the original tunica albuginea and adjacent scar tissue with long-term absorbable suture (Figure 17). An alternative approach would be to place a windsock of synthetic material over the end of the prosthesis and replace it into the corporal body as a reinforcement for the distal tunica albuginea [45]. This substitutes one foreign body close to the skin surface for another. Carson compared the two techniques natural tissue repair versus windsock and found that the former was more successful [46]. After corporoplasty the glans may be excessively mobile. Glans fixation may be necessary [47]. In addition, in certain patients following penile prosthesis placement, the glans is noted to be hypermobile, either dorsally, ventrally or in either direction, a condition called SST deformity or floppy glans. A circumcising incision can be made and the tissue under the glans dissected free. A non-absorbable 3-0 suture can then be placed through the glans substance and through the end of the tunica albuginea over the end of the inflated cylinder. The suture is tied securely. The glans is then fixed against the end of the prosthesis cylinder. This can be done in one quadrant, or all four quadrants as needed to securely fix the glans and prevent excessive mobility.
Infection associated with a penile prosthesis is considered a catastrophic event necessitating removal of the device. Today, the rates of infection are low in the range of 1-3% [27,48]. Infection associated with the prosthesis should be considered if the patient has persistent pain beyond two months following the surgery. This would be especially true if the pain is unchanging or even increasing with time. The presence of fever or erythema in the wound with fixation of parts such as the pump to the overlying skin would also be signs that would lead one to suspect an infection being present. If persistent purulent drainage occurs from the wound, especially if this is increased when pressure is placed on parts of the prosthesis such as the cylinder or pump, or if any part of the prosthesis is exposed, this would indicate an infection is present. The use of systemic antibiotics in an attempt to clear such an infection has not been successful. Many organisms which are associated with a penile prosthesis infection produce a biofilm or slim which surrounds the prosthesis parts [49]. This inhibits phagocytosis and provides a barrier to diffusion of antibiotics to the area where the organisms are present. It virtually provides a hiding place for the bacteria. When one is convinced that an infection is present, it is prudent to explore the wound and remove all the implant parts and foreign materials. This would include suture material and any graft material used to rebuild parts of the penis associated with prosthesis surgery. The traditional approach has been to return in 2-6 months, when the infection has cleared to replace a new prosthesis. In this circumstance however, the erection will be noticeably shorter, perhaps 1-2 inches and the placement of the implant cylinders would be more difficult because of development of scar tissue in the penis after infection and cylinder removal. An alternative has been advocated and is gaining popularity, termed a salvage or a rescue procedure [50, 51, 52]. This entails removal of all implant parts and foreign material, cleansing the wound with a series of antiseptic solutions and replacing the prosthesis at the same procedure (Table 1, Table 2). Long-term follow-up has shown that this has been successful in about 84% of cases. This alternative is less successful when the tissue surrounding the implant as well as the implant cavity is infected. This usually occurs soon (1-2 months) after the original surgery for placing the implant when a considerable amount of cellulitis is evident in

**Figure 14**: Extrusion of implant cylinder through end of corporal body into subcutaneous tissue.

**Figure 15**: Incision in back wall of sheath previously containing extruded Implant cylinder.

**Figure 16**: Dilation of new cavity for implant cylinder dorsal and medial to original cavity.
the wound with or without abscess formation. In these circumstances the use of systemic antibiotics (vancomycin-gentamicin) for 48-72 hours prior to the salvage has improved the chances of success. An obvious abscess or fluctuance should also be drained prior to salvage procedure. If fluid is available for culture, the organisms involved can be determined and more appropriate antibiotics substituted systemically for 48-72 hours prior to initiating a salvage procedure. Improvement or resolution of cellulitis suggests that the chance of salvage succeeding would be higher. The advantage of the salvage procedure is that most of the length of the penis will be maintained. In addition, it is easier to place cylinders while the cavities in the corpora cavernosa are open, rather than returning at a later date to create new cavities in scar tissue.

A delayed form of salvage has been advocated [53]. Using this technique, the prosthesis is removed and drains are placed in the wound though which antibiotics can be instilled for about 72 hours. The organisms involved in the infection are certain and more appropriate antibiotics can be substituted if necessary prior to drain removal. The patient is returned to the operating room after 72 hours and a new prosthesis is placed at that time. Delayed salvage involves a longer hospitalization and two operative procedures and is definitely more costly. In addition after three days of an inflammatory process, wound closure may prove difficult, especially in the very thin patient. Success with delayed salvage is similar to that of immediate salvage, and the immediate salvage has become the preferred method.

Contraindications to salvage include tissue necrosis, patients who are severely ill, such as those with life-threatening conditions such as ketoacidosis or sepsis, and those patients in whom bilateral urethral erosion of the prosthesis cylinders has occurred.

Experimental studies in Sprague-Dawley rats by Dhabuwala and Associates demonstrated that coating silicone graft material with antibiotics, particularly rifampin/minocycline, reduced the incidence of graft colonization in contaminated wounds [54]. Minocycline and rifampin have been safely used as a surface treatment in indwelling venous and urinary catheters. It has been demonstrated to be an effective method to provide broad-spectrum inhibitor activity against gram-positive and gram-negative bacteria. This combination is particularly effective against Staphylococcus.

In May 2001, American Medical Systems introduced InhibiZone antibiotic surface treatment of its three piece inflatable implants [55]. InhibiZone is a formulation of minocycline and rifampin, which is impregnated onto the outer surface of the prosthesis, resulting in a mottled orange-yellow covering (Figure 18). Antibiotics impregnated into the device surface elute from the silicone matrix when exposed to a warm, moist environment. Concentrations represent less than a common oral or IV dose. Of theoretical importance, local antimicrobial release will prevent early colonization and the development of a bacterial biofilm layer [49].
The mechanism of antimicrobial activity of minocycline (inhibits protein synthesis) and rifampin (inhibits DNA-dependent RN polymerase) may help reduce the likelihood of developing bacterial resistance to either agent [56]. In-vitro and in-vivo studies have demonstrated that minocycline is effective in retarding the emergence of staphylococcal strains that are resistant to rifampin [57]. Minocycline and rifampin also benefit from not commonly being used in the hospital setting, which may reduce the risk for bacterial resistance developing.

In the largest single clinical experience with Inhibizone, Wilson reported on 234 total inhibizone implants with follow-up of up to 18 months, 73.1% original (n=171) and 26.9% revision (n=63) [58]. There were no infections in the original series and a 1.2% infection rate (n=3) for the revision series. However, there were no staphylococcal infections and all organisms cultured (Enterococcus, Streptococcus, Candida) were resistant to the minocycline/rifampin combination.

In another local approach to prevent bacterial colonization and infection, Mentor Corporation has developed a proprietary hydrophilic coating that inhibits bacterial adherence. A number of recent publications have reported on the efficacy of antibiotic-soaked, hydrophilic-coated substrates.

In a recent study in rabbits, the ability of the new hydrophilic coating was investigated for its ability to prolong the effect of intraoperative antibiotics. Coated and uncoated discs were soaked in antibiotics and the zones of inhibition against 4 microorganisms were studied at various time points from 0 to 5 days. There was statistical benefit in limiting bacterial growth of the coated samples for up to 3 days, especially against Staphylococcus epidermis, the most common organism associated with implant infection. In theory, the anti-adherence properties and the ability to absorb water-based antibiotics will reduce the chances for infection. Mentor Corporation introduced its hydrophilic-coated prosthesis (Titan) in the fall of 2002 (Figure 19). Early follow-up has suggested a clinical benefit for patients implanted with the Titan in regards to reduced infection rates [59].

An important caveat is that the introduction of any new microbe-resisting coating should not allow an implanting surgeon to decrease his vigilance, sterile technique, and use of antibiotics to prevent implant infections. Despite the early reports of benefit from these innovations, a larger number of implantations will need to be performed by a number of different centers and surgeons, followed over time, and analyzed in order to demonstrate statistically a benefit.

Of all the currently available treatments of erectile dysfunction, the penile implant has the highest satisfaction rate. It is the most invasive and least often chosen option, but once these devices are placed, patients and partners are gratified in the vast majority of cases, with the resulting erection. Levine, Estrada, and Morgentaler, reported that 96% of patients and 91% of partners were satisfied with the results of the Ambicor prosthesis [20]. Montorsi in a series of 185 patients from a number of institutions reported on the AMS 700 penile prosthesis with a 98% patient satisfaction rate and 96% partner gratification [60]. In a multi-institutional report from Taiwan, where a
number of prostheses were used on 331 patients, 87% of patients were satisfied with the result [61]. A multi-institution report from Italy surveyed a number of patients with penile implants and Peyronie’s Disease, 79% of the patients were satisfied and 75% of the partners seemed pleased with the result [62]. The major reason for dissatisfaction in these cases was the shorter size of the erection. Others reasons for dissatisfaction include the fact that it did not feel natural, that the sensitivity and drive were not as good as they were in younger years, and that the partner did not have as great a role in creating the erection as she once did. Satisfaction rates are considerably higher than those reported for patients taking medication or using vacuum devices to restore their erections.

By stating that “the glass exhauster should be carefully applied to the part, once a day” 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 [64]. The Viennese physician Otto Lederer made the significant improvement of adding a compression ring to the use of the vacuum device to facilitate an on-demand erection. His “device for the artificial erection of the penis” was patented in Germany in 1913 and four years later in the US a patent was issued. In 1960 Geddings D. Osbon constructed the “Youth equivalent device” for his own personal use and started a company to manufacture this vacuum device in 1974. Only in 1982 he was given final permission by the Food and Drug Administration and received the US patent on March 29th 1983 [65].

The efficacy and safety of the device was first reported in the medical literature by Nadig and colleagues in 1986 [13]. Since that time numerous VCD have been approved by the Food and Drug Administration, although they all share similar device characteristics. VCD are currently recognized as the safest and least expensive treatment available for erectile dysfunction [66-70]. A total of 140 citations in Medline includes randomized controlled trials, a metaanalysis, as well as numerous prospective and retrospective studies. The committee did not review the devices used for the treatment of female sexual dysfunction.

**II. MECHANISM OF ACTION**

VCD cause rigidity by means of negative pressure suction and trapping of blood in the penis with an elastic band, disk or O ring around the base of the penile shaft [70]. Vacuum pressure > 100 mm Hg but not in excess of 225 mmHg is necessary to achieve erection in the majority of patients [71]. The blood is probably trapped in a number of different compartments in the penis, including subcutaneous tissue and the corpus cavernosum. Reduced xenon washout of the corpora cavernosa has been demonstrated with the Erec Aid system [72], and others have shown that the corporal diameters double after vacuum distension and placement of the constriction device [73]. Excessive negative pressure can cause bruising and hematoma and thus a vacuum pressure regulator is essential. Constriction sufficient to maintain rigidity can be maintained without risk for up to 30 minutes.
However, a significant decline in amplitude of the pulse volume occurs. Although persistent reduced blood flow during constriction has been described by one group using plethysmography [71], others found no arterial flow after constriction using duplex Doppler sonography [73].

### III. CANDIDATES

Almost all men with ED can successfully achieve erection with VCD [70]. Success depends on appropriate instruction, and in a recent prospective study 92% of post prostatectomy patients were able to obtain erection by the second demonstration [74]. Although one study reported that men with extensive scarring and deformity of the penis, such as after infected prosthesis, are highly likely to fail with VCD [75], expert opinion suggests that even this population may benefit from VCD. Patient time commitment to obtain and use the VCD was calculated at 1-1.5 days; individual instruction in its use should be provided [70]. Printed material and videotape instructions are less effective in ensuring successful use than demonstration by a physician or experienced medical assistant [76].

### IV. CONTRAINDICATIONS

No absolute contraindications to the use of VCD have a basis in the literature. Although the UK Panel on ED [77] mentions bleeding disorders as a potential reason not to use VCD, at least one prospective study has shown no increased risk of complications of VCD in patients taking warfarin [78]. Thus, the weight of evidence suggests safety for VCD in the face of coagulopathy or anticoagulation therapy.

### V. TYPES OF DEVICES

Only prescription equipment should be used and metal or other inelastic rings are contraindicated [70]. Consisting of a transparent plastic chamber, a manual or battery-powered vacuum and elastic band or other constriction device, the VCD must be of a length and diameter sufficient to accommodate the patient’s penis. Optimum sized openings allow the distended penis to fill the cylinder without allowing scrotal skin to be trapped in the device. A table of devices is listed below (Table 3).

### VI. INSTRUCTIONS

After applying a water-soluble lubricant to the base of the penis and the contact area of the VCD, the penis is placed in the chamber, pressing the base of the chamber tightly against the pubic bone [70]. The vacuum is applied for approximately six minutes. Improved penile rigidity results from the technique of double pumping: applying the vacuum for one to two minutes, releasing pressure and reapplying it for an additional three to four minutes.

To maintain rigidity when the vacuum is released, the constriction device is placed around the base of the penis. In men with severe corporal venoocclusive dysfunction, multiple constriction rings are required to maintain rigidity [79].

### VII. EFFICACY

The VCD causes penile rigidity sufficient for vaginal penetration in most men regardless of the cause of erectile dysfunction [80-82]. The accrued results from nearly 20 clinical trials up to 1994 have been summarized by the AUA Guidelines Panel (Table 4) [70]. The overall probability of achieving return to intercourse with VCD was of 0.757 with a 0.253 probability of drop out provides evidence for the efficacy of VCD.

In the era of oral pharmacotherapy, utilization of VCD appears to be decreasing with only a minority of patients choosing to use the devices and continuing to use them long term [74, 83-85]. In one study men using VCD were given sildenafil; of those who

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Device Name</th>
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<tbody>
<tr>
<td>Osbon</td>
<td>ErecAid</td>
</tr>
<tr>
<td>EuroSurgical</td>
<td>Post-T-vac</td>
</tr>
<tr>
<td>Genesis</td>
<td>Active II/Impulse</td>
</tr>
<tr>
<td>Owen Mumford</td>
<td>Rapport</td>
</tr>
<tr>
<td>Vet Co. UK</td>
<td>Rapport</td>
</tr>
<tr>
<td>Medwatch</td>
<td>Erectase</td>
</tr>
<tr>
<td>Mentor</td>
<td>Rapport</td>
</tr>
</tbody>
</table>

Table 3. List of VCD
successfully achieved erection with both therapies, 2/3 chose oral pharmacotherapy over VCD [86]. Men who fail sildenafil and require intracavernosal injections may be more likely to choose this modality over VCD, as was the case in a randomized crossover trial, although no statistically significant differences in patient or partner satisfaction were noted between the two treatments [78, 87].

Efficacy has been demonstrated in a number of specialized populations including spinal cord injured patients [88], cavernous venoocclusive dysfunction [79], and men with diabetes [81, 82].

Dropout rates seem to have increased compared to earlier data, with 40-65% of patients no longer using the device, despite efficacy, one year later [78, 84, 89]. The VCD should be discussed in an unbiased fashion including advantages and disadvantages [70]. Expert opinion suggests that the VCD remains effective and well accepted in certain couples, usually older and in a stable relationship.

### VIII. SPECIALIZED USES

Case series, case reports, and expert opinion suggest other potential uses for VCD. Vacuum devices have been used to enhance responses and erection quality in patients using ICI [90, 91]. One investigator was able to show an increase in buckling pressure from 117-125 with ICI alone up to 565 mm Hg in combination with ICI [92].

Others have proposed using the VCD to augment tumescence and improve erection quality in men with penile prosthesis [87]. Finally, the device has been used as a tissue expander after saphenous vein grafting of the tunica albuginea, to prevent graft contraction and enhance lengthening and girth enhancement of the penile shaft [93, 94].

### IX. PATIENT SATISFACTION

Patient and partner satisfaction appear to be closely correlated (Table 4) and also depend on successful erection [88]. Erection with VCD differs from normal vascular erection in a lower skin temperature, cyanosis, venous distension and abnormally increased girth. Destabilization of the phallus may occur at the point of constriction, which can impair penetration. Orgasm has been reported in up to 74% of patients in a retrospective case series, although ejaculation is inhibited or altered by the constriction ring [78, 95].

### X. COMPLICATIONS

The probability of discomfort, based on metaanalysis, was calculated at .188 by the AUA Guidelines panel for ED [70]. Severe pain is infrequently reported, as are dropouts for this reason. Local adverse events occur with a probability of .095. These inclu-
de petechiae, which may develop on the skin of the penis as a result of capillary rupture after use of the VCD. Ecchymosis and hematoma are uncommon, but have been reported, particularly in men taking aspirin or other anticoagulant drugs. Altered climax and impaired ejaculation are commonly reported by men using VCD.

Several case reports have documented the onset of penile curvature due to use of the VCD [96-98]. Although it has been suggested that men with spinal cord injuries and other neurological impairment of penile sensation may have complications with the constriction ring [99-101], one prospective study in this population had demonstrated no such adverse events [88].

**XI. ROLE IN TREATMENT**

The AUA Clinical Guidelines recommends that VCD should be discussed in an unbiased fashion including advantages and disadvantages, since VCD’s cause adequate rigidity for penetration in most men regardless of etiology. In order to optimize efficacy and safety, men interested in trying VCD should be given individual instruction in its use. Only VCD’s available by prescription should be used [70].

The UK Guidelines offer the following statements [77]:

Low incidence of side effects; suitable for long term use; suitable for a wide range of patients including those who have failed other therapy. Disadvantages include use in patients with bleeding disorders; lack of spontaneity and cumbersome; erections can be uncomfortable and ejaculation may be impaired; pivoting at base of penis; cold penis for partner; worse ability to attain orgasm vs. ICI with lower satisfaction for patient and partner.

**Future Directions**

Scientific studies are needed to address physiological concerns, both in terms of limits of safe constriction times as well as prospective studies to determine potential beneficial effects of distension, which currently have no scientific basis. Finally, validated anonymous instruments should be used to quantify erectile function and patient and partner satisfaction with the devices.
II. INDICATIONS AND CONTRAINDICATIONS

Evaluation for penile vascular disease and its classification ranges from simple pharmacotesting to advanced dynamic duplex ultrasonography and selective pelvic arteriography. Dynamic duplex ultrasonography is an ideal screening tool for functional assessment of arterial inflow and the corporovenous occlusive mechanism but is operator dependent and cannot provide a comprehensive 3-dimensional vascular image. Selective pudendal arteriography is more accurate in identifying the location of arterial lesions due to a significant incidence of anatomic variants. [108,109] Penile magnetic resonance angiography and multi-slice computed tomography reconstruction are less invasive anatomic studies but the current technology lacks the resolution achieved by digital subtraction angiographic techniques. [110,111]

There is no agreement in the literature on the testing regimen necessary to identify the ideal patient for revascularization procedures. [112,113] Patient selection has been wide ranging though there is an assumption of avoiding older patients, those with diffuse atherosclerosis, diabetics, and those who continue to smoke. Other series could not identify a preoperative risk factor that predicted a poor revascularization outcome [114] Corpus cavernosum electromyography, and cavernosal smooth muscle biopsy may have prognostic value but larger studies are required to determine their role in patient selection. [115] Choice of the specific procedure is generally based upon the surgeon’s preference; the only specific caution is in using dorsal artery revascularization in patients with significant corporovenous occlusive dysfunction.

III. SURGICAL TECHNIQUE

The epigastric artery is generally the inflow vessel utilized, though a short segment of reversed saphenous vein arising from the femoral vessels can also be used. Harvesting of the epigastric artery is by a paramedian incision or a laparoscopic technique [116]. The inferior epigastric artery and vein are isolated and divided at the level of the umbilicus to provide adequate length and tunneled through the subcutaneous tissue to the base of the penis. Local Paphaverine irrigation is used to prevent vasospasm and systemic heparinization is administered. The penile vessels are approached through a longitudinal incision made at the base of the penis. Buck’s fascia is incised and the vessels are prepared for anastomosis with surgical magnification with care being taken to avoid injury by division or retraction of the dorsal penile nerves.

An end-side anastomosis is performed between the epigastric artery and the proximal dorsal penile artery. (Figure 20) Interrupted sutures of 9-0 to 11-0 nylon are placed using standard microsurgical technique. The contralateral dorsal artery can be anastomosed end-side with the same vessel via a side branch of the epigastric artery or a side-to-side anastomosis can be done.

![Figure 20: Epigastric Artery to dorsal artery end to side anastomosis.](image)

IV. DEEP DORSAL VEIN ARTERIALIZATION (DDVA) PROCEDURES

The deep dorsal vein of the penis is isolated from the suspensory ligament to the distal retro-coronal plexus. In the Virag procedure the dorsal vein is opened and the venous valves rendered incompetent by a vasculotome whereas the Furlow-Fisher modification leaves them intact. The circumflex and emissary collaterals are identified and ligated. Sarramon’s modification leaves these collaterals intact. The epi-
gastric artery is anastomosed end-to-side to the proximal deep dorsal vein with interrupted sutures of 9-0 nylon. Upon completion of the anastomosis the dorsal vein is ligated proximal to the anastomosis and distally at the retrocoronal venous plexus. (Figure 21)

V. ARTERIOVENOUS REVASCULARIZATION PROCEDURES

In the original description by Hauri the vessels are prepared as above. The dorsal penile artery and dorsal penile vein are opened longitudinally for an extended length (~1.5-2.0 cm) and the adjacent wall of each closed with 7-0 continuous suture creating a common back wall. The epigastric artery is then opened for approximately 2 cm and anastomosed to the arterio-venous lumen with continuous absorbable suture to fashion a funnel shaped opening. (Figure 22) A modification of this procedure is described by Loblenz that divides the dorsal artery followed by proximal and distal end-to-side anastomoses into the arterialized deep dorsal vein [117] (Figure 23)

VI. HEMODYNAMIC CHANGES OF PENILE REVASCULARIZATION

The mechanism by which a successful outcome is achieved has not been fully elucidated. Postoperative selective angiography following dorsal artery revascularization has shown distal arterial outflow and retrograde filling of the cavernosal arteries. The original concept of correction of penile hemodynamics with increased venous outflow resistance and retrograde penile vascularization following venous arterialization has not been conclusively demonstrated. [118, 119]. Post revascularization penile perfusion and scintigraphy by Drawz demonstrates perfusion of the cavernosal bodies during erection. This functional study was consistent with Doppler anastomotic patency. There was no report of correlation with
patient reported erection improvement [120]. It has been proposed that increased intracavernosal endothelial nitric oxide synthase production as a result of the vascular shear stress and increased oxygen tension is associated with a chronic arteriovenous fistula. Additional microstructural protection may be afforded with reduction of transforming growth factor-ß1-induced collagen synthesis [121,122,123].

VII. OUTCOMES OF PENILE REVASCULARIZATION

. The available literature before 1993 contains small studies with various entry criteria and definitions of treatment success. [124] A total of seven peer-reviewed papers and one recent abstract were published and the data extracted in a manner consistent with the working documents of the 1993 AUA guidelines. (Table 5 (next page) – Table 6) To allow comparative outcome statements, the broadest definition of treatment success was used. Success was defined as a patient reporting “any” return of erectile function sufficient for intercourse. A qualitative comparison of erectile capacity was not possible to capture in a meaningful manner. Additionally, improved function was defined as a response to pharmacologic augmentation, which may include vasoactive injection or oral PDE5 inhibitors, though the proportion of each therapy was not reported. Additional data was captured through sub-group analyses, where specific populations were identified. Surgical complications, where listed, were compiled according to surgical procedure.

The goal of an invasive vascular procedure for erectile dysfunction is to provide a durable and satisfactory spontaneous erection with sexual stimulation without relying on pharmacologic augmentation.


<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>N</th>
<th>Unassisted</th>
<th>Assisted</th>
<th>Failure</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;50</td>
<td>53</td>
<td>40%</td>
<td>19%</td>
<td>42%</td>
<td>0.35</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9</td>
<td>56%</td>
<td>11%</td>
<td>33%</td>
<td>0.77</td>
</tr>
<tr>
<td>Smoker</td>
<td>26</td>
<td>62%</td>
<td>9%</td>
<td>29%</td>
<td>0.16</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>60%</td>
<td>0%</td>
<td>40%</td>
<td>0.41</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>9</td>
<td>44%</td>
<td>11%</td>
<td>44%</td>
<td>0.87</td>
</tr>
<tr>
<td>ED Duration &gt;3 yrs.</td>
<td>27</td>
<td>50%</td>
<td>8%</td>
<td>42%</td>
<td>0.9</td>
</tr>
<tr>
<td>Positive ICI test</td>
<td>10</td>
<td>60%</td>
<td>10%</td>
<td>30%</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Using this narrowest criteria success ranged from 27-94% for all procedures with no identified difference in success between the dorsal arterIALIZATION, DDVA, or arterio-venous surgeries. Postoperative vasoactive therapy allowed an additional 15-47% to achieve erections sufficient for intercourse, but it is unclear the proportion of men who were non-responders to this therapy preoperatively.

In Sarramon’s series, postoperative evaluation with the IIEF instrument showed a significant improvement in all domains compared to the control erectile dysfunction group from which the instrument was derived [125]. However, there was a significant reduction in erectile function when compared to the control population. 28% had a successful outcome using the arbitrary “normal erection” IIEF erectile domain sum score of >26, and an additional 26% were classified as “mild” (IIEF ED: 22-25).

VIII. COMPLICATIONS OF REVASCULARIZATION

Penile revascularization appears to be well tolerated and early anastomotic thrombosis is unusual. Significant complications appear to be procedure specific, particularly with venous or arterio-venous revascularization. Glans hypervascularization occurred 0-21% in 5/6 series requiring distal ligation, epigastric banding or arterial ligation in most cases (Table 7).

D. SURGERY FOR CORPORAL VENO-OCCCLUSIVE DYSFUNCTION (CVOD)

In 1873 the Italian Francesco Parona 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.126

At the turn of the century surgical dorsal vein ligation or resection was practiced by several American doctors, as e.g. Henry Raymond (1895), James Duncan (1895), Joe Wooten (1902) and mainly Frank...
<table>
<thead>
<tr>
<th>Study</th>
<th>No Pts.</th>
<th>Procedure</th>
<th>Age</th>
<th>F/U: Mos. (range)</th>
<th>% Success (Unassisted)</th>
<th>% Success (Assisted)</th>
<th>Overall Intercourse</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jarow [1]</td>
<td>11</td>
<td>Dorsal Artery</td>
<td>9</td>
<td>n/a</td>
<td>50 (12-84)</td>
<td>64%</td>
<td>28%</td>
<td>92% 10/11 patent</td>
</tr>
<tr>
<td>DePalma [2]</td>
<td>12</td>
<td>Dorsal Artery</td>
<td>n/a</td>
<td>33 (12-48)</td>
<td>27%</td>
<td>n/a</td>
<td>n/a</td>
<td>--</td>
</tr>
<tr>
<td>DePalma [2]</td>
<td>12</td>
<td>DDVA (F-F)</td>
<td>n/a</td>
<td>35 (12-84)</td>
<td>33%</td>
<td>47%</td>
<td>90%</td>
<td>--</td>
</tr>
<tr>
<td>Lukkarinen [3]</td>
<td>24</td>
<td>V5</td>
<td>6</td>
<td>n/a</td>
<td>46%</td>
<td>n/a</td>
<td>77%</td>
<td>No difference in outcomes by age at operation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hauri</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>F-F</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manning [4]</td>
<td>62</td>
<td>Virag</td>
<td>7</td>
<td>48 (19-70)</td>
<td>34%</td>
<td>20%</td>
<td>54%</td>
<td>Patency: 92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hauri Mannheim</td>
<td>1342</td>
<td>41 (18-72)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manning [6]</td>
<td>42</td>
<td>DDVA (Mannheim)</td>
<td>n/a</td>
<td></td>
<td>31%</td>
<td>26%</td>
<td>57%</td>
<td>&lt;50 Y.O.: 83% success</td>
</tr>
<tr>
<td>Kawanishi [5]</td>
<td>18</td>
<td>Dorsal art.</td>
<td>1</td>
<td>33 (1/18 &gt;50 yo)</td>
<td>94%</td>
<td>0%</td>
<td>94%</td>
<td>17/19 patent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hauri</td>
<td>5</td>
<td></td>
<td>32 (4.80)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>F-F</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Outcomes Data Table for Penile Revascularization

<table>
<thead>
<tr>
<th>Study</th>
<th>No Pts.</th>
<th>Procedure</th>
<th>Age</th>
<th>F/U: Mos. (range)</th>
<th>% Success (Unassisted)</th>
<th>% Success (Assisted)</th>
<th>Overall Intercourse</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarramon</td>
<td>114</td>
<td>Dorsal art. 44</td>
<td>47.5 (20.74)</td>
<td>17 (1-120)</td>
<td>48%</td>
<td>15%</td>
<td>63%</td>
<td>No difference in outcome by procedure (p=0.064)</td>
</tr>
<tr>
<td>Sarramon</td>
<td>38</td>
<td>DDVA (F-F)</td>
<td>52</td>
<td>61</td>
<td>25%</td>
<td>n/a</td>
<td>n/a</td>
<td>28% IIEF EF&gt;20</td>
</tr>
<tr>
<td>Vardi</td>
<td>61</td>
<td>n/a</td>
<td>20-50</td>
<td>60 (24-120)</td>
<td>48%</td>
<td>n/a</td>
<td>n/a</td>
<td>CVOD success: 64% Arterial Ds. success: 44%</td>
</tr>
</tbody>
</table>

References For Table 5:
Table 7. Complications of penile revascularization

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Pts.</th>
<th>Procedure</th>
<th>Significant Complication Reported</th>
<th>%</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jrone</td>
<td>11</td>
<td>DDVA</td>
<td>Rectos sheath hemorag. Anamotosis disruption</td>
<td>0.9%</td>
<td>–</td>
</tr>
<tr>
<td>DePalma</td>
<td>12</td>
<td>DDVA (F-F)</td>
<td>Glass hypervasc.</td>
<td>2/12</td>
<td>2/2 distal ligation</td>
</tr>
<tr>
<td>Lakkarem</td>
<td>24</td>
<td>DDVA 28</td>
<td>Wound hernia</td>
<td>1/24</td>
<td>3/3 distal ligation</td>
</tr>
<tr>
<td>Manning</td>
<td>62</td>
<td>Hausti 34</td>
<td>Shunt thrombosis</td>
<td>5/62</td>
<td>4/8 distal ligation</td>
</tr>
<tr>
<td>Kawanishi</td>
<td>19</td>
<td>F-F 13</td>
<td>Glass hypervasc.</td>
<td>2/28</td>
<td>(2/4 epigastric ligation)</td>
</tr>
<tr>
<td>Sarramon</td>
<td>114</td>
<td>DDVA 70</td>
<td>Hematuria</td>
<td>9/114</td>
<td>11/15: epigastric banding</td>
</tr>
</tbody>
</table>

Lydston (1908), who reported on 100 resections [127].

Beginning in the 1930’s Oswald Swinney Lowsley was the next protagonist of surgical treatment for corporo-veno-occlusive dysfunction. [128] 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. After his initial report in 1935, he could follow-up 273 patients of the more than 1000 patients operated upon in his later publication from 1953. [129]

After these techniques disappeared from medical literature the rebirth of corporo-veno-occlusive dysfunction surgery took place in the 1980’s as a result of the new area of investigation of erectile physiology. [130]

In the physiologic model of normal erectile function an intact veno-occlusive mechanism is necessary to maintain the mechanical erection resulting from smooth muscle relaxation and increased arterial inflow. Reduction of venous outflow may improve erectile response, assuming normal arterial inflow and the absence of significant alterations of smooth muscle function. The location and degree of venous leak is variable, and can occur anywhere along the tunica albuginea of the corpus cavernosum. [131] Diagnostic dynamic duplex ultrasound can assess arterial function and the presence of significant cavernosal venous leakage by measuring peak arterial flow and the calculated resistive index. [132] Localization and severity of veno-occlusive dysfunction may be determined by invasive dynamic intracavernosal cavernosometry and cavernosography (DICC). [133] The technical goal of therapy addresses the identified malfunctioning or ectopic deep dorsal, crural, or cavernosal veins. The surgical procedure has, over time, been expanded from simple deep dorsal vein ligation to extensive surgical exposure and vein ligation, excision, crural plication and spongiosilysis performed alone or in combination. [134] Alternatively, venous arterialization has been applied to decrease venous outflow, particularly when coupled with crural venous ligation or crural ligation and can be used in cases of mixed (arterial/venous) vasculogenic erectile dysfunction. [135,136,137,138] Antegrade or retrograde embolization with microcoils, sclerosing agents, or cyanoacrylate has been reported as a less invasive procedure. [139,140,141] The antegrade embolization is more technically demanding but in both approaches intraoperative demonstration of successful venous occlusion by cavernosography or cavernosal flow rate reduction can be identified. Combined surgical ligation and embolization has also been described. [142]

**II. OUTCOMES OF VENOUS LIGATION SURGERY**

Successful outcome of venous ligation surgery is the return to satisfactory intercourse. This implies sufficient rigidity and duration, ejaculatory control, and a supportive relationship. Improved erections can be interpreted as converting a non-responder to oral or vasoactive injection therapy or a reduction in dose required for successful intercourse. This may have a secondary benefit in ameliorating the release of intracavernosal drugs into the systemic circulation. Most studies presented are retrospective analyses, relying on the patient’s report of his sexual functioning. No study has reported use of standardized questionnaires for subjective improvement, nor has improvement in quality of life as a result of the surgical intervention been reported.

There are generally no postoperative quantitative vascular assessments, except in those cases of poor response to the intervention. There is a time related decline in successful function, presumably through incomplete ligation, recanalization, cavernosa-spongiosum leak, or unrecognized presence/progression of arterial pathology and/or smooth muscle dysfunction. [143,144]

Meaningful data comparison between surgical series is not possible due to the varying diagnostic criteria, selection criteria, surgical techniques and varied length of follow-up and outcome assessment. (Table 8) Case series with follow-up of more than one year consistently show a defined unassisted success rate of less than 50%. [145,146,147,148,149]

In an attempt to define patient selection criteria Sasso selected patients based upon mild cavernosal leak, >30% cavernous smooth muscle by biopsy, cavernosal oxygen tension >65 mm Hg, normal corpus cavernosum EMG, and age <50. Each patient met at least 3 of the above criteria and underwent ligation of the superficial, DDV, circumflex and emissary veins in addition to crural suture compression. In this highly select group 50% of patients at long term follow-up (>1 year) reported unassisted erections and 22% responded to vasoactive injections. [150]
<table>
<thead>
<tr>
<th>Study</th>
<th>Date</th>
<th># of Pts.</th>
<th>Age</th>
<th>Proced</th>
<th>Followup</th>
<th>Outcome Type</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sasso [1]</td>
<td>1999</td>
<td>23</td>
<td>20-50 (mean 41)</td>
<td>Superficial deep dorsal, Circumflex and Emissary vein ligation</td>
<td>12 months, long-term</td>
<td>Not specified</td>
<td>74% spontaneous erection at 12 months 55% long-term</td>
</tr>
<tr>
<td>Popken [2]</td>
<td>1999</td>
<td>122</td>
<td>19-78 (mean 49)</td>
<td>Superficial, deep, and circumflex vein ligation</td>
<td>70 months</td>
<td>Questionnaire</td>
<td>14% Spontaneous erections 19% ICI response</td>
</tr>
<tr>
<td>Lukkarinen [4]</td>
<td>1998</td>
<td>21</td>
<td>NA</td>
<td>Ligation DDV, +/- Cavernosal veins</td>
<td>Min. 1 yr</td>
<td>Pt report</td>
<td>29% ‘good’ 52% ICI</td>
</tr>
</tbody>
</table>

DDV = deep dorsal vein; US = ultrasonography ICI = intracavernous injection NA = not available

Adapted from RAO AND DONATUCCI Urol Cl. N.A.: 22:316, 2001 Ref. 146

References for Table 8
Surgical complications of wound infection, penile curvature, skin necrosis, and painful erections have been reported. Transient proximal penile numbness can occur, and is thought to result from neuropraxia at the time of penile suspensory ligament division.

IV. VENOUS EMBOLIZATION

Interventional radiology treatment as a minimally invasive technology for CVOD has progressed with improvements in techniques, imaging, and sclerosing agents. It has the advantage of small incisions or a percutaneous access to the offending veins, intraoperative monitoring of intracavernosal flow rates, and immediate confirmation of venous ablation. [151,152]. A transfemoral intraluminal approach provides access to multiple veins but requires significant expertise and may be limited by the number of veins that can be successfully visualized and occluded. A retrograde approach via the deep dorsal vein is technically simpler, but will not address coexisting crural venous pathology.

V. RESULTS OF VENOUS EMBOLIZATION/SCLEROSIS

Several recent small series report results on a population that is generally older than most surgical series. The results, shown in Table 9, demonstrate a long term patient reported success of 26-69%. Younger patients with a lesser degree of CVOD and near normal intracavernous oxygen tension had better outcomes [153].

VI. COMPLICATIONS

The procedures were well tolerated with transient “vascular pain” and penile edema in most patients. Mild symptoms of alcohol intoxication was reported in all patients when this treatment was used. [113]

VII. VENOUS ARTERIALIZATION FOR CVOD

Venous arterialization can be utilized for patients with significant CVOD and expands the potential candidate pool by including those patients with mixed arterial and venous pathology.

VIII. RESULTS OF VENOUS ARTERIALIZATION

The outcome data specific to venous arterialization surgical therapy for pure CVOD is limited. Results of venous arterialization of selected studies are presented in Table 10. Kayigil’s series of 25 patients include a retrospective application of IIEF Q3/Q4 for postoperative efficacy. This demonstrated a significant improvement in postoperative erectile functioning with a statistically significant improvement of mean scores. (Q3 1.55?3.44, Q4: 1.33?3.27). [154] Both studies identified a correlation between the length of follow-up and a reduction in defined success that stabilized at more than one year.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Age</th>
<th>Technique</th>
<th>Agent</th>
<th>Followup</th>
<th>Outcome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arjona, 2001 1</td>
<td>23</td>
<td>63</td>
<td>Transfemoral catheter</td>
<td>Balloons/EtOH</td>
<td>22 mos.</td>
<td>26% complete</td>
</tr>
<tr>
<td>Miwa, 2001</td>
<td>10</td>
<td>67.1</td>
<td>Open DDV cannulization</td>
<td>Absolute EtOH</td>
<td>32 mos.</td>
<td>50% complete</td>
</tr>
</tbody>
</table>

* By patient report

The concept of surgically correctable erectile dysfunction that restores sexual function without the need for pharmacological agent or implantable device is very appealing. However, the application of these procedures in the highly selected patient by surgeons experienced with the various techniques results in a variable outcome. The precise mechanism by which these procedures yield their benefit has not been fully elucidated. 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 [155,156].

There is still a need for further study with well defined diagnostic criteria, surgical techniques, and standardized patient and partner outcome assessment. Development of validated instruments to assess surgical outcomes have not demonstrated the necessary surgical simplicity and reproducibility of results to make them a widely applicable treatment option for erectile dysfunction [155,156].

IX. SUMMARY AND RECOMMENDATIONS

The concept of surgically correctable erectile dysfunction that restores sexual function without the need for pharmacological agent or implantable device is very appealing. However, the application of these procedures in the highly selected patient by surgeons experienced with the various techniques results in a variable outcome. The precise mechanism by which these procedures yield their benefit has not been fully elucidated. 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 [155,156].

There is still a need for further study with well defined diagnostic criteria, surgical techniques, and standardized patient and partner outcome assessment. Development of validated instruments to assess surgical outcomes is important and may allow comparison to currently available medical therapy. Though the greatest level of confidence identifying specific outcomes is achieved with randomized controlled trials, this is unlikely to be accomplished. Continued data collection by those surgeons performing vascular procedures must be done with attention to presenting the outcomes data clearly. This would allow capture of the pertinent data to fulfill the criteria of Evidence-Based-Medicine.

Previously, the NIH Consensus Development Conference Statement (1993) and the Clinical Guidelines Panel on ED of the American Urological Association (1996) concluded that the use of penile ligation and penile revascularization should be performed in a research setting with long-term follow-up available. [157,70] The small number of patients with well documented vasculogenic erectile dysfunction failing other treatment modalities is small and the expertise and volume required for technical success places these procedures outside of a general urological or surgical practice. 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. The committee recommends that all patients be given detailed informed consent of the current uncertainties of this procedure, alternative therapies and the need for long term follow-up. If venous or arterio-venous revascularization procedures are being considered, then additional discussion of glans hypervascularization complications and the high probability for secondary corrective surgery is required. It is the hope of this committee that as time and research progresses, the standardization of the diagnosis and treatment of penile vascular disease will determine the patient attributes and specific surgical procedure that will provide predictable and durable results.

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103. CARSTENSEN G Treatment of impotencia coeundi by reconstructing the circulation in the internal iliac artery [in German]. Langebecks arch chir (1969) 325:885-888.


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Committee 14

Pharmacotherapy for Erectile Dysfunction

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G. Christ (USA)

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| 1.II. MELANOCORTIN AGONIST: MELANOTAN II and PT-141 | 4.III. TOPICAL MINOXIDIL |
| 1.III. TRAZODONE | 4.IV. TOPICAL PAPAVERINE |
| 1.IV. DELEQUAMINE | 4.V. TOPICAL NITROGLYCERIN |
| 1.V. NALMEFENE | B. EVIDENCE-BASED REVIEW OF ED PHARMACOTHERAPIES |
| 1.VI. NALTREXONE | I. INTRODUCTION |
| 2. CENTRALLY AND PERIPHERALLY ACTIVE | II. ORAL ED PHARMACOTHERAPIES |
| 2.I. YOHIMBINE | III. LOCAL ED THERAPIES |
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| 3. PERIPHERALLY ACTIVE | 3.I. PDE 5 INHIBITORS |
| 3.II. VASOACTIVE INTESTINAL POLYPEPTIDE | 3.II. L-ARGININE |
| 3.III. ALPROSTADIL (PGE1) | 3.IV. PAPAVERINE |
| 3.V. PAPAVERINE | 3.VI. COMBINATIONS |
As is clear from the other chapters in this compendium, incredible advances have been made in the understanding, diagnosis and treatment of sexual dysfunction/disorders. In the case of erectile dysfunction, this has led to an improved understanding of the molecular and cellular mechanisms of action of nearly all of the currently used drug therapies. In the sections that follow, the basic research underlying the putative mechanism of action (MOA) of the available centrally and peripherally acting drugs is reviewed. These reviews are accompanied by two summary figures (Figures 1, 2), that provide a conceptual framework for understanding this field of medical therapy. In addition, a detailed summary table (Table 1) is given, which outlines as much as possible, the specific MOA of these drugs. In the last MOA section, which deals with the exciting developments in the PDE5 field, there are three additional figures (Figs. 3-5) and an additional Table (Table 2), to provide an exquisite level of detail about the currently most explosive area of drug research and development in erectile dysfunction.

We hope this material will assist the interested physician/health care provider in better understanding the actions of currently available drugs, and in better educating their patients about the same.
Figure 1: Schematic depiction of the general classification and putative sites of action of the currently used drugs for the treatment of erectile dysfunction.
Figure 2: Schematic diagram showing the mechanism of action and impact of currently used drugs at the level of the corporal smooth muscle cell. +: denotes stimulatory pathway, and -: denotes inhibitory pathway. Where PKA, PKC and PKG denote protein kinases A, C and G respectively, DAG denotes diacyl glycerol, MLC20 denotes myosin light chain, SMPP denotes smooth muscle myosin phosphatase, Cam denotes calmodulin, MLCK denotes myosin light chain kinase, Rho A denotes Rho A kinase, and Gq and Gs denote the G protein coupled to activation of Phospholipase C and adenylate cyclase enzymes, respectively.
Table 1: Mechanism of action summary

(Legend: IC: Intracavernosal; IU: Intaurethral; EP: Prostaglandin receptor; VIP: vasoactive intestinal polypeptide; NTG: nitroglycerine)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mode of Administration</th>
<th>Site of Action</th>
<th>Mechanism of Action</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>Oral</td>
<td>Penis</td>
<td>PDE V Inhibitor: Increased cGMP levels</td>
<td>Increased corporal smooth muscle (CSM) relaxation</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>Oral</td>
<td>Penis</td>
<td>D2-like receptor activation of oxytocinergic neurons</td>
<td>Conditioner/Increases the response to sexual stimulation</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Oral</td>
<td>Penis</td>
<td>Activation of melanocortin receptors (M1; M2; M3)</td>
<td>Conditioner/initiator of penile erection</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>Sublingual</td>
<td>Paraventricular Nucleus (PVN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanocortins/</td>
<td>Subcutaneous</td>
<td>Hypothalamus, Spinal, Penile sensory afferents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanotan H</td>
<td>Subcutaneous</td>
<td>Hypothalamus, Spinal, Penile sensory afferents</td>
<td>Activation of melanocortin receptors (M1; M2; M3)</td>
<td>Conditioner/initiator of penile erection</td>
</tr>
<tr>
<td>PGE2</td>
<td>Topical, IU, IC</td>
<td>Penis</td>
<td>EP2A receptor activation; Increased intracellular cAMP levels</td>
<td>Increased CSM relaxation</td>
</tr>
<tr>
<td>Papaverine</td>
<td>Topical, IC</td>
<td>Penis</td>
<td>Nonspecific PDE inhibitor; Increased cAMP &amp; cGMP levels</td>
<td>Increased CSM relaxation</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Oral</td>
<td>Penis</td>
<td>Blockade of postjunctional α1- &amp; α2-adrenoceptors on corporal smooth muscle cells</td>
<td>Increased CSM relaxation</td>
</tr>
<tr>
<td></td>
<td>Intracavernosal</td>
<td>Penile</td>
<td>Increase supply of NO via nonadrenergic, noncholinergic effect on NOS</td>
<td></td>
</tr>
<tr>
<td>Yohimbine</td>
<td>Oral</td>
<td>CNS</td>
<td>Blockade of prejunctional α1- adrenoceptors in hypothalamus (MPOA)</td>
<td>Conditioner</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Penile</td>
<td>Blockade of postjunctional α1- adrenoceptors on corporal smooth muscle cells</td>
<td>Increased CSM relaxation</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Blockade of prejunctional α1- adrenoceptors penile arteries</td>
<td></td>
</tr>
<tr>
<td>L-Arginine</td>
<td>Oral</td>
<td>Penile</td>
<td>Increased supply of nitric oxide (endothelial, neural)</td>
<td>Increased CSM relaxation</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Oral</td>
<td>Brain</td>
<td>Serotonin reuptake inhibitor</td>
<td>Prolonged erections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Penile</td>
<td>Blockade of postjunctional α1- &amp; α2-adrenoceptors on corporal smooth muscle cells</td>
<td>Increased corporal smooth muscle relaxation</td>
</tr>
<tr>
<td>Delequamine</td>
<td>Oral, IV</td>
<td>CNS</td>
<td>Blockade of prejunctional α1- adrenoceptors in the locus coeruleus</td>
<td>Conditioner</td>
</tr>
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<td></td>
<td></td>
<td>Penile</td>
<td>Blockade of postjunctional α1- adrenoceptors on corporal smooth muscle cells</td>
<td>Increased CSM relaxation</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Oral</td>
<td>CNS</td>
<td>Opioid receptor antagonist; attenuation of altered central opioid function (e.g., LHRH, LH, testosterone)</td>
<td>Conditioner</td>
</tr>
<tr>
<td>VIP</td>
<td>IC</td>
<td>Penile</td>
<td>Increased intracellular cAMP levels</td>
<td>Increased CSM relaxation</td>
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<tr>
<td>Minoxidil</td>
<td>Topical</td>
<td>Penile</td>
<td>K channel modulator; Increased K channel activity</td>
<td>Increased CSM relaxation</td>
</tr>
<tr>
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<td>Topical</td>
<td>Penile</td>
<td>NO donor: Increased cGMP levels</td>
<td>Increased CSM relaxation</td>
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1. CENTRALLY ACTING DRUGS

1.I. APOMORPHINE

Although the mechanisms underlying erectile function are not fully understood, 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 the central enhancer, the dopaminergic substance apomorphine. Apomorphine acts in the paraventricular nucleus of the hypothalamus as a dopamine (D2) receptor agonist. It works as a pro-erectile conditioner at this level to increase the responses of the erectile pathway following appropriate sexual stimulation. Certainly, understanding the role of central pathways/mechanisms in the control of the erectile process is critical to elucidating the mechanism of action of this newer class of orally active erectogenic agents. Chapters 10 & 11 in this volume deal in great detail with this subject, and thus, only a brief summary is given below.

Physiological erections are initiated, in large part, by central stimuli. Depending on the type of stimulus, various areas of the cortex are involved like the occipital region for visual, the rhinencephalic for olfactory, the thalamic for tactile and the limbic region for imaginative stimuli. There is good evidence that these and other stimuli from higher centers are sending inputs to hypothalamic nuclei (medial preoptic area (MPOA), paraventricular nucleus (PVN)). The MPOA contains a high density of neurons that concentrate androgens and shows an extensive interconnection to the limbic system and the lower autonomic brain stem nuclei. 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 MPOA plays an important role in the erectile response, and both pharmacological and electrical stimulation of the MPOA results in erection in anaesthetised rats (Giuliano et al., 1997; Sato & Christ, 2000; Sato et al., 2001). The MPOA is also involved in maternal behaviour (Numan, 1988) thermoregulation (Kanosue et al., 1994) and thirst (Bourque et al., 1994).

The PVN also seems to integrate the input from higher centers (Melis & Argiolas, 2002; Melis et al., 2003) and contains premotor neurones that project directly onto spinal autonomic preganglionic neurones. The PVN plays a key role in the erectile response and pharmacological or electrical stimulation of this small hypothalamic nuclei results in seminal discharge in unanaesthetised rats (Eaton, 1991) and erection and ejaculation in anaesthetised rats (Chen et al., 1997). Dopaminergic neurones belonging to the incertohypothalamic dopaminergic system are the main components of the PVN. These dopaminergic neurones impinge on oxytocin containing neurones (Bujis et al., 1984). The PVN is believed to be the nucleus where apomorphine acts as a dopaminergic substance. From the PVN, signals are then transmitted to the brainstem nuclei (periaqueductal grey (PAG), nucleus paragigantocellularis (nPgi) and raphe nuclei) and then to the periphery of the erectile axis (Marson & McKenna, 1990, 1992; Sancila et al., 2002).

Dopamine is one among a number of important central neurotransmitters involved in the initiation of erection. Dopamine is the main transmitter within the PVN (Eaton, 1991; Allard et al., 2002) that, as discussed above, 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 D3 receptor subtypes. Apomorphine has a higher affinity for the D2-like receptors (Rampin et al., 2003) that are thought to be the main site for the induction of erections in the PVN (Chen et al., 1999) 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 (Brien et al., 2002).

In summary, 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 (Melis & Argiolas, 1996). In this scenario, the presence of nitric oxide is thus mandatory in order to allow for the action of apomorphine. Apomorphine SL has recently been approved for marketing in Europe at the doses of 2 and 3 mg. The erectogenic effects are usually seen within 20 minutes of its administration; provided the presence of an adequate sexual stimulation.

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REFERENCES


1.II. MELANOCORTIN AGONIST: MELANOTAN II and PT-141

Melanotan II is a synthetic nonselective analog of α-melanocyte-stimulating hormone (α-MSH). α-MSH and adrenocorticotrophin, known as the melanocortins, are derived from proteolytic cleavage of the precursor, pro-opiomelanocortin. 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 (Thody AJ et al, 1981, van der Kraan et al, 1998). Through cloning techniques five types of melanocortin receptors (MC1, MC2, MC3, MC4, and MC5) have been characterized (Wikberg et al, 2000).

Injection of α-MSH into the rat hypothalamic periventricular region induces grooming, stretching, yawning and penile erection. Grooming, stretching and yawning but not penile erection seem to be mediated by MC4 receptors which are found almost exclusively in the central nervous system especially in the hypothalamus of the rat (Vergoni et al, 1998; Argiolas et al, 2000). A significant central role for the MC3/MC4 receptor subtypes in modulating the Melanotan II-induced intracorporal pressure increases in the rabbit has been documented (Vemulapalli et al., 2001). Another recent study (Van der Plouw et al., 2002) has provided strong support for an MC4-receptor-mediated proerectile response in spinal cord erectile centers, as well as at the level of the somatosensory afferent nerve terminals in the mouse penis. Moreover, a similar distribution of the MC4 receptor subtype has been found in the corresponding rat and human tissues. Therefore, while the melanocortin receptor subtype(s) that mediate the proerectile effects of Melanotan II/melanocortins...
Trazodone, a serotonin reuptake inhibitor, is a non-tricyclic antidepressant that has been associated with prolonged erection and priapism when administered orally in depressive patients.

In healthy volunteers trazodone dose dependently increased NPT following REM related erections and blocked the detumescence phase of erection, which is under sympathetic control, thereby prolonging the erection (Saenz de Tejada et al, 1991). In vitro, trazodone attenuated human corporal muscle contraction elicited by both electrical stimulation of adrenergic nerves and exogenous noradrenaline (Adaikan & Ratnam, 1988; Saenz de Tejada et al, 1991). Competitive radioligand binding studies indicate that trazodone has high and moderate affinity for human α1- and α2-adrenoceptors, respectively (Krege et al, 2000). In contrast to trazodone, m-chlorophenylpiperazine (m-CPP) did not significantly affect cavernosal contractions induced by electrical stimulation and exogenous noradrenaline (Saenz de Tejada et al, 1991). Thus, the proerectile action of trazodone is likely to be related to the α2-adrenoceptor blocking property of trazodone in erectile tissue.

However, m-CPP, the main metabolite of trazodone, is a serotonin agonist. m-CPP is capable of eliciting an increase in spontaneous firing of the cavernous nerve accompanied by an increase in cavernous pressure in the anaesthetized rat (Steers & de Groat, 1989).

Subcutaneous administration of m-CPP induces penile erection in rats. The proerectile property of m-CPP involves activation of 5-HT-2C receptors localized in the lumbosacral spinal level of the rat (Millan et al, 1997; Bancila et al, 1999). The neuro-modulatory role of m-CPP on penile erectile activity contributing to pharmacological action of trazodone in human is not clear.

### 1.III. TRAZODONE

Delequamine is a more specific and selective α2-adrenoceptor antagonist than yohimbine (Brown et al, 1993). α2-adrenoceptors are present on the noradrenergic cell bodies in the locus coeruleus and their presynaptic terminals throughout the brain. The central effect of α2-adrenoceptor blockade by delequamine is an increased noradrenaline level at the synapse by blocking re-uptake leading to sexual arousal (Bancroft, 2000). In rat mating experiments, delequamine dose dependently increased sexual behaviour, but unlike yohimbine, it did not affect ejaculatory function, which is mediated via 5-HT-1A receptors (Tallentire et al, 1996)

In human corpus cavernosum, norepinephrine (NE) and epinephrine may activate postsynaptic α2-adrenoceptor subtypes, in addition to activating α1-adrenoceptor subtypes, on smooth muscle cells, contributing to local control of human corpus cavernosum smooth muscle tone in vivo (Traish et al, 1997).

A centrally mediated effect of delequamine in humans is supported by the findings that intravenous infusion of low dose of the drug in the normal controls produced an increase in NPT during non-REM sleep, and with the high dose, spontaneous erections occurred just before sleep onset (Bancroft et al, 1995).

During the waking state, normal controls reported significantly higher subjective ratings of sexual arousal before erotic stimulation and increased likelihood of spontaneous erections or significant prolongation of erectile response to visual erotic stimuli following high dose of delequamine (Munoz et al, 1994).

As with the putative α2-adrenoceptor actions yohimbine (see Table 1), delequamine may also have a dual MOA. Specifically, delequamine may serve as a conditioner in the CNS by blocking the prejunctional α2-adrenoceptors and thereby increasing noradrenergic neurotransmission to enhance sexual function. In addition, delequamine may also block distinct prejunctional α2-adrenoceptors that are sympatholytic (blockade increases NO release; see discussion of yohimbine above). Finally, delequamine may provide an additional sympatholytic component via blockade of postsynaptic α2-adrenoceptors on smooth muscle cells (again, promoting relaxation; see Table 1). Obviously, clinical efficacy implies that the balance of the potential sympathomimetic and sympatholytic actions favors the later.
1.VI. NALTREXONE

Naltrexone, derived from naltrexone, is a long-acting opioid receptor antagonist. Intravenous bolus administration of naltrexone in male rhesus monkeys leads to significant increases in plasma LH and testosterone levels with no change in LH or prolactin pulse frequency or amplitude (Mello et al, 2000). Naltrexone treatment in older impotent men also increases the activity of the hypothalamic-pituitary-gonadal axis, which manifests as a significant increase in serum testosterone, LH and FSH, but no change in NPT (Billington et al, 1990).

Apart from exerting inhibitory effects on male sexual drive and performance, endogenous and exogenous opioids also exert an inhibitory influence on hypothalamic LH releasing hormone (LHRH), which stimulates the pulsatile release of LH from pituitary gonadotropes (Crowley & Simpson, 1978; Cushman, 1972; McIntosh et al, 1980, Mirin et al, 1980). Naltrexone and naloxone, which are opiate antagonists, have been shown to facilitate male copulatory behaviour (Wu & Noble, 1986; Myers & Baum, 1979). The facilitatory effect of naloxone on masculine sexual performance in the rat is associated with a drug-induced release of LHRH (Myers & Baum, 1980).

Naltrexone therapy was documented to significantly improve sexual performance in 11 out of 15 idiopathic ED patients (Fabbri et al, 1989). However, in a double blind study of 20 patients with idiopathic ED, Brennemann et al (1993) reported no significant effect on libido and frequency of intercourse. In both studies, naltrexone consistently increases the incidence of spontaneous early morning erections without significant modification of plasma gonadotrophin levels. The efficacy of naltrexone does not appear to be correlated to the hormonal effect of naltrexone.

Naltrexone therapy may, thus, be beneficial in ED patients with altered central opioid tone.

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2. CENTRALLY AND PERIPHERALLY ACTIVE

Yohimbine is an indole alkaloid from the cortex of the Coryanthe yohimbe tree, which has been claimed to have aphrodisiac activity. The principal pharmacological action of yohimbine is as an alpha2-adrenoceptor antagonist. alpha2-adrenoceptors are located both peripherally and centrally (especially in the locus coeruleus neurons; see below), which are associated with sexual arousal and response.

Peripherally, pre- and post-junctional alpha2-adrenoceptors are present in the human penile erectile tissues (Molderings et al, 1989; Traish et al, 1997). Activation of presynaptic alpha2-adrenoceptors in erectile tissue inhibits the release of noradrenaline at the sympathetic nerve endings, hence reducing the sympathetic transmission (Molderings et al, 1989).

Yohimbine then, as a presynaptic alpha2-adrenoceptor antagonist, is expected to increase sympathetic transmission and promote smooth muscle contractility. However, the occurrence of distinct pre-junctional alpha2-adrenoceptors in horse penile resistance arteries has also been reported and stimulation of these receptors inhibit nitricergic transmitter release (Simonsen et al, 1997). Blocking these pre-junctional alpha2-adrenoceptors would, therefore, effectively enhance NO release. As such, blockade of prejunctional alpha2-adrenoceptors can have both sympathomimetic and sympatholytic effects at the end organ (peripheral) level; the balance of these actions presumably favors the latter. This might be one of the mechanisms by which yohimbine induces penile arterial relaxation. Recent data also indicate that yohimbine may mediate relaxation of human and rabbit corpus cavernosum via release of nitric oxide from endothelium, which is androgen dependent (Filippi et al, 2002). Finally, antagonism of post-junctional alpha2-adrenoceptors, which mediate contractions of corpus cavernosum, by yohimbine may play a role in facilitating penile erection.

Experimental data show that central alpha2-adrenoceptors are implicated in the regulation of male sexual behaviour (Sala et al, 1990). Clonidine, a selective alpha2-adrenoceptor agonist, administered intracerebroventricularly or in the medial preoptic area of the
hypothalamus suppressed copulatory behaviour in male rats and yohimbine prevented the copulatory suppression induced by clonidine (Clark, 1991). Yohimbine has also been demonstrated to increase sexual motivation in sexually experienced male rats and induce sexual activity in sexually naive or previously inactive rats (Clark et al., 1984, 1985). In sexually exhausted intact rats, yohimbine is able to reestablish copulatory behavior whereas in rats administered a neurotoxin (DSP4, to cause a lesion in the central noradrenergic system), yohimbine, but not naloxone (opioid antagonist) or 8-OH-DPAT (5HT1A agonist) restored partially sexual performance. These findings indicate that the integrity of the central noradrenergic system is essential for sexual behaviour (Rodriguez-Manzo & Fernandez-Guasti, 1995).

The site of action of yohimbine in human as a pro-erectile agent is not well defined. Yohimbine may act peripherally by dual mechanisms:

1) a post-junctional α2-adrenoceptor antagonist, although the predominant subtype of α-adrenoceptors in penile tissue is of α1-subtype, and

2) By releasing relaxing factors such as nitric oxide.

The effect of intracavernous yohimbine has not been determined, however, intracavernous injection of another α2-adrenoceptor antagonist, idazoxan, had no erectogenic effect in man (Brindley, 1986). Yohimbine, as demonstrated in rats, may presumably act through central α2-adrenoceptor increasing noradrenergic transmission to enhance sexual function in human.

2.II. PHENTOLAMINE

Phentolamine is a non-selective α-adrenoceptor antagonist with similar affinity for α1- and α2-adrenoceptors. Both post-junctional α1- and α2-adrenoceptors mediating contractions are present in corpus cavernosum and penile vascular smooth muscle (Molderings et al., 1989; Christ et al., 1990; Traish et al., 1998; Simonsen et al., 1997). Pre-junctional α2-adrenoceptors in the corpus cavernosum modulate stimulus-evoked release of noradrenaline from sympathetic nerves in the erectile tissue (Molderings et al., 1989), whereas those in the horse penile resistance arteries regulate the release of nitricergic transmitter (Simonsen et al., 1997).

Phentolamine mesylate induced relaxation of corpus cavernosum erectile tissue is thought to occur by direct antagonism of α1- and α2-adrenoceptors, as well as by indirect functional antagonism via a non-adrenergic, endothelium-mediated mechanism suggesting nitric oxide synthase activation (Traish et al., 1998; Vemulpalli & Kurowski, 2001). 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 (Adaikan, 1979; Adaikan et al., 1986; see Chapter 10 for a full description of the role of the α-adrenoceptor pathway in penile erection and detumescence).

Oral/intracavernosal phentolamine therefore may facilitate penile erection by inhibiting the functional predominance of α1-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.

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**3. PERIPHERALLY ACTIVE**

**3.I. PDE 5 INHIBITORS**

Major research efforts have led to the production and development of compounds that are selective and potent in inhibiting particular PDEs (Corbin and Francis, 2002; Ballard et al, 1998; Rotella DP, 2002; Hellstrom et al, 2002; Klotz et al, 2001; Lue 2000; Montorsi et al, 2003; Padma-Nathan et al, 2001; Padma-Nathan et al, 2002; Hellstrom et al, 2003).

The clinical success and public interest have resulted in the generation of an enormous amount of information and data regarding the mechanism of action of these groundbreaking treatments for erectile dysfunction. The salient aspects of this ever growing database are reviewed below.

Sildenafil (Viagra™) is the first commercialized compound in this class. This class has been recently joined by vardenafil (Levitra™) and tadalafil (Cialis™). Vardenafil has a similar structure to sildenafil but the structure of tadalafil is significantly different (Fig. 3). As will be discussed below, vardenafil is more potent than sildenafil in vitro to inhibit PDE5, and this difference is explained by differences (see arrows) in molecular structures of these two compounds. We should note that potency is an in vitro measure of a drug concentration that elicits an action. It is not a direct measure of clinical efficacy. More potent does not necessarily mean more clinically efficient.

Part of the ring structure of sildenafil or vardenafil is similar to that of caffeine (see dashed ovals). This same ring structure is similar to a ring structure in cGMP. This is important since these drugs are competitive inhibitors of cGMP for PDE5, and they presumably form some of the same molecular interactions as cGMP forms with amino acids in PDE5 (hydrogen bonds, hydrophobic stacking interactions, van der Waals contacts, ionic interactions, etc). Even though the tadalafil structure differs significantly from those of the other two inhibitors, its molecular mechanism of action is believed to be similar.

The normal pathway for penile erection (Fig. 4) is initiated by sexual arousal, which stimulates release of nitric oxide at nerve endings in the penis. Another source of nitric oxide is vascular endothelial cells. As described elsewhere in this chapter, nitric oxide diffuses into vascular smooth muscle cells in the penile corpus cavernosum to cause stimulation of guanylyl cyclase and elevation of cGMP in these cells (Ignarro et al, 1990; Burnett et al, 1992). This leads to activation of cGMP-dependent protein kinase (PKG), phosphorylation of several proteins, and lowering of cell 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. The pathway shown in Fig. 4 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 this tissue is deficient/incomplete (Corbin and Francis, 1999; Jeremy et al., 1997).
There is where the PDE5 story comes into play. That is, 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. PDE5 inhibitors increase the cell cGMP by competitively inhibiting PDE5, which triggers penile erection. 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 (Robison et al., 1971), whereby caffeine 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 (Lincoln et al, 1976; Francis et al, 1980). A cartoon of the enzyme structure is shown in Fig. 5. Each of the two subunits of PDE5 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 (paired black structures), which is located very near the catalytic binding site, is brought into close proximity and 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++ (Francis et al, 1994). 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.

Although the catalytic domain of PDE5 is the direct target of PDE5 inhibitors, certain features of the regulatory domain impact the PDE5 inhibitor actions on the enzyme (Corbin et al., 2000; Corbin et al,
This domain contains allosteric cGMP-binding sites (one or two per subunit) as well as a phosphorylation site for negative feedback regulation of the enzyme. PKG phosphorylates this site about 10 times faster than does PKA. When cGMP binds to the allosteric sites, cGMP is not degraded as it is in the catalytic site, but PDE5 enzyme functions are activated by the binding reaction. Phosphorylation also activates PDE5 enzyme functions. However, when PDE5 inhibitor is present, which causes cGMP elevation and phosphorylation, PDE5 inhibitor binding at the catalytic site is expected to be stimulated. 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 100-mg dose of a particular PDE5 inhibitor might be required to induce penile erection in a particular patient.

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 needed (Corbin and Francis, 2002). 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 IC$_{50}$. Highly potent drugs are expected to have affinities (IC$_{50}$ values) in the nanomolar (nM) range. 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 tadalafl to achieve the same degree of in vitro PDE5 inhibition. Vardenafil is therefore more biochemically potent than are sildenafil or tadalafl, although not necessarily more efficacious. 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 recommended doses of tadalafl are also lower than those of sildenafil, but since these two drugs have similar biochemical potencies, the explanation for lower dosage is not clear at this time.

There are methods in addition to classical IC$_{50}$ to measure potency of a drug. The Corbin group has recently measured the strength of binding of radiola-
cGMP. Eleven distinct families have been identified (PDE1 to PDE11) that 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 25 PDE genes, and some of these genes have multiple products brought about by alternative mRNA splicing, resulting in a grand total of more than 50 PDE forms (Francis et al., 2001). 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 (Gopal et al., 2001). Sildenafil and vardenafil cross-react slightly with PDE6, i.e., their IC50s for PDE5 are only 4-10 fold lower than those for PDE6. PDE6 is expressed in the retina. This may explain the complaint of some patients that sildenafil causes visual disturbances. Tadalafil cross reacts with PDE11 to some extent, but the consequences of this effect are unknown. PDE11 is expressed in testicular cells, cardiac muscle, smooth muscle and the pituitary. Neither of the three PDE11 inhibitors cross-reacts to a large extent with any of the other PDEs except for PDE6 and PDE11, i.e., the IC50s 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 tissues outside the penile corpus cavernosum.

In addition to biochemical properties discussed above, pharmacokinetic properties of PDE5 inhibitors (ingestion, movement in the circulation, tissue uptake, elimination) have great impact on efficacy (Corbin and Francis, 2002). There are several common pharmacokinetic parameters that can be measured and quantified that describe bodily distribution of a PDE5 inhibitor (Table 2). The bioavailability, maximum plasma concentration (Cmax), the 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. The bioavailability, which is the percentage of ingested inhibitor that actually appears in the plasma, is about one-third as much for vardenafil (15%) as that forildenafil (40%). The bioavailability for tadalafil is unknown at present.

Sildenafil, vardenafil, and tadalafil have broadly similar Tmax (sildenafil and vardenafil Tmax occurs in less than 1 hour, the tadalafil Tmax occurs in 2 hours), but the Cmax of vardenafil is significantly lower than that for either of the other two inhibitors. This might be expected based on the higher biochemical potency of vardenafil. The t1/2 of tadalafil is considerably longer than that 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 provide a much longer therapeutic effect (Porst et al 2003), which may be preferred for spontaneous sexual activity, but could expose the patient to greater risk of side effects.

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. 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 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, 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 cavernosum cells. Studies of clearance of PDE5 inhibitors from plasma are documented, but studies of clearance of these inhibitors from smooth muscle cells are rare.

<table>
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<tr>
<th>Parameter</th>
<th>Tadalafil</th>
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<td>460</td>
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<td>Bioavailability, %</td>
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REFERENCES


3.II. 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 (Polak et al, 1981).

VIP co-localizes with NOS within the perivascular and trabecular nerve fibres innervating the penis (Ehmke et al, 1995). 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 (Hedlund et al, 2000). Other VIP-related peptides such as PHM, PACAP and helospectin (Hel-1) are also co-localized with VIP in nerve structures within the human cavernous tissue (Kirkeby et al, 1992, Hed-lund et al, 1995). These peptides concentration-dependently relaxed corpus cavernosum and circumflex vein preparations in vitro. Their putative roles as neurotransmitters and/or neuromodulators in the ner- vous control of penile erection are yet to be clearly established.

Though VIP is a potent relaxant of both the corpus cavernosum and penile vascular smooth muscle in vitro, the ineffectiveness of VIP-antiserum to inhibit the neurogenic relaxation in corpus cavernosum strips suggests that VIP may not be released from the
nerves during field stimulation (Adaikan et al., 1986a). Furthermore, the inability of VIP to induce penile rigidity adequate for intromission when injected intracavernously in potent (Adaikan et al., 1986a) and impotent men (Roy et al., 1990) indicates that it is not likely to be the primary neurotransmitter mediating penile erection.

The effects of VIP are mediated by a specific membrane-bound receptor linked to adenylate cyclase via a stimulatory G-protein. VIP has been shown to elevate cAMP concentrations in cavernosal tissues without affecting cGMP levels (Miller et al., 1995; Hedlund et al., 1995).

3.III. L-ARGININE

Nitric oxide, the NANC neurotransmitter of primary importance in regulating corpus cavernosum smooth muscle relaxation, is derived from L-arginine by nitric oxide synthase (NOS). As L-arginine is also a substrate of arginase, NO production is likely to be linked to the regulation of both NOS and arginase. The decreased NOS nerves and upregulated arginase II expression/activity found in diabetic corpus cavernosum, which is accompanied by a decrease in erectile function, suggests that decreased NO synthesis may play a role in diabetic erectile dysfunction (Bivalacqua et al., 2001). Alterations in the penile L-arginine-NO pathway observed in atherosclerotic and hypercholesterolaemic penile vascular bed may also result in reduction in NO bioavailability leading to ED. Recent studies show that L-arginine augments endothelium-dependent vasodilation in hypercholesterolaemic rabbits and human (Girerd XJ et al., 1990; Creager et al., 1992). The rationale for L-arginine therapy is therefore related to the supposition that dietary supplementation with NO-precursor L-arginine may normalize endothelium-dependent vasodilation and as such could have a beneficial effect in the treatment of erectile dysfunction. Based on this rationale, as with other combination therapies, it is conceivable that oral co-administration of L-arginine with yohimbine may be effective in improving erectile function in mild to moderate erectile dysfunction because of the complementary actions of the α2-adrenoceptor antagonist and the NO releasing effects of yohimbine. (see Lebret et al., 2002; see yohimbine discussion above).

3.IV. ALPROSTADIL (PGE1)

PGE1 produced relaxation of human corpus cavernosum smooth muscle and this relaxant activity was first described by Karim and Adaikan (1975) and Adaikan et al. in 1983. This was followed by the mechanism of action and use of PGE1 for the treatment of erectile dysfunction (Adaikan et al., 1986b; Ishii et al., 1986; Virag & Adaikan, 1987). Of note, the first competitive Ginestie Prize by the ISIR was awarded to PG Adaikan for identifying conventional receptors and the use of PGE1 for the treatment of erectile dysfunction in 1986, 2nd World Meeting of Impotence, Prague.

PGE1 mediates relaxation of corpus cavernosum smooth muscle via activation of EP prostaglandin receptors (EP2/4) by increasing the intracellular concentration of cAMP in corpus cavernosum smooth muscle (Palmer et al., 1994; Lin et al., 1995; Traish et al., 1997; Moreland et al., 2001). PGE1-induced relaxation of human corpus cavernosum is associated with activation of KCa channels, leading to hyperpolarisation and alterations in transmembrane Ca2+ flux (Lee et al., 1999). PGE1 may also act by inhibiting the release of noradrenaline from sympathetic nerves (Molderings et al., 1992) and suppressing angiotensin II secretion in the cavernosal tissues (Kifor et al., 1997).

PGE1 is metabolised by the 15-hydroxydehydrogenase present in the corpus cavernosum (Roy et al., 1989). 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-β1 in cultured human corpus cavernosum suggesting that PGE1 and TGF-β1 may play a key role in modulation of collagen synthesis and in the regulation of fibrosis of the corpus cavernosum (Moreland et al., 1995). This suppressant effect seems to correlate with the low incidence of local fibrotic lesions reported in PGE1 treated ED patients (Porst, 1996) and the unaltered intracavernous structures in the 5 patients with biopsies performed only after intracavernous PGE1 injection (Wespes et al., 2000).
Intracavernosal papaverine injection was the first clinically effective pharmacological therapy for ED. Papaverine is a nonopiate derivative of poppy plant (Papaver somniferum). Papaverine is a smooth muscle relaxant. In vitro, papaverine evoked 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 (Adaikan & Ratnam 1988; Kirkeby et al, 1990). In addition, in vivo studies in the rat model documented that intracavernous injection of papaverine elicited a significant and prolonged increase in intracavernous pressure (Rehman et al., 1997). Consistent with these observations, injection with 80 mg papaverine in normal volunteers and subjects with psychogenic impotence produced rigid erections. Papaverine caused marked vasodilation of the penile arteries and decreased venous outflow as recorded by Doppler (Virag et al, 1984).

Papaverine is 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 cavernous 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 (Iguchi et al, 1992; Kifor et al, 1997).

3.V. COMBINATIONS

Phentolamine, papaverine, PGE1, VIP and linsidomine 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, 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 (Kim et al, 2000). 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 α-adrenoceptors, increases the efficacy of vasodilators that initiate erection via other independent relaxatory pathways.

REFERENCES


4. **TOPICAL THERAPIES**

Topical therapy for the treatment of ED has been proposed as one means to circumvent some of the negative factors associated with ICI (intracavernous injection) and IUS (intrurethral suppositories). These therapies have an intrinsic appeal to many patients. Currently, topical therapies for the treatment of erectile dysfunction remain in clinical trials and have yet to be released for widespread use. However, topical applications have the potential to avoid the systemic effects noted with oral therapies while being perceived as minimally invasive in so far as it does not require needles or intraurethral instrumentation. Topical therapy may also provide benefit to patients unresponsive to systemic therapy or who use medications which cannot be taken along with such oral treatments (nitrate use). That is, the overall goal is the local treatment of a local problem.
GENERAL PRINCIPLES OF TOPICAL AGENTS

A short introduction to the major concepts and complications of using topical agents for the treatment of erectile dysfunction seems prudent. The transdermal route is a well established technology that provides 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, previous experience concerning the duration and onset of action employed for these other indications may not provide useful attributes. Several issues, in particular, are worth mentioning:

1) High systemic concentrations 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.

3) The vasoactive agent(s) needs to reach the corpora cavernosa in a timely fashion with the effective (highest) concentration.

Topical penile therapy, therefore, entails a unique set of anatomic and physiologic considerations. There are several anatomic/fascial layers between the penile skin and the corpus cavernosum. The tunic 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 (Becher et al., 1998; McVary et al., 1999). 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 (Gurny et al., 1993). 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. Depending on the molecular structure of the agent tested there can be nearly 100% absorption of topical agents applied to these areas. Again, exposure to the glans affords a more easily «breached» layer. Other skin regions (e.g., back and palms) are particularly impermeable (Maibach et al., 1971). An additional factor confounding efficient delivery of drug is the rich vasculature of the deep dermis which may «steal» the drugs to the systemic circulation.

With such an assortment of confounding factors one wonders exactly how gel applied to the penis could ever induce an erection. One attractive possibility is that 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 intraurethral delivery of drug (Wolfson et al., 1993; Padma-Nathan et al., 1997). The known absorptive nature of the penile skin and glans make this a real possibility (Maibach et al., 1971). If this is the case then delivery of drug to the shaft of the penis would seem superfluous and possibly only contribute to penile skin discomfort. Alternatively, the drug applied to the skin of the penis could theoretically be absorbed through the skin, the tunic of the corporal bodies and thus into the cavernous tissues. The large distance, multiple tissues layers and unknown permeability of the tunica makes this a formidable drug delivery challenge. A third more remote possibility involves the systemic absorption, recirculation and delivery of drug to the penile tissues. Systemic levels have been measured with the penile skin application of papaverine and minoxidil proving that absorption does occur. However, its presence in the systemic circulation does not prove its role in the erectile response (Kim et al., 1995; Clark et al., 1994). All of the above mentioned possibilities are expected to be inefficient at transfer of active agents thus requiring a large amount of drug to compensate the losses in the pathway.

Most of the delivery systems currently in use for topical therapy are intended for slow and steady release of the medications such as those used in hormonal, analgesic or narcotic patches. This slower process is not effective as an erection initiator as the drug flux is likely to be low. Investigators are currently trying permeation enhancers to increase drug flux speed. In order to achieve a rapid and efficient penetration the formulation needs to have sufficient penetration enhancer to help transfer (flux) the active agent with good tolerance (no significant irritation), and release the drug at the site of action (right bondage).

Several transdermal enhancers incorporated as one of the excipients in topical formulations have been reported (Becher et al., 1998; McVary et al., 1999; Kim et al., 1995; Samour et al., 1989; Pelham et al., 1995). 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 such agents enhance skin penetration by altering the fluidity of lipids in the stratum corneum, without any interaction with the chemical whose skin permeability is enhanced.

### 4.I. TOPICAL THERAPY FOR ERECTILE DYSFUNCTION – BACKGROUND

Organic nitrate donors were the first topical agents to be used in the treatment of erectile dysfunction (Mudd, 1977). Case reports have demonstrated that blood flow to the penis and tumescence are increased after application of a nitro based paste (Owen et al., 1989; Nunez & Anderson, 1993). The local effects on penile blood flow appear to be crucial since application of such gels elsewhere on the body do not induce erections. Topical minoxidil has also been reported in placebo controlled double masked trials (Clark et al., 1994; Cavallini, 1991). In one study, Cavallini reported 2% minoxidil as superior to 10% nitroglycerin cream in inducing improved penile hemodynamics and with fewer side effects.

### 4.II. TOPICAL PGE₁

Alprostadil is a natural occurring prostaglandin E1. Alprostadil and other prostaglandins in the E series are naturally present in the seminal vesicles, the cavernous tissues of males and in the placenta and ductus arteriosus of the fetus. Various formulations and injection techniques, urethral suppositories and gels using PGE-1 have been used in the treatment of erectile dysfunction over the past 15 years.

Alprostadil relaxes smooth muscle of the corpus cavernosum. As described elsewhere in this section, several mechanisms of action have been proposed. Undeniably, its effects are due to increasing the intracellular concentrations of cAMP, via a stereospecific activation of the membrane bound receptors. In particular, PGE₁ mediates relaxation of corpus cavernosum smooth muscle via activation of the EP prostaglandin receptor (EP₂/4) to increase the intracellular concentration of cAMP in corpus cavernosum smooth muscle (Palmer et al., 1994; Lin et al., 1995; Cahn et al., 1996; Traish et al., 1997; Moreland et al., 2001). PGE₁-induced relaxation of human corpus cavernosum is associated with activation of KC₃ channels, leading to hyperpolarisation and alterations in transmembrane Ca²⁺ flux (Lee et al., 1999).

Many of these actions are presumably mediated by protein kinase A. PGE₁ may also act by inhibiting the release of noradrenaline from sympathetic nerves (Molderings et al., 1992) and suppressing angiotensin II secretion in the cavernosal tissues (Kifor et al., 1997).

The physiologic endpoint is dilation of the cavernosal arteries, relaxation of the corporal smooth muscle, and therefore, is accompanied by increased arterial inflow velocity and increased venous flow resistance. As a result, the lacunar spaces expand and blood becomes entrapped secondary to compression of venules against the tunic albuginea. To achieve adequate turgescence and rigidity the tunic albuginea must be sufficiently stiff to compress the penetrating venules and thus block venous outflow. This process is also referred to as the corporal veno-occlusive mechanism. Alprostadil does not directly effect ejaculation or orgasm.

### 4.III. TOPICAL MINOXIDIL

Topical minoxidil has been recently used as an investigational drug in the treatment of erectile dysfunction. Although little can be said about its role in that regard, there is an extensive literature on its use as an antihypertensive and alopecia medication. Much of the information regarding this drug is drawn from the literature detailing its use in the former rather than latter circumstance.

Minoxidil is an antihypertensive agent while topical minoxidil (Rogaine) is used for alopecia. Due to its potency and adverse reactions, oral minoxidil is used mainly for patients with the severe drug resistant forms of hypertension. Tolerance to a prolonged therapy with oral minoxidil does not appear to be a problem. Subsequent to the oral dosage (approved by the FDA in 1979 for use in hypertension) topical formulations were approved for the treatment of alopecia in 1988. Investigation of topical formulations in the treatment of erectile dysfunction are limited and follow on the heels of its approval for alopecia.

Minoxidil does not have a direct vasodilatory effect on arterial smooth muscle. Rather, it is converted to minoxidil O-sulfate by the hepatic enzyme sulfo-transferase (McCall et al., 1983). This metabolite does have a direct vasodilatory effect on arterial smooth muscle causing a reduction in peripheral resistance and blood pressure. While the precise mechanism of action of minoxidil is not certain.
(Quast et al., 1995; Russ et al., 2003), and moreover, may vary among distinct smooth muscle cell types (Buchheit et al., 2000; Davies et al., 1996), it clearly appears to be a relatively weak corporal smooth muscle cell relaxant (Christ, 1995). In that regard, minoxidil is not known to inhibit the CNS or have adrenergic neuronal blocking effects. Minoxidil retains its activity despite adrenergic denervation. With respect to the mechanism of action, presumably at least some aspects of minoxidil-induced relaxation shares common features with other members of the K channel modulator family (i.e., pinacidil, cromakalim, etc.). In fact, in both vascular and nonvascular (including urogenital) smooth muscle, minoxidil and other K channel activators have been shown to activate $\mathrm{K}_\text{ATP}$ channels in a glibenclamide-sensitive fashion (Newgreen et al., 1990; Khan et al., 1997; Teramoto & Ito, 1999). In all these cases, activation of the $\mathrm{K}_\text{ATP}$ channel subtype results in an increased K+ efflux and cellular hyperpolarization. The net result is a physiological antagonism of transmembrane calcium flux through L-type voltage-dependent calcium channels, a reduction in the free intracellular calcium concentration, and a corresponding smooth muscle cell relaxation.

With regards to the treatment of erectile dysfunction, it is assumed that the active metabolite acts via a direct vasodilatory effect on corporal and arterial smooth muscle causing a reduction in peripheral resistance and cavernosal muscle relaxation. Presumably this promotes the veno-occlusive mechanism and results in erection. Such an effect from topical minoxidil is interesting when one considers that it is a prodrug that requires hepatic metabolism to become active (McCall et al., 1983). For this to be effective the topically absorbed minoxidil would have to be metabolized through the liver then recirculated to the penis to be active. This appears to be a substantial task. Issues regarding the site and efficacy of absorption have been addressed above.

Topical administration of minoxidil solutions should only be applied to the skin of interest. Absorption is best when the hair and the skin are dry. If applied with finger tips the hands should be thoroughly washed after applying. Systemic effects resulting from topically administered Minoxidil are unlikely but theoretically could occur if the drug is overused. Skin abrasion or irritation such as excoriations, psoriasis, or sun burn can increase the systemic absorption of topical minoxidil.

### 4.IV. TOPICAL PAPAVERINE

Since the introduction by Virag in the early 1980s, injection of papaverine into the corporal bodies for the treatment of sexual dysfunction has become a widespread and well accepted method (Virag, 1982). The use of papaverine as a topical therapy has a much shorter experience and one that has not moved beyond preliminary clinical trials.

The most characteristic effect of papaverine is relaxation of smooth muscle, especially when it has been spasmodically contracted. Papaverine acts, in large part, directly on the muscle itself. There may be several possible mechanisms by which papaverine is able to directly relax corporal smooth muscle, but the most prominent is by inhibition of the oxidative phosphorylation mediated inactivation of cAMP (via phosphodiesterase-PDE) which interferes with calcium mobilization during muscle contraction. In fact, papaverine is a nonspecific phosphodiesterase inhibitor that initiates an increase in intracellular cAMP and cGMP leading to corporal smooth muscle relaxation and penile erection; via prolongation of the half-life of these cyclic nucleotides. 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 by suppression of angiotensin II secretion in cavernosal tissue (Iguchi et al, 1992; Kifor et al, 1997)

Serum papaverine levels after topical administration have been measured in a single study (Kim et al., 1995) with a high performance liquid chromatography assay. 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. In contrast, papaverine is present in the blood at levels of 335 to 761 ng/ml within 3 minutes of IC injection of 40 mg as measured by similar techniques (Tanaka et al., 1990). The pharmacokinetics and bioavailability of topical papaverine on animal models have been studied in which 9-12.4% of the papaverine is detected in the serum. Why the marked differences between animal models and clinical trials has been blamed on gel formulation (Shaaya et al., 1992).
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 (see earlier sections in this chapter). The putative mechanism of action is described below.

Relaxation of corporal and arterial smooth muscle is the principle pharmacologic action of nitroglycerin, and presumably is dependent on activation of the NO/guanylate cyclase/cGMP/Protein Kinase G pathway. 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. This results in a reduction of left ventricular diastolic pressure. Arteriolar relaxation reduces systemic vascular resistance and arterial pressure.

The mechanistic basis for nitroglycerine-induced relaxation of human corporal smooth muscle is likely to be multifactorial, but the contribution of the major physiological entities seems quite clear. In this regard, cellular metabolism of nitroglycerine to NO and subsequent activation of soluble guanylcyte cyclase in the smooth muscle cell is the first step in the process. Activation of guanylcyte cyclase results in formation of cGMP, which in turn activates protein kinase G. Protein kinase G presumably phosphorylates a variety of target proteins, such as K channels (KCa, KATP, Kv; see Irvine et al., 2003; Archer, 2002; Bivalacqua et al., 2000; Lin et al., 2002; Spektor et al., 2002), L-type calcium channels (Adachi et al., 2001), sarcoplasmic reticulum calcium pumps (SERCA; Adachi et al., 2001), and perhaps Rho kinase as well (Chita-ley et al., 2003). Moreover, there may well be a significant cGMP-independent component to NO-mediated relaxation of smooth muscle (Adachi et al., 2001; Irvine et al., 2003). Virtually all of these reports have emphasized the important impact of the NO signalling pathway to diminish the free intracellular calcium levels, as a major mechanism of the ensuing NO-mediated relaxation response. These observations are consistent with the importance of reduced transmembrane calcium flux and/or increased calcium sequestration/extrusion mechanisms to nitroglycerine-induced relaxation. As indicated above, one major consensus point seems to be the important role played by K channel-mediated hyperpolarizing currents in this process. Furthermore, disease (diabetes)-related changes in the responsivity of isolated human corporal smooth muscle strips to nitroglycerine-induced relaxation may indicate that this compound may have diminished utility in diabetic patients. Other 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


**B. EVIDENCE-BASED REVIEW OF ED PHARMACOTHERAPIES**

### I. INTRODUCTION

Qualifications for review by the committee
Peer-reviewed scientific publications
Over 700 papers reviewed and graded
(in press included)
Excluded:
- Abstracts
- Case studies
- Review articles
- Papers in journal supplements

#### 1. GRADING THE LEVEL OF EVIDENCE

- **High (level 1)**
  - High quality RCT with high power

- **Intermediate (level 2)**
  - RCT with low power and/or less than 80% follow-up and retention
  - Good quality, non-randomized, prospective comparative study

- **Low (level 3)**
  - Uncontrolled studies
  - Non-randomized comparative studies with historical control

#### 2. CATEGORIES FOR GROUPING OF PUBLICATION REVIEWS

- General Efficacy
- Special Population Efficacy
- General and Class Specific Safety
- Cardiovascular Investigations

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### II. ORAL ED PHARMACOTHERAPIES

#### 1. PDE5 INHIBITORS: SILDENAFIL

##### 1. GENERAL EFFICACY

Ten (10) level 1 publications [1-10],
three (3) level 2 publications [11-13],
and twenty two (22) level 3 publications [14-35].

##### 2. SPECIAL POPULATION EFFICACY

- **Diabetic ED Patients**
  - Three (3) level 1 publications [36,37, 150],
  - one (1) level 2 publications [38],
  - and two (2) level 3 publication [24, 39].

- **Patients with Cardiovascular Disease (CAD, hypertension) and ED**
  - Two (2) level 1 [40]
  - and two (2) level 2 publications [41, 42].

- **Post-Prostatectomy ED Patients**
  - Seven (7) level 3 publications [43-49].

- **SSRI-Related ED Patients**
  - One (1) level 1 [50],
  - one level 2 [51]
  - and three (3) level 3 publications [52-54]

- **Depression-related ED Patients**
  - Two (2) level 1 [50, 55]
  - and one (1) level 3 publications [56]

- **Spinal Injury-related ED Patients**
  - Two (2) level 1 publications from a single trial [57, 58],
  - two (2) level 2 publications from a single trial [59, 60]
  - and three (3) level 3 publications [61-63].

- **Radiation Therapy-related ED Patients**
  - One (1) level 2 [64]
  - and eight (8) level 3 publications [65-72].

- **Spina Bifida ED Patients**
  - One (1) level 2 [73]

- **Intracavernosal Injection Therapy Failure Patients**
  - One (1) level 3 publication [74]

- **Psychiatric Outpatients with ED**
  - One (1) level 3 publication [75]
**Detailed review of important Sildenafil clinical publications**

**Table 1: Trial description (all were placebo controlled)**

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### Detailed review of important Sildenafil clinical publications

**EFD = Erectile Function Domain Score.**

**GAQ: Global Assessment Question**: has the treatment you have been taking over the past 4 weeks improved your erection?

#### Table 2: Efficacy data

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* = estimated values from the published graphs.
### Detailed review of important Sildenafil clinical publications

**Table 3: Adverse events (AE) and Comments**

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**Detailed review of important Sildenafil clinical publications**

**Question 3 and 4 of International IIEF where EF domain not reported**

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<td>1.6</td>
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<td>1.6</td>
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</tbody>
</table>

* = estimated values from the published graphs

**Question 3 : achieving an erection**  -  **Question 4 : maintaining an erection**
• Parkinson’s Disease ED Patients
  One (1) level 2 [76] and two (2) level 3 publications [77, 78]

• Psychotropic Medication Related ED Patients
  One (1) level 3 publication [79]

• Renal Failure Patients on Dialysis with ED
  Six (6) level 3 publications [80-85]

• The Elderly ED Patients
  One (1) level 2 [86] and one (1) level 3 publication [21]

• Chemotherapy and Testosterone Treated ED Patient
  One (1) level 3 publication [87]

• Post-radical Proctectomy related ED Patients
  One (1) level 2 publications [88]

• Post-renal Transplant Patients with ED
  Two (2) level 3 publications [89, 90].

3. GENERAL AND CLASS SPECIFIC SAFETY ISSUES
  Nineteen (19) level 1 [1-9, 36, 37, 40, 50, 55, 57, 91-93, 150],
six (6) level 2 [13, 41, 51, 94-96].
and twenty three (23) level 3 publications [14-17, 19-27, 31-35, 97-101].
This category includes studies related to ocular safety

4. Cardiovascular Investigations
  Thirty (30) level 1 [36, 40, 41, 94, 102-127],
twenty three (23) level 2 [96, 128-149]

SIDENAFIL REFERENCES


64. Incrocci L, Koper PCM, Hop WCI, Slob AK. Sildenafil citrate (Viagra) and erectile dysfunction following external beam radiotherapy for prostate cancer: a randomized, double-blind, placebo-controlled, cross-over study. Int J Radiat Oncol Biol Phys. 2001; 51: 1190-1195
73. Palmer JS, Kaplan WE, Firiti CF. Erectile dysfunction in spina bifida is treatable. Lancet 1999; 354: 125-6
Transplantation Proc. 2002; 34: 408-9

Bone Marrow Transplant 2002; 29: 607-610

82. Rosas SE, Wasserstein A, Kobrin S, Feldman HI. Clinical efficacy of sildenafil in patients on  


85. Juergens PH, Botev R, Wuertz D, Finkelstein SH, Smith JD, Finkelstein SO. Erectile dysfunction in  


91. Lewis R, Bennett CJ, Borkin WD, Boykin WH, Althof SE, Stecher VJ, Siegel RL. Patient and partner satisfaction with Viagra (sildenafil citrate) treatment as determined by the erectile dysfunction inventory of treatment satisfaction questionnaire. Urology. 2001; 57: 960-965


100. McCulloch TJ, Lam BL, Marmor MF, Hoffman KB, Luu JK, Feuer WJ. Acute effects of sildenafil (viagra) on blue-on-yellow and white-on-white Humphrey perimetry. J Neuroophthalmol 2000; 20: 227-228


2. PDE5 INHIBITORS: VARDENAFIL

a) General Efficacy
Five (5) level 1 publications [1-4, 12]

b) Special Population Efficacy

• Diabetic ED Patients
One (1) level 1 publication [5].

• Post-prostatectomy
One (1) level 1 publication [6].

c) General and Class Specific Safety Issues
Five (5) level 1 publications [7-10, 12].

d) Cardiovascular Investigations
One (1) level 1 publication [11]

VARDENAFIL REFERENCES


Detailed review of important Vardenafil clinical publications

<table>
<thead>
<tr>
<th>Clinical Trial Database - Vardenafil</th>
<th>Reference</th>
<th>Senior Author (List)</th>
<th>Year</th>
<th>Patient group</th>
<th>Patient Numbers</th>
<th>Trial design</th>
<th>EF</th>
<th>5 mg</th>
<th>10 mg</th>
<th>20 mg</th>
<th>Placebo</th>
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</table>
Detailed review of important Vardenafil clinical publications

<table>
<thead>
<tr>
<th>Reference</th>
<th>Senior Author (List)</th>
<th>Year</th>
<th>Intercourse Success</th>
<th>GAQ</th>
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<td></td>
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<td></td>
<td>5 mg</td>
<td>10 mg</td>
</tr>
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<td>Base</td>
<td>End</td>
</tr>
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<td>[4]</td>
<td>Hellstrom</td>
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<td>[5]</td>
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<td>2003</td>
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<td>NA</td>
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<td>[6]</td>
<td>Brock</td>
<td>2003</td>
<td>NA</td>
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<td>[9]</td>
<td>Nagao</td>
<td>2003</td>
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<td>[12]</td>
<td>Hatziychristou</td>
<td>2004</td>
<td>Sep-2 (LOCF)</td>
<td>Sep-3 (LOCF)</td>
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<td></td>
<td>Base</td>
<td>End</td>
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<td></td>
<td>Vardenafil</td>
<td></td>
<td>44</td>
<td>46</td>
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</tbody>
</table>
## Detailed review of important Vardenafil clinical publications

- **VfS** - Valid for safety
- **ITT** - Intent-to-Treat Population
- **VfE** - Valid for Efficacy
- **VPP** - Valid per protocol
- **MC** - Multicenter
- **R** = Randomized
- **DB** = Double Blind
- **PIA** = Placebo
- **IIEF-EF Domain (LOCF)**
- **GAQ** - Global Assessment question
- **SEP-2 (LOCF)** - Diary (Sexual Encounter Profile) Question 2 - (Last Observation Carried Forward)
- **SEP-3 (LOCF)** - Diary (Sexual Encounter Profile) Question 3 - (Last Observation Carried Forward)

### Clinical Trial Database - Vardenafil

<table>
<thead>
<tr>
<th>Reference</th>
<th>Senior Author (List)</th>
<th>Year</th>
<th>AE&gt;3%</th>
<th>Drop-outs due to AE</th>
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<td>[2] Porst</td>
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<td>2001</td>
<td>headache (10-22%)</td>
<td>2 (placebo)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>flushing (5-13%)</td>
<td>7 (5 mg)</td>
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<td></td>
<td>dyspepsia (1-6%)</td>
<td>2 (10 mg)</td>
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<td></td>
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<td></td>
<td>rhinitis (9-17%)</td>
<td>1 (20 mg)</td>
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<td>[4] Hellstrom</td>
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<td>flushing (9-10%)</td>
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<td>rhinitis (5-10%)</td>
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<td>headache (16-22%)</td>
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<td>flushing (19-21%)</td>
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<td>rhinitis (16-20%)</td>
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<td>sinusitis (6-7%)</td>
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<td></td>
<td>dyspepsia (4-5%)</td>
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<td>nausea (1-5%)</td>
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<td>flushing (21-36%)</td>
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<td>rhinitis (7-9%)</td>
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</table>
3. PDE5 INHIBITORS: TADALAFIL

a) General Efficacy

Three (3) level 1 publications [1-3]

b) Special Population Efficacy

• Diabetic ED Patients

One (1) level 1 publication [4].

c) General and Class Specific Safety Issues

Four (4) level 1 publications, including a sperm assessment study [1-5].

One (1) level 2 publication (open label) [6]

d) Cardiovascular Investigations

One (1) level 1 publication [7].

REFERENCES

TADALAFIL


Detailed review of important Tadalafil clinical publications (To be completed)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Trial Design</th>
<th>Patient Group</th>
<th>Patient Numbers</th>
<th>IIEF EF Domain</th>
<th>Intercourse Success = SEP 3</th>
<th>GAQ</th>
<th>AEs &gt; 3%</th>
<th>Drop-outs due to AEs</th>
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<tr>
<td>Brooks CB et al [1]</td>
<td>Single-blind randomized, placebo-controlled double-blind RCTs</td>
<td>Placebo 308 Tadalafil 2.5 mg 151</td>
<td>13.4 16.5 17% 37%</td>
<td>25% 32% 35%</td>
<td>Headache 2% Diarrhea 1% Gastrointestinal 3%</td>
<td>2.1% 1.3%</td>
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<td>Potischman M et al [2]</td>
<td>Single-blind randomized, placebo-controlled double-blind double-blind</td>
<td>Placebo 173 Tadalafil 20 mg 173</td>
<td>13.7 14.7 23% 35.6%</td>
<td>17.1%</td>
<td>Headache 3% Gastrointestinal 5%</td>
<td>3.7% 0.6%</td>
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<tr>
<td>Padma-Nathan H et al [3]</td>
<td>Single-blind randomized, placebo-controlled double-blind double-blind</td>
<td>Placebo 35 Tadalafil 2 mg 35</td>
<td>13.2 19.3 28% 43.7%</td>
<td>51.4%</td>
<td>Headache 3% Gastrointestinal 5%</td>
<td>2.4% 0.6%</td>
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<td>Serra de la Torre M et al [4]</td>
<td>Single-blind randomized, placebo-controlled double-blind double-blind</td>
<td>Placebo 71 Tadalafil 20 mg 71</td>
<td>12.1 13.2 1.6%</td>
<td>2.5%</td>
<td>Headache 3% Gastrointestinal 5%</td>
<td>3.4% 1.4%</td>
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</table>
Detailed review of important Tadalafil clinical publications (To be completed)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Trial Design</th>
<th>Patient Group</th>
<th>Patient Numbers</th>
<th>Age Mean (Range)</th>
<th>Safety Results</th>
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<tr>
<td>Holland et al</td>
<td>Placebo-controlled</td>
<td>Placebo, Tadalafil</td>
<td>297</td>
<td>58 yrs</td>
<td>Daily administration of tadalafil 10 and 20 mg had no adverse effects.</td>
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<tr>
<td>2009</td>
<td>Double-blind</td>
<td>Tadalafil 10 mg</td>
<td>109</td>
<td>51 yrs</td>
<td>No statistically significant difference from placebo in erectile function.</td>
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<tr>
<td>J.Urol</td>
<td>Placebo-controlled</td>
<td>Placebo, Tadalafil 20 mg</td>
<td>111</td>
<td>51 yrs</td>
<td>No statistically significant difference from placebo in erectile function.</td>
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<tr>
<td>Enrolment</td>
<td>Total</td>
<td>423</td>
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</table>

Abbreviations: NA = Not Applicable. Ca. = cases (about). Tx = Treatment

- IIEF = International Index of Erectile Function
- EF = Erectile Function
- > Intercourse success = SEP 3
- SEP3 = sexual encounter profile question 3 (which is a self-report of intercourse success)
- GAQ = Global Assessment Question - “did this drug or treatment improve your erection?”
4. ALPHA-BLOCKERS: PHENTOLAMINE

a) General Efficacy

Four (4) level 2 [1-4] and one (1) level 3 publication [5]

b) Special Population Efficacy

Absence of a specific publication in this category

c) General and Class Specific Safety Issues

Four (4) level 2 [1-4] and one (1) level 3 publication [5]

d) Cardiovascular Investigations

Absence of a specific publication in this category

REFERENCES

PHENTOLAMINE


5. ALPHA-BLOCKERS: YOHIMBINE

a) General Efficacy

Four (4) level 2 (one demonstrating efficacy [1] and three demonstrating non-efficacy) [2-4], and one (1) level 3 publication [5]

b) Special Population Efficacy

Absence of a specific publication in this category

c) General and Class Specific Safety Issues

Four (4) level 2 [1-4], and one (1) level 3 publication [5]

d) Cardiovascular Investigations

Absence of a specific publication in this category

YOHIMBINE REFERENCES


6. OTHER ALPHA-BLOCKER COMBINATIONS

- **Yohimbine and L-Arginine**
  One (1) level 2 publication [1] and phase 2 development status

- **L-Arginine**
  One (1) level two publication. Non-effective [2]

- **Trazodone**
  Three (3) level 2 publications [3-6] demonstrating non-efficacy and one (1) level 2 publication that was over 5 years old demonstrating some efficacy [7].

- **Trazodone and Yohimbine**
  One (1) level 2 publication [8].

### OTHER ALPHA-BLOCKER REFERENCES


7. DOPAMINE AGONIST: APOMORPHINE SL

#### a) General Efficacy

Two (2) level 1 [1,2], two (2) level 2 [3,4] and one (1) level 3 publication [5].

#### b) Special Population Efficacy

Two (2) level 2 studies not specifically designed for the subgroups [1,2].

#### c) General and Class Specific Safety Issues

Two (2) level 1 [1,2], two (2) level 2 [3,4] and one (1) level 3 publication [5].

#### d) Cardiovascular Investigations

Two (2) level 2 publications [1,2] not specifically designed to address the issue

### APOMORPHINE SL REFERENCES


### Detailed review of important Apomorphine SL publications

<table>
<thead>
<tr>
<th>Senior Author</th>
<th>Year</th>
<th>Patient group</th>
<th>Patient Numbers</th>
<th>Trial design</th>
<th>EF domain</th>
<th>Intercourse success</th>
<th>GAQ</th>
<th>AEs &gt; 3% (List)</th>
<th>Drop-outs due to AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dula [3], Eur Urol</td>
<td>2001</td>
<td>Gen population</td>
<td>296</td>
<td>Randomize, double blind, place contr, cross over</td>
<td>Drug Base 22</td>
<td>Placebo Base 48</td>
<td>Drug Base 22</td>
<td>Placebo Base 32</td>
<td>Nausea 7, Yawning 8, Dizziness 6.5, Somnolence 4.9</td>
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<tr>
<td>Dula [2], Urology</td>
<td>2000</td>
<td>Gen pop</td>
<td>569</td>
<td>Multicenter, double bind, place contr</td>
<td>Drug Base 26</td>
<td>Placebo Base 50</td>
<td>Drug Base 23</td>
<td>Placebo Base 32</td>
<td>Nausea 12, Headache 6, Dizziness 11, Sweating 10, Yawning 10, Somnolence 7</td>
</tr>
<tr>
<td>Mulhall [4], Clin Therap</td>
<td>2001</td>
<td>Gen pop</td>
<td>849</td>
<td>Multicenter open-label, uncontrolled</td>
<td>Drug Base 13</td>
<td>Placebo Base 39</td>
<td></td>
<td></td>
<td>Nausea 4.7, Headache 3.6</td>
</tr>
</tbody>
</table>
8. OTHER CENTRALLY ACTING AGENTS

- **Melanocortin Agonists/ MTII**
  Three (3) level 2 publications. Phase II development [1-3]

- **Delequamine**
  Three (3) level 2 publications [4-6].

- **Naltrexone**
  Two (2) level 2 publications [7-8]

- **Nalmefene**
  One (1) level 3 publication [9]

---

**CENTRALLY ACTING AGENTS REFERENCES**

**Melanocortin Agonists / MTH**


**Delequamine**


**Nalmefene**


**Naltrexone**


III. LOCAL ED THERAPIES

1. INTRACavernosal INJECTION THERAPY

• Alprostadil (PGE1)

a) General Efficacy

Four (4) level 1 [1-4], eight (8) level 2, [5-12] and eight (8) level 3 publications [13-20]

b) Special Population Efficacy

One (1) Level 1 [1], two (2) level 2 [11, 21] and one (1) level 3 publication [22]

c) General and Class Specific Safety Issues

Four (4) level 1 [1-4], eight (8) level 2 [23-30], and eight (8) level 3 publication [31-33, 16-20]

d) Cardiovascular Investigations

One (1) level 2 publication [34]

• Papaverine HCl and Combination Therapy

There are three (3) level 2 [21, 35-36] and one (1) level 3 publication [37].

General lack of regulatory approval despite a large clinical experience

ALPROSTADIL REFERENCES


2. **Intraurethral Therapy**

- **Alprostadil (PGE1)**

  - **a) General Efficacy**
    
    Three (3) level 1 [1-3] and two (2) level 2 publications [4, 9]

  - **b) Special Population Efficacy**
    
    one (1) level 1 [19] and one (1) level 3 [6] publication

  - **c) General and Class Specific Safety Issues**
    
    Three (3) level 1 [1-3], one (1) level 2 [4], and nine (9) level 3 [6-8, 10-15] publications

- **d) Cardiovascular Investigations**

  Absence of a specific publication in this category

**INTRAURETHRAL THERAPY REFERENCES**


3. TOPICAL THERAPIES

- **Alprostadil combined with a proprietary Permeation Enhancer**
  
  There are no Level I publications.  
  There are two (2) Level 2 [1, 2].  
  In addition 2 (1) level 2 publication exists for another combination that are in Phase II development [3,4] as well as one (1) level 2 publication [5] for topical PGE1 gel alone.  
  In addition there is one (2) Level 3 publication for a different formulation of PGE [6] as well as one (1) Level 3 publication [7] using a combination of PGE1 and papaverine.

- **Papaverine**
  
  There is one (1) level 2 publication [8].  
  Experimental

- **Minoxidil**
  
  There are three (3) level 2 publications [9-11].  
  Experimental

- **Nitroglycerine**
  
  There is one (1) level 2 [12] and two (2) level 3 publications [13, 14].  
  Experimental

TOPICAL THERAPIES REFERENCES


IV. HIGH AND INTERMEDIATE LEVEL OF EVIDENCE CARDIOVASCULAR PUBLICATIONS IN THE FIELD OF ED PHARMACO-THERAPY (graded by cardiologists on committee)

Grouped following level of Evidence, year of publication and alphabetical order of first author

I : High Level Publications

1998 - 1999


Note: Reports safety from a series of double blind and open label studies of large # of patients (4274). No difference in incidence of serious CV adverse events (including myocardial infarction) between placebo or sildenafil.

Level of Evidence: High level.


Note: Primarily an efficacy study - but it is randomized, double blind, placebo-controlled. They do present CV adverse events. 3% in sildenafil and 5% in placebo group had cardiovascular events.

Level of Evidence: High level.

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Note: Study done in chronically instrumented dogs. Sildenafil ↓ mean aortic pressure, no change in HR, LV systolic pressure or LV maximal first time derivative of LV pressure (a measure of LV contractility). Sildenafil ↑ rest and exercise myocardial blood flow.

Level of Evidence: High Level.


Note: Oral sildenafil given to men with CAD at time of catheterization. Small ↓ in systemic and pulmonary artery pressure. No effect on pulmonary capillary wedge pressure, right atrial pressure, heart rate, cardiac output. No change in coronary diameter or flow. No adverse CV effects. Slight increase in coronary flow reserve.

Level of Evidence: High level.


Note: Sildenafil increased endothelium - dependent flow mediated vasodilation (assessed by making transient arterial occlusions of the brachial artery and measuring reactive flow by ultrasound) in heart failure patients.

Level of Evidence: High level.


Note: Animal study. Sildenafil did not affect systemic blood pressure or pulmonary arterial blood pressures. Caused vasodilation in normal coronary. Did not induce ischemia in artery with critical stenosis. With nitrates ↓ systemic BP and coronary blood flow.

Level of Evidence: High level.


Note: Shows in an animal model that sildenafil improves coronary artery blood flow in the setting of a stenosis.

Level of Evidence: High level.
Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina.

Note: Men with stable angina on isosorbide mononitrate or glyceryl trinitrate given sildenafil or placebo. Sildenafil substantially potentiated hypotensive effect of nitrates.

Level of Evidence: High level.

Sildenafil is a pulmonary vasodilator in awake lambs with acute pulmonary hypertension.

Notes: Animal study. Awake lambs in which acute pulmonary hypertension is chemically induced. Cumulative sildenafil doses resulted in a cumulative decrease in pulmonary artery pressure, pulmonary vascular resistance. Only small fall in systemic arterial pressure after the highest dose. Sildenafil did not augment effect of iNO – a finding that differs from other studies.

Level of Evidence: High level.

Effect of sildenafil citrate on blood pressure and heart rate in men with erectile dysfunction taking concomitant antihypertensive medication.

Note: In men taking a variety of antihypertensive medicines, sildenafil ↓ blood pressure by -3.6/-1.9 mmHg versus -0.8/-0.1 mmHg for those on placebo. Conclusions were that short-term effects of oral sildenafil on BP and HR in men with ED were small and not clinically significant in those on antihypertensives. In men not on antihypertensives, sildenafil decrease in blood pressure was -2.2/-2.0 mmHg.

Level of Evidence: High level.

Cardiovascular safety of sublingual apomorphine in patients on stable doses of oral antihypertensive agents and nitrates.

Note: > orthostatic decrease in BP when SL apomorphine given with α blockers and Ca++ blockers (-10 and -6 mmHg vs. placebo). ↓ in BP with long acting nitrates when patients standing.

Level of Evidence: High level.

Sildenafil modulates hemodynamics and pulmonary gas exchange.

Notes: Anesthetized pigs received control or sildenafil while hemodynamics were measured. Sildenafil ↑ intrapulmonary shunt flow with marked decreases in PaO2, increased cardiac index, pulmonary artery pressure at high doses. The issue of decreased arterial O2 and increased cardiac index differs from the other studies.

Level of Evidence: High level.

Effect of sildenafil in patients with erectile dysfunction taking antihypertensive therapy.

Note: No ↑ in adverse events related to sildenafil in men on antihypertensive meds (even if on 3 or more) vs. those not on antihypertensive meds. Overall efficacy of sildenafil in this group of patients with hypertension ~70%.

Level of Evidence: High level.

Efficacy and safety of sildenafil citrate for the treatment of erectile dysfunction in men with cardiovascular disease.

Note: Important study in that many of these patients had CV disease at baseline including hypertension, previous MI, chronic ischemic heart disease, angina. Sildenafil was highly effective (71% had improvement) and no treatment related adverse CV events.

Level of Evidence: High Level of Evidence.

Effect of sildenafil citrate upon myocardial ischemia in patients with chronic stable angina in therapy with beta-blockers.

Note: Sildenafil did not worsen ischemia during exercise test.

Level of Evidence: High level.
Sildenafil citrate (Viagra) does not exacerbate myocardial ischemia in canine models of coronary artery stenosis.


Note: Experimental animal study. Sildenafil did not exacerbate ischemia in a model of coronary stenosis. It did render platelets refractory to the inhibiting effects of adenosine receptor stimulation.

Level of Evidence: High level.

Cardiovascular events in users of sildenafil: results from first phase of prescription event monitoring in England.


Note: The very important PEM study of over 5000 men in United Kingdom. Compared those on sildenafil vs. general population. Showed no increase in fatal MI or ischemic heart disease. As this was not a placebo controlled study might be intermediate level, but high n value makes this an important study.

Level of Evidence: High level.

Cardiac electrophysiologic and hemodynamic effects of sildenafil, a PDE5 inhibitor, in anesthetized dogs.


Note: Anesthetized closed chest dogs. IV sildenafil at various sub→supratherapeutic doses did not affect monophasic action potential duration or effective refractory period. Sildenafil decreased peripheral resistance; some reflex tachycardia at high dose.

Level of Evidence: High level.

Sildenafil inhibits hypoxia-induced pulmonary hypertension.


Note: Randomized, double blind study, placebo controlled. Sildenafil attenuated hypoxia – induced pulmonary hypertension in normal volunteers as well as mice.

Level of Evidence: High level.

Cardiovascular effects of sildenafil during exercise in men with known or probable coronary artery disease.


Notes: Randomized, double blind, placebo controlled study of patients with ED and known or highly suspected CAD. Symptom limited supine bicycle echocardiogram exercise tests with sildenafil or placebo. Sildenafil had no effect on symptom, exercise duration, exercise induced ischemic wall motion abnormalities. Exercise BP and heart rates were similar. 4 - 5 Mets reached (similar to intercourse).

Level of Evidence: High level.

Sildenafil effects on exercise, neurohormonal activation, and erectile dysfunction in congestive heart failure.


Notes: Carefully performed double blind, randomized, placebo controlled study showing that sildenafil was well tolerated and effective in CHF patients (mostly class II); improved exercise capacity, reduced BP and HR with exercise, improved peak VO\textsubscript{2} and exercise times.

Level of Evidence: High level.

Effects of sildenafil on cardiac repolarization.


Notes: In-vitro study of isolated guinea pig papillary muscles and canine Purkinje fibers, whole-cell patch clamp techniques in guinea pig ventricular myocytes, in-vivo ECG recordings of guinea pigs. Action potential duration not affected by therapeutic range of sildenafil. At high concentration sildenafil shortened action potential duration; QTc was not lengthened by sildenafil, in fact it was shortened in guinea pigs.

Level of Evidence: High level.

Acute and prolonged effects of sildenafil on brachial artery flow-mediated dilatation in type 2 diabetes.

Notes: Sildenafil acutely and after two weeks of therapy improved brachial - artery flow mediated dilation and it persisted for at least 24 hours after the low dose. Suggests it may improve endothelial function in diabetic patient.

Level of Evidence: High level.


Note: 16 patients with pulmonary hypertension secondary to pulmonary fibrosis. Sildenafil reduced pulmonary vascular resistance. Sildenafil improved arterial partial pressure of O₂.

Level of Evidence: High level.


Notes: Thirty patients with pulmonary hypertension in an ICU setting received inhaled NO and iloprost and were then randomized to 12.5 mg sildenafil, 50 mg of sildenafil, 12.5 mg of sildenafil plus inhaled iloprost, or 50 mg sildenafil plus inhaled iloprost. Best combination was 50 mg sildenafil plus iloprost for reducing pulmonary vascular resistance and increasing cardiac index. Iloprost alone plus 50 mg sildenafil alone were equally effective but less potent than the combination.

Level of Evidence: High level.


Notes: Study of acute effects of sildenafil in patients undergoing cardiac catheterization with normal coronaries as well as patients with coronary artery disease. Sildenafil dilated epicardial coronaries by ~ 7%. Response to acetycholine and cold pressor tests improved with sildenafil > in the CAD patients suggesting that sildenafil improves endothelial function. Platelet IIb/IIIa receptor activation was inhibited by sildenafil. In tests of endothelial dysfunction using brachial artery dilation technique sildenafil prolonged the duration of hyperemia. Isosorbide dinitrate improved myocardial ischemia during exercise testing whereas sildenafil’s response was intermediate between placebo and nitrate.

Level of Evidence: High level.


Notes: In nine patients with primary pulmonary hypertension, sildenafil caused pulmonary vasodilation and improved cardiac index. When given with inhaled NO it augmented and prolonged the pulmonary vasodilator effects of NO and prevented rebound vasoconstriction.

Level of Evidence: High level.


Notes: Thirteen patients with pulmonary hypertension had hemodynamic measures with inhaled NO, sildenafil or both. Sildenafil decreased pulmonary vascular resistance and there was an additive effect with iNO. Sildenafil improved cardiac index whereas iNO alone did not.

Level of Evidence: High level.


Notes: In a rabbit model of myocardial infarction sildenafil decrease blood pressure transiently, markedly reduced myocardial infarct size when given acutely before coronary occlusion or 24 hours before coronary occlusion. Reasonable study but we’ve been unable to reproduce these results in our lab.

Level of Evidence: High level.
Intravenous sildenafil lowers pulmonary vascular resistance in a model of neonatal pulmonary hypertension.

Notes: Animal study. Eighteen piglets in which pulmonary hypertension to meconium aspiration is mimicked (as a cause of pulmonary hypertension in neonates). IV sildenafil completely reversed the increase in pulmonary vascular resistance with no effect on systemic hemodynamics.

Level of Evidence: High level.

The effect of vardenafil, a potent and highly selective Phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction, on the cardiovascular response to exercise in patients with coronary artery disease.

Note: In this double-blind crossover, single-dose multicentre study, 41 men with reproducible stable exertional angina due to ischaemic CAD received vardenafil 10 mg or placebo, followed by ETT (5 to 10 metabolic equivalents [METS], Bruce protocol) 1 hour postdose. At peak exercise, vardenafil 10 mg did not alter blood pressure, heart rate, or rate pressure product relative to placebo. Vardenafil 10 mg did not impair the ability of patients with stable CAD to exercise at levels equivalent or greater than that attained during sexual intercourse (average of 2.5 to 3.3 METS).

Level of Evidence: High level

Effects of sildenafil citrate (Viagra) on blood pressure in normotensive and hypertensive men.

Notes: Sildenafil given to 22 hypertensive and 27 normotensive men while ambulatory blood pressure was monitored. Overall sildenafil decreased systolic by 6 mmHg and diastolic BP by -4.5 mmHg with no difference in response between normotensive and hypertensive men. All men tolerated sildenafil well without hypotensive symptoms event though 22.7% of hypertensive men and 4% of normotensive men had a decrease in systolic BP of 20 mmHg or more.

Level of Evidence: High level

Immediate and long-term hemodynamic and clinical effects of sildenafil in patients with pulmonary arterial hypertension receiving vasodilator therapy.

Note: Sildenafil has an immediate pulmonary vasodilator effect in 13 patients already receiving vasodilators for pulmonary arterial hypertension but its long-term effects on right heart function and functional status are equivocal.

Level of Evidence: High level

Effects of sildenafil (viagra) on human myocardial contractility, in vitro arrhythmias and tension of internal mammaria arteries and saphenous veins.

Note: Sildenafil exerts potent vasodilatory actions but has no direct influence on human myocardial contractility or proarrhythmic effects in vitro.

Level of Evidence: High level
The effects of sildenafil on the cardiovascular response in men with spinal cord injury at or above the sixth thoracic level.


Note: Large double blind placebo controlled crossover trial of sildenafil 50 and 100 mg. Sildenafil induces significant hypotension in people with cervical-level injuries-more so than in thoracic-level injuries-and can cause dizziness in both populations. It should be prescribed with caution and informed consent from the patient.

**Level of Evidence:** High level

Sildenafil citrate does not reduce exercise tolerance in men with erectile dysfunction and chronic stable angina.


Note: Large study. Sildenafil was well tolerated and did not adversely affect any exercise parameter in men with coronary artery disease and ED. Favorable trends in total exercise duration and times to onset of angina and limiting angina were recorded with sildenafil use.

**Level of Evidence:** High level

Timecourse of the interaction between tadalafil and nitrates.


Note: Large cross-over study demonstrating the hemodynamic interaction between tadalafil and sublingual nitroglycerin lasted 24 h, but was not seen at 48 h and beyond. Similar to other PDE5 inhibitors, tadalafil should not be administered in combination with organic nitrates.

**Level of Evidence:** High level

Clinical trials of sildenafil citrate (Viagra) demonstrate no increase in risk of myocardial infarction and cardiovascular death compared with placebo.


Note: Meta-analysis of over 120 trials. The use of sildenafil was not associated with an increase in the risk of MI or cardiovascular death (Pfizer sponsored).

**Level of Evidence:** High level

Effects of sildenafil on myocardial infarct size, microvascular function, and acute ischaemic left ventricular dilation.


Note: Open-chest rabbit study. Sildenafil reduced cardiac pre- and afterload, and parameters of left ventricular contractility. Myocardial necrosis and microvascular dysfunction were neither exacerbated nor attenuated.

**Level of Evidence:** High level

Vascular effects of sildenafil in hypertensive cardiac transplant recipients.


Note: 15 patient study. Sildenafil (50 mg) is well tolerated in hypertensive cardiac transplant recipients and improves BP, aortic augmentation index and endothelial function reducing left ventricular afterload and systolic stress.

**Level of Evidence:** High level


Note: Large study of 22,471 men identifying the safety profile of sildenafil as used in the community, showing no unexpected events. The standardized mortality ratio analysis of deaths from IH provided no evidence to suggest a higher incidence of deaths in the study cohort than in the male population in England.

**Level of Evidence:** High level

Efficacy and safety of sildenafil citrate in men with erectile dysfunction and stable coronary artery disease.


Note: Large study, placebo-controlled. Sildenafil is an effective and well-tolerated treatment for ED in men with CAD with no additional safety risks in this patient population.

**Level of Evidence:** High level
Clinical efficacy of sildenafil in primary pulmonary hypertension. A randomised, placebo-controlled, double-blind cross-over study.

Note: Randomised cross-over trial of sildenafil 25 to 100 mg tds versus placebo. Sildenafil significantly improves exercise tolerance, cardiac index and QOL in patients with primary pulmonary hypertension.
Level of Evidence: High level

Use of sildenafil for safe improvement of erectile function and quality of life in men with New York Heart Association classes II and III congestive heart failure: a prospective, placebo-controlled, double-blind crossover trial.

Note: Large crossover trial of 35 patients. Sildenafil is a safe and effective treatment for ED in men with New York Heart Association classes II and III CHF and provides relief of depressive symptoms, explaining an improvement in the perception of quality of life.
Level of Evidence: High level

Hypotensive interaction of sildenafil and nicorandil in rats through the cGMP pathway but not by KATP channel activation.

Notes: Combination of sildenafil plus nicorandil or sildenafil with nitrates potentiates hypotension in pentobarbital anesthetized rats.
Level of Evidence: Intermediate level.

Effects of sildenafil on human penile blood vessels.

Note: Uses isolated penile dorsal arteries and deep dorsal veins from 14 multi-organ donors. Sildenafil caused contraction dependent relaxation and amplified relaxation to sodium nitroprusside. Relaxation was unaffected by inhibitor of NO synthase.
Level of Evidence: Intermediate level.

Relaxation induced by cGMP phosphodiesterase inhibitors sildenafil and zaprinast in human vessels.

Note: In vitro study of human coronary, internal mammary, radial arteries, and forearm veins showing that sildenafil caused concentration -dependent relaxation in these vessels. Sildenafil amplified the effect of sodium nitroprusside.
Level of Evidence: Intermediate level.

Sympathetic activation by sildenafil.

Note: Fourteen normal volunteers received sildenafil vs. placebo. Sildenafil did not change HR, BP but did increase muscle sympathetic activity and ↑ plasma norepinephrine levels and ↑ sympathetic nerve traffic during stress.
Level of Evidence: Intermediate evidence.
Cardiovascular effects of sildenafil citrate (Viagra®): A naturalistic cross-over study.


Note: Shows sildenafil ↓ resting BP (blood pressure), reflex ↑ in HR (heart rate), No change in ECG, HR variability. Suggests sildenafil does not affect cardiac autonomic nervous system function.

Level of Evidence: Intermediate level.

Modulation of human platelet aggregation by the phosphodiesterase Type 5 inhibitor sildenafil.


Note: 100 mg oral sildenafil increased bleeding time at one hour after dose but bleeding time returned to baseline at four hours. 50 mg dose had no effect. In vitro study showed that sildenafil 50 mg or 100 mg did not inhibit ADP induced aggregation but collagen induced aggregation was reduced (note: differs from data shown in Pfizer AJC supplement).

Level of Evidence: Intermediate level.

The effect of sildenafil on nitric oxide-mediated vasodilation in healthy men.


Note: In healthy men sildenafil increased sensitivity to nitroglycerin 4 x but did not affect endothelium - dependent vasodilation in hand vein or forearm arterial vasculature. No data on men with ↓ endothelial function at baseline.

Level of Evidence: Intermediate level.

Cardiovascular safety of sublingual apomorphine in patients on stable doses of oral antihypertensive agents and nitrates.


Note: examined the pharmacodynamic interactions between apomorphine SL and commonly used cardiovascular medications in a double-blind, crossover study involving 162 men (mean age, 61 years) who had been stable on therapeutic doses of ACE inhibitors, beta blockers, α1 blockers, calcium channel blockers, diuretics, or nitrates for at least four weeks.

Level of Evidence: Intermediate level.

Nebulized sildenafil is a selective pulmonary vasodilator in lambs with acute pulmonary hypertension.


Note: Pulmonary hypertension induced by infusion of thromboxane analogue. Nebulized sildenafil ↓ pulmonary artery pressures and had an additive effect with inhaled NO.

Level of Evidence: Intermediate level.

Effect of sildenafil on blood pressure and arterial wave reflection in treated hypertensive men.


Note: Sildenafil given to eight men with well controlled hypertension reduced brachial blood pressure and reduced arterial wave reflection.

Level of Evidence: Intermediate level.

Potentiation of sildenafil-induced hypotension is minimal with nitrates generating a radical intermediate.


Note: Chronically instrumented canine study. Twenty-four hour infusion of three types of nitrates and then sildenafil. During glyceryl trinitrate sildenafil ↓ BP 21 ± 13 mmHg; during ISDN -18 mmHg; during pentaerythritol tetranitrate -6 mmHg.

Level of Evidence: Intermediate level.

Cardiac phosphodiesterase 5 (cGMP-specific) modulates β-adrenergic signaling in vivo and is down-regulated in heart failure.


Notes: This agent was used in conscious dog models including a heart failure model. They claim that PDE5 is expressed in myocardial cells. PDE5A regulation of cGMP is altered in heart failure and may blunt the beta adrenergic response.

Level of Evidence: Intermediate level.
Assessment of the efficacy and safety of Viagra® (sildenafil citrate) in men with erectile dysfunction during long-term treatment.

**Note:** Open label study of sildenafil for efficacy (n = 1008); not placebo controlled. Patients followed for 36 or 52 weeks. Treatment related CV adverse events (↑ BP, tachycardia, palpitations, angina) < 1%.

**Level of Evidence:** Intermediate level.

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Effect of inhaled iloprost plus oral sildenafil in patients with primary pulmonary hypertension.

**Note:** Small nonrandomized study showing that sildenafil reduces pulmonary artery pressure in patients with primary pulmonary hypertension and that this effect is additive with iloprost.

**Level of Evidence:** Intermediate level.

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Effect of Sildenafil on rennin secretion in human subjects.

**Notes:** Ten healthy human volunteers had unrestricted sodium intake; another 10 had restricted sodium intake. Sildenafil had only minor CV effects. Plasma rennin activity was associated with a fall after placebo but no fall after sildenafil. Results regarding renin similar between two groups. Significance of this study is not clear.

**Level of Evidence:** Intermediate level.

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Intracavernous injections for erectile dysfunction in patients with cardiovascular diseases and failure or contraindications for sildenafil citrate.

**Notes:** Success rate was 94% with injection therapy. Follow-up BPs in office did not show changes in brachial blood pressure or deterioration of CV health or change in cardiac meds.

**Level of Evidence:** Intermediate level.

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Relaxation and cGMP formation in response to sildenafil and sodium nitroprusside in saphenous veins from normotensive and hypertensive patients.

**Notes:** Study of saphenous vein rings (in vitro) from hypertensive and normotensive individuals. Sildenafil caused venorelaxation that was greater in normotensives but had a synergistic effect with sodium nitroprusside greater in veins of hypertensives. Sildenafil ↑ cGMP levels.

**Level of Evidence:** Intermediate level.

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Potential for use of pulse wave analysis in determining the interaction between sildenafil and glyceryl trinitrate.

**Notes:** Central aortic wave form measured noninvasively. Oral sildenafil augmented fall in aortic systolic pressure in healthy volunteers. There was a fall in augmentation index and pulse pressure.

**Level of Evidence:** Intermediate level.

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Sildenafil and T-1032, phosphodiesterase type 5 inhibitors, showed a different vasorelaxant property in the isolated rat aorta.

**Notes:** Study done in isolated rat aorta (in-vitro). Sildenafil caused vasodilation by both an ↑ in cGMP levels as well as an inhibition of external calcium – dependent cascade.

**Level of Evidence:** Intermediate level.

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Effects of sildenafil citrate (Viagra) on cardiac repolarization and on autonomic control in subjects with chronic heart failure.

**Notes:** In men with heart failure sildenafil decreased vagal modulations plus ↑ sympathetic modulations which may have been secondary to reflex vasodilator effect. Sildenafil had no direct effect on QT interval or dispersion. Nevertheless, authors conclude that autonomic system changes could alter QT dynamic and favor arrhythmias.

**Level of Evidence:** Intermediate level.
Interactions of sildenafil with various coronary vasodilators in isolated porcine coronary artery.

Notes: Study of isolated porcine coronary arteries in which interaction of sildenafil with various coronary vasodilators was studied. Sildenafil potentiated relaxation of arteries to drugs that were NO donors.

Level of Evidence: Intermediate level.

Sildenafil-nitric oxide donor combination promotes ventricular tachyarrhythmias in the swine right ventricle.

Notes: Eight isolated swine right ventricles – vulnerability to VT/VF tested by rapid pacing. No increase with sildenafil alone or NO donor alone, but combination increased incidence of VT/VF.

Level of Evidence: Intermediate level.

Sildenafil reverses O₂ constriction of the rabbit ductus arteriosus by inhibiting type 5 phosphodiesterase and activating BKCa Channels.

Notes: Fetal rabbit ductus arteriosus rings studied in-vitro. Sildenafil induced dose-dependent relaxation of the rings and might be an alternative or useful adjunct to prostaglandin E₁.

Level of Evidence: Intermediate level.

Sildenafil (Viagra®) augments sodium nitroprusside-induced but not nitroglycerin-induced hypotension in dogs.

Notes: Anesthetized canine preparation. Sodium nitroprusside or nitroglycerin induced dose-dependent decreases in mean arterial blood pressure without affecting heart rate. Sildenafil augmented this effect with sodium nitroprusside but not nitroglycerin. Results differ from other findings - perhaps anesthesia with thiopental blunted the effect.

Level of Evidence: Intermediate level.

Sildenafil citrate does not affect QT intervals and QT dispersion: An important observation for drug safety.

Note: Sildenafil does not prolong QT intervals or increase QT dispersion in 36 patients with erectile dysfunction.

Level of Evidence: Intermediate level.

Oral sildenafil as long-term adjunct therapy to inhaled iloprost in severe pulmonary arterial hypertension.

Note: In 14 patients with severe pulmonary arterial hypertension deteriorating despite ongoing prostanoïd treatment, long-term adjunct oral sildenafil improves exercise capacity and pulmonary haemodynamics at 9-12 months.

Level of Evidence: Intermediate level.

Sildenafil for long-term treatment of nonoperable chronic thromboembolic pulmonary hypertension.

Note: Chronic oral dosing at 6 months improved pulmonary haemodynamic and exercise capacity in 12 patients. Possible important treatment option.

Level of Evidence: Intermediate level.

Haemodynamic effects of sildenafil in patients with stable ischaemic heart disease.

Note: A single oral dose of sildenafil had no significant haemodynamic effect in 12 supine patients with stable angina. Isolated administration of sildenafil does not appear to be associated to adverse cardiovascular effects.

Level of Evidence: Intermediate level.
Effects of sildenafil citrate (Viagra) on hemodynamic parameters during exercise testing and occurrence of ventricular arrhythmias in patients with erectile dysfunction and cardiovascular disease.

Note: Sildenafil does not alter haemodynamic response to exercise or change incidence of ventricular arrhythmias in men with CVD and ED and should be safe for most patients with both these conditions.

Level of Evidence: Intermediate level

Hemodynamic response to sildenafil, nitric oxide, and iloprost in primary pulmonary hypertension.

Note: Small comparative study of 10 patients. All of the three substances, iNO, iloprost aerosol, and oral sildenafil, significantly improved pulmonary haemodynamics in patients with PPH. The most prominent haemodynamic effects and improvement of oxygenation were observed with iloprost aerosol.

Level of Evidence: Intermediate level


Note: Small study of 10 patients. Acute right heart and repeat study after 3 months of oral 50 mg tds. Pulmonary haemodynamics improved and quality of life by questionnaire.

Level of Evidence: Intermediate level

Sustained efficacy and tolerability with vardenafil over 2 years of treatment in men with erectile dysfunction.

Note: Large study of 566 men with no cardiovascular safety concerns.

Level of Evidence: Intermediate level
Committee 15

Future Treatment Targets

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Penile erection is mediated by a spinally coordinated activity in the autonomic pathways to the penis and to the somatic pathways to the perineal striated muscle, initiated by recruitment of afferent impulses. After central processing and integration of e.g., tactile, visual, olfactory, and imaginative stimuli, the signals to the peripheral tissues involved are generated. This 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, which relate to sexual function, have been defined, including the medial preoptic area (MPOA), paraventricular nucleus (PVN) (Figure 1), medial amygdala, the periaqueductal gray, and ventral tegmentum [1-4]. Studies in rats have revealed that electrical stimulation of e.g., the MPOA [5], the PVN [6], or the hippocampal formation [7] 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 [8].

The balance between factors that control the degree of contraction of the smooth muscle of the corpora cavernosa determines the functional state of the penis. Despite intensive research during the last decade, many details of neurotransmission, impulse propagation and intracellular transduction of signals in penile smooth muscles remain to be elucidated.

As evidenced by several recent reviews, the information on both central and peripheral control mechanisms involved in erection is rapidly expanding, and new details are continuously added [1-4, 9-13]. This chapter gives an update of central and peripheral mechanisms involved in the control of penile erection, and which may be targets for future treatments.

Dopaminergic neurons from various parts of the brain project to the MPOA and the PVN, [14] and dopaminergic neurons have been identified, traveling from the caudal hypothalamus to innervate the autonomic and somatic nuclei in the lumbosacral spi-
nal cord [15, 16]. Dopamine can thus be expected to participate in the regulation of both the autonomic and somatic components of the penile reflexes.

Extracellular dopamine increases in the PVN of male rats during sexual activity (Figure 2) [17]. Furthermore, when administered systemically to male rats, the dopamine receptor agonist, apomorphine, stimulating all subtypes of dopamine receptors, induces penile erection,[18] simultaneously producing yawning and seminal emission. Also 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.

Both the two major families of dopamine receptors, D1- and D2-like receptors,[19] have been associated with central erectile functions; however, the D2-like receptor subtypes seem to have the predominating effect, even if selective D1 receptor agonists have bee reported to produce erection [20].

Injection of apomorphine into the MPOA, showed that low levels of dopaminergic stimulation, via D1 receptors in particular, facilitated erections [21]. In contrast, dopaminergic antagonists injected into the MPOA decreased the number of penile reflexes [22, 23]. In the PVN, similar experiments have established that D2- rather than D1-like receptors primarily facilitate erections [1].

The erection following paraventricular D2 receptor stimulation apparently involves oxytocinergic neurotransmission. Dopaminergic neurons impinge on oxytocinergic cell bodies in the PVN, [24, 25] and apomorphine-induced penile erection is prevented dose-dependently by oxytocin receptor antagonists, [26] or by electrolytic lesions of the PVN depleting the oxytocin content [27-29]. Conversely, injection of oxytocin into the PVN induced erections that were not attenuated by dopamine receptor blockade, suggesting that dopaminergic neurons activate oxytocinergic neurons in the PVN, and that released oxytocin then accounts for the erectile response.

Injection of apomorphine into the lumbosacral subarachnoid space was reported to impair ex copula penile reflexes, slow the rate of copulation, and decrease the number of intromissions preceding ejaculation, [30, 31] suggesting an inhibitory effect on spinal erectile mechanisms. This is in contrast to recent findings, showing that injection of apomorphine intrathecal in rats evoked erection in both normal and spinalized animals [32-34]. Most probably 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. found that apomorphine injected into the PVN, but not in the the MPOA, enhanced seminal emission. [31]. Recording of intracavernous pressure in the non-anesthetized rat after systemic administration of apomorphine showed that the pressure response consisted of both smooth and striated muscle components [35]. This implies that systemically given apomorphine has effects not only on the sacral parasympathetic output, but also on somatic pathways.

Apomorphine is clinically effective in patients with erectile dysfunction (ED). However, the effect is modest compared to that of PDE5 inhibitors, and
side effects, mainly nausea, are dose-limiting. One way of increasing the efficacy of apomorphine may be combination with other agents, e.g., α-adrenoceptor (AR) antagonists, [36] or agents acting via the NO/guanylyl cyclase/cGMP pathway, e.g. sildenafil, [35] or allosteric activators of guanylyl cyclase (see below). Another possibility is to explore the effects of selective stimulation of the different dopamine receptor subtypes, with the aim of separating effect on erection and the nausea/emesis producing action. Promising results with selective D4 receptor active agents have been obtained [37].

II. MELANOCORTIN RECEPTORS

When administered intracerebroventricularly (i.c.v.), the adrenocorticotropic (ACTH) and α-melanocyte stimulating hormones (α-MSH), are able to induce penile erection (Figure 3) along with grooming, stretching, and yawning [1, 2, 38]. These effects are most probably mediated via stimulation of melanocortin (MC) receptors, of which five different subtypes have been cloned and characterized [39, 40]. α-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 MC4 receptors [38, 41]. However, it is unclear what MC receptor subtype(s) that can be linked to the erectile responses. The MC3 receptor showed a high density in the hypothalamus and limbic systems [39] regions known to be important for erectile functions. The site and mechanism of action responsible of α-MSH/ACTH seem to be different from those involving dopamine or oxytocin [9]. However, it has been reported that penile erection, produced by MC4 receptor stimulation, can be blocked by oxytocin receptor antagonists [42-44].

Martin et al., and Van der Ploeg et al. presented data that melanocortin-induced erectogenesis is mediated by MC4 receptors [42, 45]. Van der Ploeg et al. showed that MC4-receptor mediated proerectile responses may be activated through neuronal circuitry in spinal cord erectile centers and somatosensory afferent nerve terminals of the penis [45]. They also provided a basis for the existence of MC4-receptor controlled neuronal pathways that control sexual function.

Melanotan II, a synthetic analogue of α-MSH, lacking selectivity for melanocortin receptor subtypes, was shown to have potent erectile properties in animals models [44]. Given subcutaneously, melanotan II had proerectile effects also in men with erectile dysfunction [43, 44, 46, 47]. PT-141 is a novel cyclic heptapeptide analogue of alpha-MSH (and an active metabolite of melanotan II), which given intranasally had a proerectile effect in healthy volunteers. In patients with mild to moderate erectile dysfunction, PT-141 dose-dependently increased the duration and extent of penile rigidity without any reported side effects [48]. Also in patients not responding to sildenafil, PT-141 produced erection.

The therapeutic potential of α-MSH analogues seems very promising, but the clinical efficacy/side effects have to be further studied.

III. OXYTOCIN RECEPTORS

Spinal projections from the hypothalamic supraoptic and paraventricular oxytocinergic neurons associate with sacral preganglionic neurons within the autonomic and somatic nuclei controlling erection. There are reasons to believe that these neurons influence the sacral autonomic more than the somatic outflow [49-51].

Figure 3: Comparison of erectile response to intracerebroventricular (i.c.v.) α-MSH and oxytocin in anesthetized rats.
Oxytocin produces penile erection when injected into the lateral cerebral ventricle, the PVN, or hippocampus of rats. However, also intrathecal (i.t) oxytocin can initiate an erection (Figure 4). These erections can be blocked by the administration of oxytocin antagonists given intracerebroventricularly (i.c.v) or i.t, or by electrolytic lesion of the PVN [12, 52]. Also non-contact erections can be reduced by a selective oxytocin receptor antagonist, given into the lateral ventricles, which supports the view that oxytocin mediates this response [53]. The mechanism by which oxytocin elicits erection may be through autoactivation by stimulation of oxytocinergic receptors located in the cell bodies of the same oxytocinergic neurons in the PVN [52].

Oxytocin increases NO production in the paraventricular nucleus [54]. However, NO synthase (NOS) inhibitors prevent penile erection and yawning in rats induced not only by oxytocin, but also by dopamine, excitatory amino acids, the 5-HT2C receptor agonist, m-chlorophenylpiperazine (m-CCP; trazodone metabolite), and ACTH/α-MSH, suggesting that NO is essential for centrally acting erection-producing agent [12].

The effects of oxytocin and central inducers of erection are also androgen-dependent [12].

Plasma oxytocin concentrations are known to be elevated following sexual stimulation in humans [1]. However, the relevance of the oxytocinergic pathway in humans has never been established. Thus, systemic administration of oxytocin was without effect, probably due to difficulties of the peptide to penetrate into the CNS [1]. However, considering that many centrally acting agents producing erection seem to involve, directly or indirectly, oxytocinergic pathways, it would be of interest to explore the therapeutic potential of this system [55].

### IV. HEXARELIN ANALOGUE RECEPTORS

Hexarelin (Examorelin INN) is a hexapeptide originally characterized for its ability to release growth hormone (GH) in laboratory animals and humans with a potency comparable to that of the natural GH-releasing hormone (GHRH). The GH-releasing effect of hexarelin, similar to that of other GH secretagogues, is mediated by the stimulation of receptors distinct from those of endogenous GHRH [56]. This peptide also increases feeding, apparently by acting on receptors different from those that release GH and that are localized mainly in the arcuate nucleus [57].

During studies aimed at identification of the brain sites in which hexarelin acts to increase feeding, and at characterization of the receptors mediating this effect, a group of hexarelin analogue peptides was found able to induce episodes of penile erection indistinguishable from those induced by the dopamine receptor agonist apomorphine, by oxytocin, by NMDA or by NO donors when injected into the paraventricular nucleus of male rats. Active analogues include EP 50885, EP 60761, EP 80661, EP 90101, EP 91071, EP 91072. Some of the analogues were also found able to induce penile erection, although to a lesser extent, when given systemically [58, 59]. The potency of some of the hexarelin analogues (e.g. EP 80661, EP 60761 and EP 91072), when injected...
into the paraventricular nucleus, was comparable to that reported for apomorphine, oxytocin and NMDA [58]. Indeed these peptides were found capable of inducing penile erection when injected into the paraventricular nucleus of male rats at doses as low as 20 ng (Figure 5). On a molar basis, the dose of these analogues that induces 50% of the maximal response corresponds to ≈70-90 pmoles. Analysis of the amino acid sequence of the hexarelin analogues tested shows the existence of a clear structure-proerectile activity relationship [59]. Indeed, the presence of a basic C-terminal amino acid (L-Lys or L-Arg) appears to be a requisite for proerectile activity, since analogues, which lacks such a C-terminal amino acid are inactive. The C-terminal amino acid may be preceded by one or more aromatic amino acid residues, such D-Trp(2-Me) or D-Trp or D-β-(2-naphthyl)Ala-L-Phe. The N-terminal amino acid also seems to have a role in the pro-erectile activity of EP peptides. Indeed substitution of the GAB (gamma-aminobutyryl) group with the AIB (amino-isobutyryl) group not only abolishes proerectile activity, but also renders the analogue capable of preventing the proerectile activity of active analogues.

Hexarelin analogue peptides apparently induce penile erection by acting in the paraventricular nucleus of the hypothalamus by activating central oxytocinergic neurotransmission with a mechanism similar to that already described for other agents that induce erection when injected into this hypothalamic nucleus, e.g. apomorphine, oxytocin, excitatory amino acids. Accordingly, the proerectile effect of hexarelin analogue peptides was reduced by the oxytocin receptor antagonist [d(CH2)5Tyr(Me)2-Orn8]-vasotocin given i.c.v. but not into the paraventricular nucleus, by the NO synthase inhibitor L-NAME given i.c.v. or into the paraventricular nucleus, and by morphine, but not by the NMDA receptor antagonist dizocilpine ((+MK-801) or by the dopamine receptor antagonist cis-flupenthixol, all given into the paraventricular nucleus [60]. Hexarelin analogue peptides that induce penile erection also increase NO2- and NO3-concentration in the paraventricular dialysate, as measured by intracerebral microdialysis, as shown for dopamine receptor agonists, oxytocin, NMDA and NO donors. The activation of paraventricular oxytocinergic neurons mediating penile erection is apparently mediated by the stimulation of specific receptors for these hexarelin analogues possibly located in the cell bodies of oxytocinergic neurons mediating penile erection. Support for this hypothesis is provided by EP 91073, a hexarelin analogue devoid of proerectile activity, which reduces penile erection induced by active analogues not only in a dose-dependent, but also a selective manner [61]. Indeed, this hexarelin analogue is unable to reduce the proerectile effect of apomorphine, oxytocin or NMDA injected into the paraventricular nucleus. EP 91073 also reduces the increase in paraventricular NO production that occurs concomitantly with penile erection induced by active hexarelin analogues.

Receptors mediating the proerectile effect of hexarelin analogue peptides seem different from those mediating GH release and eating behavior. Accordingly, the structure-activity relationship of hexarelin analogues for penile erection differs respect to that involved in GH release and eating behavior, and elimination of the C-terminal L-Lys-NH2, which eliminates proerectile activity, is unable to reduce GH release or eating behaviour. Perhaps more important, ghrelin, an endogenous agonist of GH secretagogue receptors mediating GH release and feeding behavior, was unable to induce penile erection when injected into the paraventricular nucleus, despite its ability to induce feeding, and the effect of ghrelin on feeding was not prevented by EP 91073 [62].

No evidence is available at the moment that hexarelin analogue peptides can influence erectile function in humans. Due to the potency of these peptides when injected into the paravenricula nucleus of male rats, the possibility of application of hexarelin analogue peptides in the treatment of erectile dysfunction should be examined. However, a significant amount of work will still be needed to address questions related to potency, bioavailability, half-life, toxicity and route of administration.

Figure 5: Erections induced by hexarelin and some analogues in the awake rat
In the brain, 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. Bulbospinal neurons containing 5-HT project to the autonomic and somatic nuclei in the spinal cord of e.g., rats and cats [1]. Some serotonergic fibres were found in close apposition with retrogradely-labelled sacral preganglionic neurons and motoneurons, and synapses have been demonstrated at the ultrastructural level, [49] supporting the involvement of 5-HT in both the supraspinal and spinal pharmacology of erection, with participation in sympathetic, parasympathetic as well as somatic outflow mechanisms.

In animals, 5-HT seems to exert a general inhibitory effect on male sexual behavior, [63] although the amine may be inhibitory or facilitatory depending upon action at different sites and at different 5-HT receptors within the CNS [64, 65]. This may explain conflicting reports of 5-HT receptor agonists either enhancing or depressing sexual function. Yonezawa et al. found that p-chloroamphetamine (PCA), an indirect 5-HT receptor agonist, elicited simultaneously both penile erection and ejaculation in anesthetized rats [66]. It was suggested that these effects were mainly produced by the release of 5-HT, 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 [11, 12].

5-HT2C (previously 5-HT1C) receptors seem to mediate erectile responses, [67] and in rats stimulation of 5-HT2C receptors increased circulating oxytocin [68]. NOS inhibitors given i.c.v. prevented 5-HT2C-receptor mediated erectile responses [69]. These findings suggest that both oxytocin and NO are involved in 5-HT2C-receptor mediated erections.

Undoubtedly, 5-HT mechanisms are involved in the control of erection, which makes them attractive as targets for potential erection-modulating drugs. However, so far no drugs interfering exclusively with the 5-HT mechanisms involved in erectile control have proven clinically useful.

The information on noradrenergic mechanisms involved in the central neuromediation of penile erection is sparse. The spinal cord contains proerectile autonomic motoneurons destined to the penile tissue and its vasculature, and somatic motoneurons destined to the perineal striated muscles [70]. Current data suggest that increased noradrenergic activity stimulates, whereas decreased noradrenergic activity inhibits, sexual function [63, 71, 72]. Chang et al. suggested that in the hippocampal formation there is a negative feed back mechanism for the regulation of penile erection, which is triggered by ascending sensory inputs initiated by tumescence of the penis (Figure 6) [73]. They also suggested that the noradrenergic innervation of the hippocampal formation that originates from the locus coeruleus may play an active role in this negative feedback regulation, engaging at least $\alpha_1A/D^+$-, $\alpha_2B^+$-, and $\alpha_2C^+$-adrenoceptors (ARs) in the hippocampus. [74]. Theoretically, such a negative feed-back mechanism could be the site of action of the $\alpha_2$-AR antagonist, yohimbine.

Yaici et al. demonstrated neurons and fibers immunoreactive for $\alpha_2A$ and $\alpha_2C$-AR subtypes were mainly present in the intermediolateral cell column, the dorsal gray commissure and the ventral horn of the T12-L2 and L5-S1 spinal cord [75]. Pseudorabies virus-infected neurons in the autonomic nuclei were both immunoreactive for $\alpha_2A^+$- and $\alpha_2C^+$-AR subtypes and closely apposed by $\alpha_2A^-$ and $\alpha_2C^-$-immunoreactive fibers. Yaici et al. suggested that there is an intraspinal modulation of the noradrenergic and adrenergic control of the autonomic outflow to the penis by pre- and postsynaptic $\alpha$-ARs [75].

It may thus be possible to modulate penile erection via $\alpha_2$-ARs both at a spinal and supraspinal site. Whether subtype selective $\alpha_2$-AR antagonists have better effects than yohimbine remains to be established.

In the CNS, NO function is essential for erectile responses (Figure 7). NO can modulate sexual behavior and penile erection. [69, 76-79] and may act in several discrete brain regions, e.g., in the MPOA [78, 79].
Figure 6: A negative feedback mechanism for the regulation of penile erection in the hippocampal formation. The mechanism is triggered by ascending sensory inputs initiated by tumescence of the penis. The noradrenergic innervation of the hippocampal formation originating from the locus coeruleus exerts a negative feedback involving at least α1A/D-, α2B-, and α2C-adrenoceptors (ARs) in the hippocampus (after data from Chang et al 2001).

Figure 7: Nitric oxide and androgens are important for central mediation of erection, no matter what system initiates the process.
and the PVN [69, 80]. Injection of NOS inhibitors i.c.v. or in the PVN prevented penile erectile responses induced by dopamine agonists, oxytocin, and NMDA in rats, and NO may also mediate the actions of ACTH/α-MSH and 5-HT2C agonists [69]. The inhibitory effect of NOS inhibitors was not observed when these compounds were injected concomitantly with L-arginine, the substrate for NO [69]. NO production increased in the PVN 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 PVN [77].

It is well established that the hypothalamus plays an essential role in the integration and control of male reproductive and sexual functions [1]. The gonadotropin-releasing hormone (GnRH) is synthesized and secreted in the MPOA, and as pointed out by Ferrini et al., the hypothalamus controls pulsatile gonadotropin secretion and serum testosterone levels necessary to maintain spermatogenesis, libido, and, at least in the rat, the function of the CC smooth muscle and the perineal muscles involved in penile erection [81]. In the rat, the hypothalamus also plays a fundamental role in the control of copulatory behavior, penile erection, and ejaculation through the transmission of central stimuli originating mainly from the MPOA and PVN [8]. The number of oxytocinergic neurons in the rat PVN and supraoptic nucleus decreases substantially with aging, [82] and this decline may impair sexual function, since penile oxytocinergic neurons have been postulated to have an important role in erection and ejaculation.

To explain selective neuronal loss in the brain, including the hypothalamus, it has been proposed that there is an increase in the rate of programmed cell death by oxidative and nitrosative stress in these neurons [83]. Peroxynitrite, the product of the reaction between NO and superoxide, is a strong oxidizing and nitrating agent that can react with all classes of biomolecules. A high level of peroxynitrite has been observed in the brain with aging. Vernet et al. showed that in the rat MPOA and other regions of the brain, this might be due to the expression of inducible nitric oxide synthase (iNOS) [84]. Ferrini et al. investigated by quantitative immunohistochemical analysis the regional differences in the aging-related expression of iNOS in the hypothalamus [81]. They also studied whether these changes were associated with similar variations in peroxynitrite formation and the rate of apoptosis and examined whether iNOS induction occurs in GnRH- and oxytocin-containing hypothalamic neurons. They found an aging-related iNOS expression in the hypothalamus of the male rat, which they concluded affected regions known to control the synthesis and release of GnRH and oxytocin and the factors regulating penile erection. Their observations suggested that iNOS may play a role in the reduction in GnRH and oxytocin neuronal secretion, resulting in reproductive dysfunctions, such as lowered serum testosterone levels and diminished copulatory function in the aging male animal.

C. PERIPHERAL TARGETS

I. NORADRENALINE AND α-ADRENOCEPTORS

Penile arteries and veins and cavernosal smooth muscle receive a rich adrenergic innervation, and it is generally accepted that the penis is kept in the flaccid state mainly via a tonic activity in these nerves [12]. Released noradrenaline stimulates α-ARs in the penile vasculature and in the trabecular smooth muscle of the CC. The postreceptor mechanisms involved include activation of phospholipase C and generation of inositol triphosphate (IP3) and diacylglycerol. In addition, α-AR agonists induce a higher force/Ca2+ ratio than does a depolarization-induced increase (ie, potassium chloride) in intracellular Ca2+, suggesting a “calcium-sensitizing” effect of the agonists (see below). The effect of calcium-sensitizing agonists are mediated by guanosine triphosphate (GTP)-binding proteins recruiting other messenger systems [85].

Hashitani et al. investigated the cellular mechanism of NO-induced relaxation in CC smooth muscle from the guinea pig [86]. They found that in noradrenaline- precontracted preparations, the NO donor, SIN-1, inhibited 80% of the contraction and decreased [Ca2+](i) by 20%. In contrast, the calcium antagonist, nifedipine, reduced [Ca2+](i) by 80%, whereas the level of contraction was decreased by only 20%. In high potassium precontracted preparations, SIN-1 inhibited 80% of the contraction and reduced [Ca2+](i) by 20%. Hashitani et al. suggested that decreasing the sensitivity of contractile proteins to Ca2+ may be the key mechanism of NO-induced relaxation in CC smooth muscle [86].

Many factors, including androgens, may regulate the α-AR responsiveness of cavernous smooth muscle.
Compared with normal rats, castrated animals showed an enhanced reactivity to $\alpha_1$-AR stimulation [87]. In animals with long-term (1-year) streptozotocin-induced diabetes, there was a failure to respond to $\alpha_1$-AR stimulation in the cavernous circulation [88]. The clinical importance of these observations has so far not been established.

It is known that men with hypertension have a higher prevalence of ED than the general population. Behr-Roussel et al. found in the spontaneously hypertensive rat a reduced response to cavernous nerve stimulation, a reduced contractile CC response to phenylephrine, and impaired endothelium-dependent relaxation to acetylcholine [89]. Indomethacin improved the acetylcholine-induced relaxations. The investigators suggested that ED in hypertension was due to a dysregulated balance between vasoactive substances, with an increase in vasoconstrictor prostanoids and a defect NO availability. Since the spontaneously hypertensive rat has an increased peripheral sympathetic nervous activity, it may be that NO fails to override the concerted effects of the contractile factors in the penis (see below).

### II. ENDOTHELINS AND ENDOTHELIN RECEPTORS

ET-1, which potently induces slowly developing, long-lasting contractions in the CC and penile vessels, has been suggested to contribute to the maintenance of CC smooth muscle tone [12, 90]. Contractions can be evoked in human CC tissue also by ET-2 and ET-3, although these peptides have a lower potency than ET-1 [91]. The contractions induced by ET-1 may be dependent on transmembrane calcium flux (through voltage-dependent and/or receptor-operated calcium channels), the mobilization of IP3-sensitive intracellular calcium stores [92, 93], and calcium sensitization of the contractile machinery. In bovine retractor penis muscle and penile artery, the contraction induced by ET-1 was mediated primarily by ETA-receptors [94]. This was also the case in human CC [95]. In the pithed rat, intravenously injected ET-1 had a vasodilator action (increase in corporal pressure) at low, but a vasoconstrictor action at high, doses [96]. ET-3 had mainly vasodilator effects, and it was suggested that the vasodilator actions were mediated by activation of ETB receptors on the endothelium and local release of NO, since these actions were inhibited by NG-nitro-L-arginine methyl ester (L-NAME).

Dai et al. used selective receptor antagonists to examine the role of ET-1 in erection in rats [97]. Their results confirmed that cavernosal tissue of the rat penis is highly responsive to ET-1. However, blockade of the ETA or the ETB receptor had no effect on the erectile response induced by maximal ganglionic stimulation in vivo. The failure of the ET-1 antagonists to affect penile erection seemed to reflect a minimal role of ET-1 in the erectile response in the rat. Kim et al. evaluated in a pilot study the ETA receptor antagonist BMS-193884 as a treatment for ED in an animal model (rabbit) and in men with mild-to-moderate ED [98]. Experimentally, BMS-193884 facilitated cavernosal smooth muscle relaxation ex vivo and prolonged penile tumescence in vivo. In contrast, the clinical study failed to show enhancement of erectile responses in men with ED. However, this disparity between the laboratory and clinical results does not rule out that ETs may play a role in keeping the penis in a flaccid state or that ETs may be associated with ED. Further clinical studies with selective antagonists of ET receptors have to be performed to assess the role of ETs in erectile function and ED.

Even if a role for ETs as long-term regulators of corporal smooth muscle tone has not been definitely established, they may have important effects in penile physiology and pathophysiology, for example, as modulators of the effect of other contractile agents (eg, noradrenaline) [92, 99, 100] as modulators of cellular proliferation and phenotypic expression [101].

### III. PROSTANOID RECEPTORS

Human corpus cavernosum tissue has the ability to synthetize various prostanoids, and has also the ability to locally metabolize them [1, 102, 103]. 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$_{2\alpha}$, PGI$_2$, and TXA$_2$, there are five major groups of receptors mediate their effects, namely 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 established [102, 103]. Prostanoids may be involved in contraction of erectile tissues via PGF$_{2\alpha}$ and thromboxane A$_2$, stimulating TX and FP receptors and ini-
tiating phosphoinositide turnover, as well as in relaxation via PGE₁ and PGE₂, stimulating EP receptors (EP2/EP4) and initiating an increase in the intracellular concentration of cAMP. Prostanoids may also be involved in inhibition of platelet aggregation and white cell adhesion, and recent data suggest that prostanoids and transforming growth factor-β₁ (TGF-β₁) may have a role in modulation of collagen synthesis and in the regulation of fibrosis of the corpus cavernosum [104].

Whether or not inhibition of contraction-mediating prostanoid receptors will be useful as a therapeutic principle for treatment of ED remains to be established.

IV. THE RHOA/RHO-KINASE SIGNALING PATHWAY

It is generally accepted that vascular smooth muscle contraction is dependent on the extent of myosin light chain phosphorylation. Vasoconstrictor ligand binding elevates cytosolic free calcium ([Ca²⁺]ᵢ) by causing the opening of membrane Ca²⁺ channels as well as the release of Ca²⁺ stored in the sarcoplasmic reticulum [105]. The Ca²⁺ binds to calmodulin and the resulting complex activates myosin light chain (MLC) kinase (Figure 8). When active, MLC kinase phosphorylates MLC (i.e., MLC-P) permitting myosin - actin cross bridge formation and contraction. MLC phosphatase is responsible for removal of the phosphate and in the non-phosphorylated state the myosin cross bridge detaches and relaxation results. Thus, the relative activity of MLC kinase and MLC phosphatase determines the state of contraction or relaxation. Recent studies have, however, demonstrated that in vascular smooth muscle, the relationship between [Ca²⁺]ᵢ and agonist-induced force generation is not a simple one [106] and suggest a Ca²⁺-independent regulation, which is also activated during agonist-induced smooth muscle contraction. In addition to increasing cytosolic Ca²⁺, vasoconstrictor agents may also activate this Ca²⁺-independent mechanism, i.e., Ca²⁺ sensitization. The Ca²⁺ sensitization appears to result from the inhibition of MLC phosphatase activity, and when MLC phosphatase activity declines, there is a net increase in the extent of MLC phosphorylation resulting in sustained contraction despite the moderate to low levels of [Ca²⁺]ᵢ.

Except during periods of sexual excitement or episodes of nocturnal penile erections, the smooth muscle cells of the penile vasculature are primarily contracted resulting in minimal blood flow through the erectile tissue. In order for the penis to become erect, this vasoconstriction must be overcome to permit relaxation of the arteriolar and sinusoidal smooth muscle cells [12, 107]. The primary agent responsible for this cavernosal smooth muscle relaxation is thought to be nitric oxide (NO) released from penile nerves and from cavernosal endothelial cells [12]. NO diffuses into smooth muscle cells where it activates soluble guanylate cyclase (sGC) to elevate intracellular levels of cGMP and increases cyclic GMP-dependent protein kinase (PKG or cGK I) activity [108]. The NO/cGMP/PKG signaling pathways lead to relaxation through a variety of mechanisms including: (1) inhibition of L-type Ca²⁺ channels, (2) activation of Ca²⁺-dependent ATPase in sarcoplasmic reticulum, (3) stimulation of the opening of membrane K⁺ channels to hyperpolarize the cell membrane [109] (4) suppression of the Ca²⁺ sensitization pathway [110].

Cyclic AMP-dependent relaxation may also contribute to relaxation of cavernosal smooth muscle. Erection resulting from the actions of e.g., vasoactive intestinal peptide are considered to be mediated by cAMP-dependent processes [12, 111]. Furthermore, prostaglandin E₁, widely used in the treatment for ED, acts via a cyclic AMP-dependent mechanism [112]. Although less extensively studied, the mechanisms involved in cyclic AMP-dependent vasorelaxation appear to parallel those described for cyclic GMP-dependent mechanisms.

While there is ample published evidence supporting the role of [Ca²⁺]ᵢ in cavernosal smooth muscle contraction, [105] pathways which regulate Ca²⁺ sensitivity have only recently been examined in the vascular tissue of the penis [113]. Ca²⁺ sensiti-
zation is regulated in other vascular tissues by the monomeric GTP binding protein, RhoA and its downstream target, Rho-kinase [85, 105, 108]. Figures 8, 9 and 10 will illustrate these pathways.

RhoA is a small, GTP-binding protein which regulates a wide range of cellular processes including cytoskeletal function, secretion and smooth muscle contraction [105]. In the inactive state, RhoA binds GDP, but with vaso-constrictor ligand binding, GDP is exchanged for GTP. Activation of RhoA is completed with post-translational geranylgeranylation and RhoA migration to the cell membrane. These steps, resulting in RhoA activation, are regulated by three groups of proteins, which are found in most cells (Figure 9) [114, 115]. The GTPase activating proteins (GAP) increase intrinsic GTPase activity to maintain RhoA in the inactive form. Guanine nucleotide dissociation inhibitor (GDI) proteins inhibit GTPase activity to maintain RhoA in the GDP bound (inactive) state. Guanine nucleotide exchange factors (GEF) promote dissociation of RhoA-GDP to facilitate binding of GTP and RhoA activation. GEF proteins are considered to be the primary regulators of RhoA activation and hence the activity of the RhoA/Rho-kinase pathway (Figure 10).

Once activated, RhoA has several downstream targets, but of interest to this discussion of smooth muscle contraction is the downstream target, Rho-kinase. Rho-kinase, in turn, phosphorylates MLC phosphatase which results in the loss of phosphatase activity. When MLC phosphatase activity is inhibited, the phosphorylated form of MLC (i.e., MLC-P) is maintained and smooth muscle remains contracted. Rho-kinase has been reported to exist in two isoforms (α and β, but the β is considered to be the more important in cavernous smooth muscle contraction [116, 117].

Reports from several laboratories have demonstrated that there is considerable activity of the RhoA/Rho-kinase signaling pathway in penile tissue. These studies have utilized western analysis and immunocytochemistry to demonstrate both RhoA and Rho-kinase proteins in cavernous smooth muscle cells (Figure 11) [113, 118-121]. In addition, the selective Rho-kinase inhibitor, Y-27632 [(-)-(R)-trans-4-(1-Aminoethyl)-N-(4-pyridyl) cyclohexanecarboxamide dihydrochloride, monohydrate], has been used to demonstrate RhoA/Rho-kinase activity in the cavernous vasculature and during the erectile response [113, 118, 121]. Y-27632 competes with ATP for binding to the ATP binding site on Rho-kinase and, in this way, prevents the phosphorylation, and thus, inactivation of MLC phosphatase. In the presence of Y-27632, MLC phosphatase is activated so that MLC-P is de-phosphorylated to promote smooth muscle relaxation. Injection of Y-27632 into the cavernous sinuses of the rat penis produced increased intracavernosal pressure (ICP) in a dose-dependent fashion (Figure 12) as shown by Chitaley et al [113]. In this study, prior treatment of the penile vasculature with inhibitors of NO synthesis (ie., L-NAME) or guanylate cyclase (ie., ODQ) failed to alter the vasodilatory action of Y-27632, demonstrating that the inhibitor does not cause erection by activating NO-dependent vasorelaxation mechanisms. In other studies of the RhoA/Rho-kinase signaling pathway in the penis, methoxamine (α-AR agonist) or ET-1, was injected into the cavernous sinuses before, and again after, treatment with Y-27632 [121]. Both methoxamine and ET-1 strongly inhibited the erectile response by constricting the arterioles and cavernous sinuses and thereby limiting blood flow into the erectile tissue. However, when injected
in combination with Y-27632, the vaso-constrictor effects were prevented and erection occurred normally [121]. These whole animal studies suggest that the RhoA/Rho-kinase pathway mediates both α-AR and ET-1-mediated vasoconstriction in the penile circulation. In *in vitro* studies from several laboratories, strips of human, rabbit or rat cavernous tissue which had been contracted with phenylephrine or ET-1, were demonstrated to relax in a dose dependent fashion in response to the addition of Y-27632 [113, 117, 119, 120].

Additional evidence supporting a critical role of the RhoA/Rho-kinase pathway in the maintenance of vasoconstriction in the cavernosal circulation has recently been presented [122]. In these studies, an adeno-associated viral gene was used to transfer a dominant negative RhoA mutant to the cavernosal smooth muscle cells of normal rats. The mutant form of RhoA exchanges GDP for GTP, is geranylgeranylated and migrates to the cell membrane apparently normally. However, the dominant negative form of RhoA fails to activate Rho-kinase so that MLC phosphatase remains active to dephosphorylate MLC~P and permit smooth muscle relaxation. Western analysis of penile proteins and immunohistochemistry showed that following injection of the dominant negative RhoA into the cavernosal sinuses of rats, cavernosal smooth muscles became infected. In the infected animals, the basal ICP was increased and the erectile response to ganglionic stimulation was strongly enhanced relative to the response in animals infected with the adeno-viral vector only. Systemic blood pressure was unaffected by the treatment. This novel finding strongly supports the hypothesis that the RhoA/Rho-kinase pathway is critically involved in the maintenance of the penis in the non-erect state. In addition, these studies point to the possibility that genetic manipulation of RhoA mediated activation of Rho-kinase could be developed as a potential mode of ED treatment.

It is clear that for erection to occur, Rho-kinase-mediated vasoconstriction must be overridden by a NO/cGMP/PKG dependent process. Prior studies have shown that potent vaso-constrictor agents (methoxamine, ET-1) have no effect when administered directly into the cavernous sinuses of the rat penis made erect by ganglionic stimulation or from injection of a NO-donor drug [87, 97]. These findings can be interpreted to mean that NO, released from penile nerves, endothelial cells, or from intracavernous injection of NO or NO donors, activates pathways which block the actions of vasoconstrictor agents [123, 124]. Furthermore, the experiments suggest that an important action of NO is to directly inhibit RhoA activation or Rho-kinase-regulated phosphorylation of MLC phosphatase.

A review of the literature reveals that there is support for a direct inhibitory effect of NO on the RhoA/Rho-kinase pathway in other vascular beds. The studies of Sauzeau et al showed that NO regulated vasodilation resulted, in part, from the PKG-dependent phosphorylation of RhoA [108]. The phosphorylation of RhoA is thought to destabilize membrane binding thereby preventing its activation. In other studies of NO and Rho-kinase interactions, rat aorta strips were contracted with phenylephrine and found to readily relax in response to Y-27632 treatment. If, however, the tissue was first denuded of endothelial cells to remove the primary source of NO, the Y-27632-induced relaxation was reduced [125]. However, the relaxing effect of Y-27632 was fully restored when a NO-donor was added to the endothelium-denuded tissues. Based on these stu-
dies, the authors suggest that NO-mediated inhibition of RhoA/Rho-kinase is an integral part of vascular smooth muscle relaxation.

In animal studies, the erectile response to intracavernous injection of an NO donor was measured immediately before and immediately after administration of a near-threshold dose of Y-27632 [126]. Y-27632 treatment significantly enhanced the NO-stimulated rise in ICP even though there was virtually no measurable response to the Y-27632 when given alone. Furthermore, the response to the combination of the NO-donor and Y-27632 was significantly greater than the response to either drug alone or to the sum of the responses to the two drugs when given separately. These findings support the hypothesis that NO/cGMP/PKG-dependent processes inhibit RhoA/Rho-kinase signaling, and in doing so, reduce vasoconstriction as a critical part of the normal erectile response [113].

In addition to studies demonstrating that it mediates the actions of several vasoconstrictors, there is also the suggestion that the RhoA/Rho-kinase signaling pathway may inhibit NO production [127, 128]. In another vascular bed, Rho-kinase mediated phosphorylation of eNOS inhibits NO production by endothelial cells [129, 130]. This action of Rho-kinase would suppress the production of NO to keep the arterioles constricted and limit blood inflow.

Activity of the RhoA/Rho-kinase pathway has been examined in the corpora cavernosa of animal models of erectile dysfunction. In these studies, immunohistochemical techniques were used to quantify changes in RhoA and Rho-kinase proteins in penile tissue and animals have been treated with Y-27632 to determine if suppression of Rho-kinase mediated vasoconstriction reverses the impaired erectile function. In some studies, cavernosal tissues were incubated in vitro and the relaxation in responses to Y-27632 were determined. Based on their studies, several investigators have suggested that up-regulation of the RhoA/Rho-kinase signaling pathway may be a significant factor in the development of erectile dysfunction [113, 116, 118-120, 131-133].

The severe hypogonadal state following castration of rats results in a marked suppression of the erectile response; androgen replacement in the castrated animals fully restores the response [134-136]. Recently, the role of the RhoA/Rho-kinase pathway in the development of this castration-related erectile dysfunction has been investigated [137]. In these experiments, western analysis of RhoA and Rho-kinase protein in cavernosal tissue revealed a significant upregulation of these proteins in castrated rats. Testosterone replacement in the castrated rats fully restored the erectile response although it failed to fully restore the quantity RhoA or Rho-kinase protein. A single intracavernous injection of Y-27632 increased the magnitude of the erectile response in castrated rats to levels measured in intact control rats and testosterone-treated, castrated animals. Similarly, the in vitro contractile response to the α-AR agonist, phenylephrine, was markedly increased in the cavernosal tissue from the castrated rats and the response to this α- adrenergic agonist was inhibited by Y-27632.

The erectile response in two models of erectile dysfunction associated with hypertension has been reported [138]. In both spontaneously hypertensive rats which are also stroke prone (SHRSP), and rats made hypertensive by removal of one kidney, deoxycorticosterone acetate (DOCA) treatment and saline drinking water (DOCA-salt), MAP was increased to 180 - 200 mm Hg. In these severely hypertensive animals, the erectile response to ganglionic stimulation was sharply reduced. When animals in either group received a single intracavernous injection of Y-27632, the erectile response was significantly improved and MAP was suppressed to near normal levels. Western analysis of pathway proteins showed an upregulation of both RhoA and Rho-kinase in both SHRSP and DOCA-salt animals. Similar results have been reported for spontaneously hypertensive rats (SHR) [131]. Interestingly, treatment of SHRSP rats with the ACE inhibitor, captopril, improved the erectile response and reduced MAP [139]. The effect of captopril on the RhoA/Rho-kinase signaling pathway was not determined.

Recently published results support a significant role for the RhoA/Rho-kinase pathway in the erectile dysfunction associated with diabetes in rabbits [116] In vitro, corpus cavernosum tissue from these animals showed increased expression of both ETa and ETA receptors and showed increased sensitivity to the contractile effects of ET-1. The ET-1 induced contractions were completely prevented by treatment of the tissues with Y-27632 suggesting that the ET-1 effect was mediated by the RhoA/Rho-kinase pathway. Furthermore, western analysis of cavernosal tissue showed that the α isoform of Rho-kinase was unaffected whereas the β form was significantly upregulated in diabetic tissues. Based on their findings, these authors suggested that increased sensitivity to ET-1 in the diabetic model is mediated by Rho-kinase and this could account for the impaired erectile
function in this disease. Very recently, gene transfer was used to show that inhibition of Rho-kinase activation was effective in reversing the impaired erection in diabetic rats [133]. These investigators infected cavernosal tissue with the dominant negative form of RhoA in diabetic rats and showed that in the infected animals, the erectile response was fully restored to normal levels while MAP remained unaffected. The authors suggest that inhibition of RhoA/Rho-kinase signaling may provide a potential gene target for the treatment of diabetes related ED.

The relationship between benign prostatic hypertrophy (BPH) and the erectile dysfunction has been investigated using a rabbit BPH model in which the bladder outlet was partially obstructed [132]. Isolated corpus cavernosum from these animals exhibited a greater phenylephrine-induced contraction in vitro than cavernosal tissue from control animals. Furthermore, when Y-27632 was added to the incubation, the tissue from the partially obstructed rabbits relaxed less suggesting higher Rho-kinase activity. Immunofluorescence indicated that both the α and β forms of Rho-kinase were over-expressed in penile tissue with bladder neck obstruction. These results support the hypothesis that up-regulation of the RhoA/Rho-kinase pathway contributes to the ED associated with BPH.

A major problem in the development of treatments for ED is hypotension. In the rat model, injection of Y-27632 over the dose range of 2 - 200 nmol/kg, failed to cause any significant change in MAP even though the treatment increased ICP in a dose dependent fashion. However, at the maximum dose of 400 nmol/kg, ICP was not increased further but arterial blood pressure was significantly reduced [113, 121]. When dissolved in DMSO and applied topically to the rat penis, Y-27632 increased ICP, although about 70-fold more drug was required compared to the response to intracavernous injection of the inhibitor. Topical application of high doses of Y-27632 had a significant hypotensive effect although there are large blood vessels close to the skin surface in the rat penis and this may contribute to systemic effects of the drug [140].

At this stage of investigation, it is not possible to predict whether or not inhibitors of Rho-kinase or drugs which interfere with the activation of RhoA will be of value in the future treatment of erectile dysfunction. This strategy for the treatment of ED would have several advantages:

1. Since the RhoA/Rho-kinase pathway appears to mediate vasoconstriction stimulated by α-adrenergic agonists, endothelin-1 and other agents, a Rho-kinase inhibitor would be effective in ED resulting from a wide range of etiologies.

2. Based on animal models, evidence suggests that the up-regulation of the pathway may be present in several ED-related diseases including diabetes, hypertension, hypogonadism and bladder neck obstruction.

3. Inhibition of RhoA/Rho-kinase mediated vasoconstriction results in erection via pathways which are independent of NO/cGMP/PKG pathways so concurrent nitrate containing drug use would not be contraindicated.

While Rho-kinase inhibitors such as Y-27632 may have future value as treatments for ED, the proteins that regulate the activation of RhoA may represent the more attractive target for controlling vasoconstriction in the penis. GDI and GAP proteins act to suppress the RhoA activation by binding to RhoA and by increasing GTPase activity (see Figure 9). It may be possible to suppress the activity of these proteins with antibodies, specific drugs or alterations of their genetic expression. The more likely targets for intervention in the RhoA activation mechanism are the guanine nucleotide exchange factors (GEF). These factors enhance the dissociation of the GDP bound to RhoA and thereby promote the replacement of GDP by GTP, a critical step in the activation of RhoA. GEF activity may be under the control of several signaling pathways including phosphatidylinositol kinases, other protein kinases or simple dimerization [142]. Of potential interest in this discussion of the NO-mediated erectile response are the reports that RhoA activity is also under the regulatory control of G proteins [143, 144].

Potential problems, which could limit the development of inhibitors of RhoA activation and/or Rho-kinase activity as a treatment for erectile dysfunction, stem from the wide cellular distribution of this pathway. This distribution makes it difficult to target RhoA and/or Rho-kinase activity in the corpus cavernosum without effecting activity in other vascular tissues. The finding that Rho-kinase exists in two isoforms (α and β) raises the possibility that other
isoforms exist, which are specific to vascular beds such as the penile vessels. If this is the case, specific drugs could be designed which target penile tissue without adverse effects elsewhere. Similarly, penis specific isoforms of RhoA may exist.

**V. NO, GUANYLYL CYCLASES, AND THE cGMP PATHWAY**

Many endogenous vasodilators have been shown to have relaxant effects on isolated CC and penile vascular preparations preparations, and some of them have been shown to be clinically efficacious. However, their role in normal erection and in the pathophysiology of ED has not been established [1, 12]. The main relaxant pathway is the L-arginine/NO/guanylyl cyclase pathway. Synthesis of NO and the consequences of NO binding to sCG are essential for the erectile process and there are several steps in the pathways after sGC that may change in ED. The endothelium and/or the nerves innervating the CC may be the source of NO, and thus, more than one isoform of NOS can be involved. Both neuronal NOS (nNOS) and endothelial NOS (eNOS) are activated by calcium entry into the cell, binding to calmodulin associated with the enzymes. Whereas physiologic penile erection lasts several minutes, the calcium-dependent activation of nNOS or eNOS is transient.

Several groups have shown that the phosphatidylinositol 3 kinase (PI3 kinase) pathway that activates the serine-threonine protein kinase Akt (also known as PKB) causes direct phosphorylation of eNOS, reducing the enzyme’s calcium requirement and causing increased production of NO [145-147]. This pathway is responsible for both shear stress and growth factor enhancement of blood flow that can last for hours [148-150].

As mentioned previously, NO can be formed by both nNOS and eNOS in penile erectile tissues. eNOS is activated by viscous drag or shear stress in blood vessels to produce NO continuously, a process mediated by the PI3 kinase/Akt pathway. Hurt et al. showed that PI3 kinase/Akt physiologically mediates erection [151]. Both electrical stimulation of the cavernous nerve and direct intracavernosal injection of papaverine caused rapid increases in phosphorylated (activated) Akt and eNOS. Phosphorylation was diminished by wortmannin and LY294002, inhibitors of PI3 kinase, the upstream activator of Akt. The two drugs also reduced erection. Penile erection elicited by papaverine was reduced profoundly in mice with targeted deletion of eNOS. The findings of Hurt et al. support a model in which rapid, brief activation of nNOS initiates the erectile process, whereas PI3 kinase/Akt–dependent phosphorylation and activation of eNOS lead to sustained NO production and maximal erection [151]. Consistent with this model, penile production of NO after electrical stimulation persists much longer than the duration of the stimulus.

It has been well demonstrated that NOS abnormalities may play a role in ED associated with, for example, aging and diabetes, conditions for which Cartledge et al. demonstrated in the rat impaired NO-mediated relaxation [152]. Garbal et al. found that the soluble NOS activity decreased significantly in penile tissue from senescent rats [153]. Lower NOS messenger RNA expression was found in old than in young rats [154]. In another rat model of aging, the number of NOS-containing nerve fibers in the penis decreased significantly, and the erectile response to both central and peripheral stimulation decreased [155]. In the aging rabbit, endothelium-dependent CC relaxation was attenuated; however, eNOS was up-regulated in both vascular endothelium and corporal smooth muscle [156].

ED in diabetes may be associated with peripheral nerve damage but may involve diminished endothelial production of NO as well [157]. Cellek et al. demonstrated in rats with experimental (streptozotocin-induced) diabetes a selective degeneration of nitrergic nerves [158]. This was suggested to be due to NO, since inhibition of NOS was shown to be neuroprotective. Escrig et al. suggested that the diabetes-induced reduction in corporeal NO levels could be mainly due to the lack of some essential cofactors for NOS activity rather than to changes in the amount of enzyme proteins [159].

Penile NOS activity and penile NOS content were reduced in rat models of both type I and type II diabetes with ED [160]. However, in streptozotocin-induced diabetic rats, NOS binding increased,[161] and NOS activity in penile tissue was significantly higher than in controls, despite a significant degradation of mating behavior and indications of defective erectile potency [162].

In isolated CC from diabetic patients with ED, both neurogenic relaxation and endothelium-dependent relaxation were impaired [163]. In humans, the diabetic ED was suggested to be related to the effects of advanced glycation end products on NO formation [164]. This was also found in rats [152]. Cartledge et
al. found in rats that glycosylated human hemoglobin impaired CC smooth muscle relaxation by generation of superoxide anions and extracellular inactivation of NO [165]. Hyperglycemia decreases NO production by eNOS via O-linked glycosylation of eNOS at the Akt target S1177 in hyperglycemic cell culture conditions and in animal models of diabetes [166].

The guanylyl cyclases (GCs), comprising both membrane bound (particulate) and soluble isoforms, are expressed in nearly all cell types [167]. However, in the penis, soluble sGC is probably the most important receptor for NO as a signalling molecule. The enzyme consists of two different subunits, and contains a prosthetic heme group that mediates up to 400-fold activation by NO. Even if NO seems to be the most effective stimulator of sGC, there are other ways of stimulating the enzyme.

The benzyldiazolderivate 3(5’-hydroxymethy-2´-furyl-benzyl indazol (YC-1), which binds to an allosteric site on the enzyme (Figure 13), was shown to produce a direct activation of sGC by increasing the affinity for GTP and increasing the maximal enzyme activity, leading to increased cGMP levels in smooth muscle cells [168]. Moreover, YC-1 caused a large activation in the presence of the NO donor, sodium nitroprusside, which lead to a remarkable 2200-fold stimulation of the human recombinant sGC [169]. In addition YC-1 enhances the sGC stimulating effect of CO (31-34-fold above CO alone [170]. Besides NO, YC-1 represents the first drug activating sGC in a biological environment. In addition, YC-1 seems to be able to stimulate NO-synthesis and release, [171] and to inhibit cGMP hydrolysing phosphodiesterases, [172] enhancing the overall effect of cGMP.

YC-1 caused concentration-dependent relaxant responses in NA-contracted rat corpus cavernosum preparations, and enhanced responses to electrical field stimulation. YC-1 also enhanced the relaxant response induced by carbachol. In vivo, YC-1 elicited not only dose-dependent erectile responses when administered intracavernously, but also increased the effects on intracavernous pressure produced by stimulation of the cavernous nerve [173]. In addition, it enhanced the effects of subthreshold doses of apomorphine (Figure 14).

YC-1 and other non-NO dependent sGC stimulators represent an interesting pharmacological principle that may be useful for treating erectile dysfunction, given alone or in combination with e.g., a PDE 5 inhibitor or a centrally acting agent, particularly in patients lacking NO [174].

Kim et al. demonstrated production of cGMP by particulate GC in the corpus cavernosum membranes of rabbit and rat stimulated by C-type natriuretic peptide 1-22 CNP), atrial natriuretic peptide 1-28 (ANP) and brain natriuretic peptide 1-26 [175]. In addition, CNP, but not ANP relaxed precontracted isolated preparations of rabbit corpus cavernosum. Kuthe et al. demonstrated mRNA transcripts encoding for guanylyl cyclase-B, a receptor of the peptide hormone C-type natriuretic polypeptide, in human corpus cavernosum [176]. This finding was verified at the protein level by immunohistochemistry that demonstrated guanylyl cyclase B in corpus cavernosum and helical artery smooth muscle cells. They further showed that C-type natriuretic polypeptide increased intracellular cGMP. In organ bath studies with corpus cavernosum muscle strips C-type natriuretic polypeptide caused relaxation Kuthe et al. suggested a role for C-type natriuretic polypeptide and its receptor in the induction of penile erection and its possible future therapeutic use for erectile dysfunction [176].

It seems that a main cause of diabetic ED may be that reduced NOS activity, and a reduced production of NO, cannot compensate for an increased contractile effect of, for example, noradrenaline and ET-1, mediated via an up-regulation of the Rho kinase.
pathway. NO generated from nerves and/or endothelium stimulates sGC, with a resulting increase in cGMP levels. CGM, in turn, signals via three main receptors in eukaryotic cells: ion channels, phosphodiesterases, and protein kinases [167]. At present, however, the molecular targets, which are activated by cGMP and finally execute the relaxation of penile smooth muscle, are only partly known. Mills et al. suggested that NO exerts two distinct and specific actions, both mediated by cGMP-dependent protein kinase (PKG or cGK I) [177]. cGK I may reduce calcium by inhibiting membrane and sarcoplasmatic reticular Ca2+ channels. Ammendola et al. showed that a regulatory protein associated with the IP3-receptor (inositol 1,4,5-trisphosphate receptor-associated cGMP kinase substrate, IRAG) is phosphorylated by cGK I [178]. This will lead to a decreased IP3-induced calcium release. If this occurs in the CC, the consequent decrease in [Ca2+]i will result in a decline in MCL kinase activity, reduced levels of phosphorylated MLC, and decreased contraction of the CC smooth muscle. cGK I may also reduce Rho kinase activity and thus prevent the suppression in MLC phosphatase activity.

Inactivation of cGK I in mice [179] resulted in a low ability to reproduce. CC tissue from these mice has an inability or markedly reduced ability to relax in response to neurally or endothelially released or exogenously administered NO [180]. The expression of cGK I in penile tissue from cGK I+/+ mice, as revealed by immunohistochemical analysis, was confined to the smooth muscle of the walls of the central and helicine arteries and to the smooth muscle of the trabecular septa surrounding the cavernous spaces. This is in line with its presumed role in the erectile events.

Analysis of the NO/cGMP–induced relaxation clearly showed that cGK I is the major mediator of the cGMP signaling cascade in CC tissue. Its absence cannot be compensated for by the cyclic adenosine monophosphate signaling cascade that relaxes normal and cGK I–null penile erectile tissue to a similar extent. Taken together, these findings suggest that activation of cGK I is a key step in the signal cascade leading to penile erection. The expression of cGK I was examined in CC specimens from patients with and without ED [181]. In all specimens of cavernosal tissue, a distinct immunoreactivity was observed in different parts and structures, with a high expression in smooth muscle cells of vessels and in the fibromuscular stroma. No clear immunoreactivity against cGK I was found in the endothelium. There was no distinct difference in immunoreactivity and cellular distribution between potent and ED patients. This does not exclude that dysfunction of cGK I can be a cause of ED in humans. cGK I occurs in two isoforms, I-α and I-β. cGK I-α is the physiologically more active isoform, which decreases the noradrenaline-stimulated cytosolic Ca2+ level [182]. In alloxan diabetic rabbit CC smooth muscle, the
expression of the cGK I-α isoform was significantly reduced [183]. This is an important finding demonstrating that changes in the pathway downstream of cGMP can contribute to ED. It also implies that further targets for future treatments can be defined.

VI. PHOSPHODIESTERASES

The use of phosphodiesterase (PDE) inhibition to treat erectile dysfunction (ED) has been proven as effective therapy. It is a misconception that the use of PDE inhibitors to treat ED is new. The Chinese herbal medicine, Yin Yang Huo (Epimedii herba), has been used to treat sexual disorders for over a thousand years. One ingredient of this herbal remedy is the weak PDE 5 inhibitor Icarrin [184]. Since the 1980s, intracavernous administration of the PDE inhibitor, papaverine, has been used to treat ED. Experimentally, manipulation of PDEs relaxes human and animal cavernous smooth muscle. However clinical interest in PDE inhibitors to treat ED rose dramatically following the approval of the PDE 5 inhibitor, sildenafil, in March of 1998 in the United States. With worldwide sales exceeding $1.5 billion in 2001, for a disorder that less than 10% of men seek medical attention, the potential market for PDE inhibitors is enormous [185, 186]. Improvements in efficacy and reductions in side effects are highly likely by exploiting recent data concerning isofoms, splice variants, structure/function medicinal chemistry, tissue distribution, and cyclic nucleotide cross talk. Recent discoveries and combination therapies using other classes of drugs acting through different mechanisms, suggests the full potential for therapies based on PDEs has yet to be realized.

Phosphodiesterases are intracellular enzymes that catalyze the breakdown of cAMP and cGMP [187, 188]. These cyclic nucleotides are ubiquitous and occur in many diverse tissues including nerves and all smooth muscles. However the distribution of isoforms and splice variants allow relative tissue specificity for agents targeted at PDEs [184]. In the human genitourinary tract, penis, clitoris, bladder, prostate, vas deferens contain PDEs. In smooth muscle PDEs regulate contractility. Neurotransmitters released by autonomic nerves in the penis can raise either cAMP or cGMP that are subsequently hydrolyzed by PDEs. For example, vasoactive intestinal polypeptide (VIP), calcitonin gene related peptide (CGRP) and pituitary adenylate cyclase (PACAP) raise cAMP, while nitric oxide (NO) stimulates cGMP[189] via adenylyl cyclase and sGC respectively. Recent discovery of membrane bound guanylate cyclase linked to the C-type natriuretic polypeptide in the human CCSM presents alternative ligand targets that can be manipulated and combined with PDE inhibition [176].

Specific PDEs hydrolyze cAMP, cGMP or both nucleotides [184] PDEs 4, 7 and 8 are specific for cAMP (Table 1). PDEs 5, 6, and 7 are specific for cGMP. However, PDEs 1, 2, 3, 10 and 11 are non-selective. cGMP specificity is confirmed by the more hydrophobic amino acids at the binding site.

The human genome contains 21 genes that encode for 11 PDE proteins [184, 186] PDEs 2, 5, 9,10, and 11 are encoded by one gene. In contrast, multiple genes encode for PDEs 1, 3, 4, 6, 7 and 8. Adding to this complexity, multiple splice variants exist for each PDE. These PDE splice variants vary in different tissues. This tissue specificity for splice variants may allow the design more tissue selective PDE inhibitors.

Thirteen PDE mRNAs are expressed in the human CCSM. In the human penis, PDEs 1, 3, 4 and 5 are of primary interest because of their known ability to influence contractility of CCSM. Pharmacological data must be obtained using human CCSM tissue because of significant species differences in PDE expression. For example, PDE 3-4 is found in greater quantities in the human than rabbit CCSM. This explains preclinical data demonstrating that the PDE 3 inhibitor milrinone relaxes contracted human, but not rabbit CCSM. Despite known tissue and species differences in PDE expression, further analysis is needed to optimize drug development.

In 1980, PDE 5 was purified by Francis and coworkers. Yet it wasn’t until 1993 that the gene for PDE 5 was cloned by McAllister-Lucas and colleagues. PDE 5 is a 200 kD homodimer possessing two allosteric binding sites for cGMP [190]. One site is found at the amino terminal. The other binding site for cGMP resides at the conserved zinc finger-binding motif. Current PDE 5 inhibitors compete with cGMP for binding at the catalytic site. Both PKA and PKG phosphorylate PDE 5 to enhance binding activity. Transmitters or drugs that repeatedly activate either the guanylate cyclase or adenylate cyclase may up-regulate PDE 5 in CCSM. Recent unpublished work suggests that relatively high concentrations of PDE 5 inhibitors, exceeding therapeutic serum levels, may reduce PDE 5 expression.

PDE 5 exists as three isoforms- PDE 5A1, PDE5A2
and PDE A3 (Lin et al., 2003). The A3 isoform is restricted to smooth muscle. The specificity of sildenafil for PDE 5A3 isoform is equivalent to A2 isoform, but exceeds that for the A1 isoform. Drugs more selective for the PDE 5 A3 isoform may possess greater selectivity for the CCSM thereby reducing side effects, such as flushing, headache or backache.

Sildenafil is the first PDE 5 inhibitor approved for the treatment of ED that possesses efficacy, safety, reliability and minimal side effects [191]. Two new PDE 5 inhibitors, tadalafil and vardenafil, are recently approved for clinical use in the United States [185, 191]. Sildenafil and vardenafil are more similar in structure to cGMP than tadalafil. Phase 3 clinical trials for tadalafil and vardenafil demonstrate comparable efficacy to sildenafil [185]. Other PDE 5 inhibitors in preclinical trials include UK 369993 (Pfizer), TA 1790 (Vivus/Tanaka), DA 8159 (Dong A), and E 8010/4010 (Eisai) [186]. It is important to understand that until randomized, prospective, comparator trials are performed, it is difficult to compare efficacy and side effects for the same class of drug. Moreover, differences in specificity and pharmacokinetics do not universally translate into improved efficacy or reduced side effects. Indeed, side effects and efficacy appear to be similar for these three PDE inhibitors, despite differences in selectivity and potency for PDE 5. Selectivity for antagonists is often expressed as a ratio of EC50s. The EC50 of a compound is that concentration that inhibits activity by 50%. The IC50 of a drug may vary depending on the tissue source for the PDE 5 protein as well as its purity. Potency is an in vitro measure of a drug concentration that exerts an action. Neither selectivity nor potency is direct measures of clinical efficacy.

It is also possible that a PDE 5 inhibitor exerts non-

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<td>5A</td>
<td>cGMP</td>
<td>CCSM, platelets, visceral/smooth SM</td>
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CCSM = corpus cavernosum smooth muscle SM = smooth muscle
PDE effects that influence smooth muscle efficacy for ED. For example, sildenafil at high concentrations in vitro inhibits L-type Ca²⁺ channels and opens KATP channels in CCSM [192]. These actions may theoretically augment CCSM relaxation, although contribute to non-selectivity.

Because NO is involved in other physiological processes besides penile erection, and PDE 5 expression is not limited to the CCSM, the use of PDE 5 inhibitors may be expanded to include disorders that may benefit from elevations in intracellular cGMP, such as cystic fibrosis, achalasia, pulmonary hypertension and cerebral ischemia.

The structural complexity of the PDE family, the ubiquitous presence of PDEs and the potential for crosstalk between PDE signal transduction pathways represent major challenges for drug design and usage. Many PDE inhibitors fail to progress through clinical trials due to unwanted overlapping enzymatic activities, PDE tissue distribution and drug selectivity. Non-selectivity may result in unwanted side effects.

Preclinical data exists for a variety of PDE 5 inhibitors. FR 226807 (Fujisawa) is a selective PD5 inhibitor. T-1032 (Tanabe) is structurally similar to sildenafil with greater potency [192]. KF 31327 is a non-selective PDE 5 inhibitor with some selectivity for PDE 3. Other sildenafil analogues (SK Chemical) have increased potency but decreased sensitivity for PDE 5. Differences in tissue distribution, isoform specificity, enzymatic activity, and drug sensitivity among these and other agents present the potential for either enhanced efficacy or a better therapeutic index. However, it is possible isoform specific drug design cannot be achieved. In this regard, molecular approaches to block PDE 5 isoforms include antisense deoxyligonucleotides that bind the mRNA for the specific isoform cells. CCSM could be induced to generate endogenous RNA fragments called interference RNA to block mRNA translation of the PDE protein. Third generation PDE 5 inhibitors may possess regenerative or prophylactic capability and allow local application.

Some side effects of sildenafil are attributed to lack of selectivity for PDE 5 over other PDEs at therapeutic serum concentrations. Changes in color vision have been attributed to an action at PDE 6. Bakache, headaches or flushing has been postulated to be due to an action at PDE 1 found in blood or PDE 5 in non-penile tissues [186]. Because inhibition of PDE 3 in humans CCSM leads to augmented relaxation, PDE 3 inhibitors represent potentially useful drug for ED. However, one limitation of agents that inhibit PDE 3 is the effect of cAMP on myocardial contractility and vascular tone. Thus, cardiovascular side effects limit the introduction of drugs that target PDE 1 or PDE 3. Some of these worries may be mitigated by isoform or splice variant specific compounds specific for penis. Alternatively, local administration may be attempted. Another strategy is to use combination therapy to lower the dosage of PDEs 1, 3, and 4 inhibitors.

Combination drug strategies for ED can be based on 1) pharmacology, 2) site of action, 3) side effects, and 4) route of administration. Targeting the CNS and CCSM enhances two physiologic sites involved in penile erections. This approach may also be reasonable if ED results from several stimuli deficits. In experimental models, the action of the dopamine agonist, apomorphine, is enhanced by sildenafil [35]. The apomorphine/sildenafil regimen combines different mechanisms, sites of action, routes of administration, and some differing side effects (e.g. nausea). Nevertheless, common side effects of flushing, hypotension or headache suggests that this particular combination may possess serious risks.

Drugs that selectively increase cAMP or cGMP or non-selectively increase both cyclic nucleotides relax CCSM. Upstream and downstream targeting one cyclic nucleotide signaling pathway is feasible and provides tremendous flexibility. An agent that increases selective cGMP plus the substrate for guanylate cyclase, such as an NO donor or enhancer of GTP binding has been examined experimentally [174]. Sildenafil nitrate provides NO plus inhibiting PDE 5 and is undergoing clinical evaluation.

Significant crosstalk occurs in smooth muscle between signal transduction pathways for cAMP and cGMP. Interactions between cyclic nucleotide pathways may produce potential synergies. In vitro high concentrations of cAMP can inhibit PDE 5 [193]. Conversely, high concentrations of cGMP can inhibit PDE 3 [193]. Thus, maximal stimulation of either pathway, although not directly activating the other, could amplify the response when the corresponding pathway is turned on. Intracavernous papaverine inhibits several PDEs to achieve erection. Whereas, intracavernous prostaglandin E1 (PGE 1) activates adenylate cyclase to raise cAMP. High local concentrations of cAMP are capable of triggering a rise in cGMP through inhibition of PDE 5. At high doses the PDE 5 inhibitor, sildenafil, raises cAMP in cultured human corpus cavernosum smooth muscle.
adenylate cyclase activator, prostaglandin E1
erections with intracavernous injections (ICI) of the PDE 5 inhibitor, sildenafil, often obtain better benefits. For example, men who fail to achieve full rigidity with cAMP avoids cardiovascular side effects. For
cyclic nucleotides in human CCSM using one or more PDE inhibitors may be useful to treat ED without producing dose limiting side effects.

PDE 3, 4 and 5 inhibitors administered as single agents intracavernously cause a modest increase in intracavernous pressure (ICP) in cats [112, 193]. Unfortunately, the rise in intracavernous pressure is less than that observed with intracavernous trimix (PGE1, phentolamine, papaverine). This latter combination works through 3 different mechanisms: 1) activation of adenylate cyclase, 2) nonspecific blockade of phosphodiesterases, and 3) antagonism of α-ARs. By comparison, the ICP response to the combined activation of guanylate cyclase using an NO donor plus a PDE 5 inhibitor remains below that achieved with the combination of a PDE 5 inhibitor and activation of adenylate cyclase. It is tempting to speculate that combined activation of both cAMP and cGMP pathways with inhibition of their respective PDEs achieve greater enhancement of erectile function than activation of either pathway alone or activation of either pathway plus blockade of the corresponding PDE inhibitor.

Cyclic nucleotides may also influence other mechanisms involved in erectile function. For example, cAMP dampens the action of norepinephrine at α1-AR. cAMP acting within noradrenergic nerve terminals can reduce the release of NE. In addition, chronic elevation in cytosolic cAMP in rabbit CCSM upregulates nitric oxide synthase (NOS). This implies that even monotherapy if given chronically may trigger other long-term processes leading to sustained improvements in erectile function. These concepts also highlight the difficulty comprehending the precise mechanisms involved in combination drug therapy or predicting adverse events.

Clinical experience has revealed that patients who fail to respond to an agent that inhibits PDE 5 may benefit from the addition of agents that raise cAMP. This suggests combination PDE 5/3 inhibitors may be useful. Local administration of the drugs that raise cAMP avoids cardiovascular side effects. For example, men who fail to achieve full rigidity with the PDE 5 inhibitor, sildenafil, often obtain better erections with intracavernous injections (ICI) of the adenylate cyclase activator, prostaglandin E1 (alprostadil or PGE1) [195]. Shabsigh et al. found that 90% of men with suboptimal responses to sildenafil achieved further improvement in erection with alprostadil [196]. Conversely, 15-20% of ICI PGE1 failures may still respond to sildenafil [197-198]. In a study of diabetic men with ED, 39% on ICI PGE1 responded to sildenafil [183]. Another strategy is to provide the cAMP system with ICI then try PDE inhibitors.

In a small, complex clinical trial Lammers et al. performed a 4-way crossover study of 4 oral agents: placebo, sildenafil, papaverine and phentolamine [200]. Although no differences between groups were statistically significant when using the sexual encounter profile (SEP), visual analog scale of erection, or a global efficacy questionnaire, several issues remain. First, the study was woefully underpowered to detect subtle differences (e.g. 10-20%) between groups. Even placebo and sildenafil were no different. Second, papaverine is essentially not absorbed by the gastrointestinal tract. This study highlights the profound need to perform a large multi-institutional trial of combination therapy for ED.

Besides cost, there are serious concerns about the use of combination therapy for ED. As with the original phentolamine/papaverine mixture for intracavernous therapy, priapism is possible. Several reports of priapism have been associated with sildenafil combined with ICI, PGE1, or an oral erectogenic agent such as trazodone [201, 202]. Although priapism from sildenafil alone is exceedingly rare, in combination with other drugs this morbidity appears to increase. Because many of the agents used to treat ED relax an array of smooth muscle, including vascular smooth muscle, hypotension, and gastroesophageal reflux may occur following use of drug combinations. Cyclic nucleotides also influence cardiac function, raising the specter of arrhythmias or altered cardiac function with certain combinations. Related issues such as whether sequential or combination approaches reduce the likelihood of tachyphylaxis needs to be examined. Similarly, little is known about the chronic effects of persistent elevations in NO or cyclic nucleotides on the function of CCSM. Loss of effectiveness of combination intracavernous therapies has been usually attributed to progression of disease. Yet the theoretical concern remains that persistent activation of certain signal transduction pathways could lead to tachyphylaxis [203, 204]. Preliminary reports of patient failures with single agents for ED being rescued with combination thera-
pies are receiving increased scrutiny. These reports must be viewed with some degree of skepticism because of the lack of randomized drug-comparator trials with sufficient patient numbers. Further, in designing such studies it is difficult to control for a placebo effect when two routes of administration or two agents with very different side effects are used.

Patients who fail an oral PDE 5 inhibitor, but are not enthusiastic about more invasive therapies, represent a therapeutic challenge. Preliminary reports suggest that combining strategies drugs able to raise both cAMP and cGMP may salvage patients refractory to sildenafil in the treatment of ED. It remains unknown whether PDE 1, 3, and 4 inhibitors alone or combined with PDE 5 inhibitor will lead to increased efficacy without serious side effects, such priapism, hypotension or cardiac effects. Prospective and randomized clinical trials are needed with adequate patient numbers to ascertain the true benefits and possible morbidities of combination strategies.

D. OTHER APPROACHES

The future of clinical therapeutics for erectile dysfunction will be developed predictably along several biological levels associated with the structural and functional characteristics of the penis. Conceivable therapeutic “targets” range across tissueal, cellular and molecular levels, and progress made in each of these areas in recent years suggests that multiple treatment options for erectile dysfunction will ensue in the short time to come. Such prospects include cellular protection and regeneration, growth factor interventions, neurovascular reconstruction, erectile tissue engineering, and gene therapy.

Treatment possibilities on the cellular level are consistent with the homeostatic, proliferative and regulatory properties of the penis. It is axiomatic to mention that the biological integrity and function of cellular components of the penis fundamentally relates to the preservation of erectile responses. Further, objectives to preserve and revitalize nerves, endothelium and smooth muscle can be readily presumed to translate into new avenues for treatment of erectile dysfunction.

Concepts of tissue reconstitution applied to erectile dysfunction are based on the recognition that a number of disease processes and assorted trauma of the pelvis and genitalia bring about such destructive effects on the cells and tissues of structures relevant to the function of the penis that reversal or correction with medical therapies is unfeasible. Tissue grafting, cell transplantation, materials science and bioengineering are receiving attention as innovative approaches to restore erectile function in these circumstances.

Considerations for somatic gene therapy have arisen primarily from the idea that genes or sets of genes/gene products can be targeted and altered according to their expression or function to preserve erectile potency. The implication is that techniques can be directed toward particular molecular alterations identified to be associated with erectile impairment or otherwise the strategy can be applied nonspecifically with gene products that nonetheless yield erectile improvement.

I. NEUROPROTECTION

Neurogenic origins represent a leading categorical cause of erectile dysfunction, including diverse neurological disorders and even iatrogenic conditions relating to genitourinary and pelvic surgeries. One strategy to address neurogenic erectile dysfunction is based on neurogenesis, the developmental biology process that refers to the growth and regeneration of neurons in organ systems.

In the penis, therapeutic neurogenesis has been explored with the premise that nerve development is required for preserving neural functions that govern the erectile response and for opposing mechanisms involved in programmed neuronal cell death within the organ. In experimental rat models of cavernous nerve grafting, the neurotrophins nerve growth factor (NGF) and acidic fibroblast growth factor (FGF) enhance nerve recovery in the penis and electrophysiologically induced erectile responses [205, 206]. Assorted growth factors have been localized in rat corporal tissue and associated with neurite outgrowth–promoting activity including basic FGF [207] and insulin-like growth factor-1 and transforming growth factor ? [208]. Atypical growth factors that have shown neurotrophic effects on the penis include growth hormone, [209] the glial cell line derived factor neurturin, [210] immunophilin ligands, [211] the neuronally derived signaling molecule Sonic hedgehog protein, [212] and even vascular endothelial growth factor (VEGF) [213]. Since the metabolic environment may also influence neuroprotection in the penis, consideration may be given to promoting the action of key endogenous nutrients and inso-
luble extracellular matrix molecules such as laminin, fibronectin and some forms of collagen that are associated with nerve growth and regeneration [214]. Biochemical processes involved in nerve protein modifications after injury could also be exploited for promoting nerve-mediated function. [215].

These descriptions indicate that a number of possibilities may serve as effective targets for neurobiologic interventions in the penis. It is worth emphasizing that this therapeutic direction offers a corrective approach to the problem of erectile dysfunction related to a neuronal defect, with the intent to restore naturalness and normalcy of sexual function. Key issues are whether therapies related to this field can be administered without causing untoward proliferative effects on structures elsewhere in the body. A controlled manner of their effects on nerve growth is also essential.

II. VASCULOPROTECTION

Cardiovascular disorders including hypercholesterolemia-induced vascular disease and atherosclerosis have been associated with erectile dysfunction with the implication that endothelial dysfunction is the key pathogenic factor underlying these clinical manifestations. The relevance of the vascular endothelium to the physiology of the penile vasculature is consistent with its roles in other vasculature, in which the structure contributes to biological processes related to vascular homeostasis and hemodynamic regulation.

A role for angiogenic factors in the molecular regulation of penile vascularization has been postulated. VEGF is a strong candidate since it is a direct-acting specific endothelial cell mitogen that stimulates angiogenesis and regulates embryonic vessel development in a gene-dosage-dependent manner [216]. VEGF splice variants have been identified in rat and human cavernosal tissue [217-219]. Corporal smooth muscle cells express the VEGF receptor VEGFR-1 and respond in vitro to VEGF stimulation by proliferation and migration [220-221]. In rat and rabbit models of vasculogenic erectile dysfunction, intracavernous delivery of VEGF restored erectile function within a few weeks and was associated with increased corpus cavernosal endothelial cell content [213, 222,223]. Basic FGF has also been shown to have angiogenic effects in cavernosal tissue, apparently by increasing VEGF levels [224]. These findings would suggest that angiogenesis and possibly trophic effects on smooth muscle cells serve as likely mechanisms for the observed VEGF-induced recovery of erectile function at least in the long term.

While a host of molecular mechanisms are involved in the integrity and function of endothelium, the signaling function associated with endothelial NOS in the penis would appear to be quite relevant since the enzyme synthesizes the erection mediator nitric oxide from penile vascular and sinusoidal endothelium [225]. As an alternative explanation for VEGF treatment effects in cavernosal tissue, the growth factor may act via endothelial NOS-regulated mechanisms in the penis. VEGF appears to induce endothelial NOS mRNA and protein levels in penile homogenates [226]. Recent work has further shown that VEGF-induced erection recovery within one week in a mouse model of vasculogenic erectile dysfunction is associated with the activation of a constitutively active phosphorylated form of endothelial NOS, which is primed to generate nitric oxide continuously in the penis [227]. Since “activated” endothelial NOS has been described as a major determinant of the erectile response,[251] it will be interesting to identify other experimental strategies that target this molecule in the penis for the treatment of erectile dysfunction.

Several proposals have been put forward that relate to the restoration or promotion of vascular/endothelial mechanisms and particularly the production of endothelial nitric oxide in the penis. As such is the case for therapeutic neurogenesis, strategies devised to promote the growth and function of the penile vasculature offer likely opportunities to restore normal and natural function according to established concepts of erection physiology.

III. NERVE RECONSTRUCTION

The structural repair or reconnection of nerves after injury involving the autonomic nerve supply of the penis has generated great interest recently to restore neurological function of this organ. Studies have been carried out both on preclinical and clinical levels suggesting the feasibility of such interventions. In cavernous nerve-ablated rats, assorted nerve grafting conduits have been effectively applied including the genitofemoral nerve,[227] amniotic membrane grafts, [205] and silicone nerve tube conduits [206]. Similarly, early results have shown that intracorporeal autotransplantation of pelvic ganglia in rats may offer a means to treat neurogenic
erectile dysfunction [229]. In humans, cavernous nerve interposition grafting has been investigated following radical prostatectomy using the genitofemoral nerve [230] and the sural nerve [231]. In the latter, success has been shown in early trials while various technical enhancements such as cavernous nerve electrical stimulation have also been evaluated to improve upon the technique and functional outcomes [232].

These demonstrations lend support for the role of tissue grafting to restore erectile function after injury or loss of nerve supply of the penis. The availability and suitability of synthesized grafting material opposed to autogenous sources are issues worthy of consideration. An additional matter for consideration is the technical feasibility of grafting procedures to reconstitute the autonomic penile innervation, which is far more complex in the human than in rodents. The success of nerve reconstruction, and tissue reconstruction in a broader context, may also hinge on supplementary growth factor strategies that will favor graft “take” and function.

IV. TISSUE ENGINEERING

An early accomplishment in the endeavor to re-create erectile tissue was the formation of a corporal smooth muscle syncytium de novo on biodegradable polymer scaffolds in athymic mice from primary human cells in culture [233] (Figure 15). Subsequent experiments combining endothelial cells with corporal smooth muscle reconstruction in vivo established the real possibility of engineering vascularized neo-corpora [234] (Figure 16). Further work has shown that cartilage penile rods can be engineered as natural penile prostheses [235] (Figures 17 and 18). The discipline has also advanced delivery methods for genes and growth factors that promote organogenesis. In this area, polymeric microspheres containing VEGF secreting cells were shown to induce neovascularization in a controlled manner in vitro and in vivo in an animal model [236].

In recognition that endothelial cells make up a substantial component as well as subserve a critically functional role in the corpus cavernosum, basic investigations have been undertaken to evaluate the possible introduction of extrapenile endothelial cells into the corpus cavernosum to recover endothelial-mediated function [237]. These experiments have shown that harvested microvascular endothelial cells from the rat epididymal fat pad injected into the rat corpus cavernosum remain viable for up to 2 weeks after transplantation. The concept is extended by the possibility of genetically modifying the cells ex vivo to enhance their biological potential prior to delivery.

Prior to bringing these concepts to the clinical arena, further tissue engineering developments must be achieved. The actual creation of genital structures will require not just the admixing of smooth muscle and endothelial cells but rather the full assembly of all components of erectile tissue including nerves and connective tissue. It will also involve fulfillment of the architectural, biomechanical and functional requirements of native corpora cavernosa. Additional development of cell delivery vehicles and delivery systems for introducing developmental factors will be paramount for advancing the field.

V. GENE THERAPY

The concept of gene therapy refers to the introduction of foreign genetic information into human cells
Figure 16: Cavernosometric recordings of rabbit corporal bodies 3 months after native corporal tissue was excised and replaced with matrices either containing tissue engineered implants or matrix alone. Results are compared with normal rabbit cavernosometry. (courtesy A Atala).

Figure 17: Light microscopic depiction of engineered corporal tissue, showing histologically intact sinusoidal spaces, lined with endothelium and smooth muscle (courtesy A Atala).

Figure 18: Photomicrograph of polymer scaffolds seeded with human cartilage cells (courtesy A Atala).
for the purposes of either restoring or supplementing normal cellular function that is defective, or conversely, functionally antagonizing the effects of expression of a mutant genetic phenotype [238]. In particular, somatic gene therapy applies to the genetic modification of differentiated target cells, in contrast to modifying more pluripotent (less differentiated) germ line cells, resulting in a desired cellular response.

Gene therapy approaches can be categorized according to their delivery designs, using non-viral (naked DNA, plasmid DNA, liposomes) or viral (e.g., adenoviruses, adeno-associated viruses, retroviruses) vectors or other cell-based (e.g., myoblasts, endothelial cells) delivery systems [239]. Their roles are commonly assessed according to several properties including transfection efficiency, durability, and safety profile. Non-viral vectors, in general, can be generated plentifully and they carry low risks of immune or inflammatory responses. However, they produce low transgene expression and have shown limited effects in vivo. Viral vectors, in contrast, offer high cellular transduction efficiency. However, they risk insertion into the DNA of dividing cells and may trigger immune and inflammatory responses while their conduciveness to high titer production can be difficult. Interest in adenovirus vectors has been enhanced with the development of second-generation (gutless) adenovirus vectors, having all viral genes deleted, which minimizes the risk of host immune responses, increases cloning capacity, and allows repeated administrations over time. Interest in adeno-associated viral vectors has generated from several characteristics including their limited pathogenicity and ability to transduce nondoning cells. Cell-based gene therapy offers the stable delivery of genetic material via an altered cellular vehicle and relies on the adherence and persistence of the cell within the incorporated tissue.

The penis has lent itself to such therapy on the grounds that a number of molecular mechanisms underlying erection physiology have been defined such that the introduction of genes/gene products related to these mechanisms to the organ can be performed in such a way to achieve a desired pro-erectile effect. In addition, the penis offers several unique properties that are most suitable to the performance of gene therapy: its accessibility as a mostly external organ, its separateness from the rest of the body which allows efficient genetic manipulation while limiting systemic effects, its content of corporal smooth muscle cells in which only a small fraction seemingly require modification to restore normal tissue function, and the low turnover rate of these cells which allow a desired gene to be expressed for long durations.

Several gene therapy approaches for treating erectile dysfunction have been studied at the preclinical level. Attractive molecules for such therapy have included NOS genes, growth factors, and other effectors of cavernosal tissue function. The first demonstration of this therapy was the intracavernous administration of naked complementary DNA (cDNA) encoding the inducible NOS gene to aged rats, which showed erectile improvement in response to the therapy [240]. Similarly, intracavernous injection of cDNA encoding neuronal NOS elevates erectile function in rats [238]. Intracavernous injection of hSlo cDNA, which encodes for the large-conductance calcium-sensitive maxi-K channel, improves erectile function in aged and diabetic rats [241, 242] (Figure 19). Adenoviral gene transfer has also been applied using endothelial NOS, which effectively improves erectile function in aged and diabetic rats [243-245]. Plasmid and adenoviral gene transfer of inducible NOS also yields erectile improvement in rats although adenovirus-transduced myoblasts were found to be more effective in this regard [246]. Success with adeno-associated virus gene therapy has been shown for delivery of VEGF to improve erectile function in rats with vasculogenic erectile dysfunction [247]. The gene transfers of calcitonin gene-related peptide, penile neuronal NOS, and brain derived neurotrophic factor with erectogenic effects in animal models of erectile dysfunction have also been demonstrated.

It is clear that gene therapy for the treatment of erectile dysfunction carries enormous promise. At this
time, an assortment of gene constructs has been evaluated to add to the pioneering investigations in the field, suggesting that a whole host of possibilities may be considered for molecular targeting using the gene therapy approach. Attention will need to be given to the selection of a preferred gene product or combination thereof that will be either broadly useful or specifically advantageous for select presentations of erectile dysfunction for maximal benefit clinically. Besides overcoming major safety hurdles, some other challenges also require attention prior to bringing this intervention to a clinical level. First, it is recognized that penile erection is a conditional response such that gene therapy constructs that result in constitutive expression present risks of prolonged erection or priapism. Considerations for the future must pertain to the control of the treatment as having ‘on-demand’ applicability. Second, there is the contention that redosing may still be required despite the long-term efficacy of treatment. Future delivery optimization must be considered. Third, gene therapies may be limited by significant destructive changes in some presentations of erectile dysfunction, such as “end-stage” penile fibrosis and tissue loss.

E. CONCLUSIONS AND RECOMMENDATIONS

Even if the information about the mechanisms of erectile function and dysfunction has increased markedly during the last decade, there are still many details which need to be clarified. Despite the therapeutic success of sildenafil and other PDE 5 inhibitors, current therapies can be improved. New targets in the CNS and peripherally seem promising. Thus, melanocortin receptor agonists seems currently to be a most promising approach, and by selective dopamine receptor stimulation, the disadvantages with apomorphine may possibly be avoided. Since most of the centrally acting agents seem to involve oxytocinergic pathways or receptors, this system is an attractive target once the problems of penetration into the CNS have been overcome. Rho-kinase inhibition is at present difficult to apply as a therapeutic principle, having in mind the wide distribution of the enzyme. However, interventions upstream Rho-kinase may provide the selectivity for penile tissues necessary for making this principle clinically useful. There is a rational for combinations of therapies and this may be a niche for non-NO-dependent guanylyl cyclase stimulators. New, still more selective PDE 5 inhibitors seem to be possible to develop. These, and other approaches, including neuroprotection, vasculoprotection, nerve reconstruction, tissue engineering, and gene therapy mean that the spectrum of future possibilities to treat complicated ED will be considerably increased.

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Summary of the Recommendations on Sexual Dysfunctions in Men

Chairman: T.F. LUE
Vice Chair: R. BASSON, F. GIULIANO, F. MONTORSI, R. ROSEN
Secretary: S. KHOURY

Scientific Committee: J. BUvat, M. GANEM, A. JARDIN, A. MELMAN, P. QUENEAU, L. TIEFER, G. WAGNER

and the Representatives of the Collaborating Organisations

The 2nd International Consultation on Sexual Dysfunction in men and women was convened in Paris, France June 28 - July 1, 2003. Its mission was to update the present knowledge in this fast developing area of medicine and develop recommendations for the evaluation and management of Sexual Dysfunction in men and women.

This summary encompasses the recommendations concerning Sexual Dysfunction in men. The recommendations are based on a thorough review of the available literature following the Evidence-based Medicine principles as developed by the Consultation in collaboration with the Oxford and Cochrane institutions.

The focused recommendations of the 16 committees were discussed in an open session in Paris by a large audience of experts. The final recommendations were refined by the Scientific Committee consisting of the chairpersons of each committee and representatives of the medical associations co-sponsoring the Consultation.

These recommendations published in 2004 will be periodically re-evaluated in the light of clinical experience and progress within the field.

«There exists fundamental rights for the individual, including the right to sexual health and a capacity to enjoy and control sexual and reproductive behavior in accordance with a social personal ethic - freedom from fear, shame, guilt, false beliefs and other factors inhibiting sexual response and impairing sexual relationships - freedom from organic disorders, disease and deficiencies that interfere with sexual and reproductive function. » WHO 1994

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Sexuality is a complex bio-psycho-social process. Physiological aspects of sexual response (e.g. erection, ejaculation) should be understood in the context of interpersonal and cultural factors. The treating physician and collaborating specialists should possess broad knowledge about human sexuality. Problems may be lifelong or acquired, global or situational. Adequate attention to these aspects during the history taking will educate the often uninformed patient regarding the complex nature of sexuality, and prepare him for understanding treatment and outcome realities. Patient and partner expectations, needs and priorities will be significantly influenced by cultural, social, ethnic, religious and national/regional factors. The rational selection of therapy by patients is only possible following appropriate education, including information about sexuality and all treatments options for sexual/erectile dysfunction. Although not always possible on the first visit, every effort should be made to involve the patient’s sexual partner early in the therapeutic process.

Erectile dysfunction (ED) is defined as the consistent or recurrent inability of a man to attain and/or maintain a penile erection sufficient for sexual activity.

The diagnosis of ED is made by the clinician based on results of diagnostic evaluation. Although the diagnosis may be supported by objective testing (or partner reports), these measures cannot substitute for the patient’s self-report in classifying the disorder or establishing the diagnosis.

The necessary reliance on patient reports implies that cultural factors and patient-physician communication will be important determinants in defining and diagnosing the disorder.

◆ Consistency is an important component of the definition of ED. Erectile difficulties must be reported to occur on a consistent or recurrent basis in order to qualify for the diagnosis of ED. A 3-month minimum duration is generally accepted for establishment of the diagnosis. In some instances of trauma or surgically-induced erectile dysfunction ED (after radical prostatectomy), the diagnosis may be given prior to 3 months.

ED may occur at any age after puberty with a sharp increase after the age of 60. There are many etiological profiles in ED. It is noteworthy that ED might not be the primary complaint and / or may be associated with other medical and sexual problems.
All men with ED should be evaluated by a health care professional with a sensitivity toward cultural, ethnic and religious factors. A multidisciplinary approach may be required in some cases. Following a careful medical, sexual and psychosocial evaluation, treatment options such as psychosexual and/or relationship therapy, pharmacological, or in very specific cases surgical interventions should be considered. A patient-centered approach is emphasized throughout, as physicians and patients collaborate in the assessment and management of the patient’s sexual dysfunction.

The diagnostic tests utilized in the assessment of the patient with ED may be stratified as:
◆ Basic evaluation: an assessment necessary in all patients. All patients with ED should receive a medical, sexual and psychosocial history, physical examination and focused laboratory tests.
◆ Optional tests: tests of proven value in the evaluation of specific patient profiles, with use based on the clinical judgment of the treating physician in general practice
◆ Specialized tests: tests of value in select patient profiles in specialized settings

The rationale for testing and potential impact of a positive test should be explained to the patient (e.g. an abnormal fasting glucose result may lead to the diagnosis of diabetes).

The sexual, medical and psychosocial history are the most important elements in the basic evaluation and should be obtained in all patients presenting with complaints of SD in general and ED in particular. (A questionnaire to be filled out by the patient is provided in this document. This questionnaire may help to initiate physician/patient dialogue).

**1 BASIC EVALUATION**

**a) Sexual Function Assessment**

The essential components of sexual function assessment should include:
◆ erectile insufficiency (onset, duration, progression, severity of the problem, qualification of ED as it relates to sex with a partner, nocturnal/morning erections, self-stimulatory and visual erotic induced erections)
◆ altered sexual desire
◆ ejaculation
◆ orgasm
◆ sexually-related genital pain disorders
◆ and partner sexual function, if available.

**Sexual Function Scales and Questionnaires**

Brief symptom scales or questionnaires may assist the clinician in recognizing and diagnosing the sexual problem. These measures may also permit patients to acknowledge the problem and to initiate a clinical discussion with their health provider. Scales and questionnaires are also a valuable tool in clinical trials and outcomes research on ED.

Several brief symptom scales are available for the assessment of male sexual dysfunction*. A new screening tool for male sexual function (Male Scale) is in the final stage of validation and will be available shortly specifically for use in screening male patients for symptoms of sexual dysfunction. This brief questionnaire provides clinically-relevant information on a variety of sexual function domains (erection, ejaculation/orgasm, desire, pain, satisfaction). It also provides

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* These include the International Index of Erectile Function (IIEF) (Rosen et al., 1997); The Sexual Health Inventory for Men (SHIM) (Rosen et al., 1999); the Brief Male Sexual Function Inventory (BMSFI) (O’Leary et al., 1995); and the Center for Marital and Sexual Health questionnaire (CMASH) (Corty & Althof, 1996)
an index of bother or distress associated with sexual dysfunction. This tool can be used as a screening tool in primary care settings, or for monitoring an individual patient’s response to treatment over time.

Although valuable in recognizing and identifying sexual dysfunction, screening tools and questionnaires should not substitute for a careful sexual, medical, and psychosocial history.

For patients with ED and other sexual symptoms (e.g. lack of desire, anorgasmia, pain during intercourse), further evaluation of these symptoms is recommended prior to initiating ED therapy (See Diagnostic Algorithm). Whenever possible, the temporal association or causal relationship between the symptoms should be assessed.

b) Psychosocial Assessment

The patient’s psychological state needs to be assessed with special attention to symptoms of anxiety or depression, altered self esteem and coping skills, past and present partner relationships, history of sexual trauma/abuse, occupational and social stresses, health issues in either partner infertility, child-rearing difficulties, economic status, and educational level.

Patient expectations

A critical aspect of assessment is the identification of patient needs, expectations, priorities and treatment preferences, which may be significantly influenced by cultural, social, ethnic and religious perspectives. Patient education is also important in fostering a therapeutic relationship, facilitating patient-physician communication and enhancing treatment compliance.

Partner involvement

Although not always possible on the first visit, effort should be made to involve the patient’s partner early in the process. Partner participation may be influenced by cultural and social expectations as well as patient needs and preferences.

When psychosocial assessment reveals the presence of significant psychological distress, relationship problems or partner conflict, further evaluation and management may be necessary either prior to, or in conjunction with treatment of ED (See Diagnostic Algorithm). Referral to an appropriate mental health professional may be indicated in some cases.

c) Medical History

The essential components of this history should include an assessment of the following:

- lifestyle factors (smoking, alcohol, recreational drugs)
- chronic medical illnesses: • hypertension, • diabetes mellitus, • cardiovascular risk factors including hyperlipidemia, • renal or hepatic dysfunction , • neurological disease, • endocrine disease
- medications/recreational drug use
- psychiatric illness including depression
- pelvic/ perineal/ penile trauma and surgery
- pelvic radiotherapy

For patients with reversible risk factors for ED, such as uncontrolled hypertension or hyperlipidemia, these factors should be assessed and managed prior to or in conjunction with the initiation of ED treatment (See Diagnostic Algorithm).

Particular attention should be given to patients with unstable cardiovascular disease (e.g., recent MI, unstable angina). These patients may require further medical evaluation and management prior to initiating ED therapy (See Diagnostic Algorithm). Additionally, patients with a history of pelvic or perineal trauma may require additional imaging and vascular studies as part of their diagnostic assessment. This is particularly relevant in younger patients with relatively recent injuries. In such cases, patients should be referred to a specialist familiar with the use of these tests (See Diagnostic Algorithm).

Focused Physical Examination

A focused physical examination should be performed on every patient with ED. The physical examination may corroborate aspects of the medical history and may occasionally reveal unsuspected physical findings. This examination should include:

- an assessment of body habitus (secondary sexual characteristics),
- an assessment of the cardiovascular, neurological and genito-urinary system focusing on penile, testicular and rectal exam. Blood pressure and heart rate should be measured if not assessed in the previous 3-6 months. In conducting the physical examination, special attention should be given to signs of penile abnormality (e.g., Peyronie’s Disease), prostatic enlargement or other abnormalities, and signs or symptoms indicative of hypogonadism (See Diagnostic Algorithm). In such cases, further diagnostic evaluation should be undertaken by the primary care physician, if qualified, or a suitable specialist.
# DIAGNOSIS: I. Basic Evaluation

## Medical History

**ILLNESS**  
*Has a doctor ever diagnosed any of the following illnesses?*

- High blood pressure
- Heart disease (heart attack, chest pain with exercise or sex)
- Diabetes (high blood sugar)
- Hyperlipidemia (elevated cholesterol or triglycerides)
- Vascular disease (stroke, mini-stroke, blockage of arteries, aneurysms)
- Emotional problems (depression, anxiety or other psychiatric conditions)
- Hormone problems (testosterone, thyroid, steroids)
- Kidney disease
- Neurological problems (Parkinson’s, multiple sclerosis, spine injury)
- Trauma or injury to: penis, pelvis, perineum, testes, or rectum
- Prostate problems (enlargement, BPH, elevated PSA, infection)
- Urinary problems (urgency, frequency, hesitancy, weak stream, infection)
- Sleep apnea (severe snoring, daytime sleepiness)
- Chronic fatigue or weakness
- Cancer (bladder, prostate, rectum or other)
- Radiation of the bladder, prostate or rectum
- Unexplained weight loss
- Joint pains (severe or chronic problems moving or changing positions)
- Sexually transmitted diseases

## Psychosocial Assessment

**IN MY PERSONAL LIFE**  
*CHECK FOR YES*

- I have sexual fears or inhibitions
- I have problems finding partners
- I am uncertain about my sexual identity
- I have been subjected to emotional or sexual abuse
- I have significant relationship problems with family members
- I have been under considerable emotional or physical stress
- I often get depressed and anxious
- I am a nervous person

## My sexual partner has problems with

- Health
- Sexual interest
- Sexual performance
- Sexual fears, inhibitions
- History of sexual abuse
- Depression

### DRUGS

*Have you taken drugs of any kind in the last 3 months?*

1. **PHARMACEUTICALS:**
   - Sedatives
   - For hypertension
   - Hormones
   - Drugs for ulcer
   - Other

2. **RECREATIONAL:**
   - Alcohol -
     - Tobacco (cigarettes a day......)
     - Marijuana
     - Cocaine
     - Other
MEDICAL, PSYCHOSOCIAL AND SEXUAL ASSESSMENT QUESTIONNAIRE (Ctd)

**Arousal/Performance a) Chronology**
- When was the last time you had a satisfactory erection?
- Was the onset of your problem gradual or sudden?
- When was your last normal erection?

**Arousal/Performance b) Quantify**
- Do you have morning or night time erections?
- On a scale of 1 to 5 rate your rigidity during sex?
- With sexual stimulation can you initiate an erection?
- With sexual stimulation can you maintain an erection?

**Arousal/Performance c) Qualify**
- Is your erectile dysfunction partner or situational specific?
- Do you lose erection before penetration, or before climax?
- Do you have to concentrate to maintain an erection?
- Is there a significant bend in your penis?
- Do you have pain with erection?
- Are there any sexual positions that are difficult for you?

**7. Libido / Interest**
- Do you still look forward to sex?
- Do you still enjoy sexual activity?
- Do you fantasize about sex?
- Do you have sexual dreams?
- Are you easily sexually aroused (turned on)?
- Do you have a strong sex drive?

**8. Ejaculation / Orgasm / Satisfaction**
- Are you able to ejaculate when you have sex?
- Are you able to ejaculate when you masturbate?
- If you have a problem with ejaculating, is it:
  - You ejaculate before you want to?
  - You ejaculate before your partner wants you to?
  - You take too long to ejaculate?
  - You feel that nothing comes out?
- Do you have pain with ejaculation?
- Do you see blood in your ejaculation?
- Do you have difficulty reaching orgasm?
- Do you find your orgasm satisfying?
- What percentage of sexual attempts are satisfactory to your partner?

**3a. The problem with your sexual function concerns: (mark one or more)**
- Problems with little or no interest in sex
- Problems with erection
- Problems ejaculating too early during sexual activity
- Problems taking too long, or not being able to ejaculate or have orgasm
- Problems with pain during sex
- Problems with penile curvature during erection
- Other: ...................................................

**3b. Which problem is most bothersome (circle) 1 2 3 4 5 6 7**

4. What effect, if any, has your sexual problem had on your partner relationship/s?
- Little or no effect
- Moderate effect
- Large effect

5. What is the most likely reason for the sexual problem
- Medical illness or surgery
- Prescription medications
- Stress or relationship problems
- Don’t know

6. Arousal/Performance - a) Chronology
- When was the last time you had a satisfactory erection?
- Was the onset of your problem gradual or sudden?
- When was your last normal erection?

6. Arousal/Performance - b) Quantify
- Do you have morning or night time erections?
- On a scale of 1 to 5 rate your rigidity during sex?
- With sexual stimulation can you initiate an erection?
- With sexual stimulation can you maintain an erection?

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- Do you still look forward to sex?
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  - You ejaculate before your partner wants you to?
  - You take too long to ejaculate?
  - You feel that nothing comes out?
- Do you have pain with ejaculation?
- Do you see blood in your ejaculation?
- Do you have difficulty reaching orgasm?
- Do you find your orgasm satisfying?
- What percentage of sexual attempts are satisfactory to your partner?

9. Previous Consultations
- Have you consulted a physician or counselor for your sexual problems?
- If yes, what type of physician or counselor have you consulted (check all that apply):
  - General practitioner
  - Urologist
  - Other specialist
- Are you taking any medication or receiving medical treatment for the problem?
  - If yes, what medical or other non-medical treatments are you using?
  - How effective has the treatment been?
  - Not at all effective
  - Somewhat effective
  - Very effective
The physician must **tailor the laboratory work-up** based on patient **complaints** and **risk factors** outlined by the history and taking into account the cost and availability of testing resources. These tests **include** the following focused laboratory tests:

**a) A fasting glucose and lipid profile**

If not available within the previous 12 months to rule out diabetes mellitus and hyperlipidemia. If these test results indicate significant abnormalities (e.g., hyperlipidemia, diabetes), these conditions should receive further diagnostic evaluation and management, as indicated (See Diagnostic Algorithm).

**b) An evaluation of the hypothalamic-pituitary-gonadal axis with a testosterone assay.**

In patients with sexual dysfunction and at risk of or suspected of **hypogonadism**, the following biochemical investigations are recommended:

A blood sample for **testosterone** (T) determination between 8:00 and 11:00 AM. The most accessible and reliable assays to establish the presence of hypogonadism are the measurement of **bio-available T** or the **calculated free T** (cFT). Assays for total testosterone, particularly in the elderly, may not reflect the man’s true androgenic status. If T levels are below or at the lower limit of the accepted normal values, it is prudent to **confirm** the results with a second determination together with assessment of **luteinizing hormone** (LH).

Before considering specialized evaluation and diagnostic testing the physician should consider whether the patient case profile meets the indications for **specialist referral**.

The physician must also consider the ability of his clinic facility to provide and support specific hormonal, vascular, neural and psychological testing. They include the following:

- In depth psycho-sexual and relationship evaluation
- **Psychiatric evaluation**
- **Nocturnal penile tumescence and rigidity (NPTR) assessment**
- Vascular diagnostics:
  - In office penile injection pharmacotesting
  - Penile Doppler ultrasound,
  - Dynamic infusion pharmacocavernosometry and pharmacocavernosography
  - Penile arteriography
  - CT and MR imaging (to evaluate trauma and infection)
- Nuclear imaging
- Specialized endocrinologic testing: thyroid function studies, hypothalamic-pituitary-gonadal function studies, MRI sella turcica
- Neuro-physiologic testing: vibrometry, bulbocavernosus reflex latency, cavernosal EMG and somatosensory evoked potential testing, pudendal and sphincter EMG

**CONCLUSION**

II **OPTIONAL AND/OR SPECIALIZED DIAGNOSTIC TESTING**

As indicated in the Diagnostic Algorithm, these tests are to further evaluate specific etiological conditions or factors, or to evaluate potential contraindications to direct therapies for ED (e.g. unstable cardiac disease). Patients should be fully informed as to the rationale for these tests and the results of testing should be reviewed with the patient, when available. While the majority of patients with ED can be managed within the primary care setting by a physician educated in male sexual dysfunction, specific circumstances may dictate the need for referral for specialized testing and/or treatment (see Diagnostic Algorithm).
1. Patient requests referral for specific testing or treatment.
2. Patient requiring vascular, neurological or cardiologic evaluation
3. Young patient with pelvic, perineal or penile surgery or trauma who may be a candidate for reconstructive vascular surgery.
4. Patient with Peyronie’s disease and/or a significant penile bend or deformity that might require surgical correction.
5. Patient with refractory depression, bipolar disorder, psychosis or history of sexual abuse or trauma and those patients with complicated psychiatric or psychosexual disorder as well as those with complex relationship issues.
6. Patient with a complicated endocrinopathy including complicated diabetes mellitus.
7. Patient with treatment failures who may be a candidate for intracavernosal injection therapy or penile implant surgery.
C. Treatment Strategy of Erectile Dysfunction

The clinician has a variety of treatment options available, including medical, psychosocial and surgical treatments for ED. Wherever possible, the selection of therapy should be based on a careful matching of patient needs and preferences with the available treatment options. The selection of therapy is strongly influenced by personal, cultural, ethnic, religious and economic (affordability) factors. As noted above, all patients should receive a medical, sexual and psychosocial history, physical exam and focused laboratory testing in conjunction with, or prior to the initiation of therapy. Treatment options should be carefully reviewed with the patient and patient’s partner, if available. Patients should be educated carefully about available treatment options and their associated risks and benefits. The goal of therapy should be viewed as restoration of a satisfactory sexual life, not only a rigid erection.

The main steps of the treatment strategy are:

1. address risk factors and comorbidity
2. counsel and educate the patient and partner if available
3. medical treatment: oral and local
4. surgical treatment

ADDRESS RISK FACTORS AND COMORBIDITIES

In parallel to direct treatment for ED, good medical practice recognizes the value of altering modifiable risk factors. Although frequently insufficient to reverse ED completely, this step may be of great value in select patients. Since ED may be a marker of underlying cardiovascular, metabolic or depressive illness, these comorbidities should be addressed whenever possible.

Potentially modifiable risk factors and comorbidities include the following:

LIFESTYLE AND PSYCHOSOCIAL FACTORS

- Lifestyle factors, such as obesity, cigarette smoking, alcoholism or substance abuse may require priority management specific to the particular issue.

Psychosocial factors include relationships issues e.g. partner conflict, mood problems and depression, or other psychosexual dysfunctions.

PRESCRIPTION OR NON-PRESCRIPTION DRUG USE

Commonly used antihypertensive agents (e.g. diuretics, beta-blockers) psychotropic drugs (e.g. antidepressants, neuroleptics), in addition to antiarrhythmics, antiandrogens and steroids.

Alterations in drug dosages or classes may be of significant benefit in select patients but this should be coordinated with the primary physician wherever possible.

HORMONE REPLACEMENT THERAPY

for hormonal abnormalities (e.g. hypogonadism, hyperprolactinemia)

In men with ED and/or diminished interest, a clear indication of hypogonadism (a clinical picture together with biochemical evidence of hypogonadism) should exist prior to initiation of androgen therapy. Since androgen replacement therapy is typically chronic or life-long, it is essential that all patients receiving androgen therapy be followed on a regular basis.

The treating physician must be familiar with the diagnostic, therapeutic and monitoring aspects of androgen therapy.

- The patient should be monitored closely for possible side effects or contraindications, such as abnormal liver function, hyperlipidemia, polycythemia, prostate abnormalities (prostate cancer or severe bladder outlet obstruction), hyperactivity or aggressive behaviour, and sleep apnea.

- Inadequate therapeutic response or the appearance of significant adverse effects call for reassessment of treatment indications.
Psychological counseling addresses the predisposing, precipitating, maintaining and contextual factors associated with the presenting sexual dysfunction. These include specific psychological or interpersonal factors such as anxiety or depression, abuse history, relationship distress, sexual performance concerns, dysfunctional communication patterns and/or comorbid sexual conditions. Counseling or brief sex therapy might be considered as a potential adjunct to medical or surgical treatments for ED, and may improve outcomes in selected cases. Counseling can address psychological or interpersonal consequences associated with loss of potency or sexual intimacy, long-standing couple’s issues or individual psychological problems, such as depression or anxiety. The principal advantages of psychosexual therapy are its noninvasive nature and broad applicability. Disadvantages are its variable efficacy, lack of appeal for many patients and partners, cost and acceptability factors, and lack of qualified providers. Psychosexual counseling can be considered prior to, in conjunction with, or following after the use of medical/surgical therapy, as indicated.

The P-LI-SS-IT model is often used to classify the level of psychological intervention. This well-known model includes four levels of intervention: (P) Permission is given to all patients to enquire about sexual concerns, to request information relevant to their condition, and to seek help for their problem. Limited information (LI) is provided to most patients, and to partners where possible, regarding availability and choice of specific treatments (e.g. PDE-5s), associated risks, benefits and cost factors, and the potential relationship of ED to known risk factors (e.g. obesity). Specific suggestions (SS) are used in a minority of cases for improving partner communication, control of erection or premature ejaculation, self-stimulation or developing sexual responses in the partner. Lastly, intensive therapy (IT) is reserved for treating more deep-seated psychological problems, such as primary depression or obsessive-compulsive disorders. Medications (e.g. SSRIs) are useful in treating such cases, along with psychological counseling when available.

In Summary

Psychosexual therapy may be offered alone or in combination with medical treatment as first-line management for men with ED or other sexual problems.

For this reason, all health-care providers should be familiar with the basic concepts and principles of psychosexual and couple therapy. For some patients, brief education, support and reassurance will be sufficient to restore sexual function.

For others, referral for more specialized and intensive counseling is necessary. In either case, physicians should identify those individuals who may benefit from psychosexual or couple therapy, and make appropriate referrals when indicated. If specialized referral is not available, patients should be provided with simple counseling and education as needed.

III MEDICAL TREATMENT FOR ED

1 General Principles

The majority of patients will need to consider direct treatment options for ED

a) Shared decision making

Decision to treat depends mainly on the distress ED provokes in the patient and/or his partner.

The development of ED can significantly affect the quality of life, but it is not a life-threatening disease. Consequently it is reasonable to discuss the benefits, risks, and costs of the available treatment strategies with the patient and have the patient actively participate in the choice of therapy.

b) Cardiovascular safety

There is a documented correlation between cardiovascular diseases and ED. In a significant number of patients ED may be sign of endothelial vascular dysfunction.

An important issue prior to the institution of any therapy and the subsequent resumption of sexual activity is the overall cardiovascular condition of the patient. Is this patient able to resume the exercise of sexual activity? If not, priority cardiovascular assessment and intervention may be appropriate.
c) Partner issues

The partner’s sexual function can interact with the patient’s sexuality and if possible should be considered prior to initiating therapy. Partner’s health and psychological functioning should also be considered.

d) Which drugs for ED treatment?

Only those pharmacological treatments that have been thoroughly tested in randomized clinical trials, with subsequent publication of results in peer-reviewed literature, should be considered for general use. Long-term follow-up of all treatment options must be performed to demonstrate durability and continued efficacy and safety as well as patient and partner acceptability.

e) Criteria of selection

The treatment selected by a patient will be influenced not only by issues such as efficacy and safety but also by the patient’s cultural, religious and economic background.

Additionally, the following factors may influence the patient’s or partner’s selection of therapy:
1. ease of administration,
2. invasiveness,
3. reversibility,
4. cost,
5. the mechanism of action (peripheral vs central, inducer vs enhancer) and
6. regulatory approval and availability

f) The use of internet

The use of the internet to prescribe therapies for erectile dysfunction should be strongly discouraged since it fails to meet the need for direct physician-patient contact in the assessment of all patients presenting with this complaint.

2 ORAL AGENTS

Oral therapies may be considered first-line therapies for the majority of patients with ED because of potential benefits and lack of invasiveness.

They demonstrate a good risk to benefit ratio.

Several agents are registered for this indication (selective PDE5 inhibitors, apomorphine and yohimbine).

a) Phosphodiesterase type 5 (PDE 5) inhibitors

PDE 5 is the enzyme responsible for the breakdown of the intracellular second messenger of nitric oxide i.e. cyclic guanosine monophosphate (cGMP) in the corporal smooth muscle. PDE5 inhibition increases the concentration of cGMP and promotes corporal smooth muscle relaxation and erection in response to sexual stimulation.

PDE5 inhibitors are associated with the broadest efficacy and tolerability of oral ED therapies. Accordingly PDE5 inhibitors are considered as the reference class for oral treatment. Three members of this class are available today, sildenafil, vardenafil and tadalafil. Sildenafil was approved worldwide in 1998 and vardenafil and tadalafil in 2003.

PDE5 inhibitors are effective and well tolerated as demonstrated in controlled clinical trials and clinical practice experience. In general ED, a high level of evidence exists for the efficacy of all three drugs. The long-term effectiveness and safety of sildenafil has been demonstrated in controlled clinical trials, open label studies, and post-marketing experience.

The clinical action of PDE5 inhibitors may be visible with the first intake. Nevertheless there is a necessity for patient education on how to optimally use the drug because of the need for sexual stimulation and adequate dosing. For this reason, results of treatment improve with repeated dosing.

PDE5 inhibitors are strictly contraindicated in patients receiving organic nitrates and nitrate donors.

In patients receiving concomitantly an α-blocker, recommendations may vary from caution to contraindication depending on the PDE5-inhibitor and the α-blocker to be used. Physicians must carefully follow the label instructions of these drugs.
PDE5-inhibitors undergo hepatic metabolism via cytochrome P450CYP3A4. **CYP3A4 inhibitors** such as erythromycin, ketoconazole, and protease inhibitors, can increase the levels of PDE5-inhibitors. In patients taking these drugs, consider administering PDE5-inhibitors at the **lowest available dosage**. Concomitant grapefruit intake should be avoided because of its CYP3A4 effect.

The three PDE5 inhibitors are associated with **class-related side-effects** including headache, dyspepsia, facial flushing, and nasal stuffiness. Other side-effects such as altered vision (due to PDE6 inhibition), myalgia and back pain may vary according to the specific compound in discussion. These side-effects are predominantly **mild** to **moderate**.

There is variability of **onset of action** for these three drugs (which may be at least 15 to 30 minutes). The **duration of action** is about 5 hours for sildenafil and vardenafil and up to 24-36 hours for tadalafil.

**b) Apomorphine SL**

Apomorphine SL (sublingual) is a **centrally acting** non-selective dopamine agonist with **modest efficacy** and **good tolerability** in **mild ED**. It is associated with mild to moderate nausea and rare bradycardia/syncope (vasovagal) syndrome. Apomorphine SL is registered in various countries since 2002.

**c) Yohimbine**

Yohimbine is both a **peripherally and centrally acting alpha-blocker** associated with **low level of evidence for efficacy** in general ED.

Conclusion: advantages and disadvantages of oral treatment

The advantages of oral drug therapies include **broad patient acceptance**, **ease of administration** and **relative efficacy**.

The disadvantages include **specific contraindications** such as the concomitant use of nitrates with respect to PDE5 inhibitors, the **relative cost**, and the moderate discontinuation rate. Also the potential for misuse should be considered.

**3 Local Therapy**

Local therapies include **intracavernosal injection therapy**, **intraurethral/topical therapy** and **vacuum device therapy**. Patients who fail oral drug therapy, who have **contraindications** to specific oral drugs or who experience adverse events from oral drugs might consider these local therapies. Additionally, individual **preferences** may direct a patient to consider local therapies prior to or as an alternative to an oral drug therapy.

**a) Intracavernosal Injection (ICI) Therapy**

**Alprostadil (Prostaglandin E1)**

**Alprostadil**, the synthetic formulation of the endogenous prostanoid **prostaglandin E1**, is delivered by local injection into the corpora cavernosa. It affects **smooth muscle relaxation** primarily by increasing levels of cyclic AMP within the corporal smooth muscle. It is associated with **high efficacy** and **modest tolerability** in general ED.

The **adverse events** associated with alprostadil injection therapy are primarily **local** and include, **acutely**, penile pain and priapism (rare) and, **chronically**, penile fibrosis or curvature (both of which are uncommon).

**Papaverine and combination+Penthalamine**

**Papaverine hydrochloride alone** or in **combination** with phenolamine or a combination of papaverine, phenolamine and alprostadil has been **extensively and successfully utilized** in clinical practice. However this is not an approved therapy.

**Intracavernosal injection therapy** is **contraindicated** in patients with sickle cell anemia and with other conditions that predispose to priapism. Anticoagulant therapy is not an absolute contraindication but extra care must be taken to avoid excessive bruising.

The **advantages** of penile injection therapy include broad efficacy, relative safety and the rapidity of onset of action. The **disadvantages** include invasive local administration and relative cost.

**b) Intraurethral therapy**

**Intraurethral alprostadil** therapy is associated with **moderate efficacy** and tolerability in the management of general ED. In addition to similar **adverse events** associated with alprostadil ICI therapy, the intraurethral administration of alprostadil is also associated in rare cases with hypotension and syncope.
The advantages of intrarectal therapy include its less invasive nature. The disadvantages include local as well as systemic side-effects (rare), relative cost and partner related vaginal irritation. A condom should be used in case the partner is pregnant.

c) Intrameatal therapy

The topical (intrameatal) application of the combination of alprostadil and a dermal permeation enhancer is associated with a certain efficacy and tolerability that need to be confirmed by further studies. It is has been approved in some Asian countries.

d) Vacuum Constriction Devices

Vacuum constriction devices (VCD) are widely available including over-the-counter (without prescription) in some countries. They are of appeal to a group of men who are not interested in pharmacological therapies or have specific contraindications to these therapies. VCD’s apply a negative pressure to the pendulous penis, thus drawing blood into the penis, which is then retained by the application of an elastic band at the base of the penis.

The side-effects associated with VCD therapy include penile pain, penile numbness, bruising and trapped ejaculation. Anticoagulant therapy is a relative contraindication.

The advantages of VCD therapy include its non-pharmacologic nature, on demand use and cost. The disadvantages of VCD therapy include their cumbersome utilization and minor local side-effects.

2 Penile implants

The final treatment option for ED is the surgical implantation of a malleable or inflatable penile prosthesis. This option is highly invasive and irreversible and should therefore be reserved for select cases failing other treatment modalities. However, under unique and uncommon circumstances a penile implant could be selected as a primary option. When properly selected, penile prostheses may be associated with high rates of patient and partner satisfaction.

Penile implant surgery is uncommonly associated with prosthesis infection (1-5%) but such cases usually require explantation and may result in severe scarring and penile deformity. Mechanical failures are now less than 5% in the first year, about 20% at 5 years and 50% at 10 years.

The advantages of penile prosthesis implantation include relative long lasting effect and high patient’s satisfaction. The disadvantages of penile prostheses include irreversibility, invasiveness, surgical complications and mechanical failure.

3 REASSESSMENT AND FOLLOW-UP

Reassessment and follow-up should be conducted at regular intervals with every patient receiving treatment for ED. The goals of follow-up include:

1. The need for dose titration or substitution of another treatment intervention should be considered at each treatment follow-up visit. Patients may change treatment preferences, seek new information, or wish to reevaluate their current treatment choices.

2. Patient communication. Patients may have concerns regarding treatment administration, other sexual dysfunctions (e.g. premature ejaculation), partner issues (e.g. anorgasmia) or lifestyle factors (e.g. emotional stress).

3. Patients may change medication regimens, either for ED or a concomitant medical disorder. The possibility of adverse drug reactions or drug interaction with oral ED drugs should be carefully monitored.

4. General medical and psychosocial reassessment should occur at regular intervals, depending upon the patient’s health, physical and psychosocial needs. Follow up also provides an additional opportunity for patient education.
TREATMENT STRATEGY OF ERECTILE DYSFUNCTION (ALGORITHM)

1. Educate the Patient About Risk Factors and Comorbidities
   Provide Appropriate Education and Counseling to the Patient and Partner
   Consider Treatment Options

2. INITIATE MEDICAL TREATMENT
   Treatment is Selected Taking Into Account the Medical and Psychosocial Contraindications/Patient Preference and Availability
   Conjoint Psychosocial and Medical Treatment May be Indicated

   Other oral Treatments
   NOT SATISFIED

   PDE5 Inhibitors*
   NOT SATISFIED

   Local Therapies
   - Pharmacological
   - Mechanical
   NOT SATISFIED

   REEVALUATE AND ADJUST THERAPY
   • Treat Hypogonadism if Present
   • Dose Titration
   • Instruct Patient on Optimal Use of Treatment
   NOT SATISFIED

3. Consider Alternative Oral or Local Therapy as Above
   Additional Education and Counseling
   NOT SATISFIED

4. REFER TO A SPECIALIST
   Depending on the Predominant Etiology and Circumstances the Specialist could be a:
   • Urologist: Penile Prosthesis, Penile Revascularization or Correction of Penile Deformity
   • Psychosocial Therapist or Psychiatrist: Treatment of Complicated or Treatment-Refractory Problems
   • Other Medical Specialist

*PDE5 inhibitors are the preferred treatment option in the large majority of patients
I PREMATURE EJACULATION (EARLY EJACULATION) (PE)

1 DEFINITION

Premature ejaculation, also referred to as rapid or early ejaculation, is defined as “premature ejaculation is the recurrent or persistent ejaculation with minimal sexual stimulation, that occurs before, at or shortly after penetration, upon which there is little or no voluntary control, and which causes bother to the patient and/or his partner”.

This definition has 3 essential criteria:

a) brief ejaculatory latency; b) loss of control; and c) psychological bother in the patient and/or partner.

Ejaculatory latency of two minutes or less may qualify a man for the diagnosis, which should include consistent inability to delay or control ejaculation, and marked distress about the condition. All three components should be present to qualify for the diagnosis. Subtypes of the disorder are symptom-based, including lifelong versus acquired, global versus situational PE, and the co-occurrence of other sexual problems, particularly ED. About 30% of men with PE have co-occurring ED, which typically results in early ejaculation without full erection. A wide degree of severity is seen, with patients ejaculating on or prior to penetration in the most severe cases.

2 ETIOLOGY

The etiology of the disorder is uncertain in most cases, and likely includes a combination of organic and psychogenic factors. Negative conditioning and penile hypersensitivity are the most frequently cited etiological factors in PE, although neither mechanism has received adequate experimental support to date.

3 PREVALENCE

PE is a highly prevalent disorder; however accurate population-based data are not available. Although usually associated with less bother than ED, the disorder may cause substantial bother in some instances. It may be associated with sexual problems in the woman partner, particularly anorgasmia or a sexual pain disorder (e.g., vaginismus). In such cases, couples or sex therapy approaches may be of particular value. These may be combined with pharmacotherapy for treatment of PE in the male.

4 DIAGNOSTIC ASSESSMENT

1. All men who meet diagnostic criteria for PE should receive a medical and sexual history, physical examination and investigations of causal or maintaining factors for the patient’s PE, such as anxiety or interpersonal factors. The developmental history of the disorder should be carefully assessed, such as whether the rapid ejaculation is global or situational, lifelong or recent in its development, and the presence or absence of other sexual dysfunctions, such as ED. If ED is present, this should be evaluated according to the guidelines above.

2. Details of the patient’s ejaculatory response should be obtained, particularly the subjective assessment of ejaculatory latency, sense of ejaculatory control and level of sexual dissatisfaction or distress should be fully evaluated. Sexual and emotional responses of the partner need also to be assessed, particularly the presence or absence of sexual dysfunction or pain in the partner. Questionnaire measures or brief symptom scales are available for assessing PE, although these are not well-standardized to date. Laboratory-based evaluations (e.g. biothesiometry) are not recommended for routine evaluation.

5 TREATMENT

As indicated in the following algorithm, several management options are available following initial assessment and diagnosis. In particular, men with premature ejaculation secondary to ED, other sexual dysfunction or genitourinary infection should receive appropriate etiology-specific treatment. Men with lifelong premature ejaculation should be managed with pharmacotherapy, while those with acquired or situational PE can be treated with pharmacotherapy and/or behavioural therapy according to patient/partner preference. Men with significant contributing psychogenic or relationship factors may benefit from concomitant behavioural therapy. Recurrence of premature ejaculation is highly likely to occur following withdrawal of treatment. Behavioural therapy may augment pharmacotherapy to enhance relapse prevention. A flow-chart model for office management of PE is shown below.

Pharmacological treatments for PE include use of selective serotonin reuptake inhibitors (SSRIs) (e.g., paroxetine, sertraline, fluoxetine clomipramine), topical local anaesthetics (e.g., lidocaine), and PDE-5 inhibitors (e.g., sildenafil). None of these drugs have received regulatory approval for treatment of PE, although clinical trial data supports their use in individual cases. SSRIS should not be prescribed in patients under 18 years of age.
MANAGEMENT OF PREMATURE EJACULATION (PE)

PATIENT COMPLAINING OF PREMATURE EJACULATION (PE)

**PATIENT/PARTNER HISTORY**
- Establish presenting complaint
- Intravaginal Ejaculatory Latency Time
- Perceived degree of ejaculatory control
- Degree of patient/partner distress
- Onset and duration of PE
- Psychosocial history
- Medical history
- Physical Examination

**TREATMENT**

**BEHAVIORAL THERAPY**
- Stop/Start
- Squeeze Technique
- Sensate Focus

**RELATIONSHIP COUNSELING**

**PHARMACOTHERAPY**
- SSRI agents *
- Topical anesthetics

**COMBINATION TREATMENT**

Counsel the patient and discuss treatment options and patient’s preference

PE SECONDARY TO ED OR OTHER SEXUAL DYSFUNCTION

MANAGE PRIMARY CAUSE

*Selective serotonin re-uptake inhibitors (SSRIs)*
Paroxetine, sertraline, fluoxetine, clomipramine
Administration:
- Daily treatment
- On demand treatment
- Low daily doses + as needed higher dose 3-6 hours before intercourse.

Side effects: fatigue, yawning, mild nausea, perspiration (gradually disappear over 2-3 weeks)
Withdrawal should be gradual (i.e. 2-3 weeks).

* None of these drugs have so far received regulatory approval for treatment of PE, although clinical trial data supports their use in individual cases

Withdrawal should be gradual (i.e. 2-3 weeks).
Male orgasmic dysfunction (MOD) includes a spectrum of disorders in men ranging from delayed ejaculation to a complete inability to ejaculate, anejaculation, and includes retrograde ejaculation.

**Etiology**

Multiple etiological factors have been identified, including both organic and psychogenic factors. Any medical disease, drug 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.

Ejaculatory dysfunction and loss of orgasmic sensation commonly occur following prostate or bladder surgery and have been reported in association with lower urinary tract symptoms (LUTS) in aging men.

Commonly used drugs, such as alpha-blockers (e.g. tamsulosin) and serotonin-uptake inhibitors (e.g. paroxetine) have been associated with loss of orgasm or ejaculation. Precise prevalence data for these disorders are not available, although recent studies suggest that MOD may be almost as prevalent as ED in aging men. Loss of ejaculation is often age-related and may be associated with other sexual dysfunctions in the male, particularly ED.

**Diagnostic Assessment**

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. A flow-chart model is shown below.

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 degree of sexual stimulation,

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 and the sensation of the genitalia.

6. The partner’s assessment of the situation, including whether the partner suffers from sexual dysfunction, and

7. Assessment of the sexual and overall relationship

**Treatment**

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. Management involves identification of the etiology and disease specific treatment. Men who occasionally achieve orgasm and ejaculation are usually suffering from psychogenic inhibited ejaculation or penile hypoanaesthesia secondary to age or spinal cord disorder related degeneration of the afferent penile nerves.

The former is managed with behavioural therapy and/or psychotherapy. Men with age related penile hypoanaesthesia should be educated, reassured and be instructed in revised sexual techniques which maximise arousal. The majority of men who always achieve orgasm but never experience prograde (antegrade) ejaculation or have a greatly reduced prograde ejaculatory volume, have 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 (with alpha adrenergic agonist) 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. Wherever possible, medical and psychological approaches should be combined in the treatment of MOD.
DELAYED EJACULATION-ANEJACULATION-ANORGASMIA

FAILURE OF ORGASM
• Neurogenic
• Metabolic
• Drug Adverse Effect
  → Disease Specific Management

INHIBITED MALE ORGASM
→ Psychosexual therapy

INHIBITED MALE ORGASM
With Nocturnal/Masturbation Emissions
→ Psychosexual Therapy
AGE RELATED INSENSITIVITY
→ Reassure/alter sexual technique

IS THERE ORGASM?

NEVER

SOMETIMES

ALWAYS

IS THERE EJACULATION?

YES

ARE SPERM PRESENT IN URINE AFTER ORGASM?

NO

ASPERMIA
→ Ejac.Duct Obstruction
Urological Consultation

RETOGRADE EJACULATION
→ Reassure/Educate
→ Pharmacotherapy
→ Surgery

NO

YES
PRIAPISM

I DEFINITION

Priapism is a relatively rare condition in men, which 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 may be distinguished, although there may be some overlap among categories.

1. Low flow (no flow) or ischaemic priapism. This is the most common form 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.

2. High flow, well oxygenated priapism. This is less common than the first type and may occur following surgical treatment or pelvic trauma. It may also be congenital or idiopathic in origin.

3. Recurrent or stuttering priapism commonly occurs in men with sickle cell disease but is not confined to them. Such a priapism is usually high flow but may become low flow and anoxic.

II DIAGNOSIS AND INITIAL MANAGEMENT

A 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, severity of pain and presence of potential causative or comorbid factors, such as a secondary tumor in the penis. A blood sample should be taken in all cases to exclude sickle cell disease, thalassaemia major, and leukaemia. These conditions require appropriate management at an early stage.

III FIRST AID MANAGEMENT OF PRIAPISM

First aid measures may be initiated by the patient or health practitioner prior to medical examination and diagnosis. Cold showers or ice packs may be beneficial during the early stages. Exercise and micturation are occasionally helpful. Analgesics should be given as appropriate. Pharmacologic oral therapies include terbutaline, pseudoephedrine, etilephrine and procyclidine.

IV UROLOGIC MANAGEMENT OF ANOXIC PRIAPISM

If ischemic priapism is diagnosed based on presenting symptoms and physical examination, it is essential to decompress the corpora as soon as possible. This is typically achieved by aspiration of at least 5 ml of blood with a 19 to 21 gauge buttefly needle. The colour of the blood aspirated in an anoxic priapism is almost black and the blood gases will confirm the hypoxic state of the penile corpora. It is necessary to slowly aspirate until oxygenated red blood is obtained before injecting an alpha-adrenoreceptor agonist in an attempt to cause contraction of the smooth muscle. This process may take 1 hour to occur and the pulse and blood pressure should be monitored. It is doubtful whether irrigation of the corpora is of any benefit. Surgical intervention may be required if repeated aspiration is not successful (See Table below).

V MANAGEMENT OF HIGH FLOW PRIAPISM

The erection is less rigid and pain is typically less severe in this form of priapism. The condition is typically self-limiting and prognosis is generally favorable, in contrast to ischemic priapism. Conservative treatment is recommended in most cases. A high flow priapism is indicated by aspirating bright red arterialised blood from the corpora and the diagnosis is then confirmed by Doppler examination. When associated with traumatic injury, treatment of high flow priapism may include selective embolisation with autologous blood clot. This is usually successful and may be repeated. Surgical ligation of the fistula may be successful but it is more difficult and invasive. It should be remembered that an idiopathic high flow priapism may convert to a low flow one and urgent intervention is then required.

VI MANAGEMENT OF RECURRENT (“STUTTERING”) PRIAPISM

This condition is uncommon, not confined to men with sickle cell disease, and poorly understood. The onset of the prolonged erection is usually during sleep and detumescence does not occur immediately upon waking. The mechanism is obscure and management of recurrent priapism is difficult as the episodes may be ischaemic or non ischaemic in the same patient. Sickle cell disease, if present, requires haematological management which may reduce the frequency or severity of attacks. The condition is usually benign, although a full blown ischaemic episode may occur which requires urgent intervention. Patients should be informed about this eventuality. Pharmacologic agents used in the treatment of recurrent priapism include terbutaline, procyclidine, clonazepam, etilephrine, LHRH agonists, baclofen and phenylephrine implants.
PRIAPISM

INITIAL MANAGEMENT
- HISTORY
- CLINICAL EXAMINATION
- HAEMATOLOGY
- DOPPLER IF EASILY AVAILABLE
- ASPIRATION IF NECESSARY

FIRST AID MEASURES
- ANALGESIA
- PHYSICAL METHODS
- ORAL DRUGS (e.g. terbutoline 5-10 mg)

NO FLOW ISCHEMIC

Evacuate old blood with a 19 or 21 gauge butterfly needle inserted through the glans to the corpus cavernosum

FAILURES

Intracavernous injection of an α-adrenergic agonist*

FAILURES

Biopsy and shunt surgery

FAILURES

Discuss penile prosthesis

HIGH FLOW NON-ISCHEMIC

Expectant Compression Embolisation (surgery)

LATE PRESENTATION

Normal red blood

Black blood

* Inject 250 to 500 mcg of diluted phenylephrine into the corpus cavernosum every 3-5 minutes until detumescence occurs or until 10 mg total is reached. In older patients blood pressure and pulse should be monitored.
Peyronie’s disease is named after the French surgeon François de La Peyronie and is an acquired disorder of the tunica albuginea characterised by the formation of a plaque of fibrous tissue and often accompanied by penile pain and deformity on erection. There may be difficulty of penetration as a result of the curvature and the condition may be accompanied by some impairment of erectile capacity.

Peyronie’s disease should be differentiated from localised cavernous fibrosis associated with direct external trauma to the corpus, injury from a fractured penis, or damage to the cavernous tissue due to intracavernous injections. Atypical areas in the crura are typically associated with external trauma.

Peyronie’s disease is usually easy to diagnose by clinical history and examination and it should be differentiated from congenital abnormalities (vide infra) and extremely rare secondary tumours in the penis.

A history and physical examination are usually sufficient to make the diagnosis of Peyronie’s disease, and further investigation is only necessary in selected patients. Plaque size is measured in the flaccid penis, and may be confirmed by means of ultrasound, CT or MRI testing, although these methods have not been shown to be superior to clinical examination. Deformity is better studied after vacuum or pharmacologically induced erection. A careful medical and sexual history should be obtained, including the patient’s ability to achieve and maintain erection. Most cases are self-limiting and benign, requiring no more than education and reassurance of the patient.

Many patients do not require medication and although many pharmacological treatments have been described, few have shown clinically significant treatment effects compared to placebo. A combination of colchicine and vitamin E was shown to be beneficial in one study, but further research is necessary. The combination is relatively “inexpensive and safe”. Procarbazine, paraaminobezoate (Potaba), tamoxifen, verapamil and acetyl esters of carnitine have also been recommended, but have not demonstrated adequate safety or efficacy to date. Intraplaque injections with betamethasone, collagenase or verapamil have also been shown to have limited benefit in some studies.

Surgical procedures for correction of Peyronie’s disease are available and can be employed in severe cases. Surgical correction of the penile deformity should not be considered for at least 12 months following initial diagnosis, and after symptoms have been stable for 3, and preferably, 6 months. The deformity should make intercourse difficult and the quality of erection should be adequate. Indications for surgery are shown in the Table below. Patients should be fully informed about the nature of their condition and anticipated outcome of surgery.

A number of surgical procedures are available. The Nesbit excision technique usually provides the best results and is the method of choice for most men. Plication techniques have also been used, but with less favorable results. Plaque incision and vein grafting procedures offer effective straightening of the penis, but with an increased risk of postoperative erectile dysfunction. These procedures should only be used in selected patients. Penile prosthesis may be the treatment of choice for the older man with vascular impairment, erectile dysfunction and an erectile deformity. The final algorithm for management of Peyronie’s disease is shown below.

**Indications for Surgery**

- Disease present for at least 12 months
- Stable for at least 3 months (preferably 6 months)
- Deformity makes intercourse difficult
- Quality of erection important
to decide between reconstruction or Prosthesis
- Patient expectation and informed consent
PEYRONIE’S DISEASE MANAGEMENT

PRESENTING SYMPTOMS
- Penile pain (during erection)
- Penile deformity
- Presence of a penile plaque or induration
- Erectile dysfunction

ASSESSMENT
- Medical, sexual, family, history of penile trauma
- Physical examination
  - Measurement of plaque, location
  - Clinical evaluation of deformity
  - Look for Dupuytren’s disease
  - Evaluate quality of erection

TREATMENT
Shared decision-making:
- Explain natural history
- Reassure the patient that the “lump” is not a malignant disease.
- Discuss treatment modalities and their outcomes and side effects

No ED
- Mild or no deformity
  - Conservative treatment
- Moderate or severe deformity
  - Consider plastic surgery with the patient

ED Present
- Treat ED
  - Successful
  - Failure
    * In the flaccid penis or after pharmacologically or vacuum induced erection
CHAPTER 18  Committee 6b Standards for Clinical Trials in Sexual Dysfunctions of Women: Research Designs and Outcomes Assessment
J. R. Heiman (USA), M. K. Guess (USA), K. Connell (USA), A. Melman (USA), J. S. Hyde (USA), T. Segraves (USA), M. G. Wyllie (U.K)

CHAPTER 19  Committee 7 Physiology of Female Sexual Function and Pathophysiology of Female Sexual Dysfunction
I. Goldstein (USA), A. Giraldi (Denmark), A. Kodigliu (Turkey), HW van Lunsen (The Netherlands), L. Marson (USA), R. Nappi (Italy), J. Pfaus (Canada), A. Salonia (Italy), A.M. Traish (USA), Y. Vardi (Israel)

CHAPTER 20  Committee 12b Endocrine Aspects of Female Sexual Dysfunction
S.R. Davis (Australia), A.T. Guay (USA), J.L. Shifren (USA), N.A. Mazer (USA)

CHAPTER 21  Committee 9b Women’s Orgasm
C.M. Meston (USA), E. Hull (USA), R.J. Levin (UK), M. Sipski (USA)

CHAPTER 22  Committee 16 Women’s Sexual Desire and Arousal Disorders and Sexual Pain
R. Basson (Canada), W.C.M. Weijmar Schultz (Netherlands), Y.M. Binik (Canada), L.A. Brotto (USA), D.A. Eschenbach (USA), E. Laan (Netherlands), W.H. Utian (USA), U. Wesselmann (USA), J. Van Lankveld (Netherlands), G. Wyatt (USA), L. Wyatt (USA), S. Leiblum (USA), S.E. Althof (USA)

CHAPTER 23  SUMMARY OF THE RECOMMENDATION FOR WOMEN
Committee 6 B

Standards for Clinical Trials in Sexual Dysfunctions of Women: Research Designs and Outcomes Assessment

Chair
J. R. Heiman (USA)

Members
M. K. Guess (USA),
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A. Melman (USA),
J. S. Hyde (USA),
T. Segraves (USA),
M. G. Wyllie (U.K.)
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DEFINING THE DISORDER OF THE PATIENT POPULATION

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GLOSSARY OF KEY TERMS

APPENDIX A. THE FEMALE SEXUAL FUNCTION INDEX (FSFI)

REFERENCES
I. INTRODUCTION

In contrast to the burgeoning data on men, clinical trials on sexual dysfunctions in women are few, -this in spite of the fact that sexual dysfunctions are likely more common in women than in men. Currently there are no medications approved for treatments in women, and there is limited data on drug efficacy or psychological efficacy in well-controlled studies. However, there is considerable ongoing interest in and early efforts at identifying peripheral- and centrally acting agents.

To date, there has been attention to diagnostic precision, assessment tools and outcome measures. However, most of the efforts to address women’s sexual dysfunction have relied on the agents that were first tested in men—a rational but potentially distracting strategy that fails to account for existing differences between the sexes. The remaining unsolved issues in these areas will be pointed out here as they impact clinical trial development.

Our focus is on the design and conduct of clinical trials for female arousal disorder (FAD) and female desire disorder (particularly hypoactive sexual desire disorder, FHSD). Although female orgasmic disorder (FOD) is important, it will only be mentioned indirectly, as too little clinical trial activity for this disorder exists to formulate clear standards. At times we may refer to these conditions in this chapter more broadly as female sexual dysfunction (FSD), in keeping with the diagnostic systems currently in place.

FSD does not exist as a single diagnosis; it is a summary category under which specific disorders are classified. For our purposes in this chapter, we are assuming definitions compatible with the DSM-IV-TR [3] and, to a lesser extent, the Consensus Conference [4]. We will address study design issues, sample (clinical and non-clinical) selection, duration and timing of the trial, diagnostic methods, assessment measures and outcome variables important to measure and statistical analyses.

We review Phase I-IV clinical trial design purposes and provide some initial guidelines for protocol development, ethical and clinical issues, research reports and publications.

A major goal for the chapter is to review the current standards for the design and conduct of clinical trials. General principles that apply to all clinical trials are presented, along with specific issues that have to do with the applications to sexual conditions. For example, physiological and self-report measures of sexual function are discussed, but physiological measurement for women is not always possible, given the inadequacies in measuring development for desire and, in particular, orgasm. In addition, issues involving partner, quality of life, and personal distress measures will be addressed. The focus will be on general guidelines and principles with selected examples of diagnosis-specific variations. Many of the principles discussed here also apply to the development of non-pharmacological treatments, such as physical therapy and psychological regimens, but our focus is on standards for the former.
II. RATIONALE AND DESIGN OF CLINICAL TRIALS

The development and regulatory approval of a new treatment is usually described in four phases, which we will discuss below. Clinical trials are intended to demonstrate diagnosis-specific efficacy and safety for regulatory purposes. They should also provide some information about the risks and benefits when the product reaches the broader clinical environment.

1. PHASE I

This phase tests the first exposure of the experimental agent or device in humans, and Table 1 outlines the range of potential studies relevant to FSD in this phase. Typically, testing begins with healthy volunteers, excluding women of childbearing capacity unless there is a specific reason to consider them. It is important to recognize that an agent already tested in men still requires the Phase I testing in women, with attention to dose, timing, and possibly hormonal status. This will also depend on the pre-clinical data available in both male and female animals, formulation changes, and comparative doses.

An important issue is the required reproductive toxicity studies, particularly if agents will be used in women of childbearing age. The initial goal is to assess for tolerability and safety on key parameters. First-dose exposures are selected based on animal studies, with particular markers noted such as liver metabolism and lipid profiles in vitro. First-dose studies begin with a very low single dose, 20-100 times lower than the predicted threshold efficacy dose in humans, and titrate upwards, by multiples of 2 to 5.

Poor toleration may stop this stage of development; adequate toleration, measured by physical or subject reported parameters, would move it toward multiple dose studies. Dosing frequency is selected by the specific type and action of the novel agent. Multiple dose studies test the ability of subjects to tolerate dosage over time. In both single and multiple toleration studies, assays of plasma drug levels are useful and should be monitored. However, plasma levels are not always available. Even when available, as in endocrine panels for hormonal agents, the reliability of these tests may be difficult to guarantee [5].

Paralleling these initial dosing studies, pharmacokinetic and drug metabolism studies should be initiated in order to make sure that metabolic pathways are known. Concerns would be around the detection of dose-dependent tissue drug accumulation and possible drug interactions. It is important to ensure that there are no dose-dependent tissue drug accumulations and that the metabolic pathways for major drug interactions are known.

Phase I clinical pharmacology studies in healthy volunteers can expedite dose selection and the overall drug development process and even provide limited efficacy information. In addition, Phase I studies may also focus on specific populations. For example, menopausal or oophorectomized women may be of special interest to see if they display different pharmacokinetics and tolerability (Table 1).

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Dose</td>
<td>Assessment of tolerability after a single dose administration</td>
</tr>
<tr>
<td>Multiple Dose</td>
<td>Assessment of tolerability over likely dosing period</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Assessment of kinetics and metabolites predictability in pre-clinical studies</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>Indirect assessment of efficacy to ensure adequate pharmacodynamic/pharmacokinetic relationships</td>
</tr>
<tr>
<td>Special Populations</td>
<td>Pre-and postmenopausal on hormonal products; very elderly; may display different tolerability/pharmacokinetics</td>
</tr>
</tbody>
</table>

2. PHASE II

Efficacy testing begins in Phase II, where the primary objective is identifying an effective dose range that will be more fully evaluated in Phase III. Clinical samples rather than healthy subjects are the focus of the evaluation. Since tolerability has been established in Phase I, the dose range tested usually begins at 5-20% of maximum, with continued data on tolerability being collected. The lowest effective dose should be established. Risk/benefit estimates continue to be examined.

Crossover designs are often preferred to parallel designs for Phase II studies. The main advantage of a crossover design is that each subject serves as her own control, thus reducing between-subject variability and allowing for within-subject com-
parisons. The increased statistical power may allow for a smaller sample size to be tested. However, there are a number of disadvantages. A crossover design is only viable if the evaluation of treatment involves short-term relief of symptoms of a chronic condition. One potential problem with the design is that the effect of the first treatment may carry over to the second period and hence interferes with the second treatment. Thereby, it biases any comparison between treatments. Although this can be minimized by allowing a suitable wash-out period, it may create problems of interpretation when the onset of action of treatment is relatively slow and off set is long; for example, with hormonal manipulation. These issues may arise in situations where diagnostic categories are difficult to differentiate completely or are imprecise, as they often are within FSD. An example is the extensive overlap in diagnosis between arousal (FSAD) and desire disorders (FHSD) [4]. There are also many variables in women that in a single study may be difficult to control (e.g., diet, BMI, alcohol intake, mood variability, menstrual cycle phase, precise hormonal status, and psychosocial variables), but the crossover study helps reduce the impact of error introduced by subject variability. The data can be examined post-hoc for variables such as age, medical status, and hormonal condition, in order to better plan the Phase III designs. In addition, drug interaction studies may be examined at this time. For example, the discovery that sildenafil citrate required an adequate androgen and estrogen environment to be effective for women was an important finding that impacted subsequent Phase III designs. The disadvantage to crossover designs is potential carryover effects from one treatment to the other, a not unlikely scenario wherein the etiology is both psychogenic and physiologic, as many sexual disorders can be. This is further exacerbated by three or more treatment conditions, or when the outcome variables depend on the availability and cooperation of the woman’s partner. Switching between conditions may prove quite disruptive to sexual interactions. Thus, in-clinic studies that look at specific responses to visual or vibratory sexual stimulation may be more useful and practical at this phase.

Crossover designs test each subject in response to a specific dose and placebo over two-week to two-month treatment periods separated by a brief (one day to one month) washout period. The choice of timing of treatment and washout periods depends the pharmacokinetics and metabolism of the drug and on the level of individual psychological and couple variables impacted. For example, testing sildenafil citrate permits a shorter treatment and washout period than does the testing of a systemic androgen, given the amount of time androgenic compounds appear to require to achieve a sustained blood level and potentially interact with other neuroendocrine processes.

Phase II studies may involve evaluation in special populations. For example, the common anorgasmia side effect of the antidepressants, particularly of the selective serotonin reuptake inhibitor (SSRI) drugs, coupled with the high prevalence of SSRI use in women, may warrant early stage characterization of the potential effects of a new agent on FSD in this sample of women. Further drug interaction studies may be undertaken during this phase as well.

3. Phase III

Regulatory approval requires at least one large-scale, well-controlled and adequately powered pivotal study with clearly defined and carefully selected patient groups. Parallel designs are the usual choice in Phase III studies. This design is most suitable when the treatment is expected to change the course of the disease and make an appreciable difference to the patient's condition. In addition the long-term effects of treatment can also be assessed using this design carrying on over a number of years. In addition to the classical parallel design, a combined parallel and crossover design is also appropriate with some agents.

For example, comparing the effectiveness of a different doses of a topical genital vasocongestive agent with a short half life to placebo can be provide good efficacy data, though it might take longer than a straight parallel design. Large samples usually mean that these pivotal phase III trials are multi-center, randomized, double-blind, prospective studies testing two or more doses of the novel drug in comparison to a placebo control. Treatment duration is often 12-16 weeks, although longer trials of 6 months or more are increasingly preferred. A minimum of 8 weeks is recommended, although this timeframe is more appropriate for Phase II studies. Longer trials are more vulnerable to subject attrition, especially in the placebo arm. Each patient is randomly assigned to a specific treatment group and comparisons are made between the treatments at various time-points, particularly comparing treatment to baseline changes. Baseline assessments themselves are used to confirm whether subjects still meet inclusion criteria, to check the effectiveness of
randomization for comparability of groups, and to see what variables might contribute to treatment response. It is thus important to make baseline assessments of all patients in order to make the groups as equivalent as possible prior to randomization.

In is not uncommon to precede the parallel treatment conditions with a single-blind, placebo or no treatment run-in phase before randomization. This establishes a reproducible baseline and helps to screen out patients who might demonstrate clear placebo responses. At the end of treatment an open label-extension may be offered, in order to gather additional safety and efficacy data and to offer individuals in the control group access to active treatment (thus aiding their motivation to remain in the trial). The open-label extension may last from 6 months to several years.

A comparison drug or treatment may be tested in this phase, although they are not required for regulatory approval. All Phase III studies should be prospective and placebo-controlled and carefully define of the population to whom the agent could be effective, via the inclusion and exclusion criteria. Primary and secondary efficacy endpoints need to be clearly specified, though these studies are usually powered only for the primarily endpoint.

4. PHASE IV

Phase IV studies are undertaken during the drug registration process or following approval. Overall, Phase IV studies are designed to increase understanding of the overall treatment profile in the target populations. These studies may not include all of the controls used in Phase III trials, but comparator agents and special population groups are more likely to be included in trial designs in this phase. One rationale for this phase is “post marketing surveillance” studies designed to provide long-term tracking of patients on active drug in order to expand the safety database.

5. DRUG INTERACTION STUDIES

Women are likely to be receiving drug therapy, or to be taking nutritional supplements, that interact with the novel agent in some way. The most common examples are hormonal agents in the form of oral contraceptives or hormone replacement, antidepressants, or allergy medications. Key drug interactions should be examined and fall into two major categories: pharmacokinetic and pharmacodynamic interactions.

Pharmacokinetic drug interaction studies are designed to evaluate acute effects of the new agent on the plasma levels of other concomitantly administered drugs (e.g., hormones, anticholesterolemic). If the novel agent is known to be an inducer or inhibitor of cytochrome-dependent liver metabolizing systems, specific drug interaction studies may be required.

Pharmacodynamic interaction studies are particularly relevant to investigate the potential of a novel agent to impact positively or negatively on the efficacy of ongoing medications taken to control serious conditions such as hypertension, hyperlipidemia or diabetes. Alterations in blood pressure in a patient with controlled hypertension or endocrine control in a diabetic patient would be undesirable and should be evaluated during Phase I or II studies.

• SUMMARY POINTS:

The process of new drug or device development is categorized into four phases. Each phase is concerned with safety, though I-III are the most rigorously attentive to this issue, and efficacy in Phase II and III. Phase I studies are usually performed in healthy volunteers to evaluate pharmacokinetic properties and tolerability of different doses of new drugs. Phase II studies provide initial efficacy and dose ranging information. Phase III studies are large-scale, prospective studies of efficacy and safety. Phase IV studies are post-approval or special population studies.

Crossover designs are often employed in Phase II studies with the advantages of controlling for subject variability and increased statistical power. Parallel or combination parallel-crossover designs are preferred in Phase III or IV studies. Phase III studies should always be double-blinded and placebo controlled with careful assessment at baseline functioning prior to randomization. The minimum duration of treatment is usually 12-16 weeks.

Drug interaction studies are important in evaluating possible pharmacokinetic and pharmacodynamic interactions between FSD agent and other drugs used in the treatment of common comorbidities (hyperlipidemia, hypertension, depression) or hormonal regulation (menstrual cycle, menopause).
III. STUDY POPULATIONS

Clinical trials require precise definitions in the inclusion and exclusion criteria of the types of patients who are eligible for the study. Three general principles guide the definition of study populations:

1) The study population should represent the overall patient population for whom the treatment under investigation is intended,

2) The disorder under investigation must be well characterized and well defined so that unambiguous inclusion and exclusion criteria can be used, and

3) A logical and reasonable balance must be struck between the safety of the enrolled patients and the breadth of the exclusion criteria.

Psychosocial factors complicate the definition of appropriate populations for the study of pharmacological treatments for female sexual dysfunction. Female subjective sexual experience is mediated to a certain extent by expectations, which are the product of prevailing societal values, familial values, and partner expectations. Societal expectations concerning female sexuality have undergone rapid change particularly in Western cultures in the twentieth century. Thus the definition of what constitutes a disorder may vary from one cultural subgroup to another.

A variety of different factors render the search for biological therapies of female sexual disorders more difficult. The scientific knowledge base concerning female sexual disorders lags behind that of male sexual disorders. This greatly complicates identification of biological contributors to female sexual disorders. Also, the search for treatments of female sexual dysfunctions is taking place prior to basic research concerning the neurophysiological and psychological basis for individual differences in female sexual responsivity. The diagnostic system for female sexual disorders was developed for the diagnosis of psychiatric disorders. This system has been adopted and slightly modified for the classification of disorders of biologic, mixed etiologies, or more commonly unknown etiologies and is currently under further scrutiny and review. It is unclear whether this is the appropriate approach.

Research to date has found considerable overlap between disorders of the various levels of female sexual response (e.g. women diagnosed with libido problems also frequently have arousal disorders), which complicates study of compounds targeting any one aspect of the female sexual response cycle. Whether this represents a genuine overlap between different disorders or imperfection of the current nosological system is unclear.

In view of the current state of knowledge, certain general recommendations can be made concerning research populations. It is critical that the population being studied be precisely defined, preferably by operationalized criteria with clear specification of duration of problem and frequency of problem. As numerous population surveys have indicated strong relations between psychosocial stressors, marital discord, and dysphoric mood, it is critical that these variables be assessed as they may obscure the effect of any biological intervention. Because of the overlap between female sexual disorders, trials of any specific disorder should include measures of other sexual disorders as it is possible that a given compound may be effective in only small subsets of a specified patient group. It is recommended that one disorder group be selected as the target population. One should attempt to study patients meeting diagnostic criteria for one disorder and not others if possible. For example, one might attempt to study women meeting criteria for hypoactive sexual desire disorder who do not meet criteria for sexual arousal disorder or orgasmic disorder. This complicates recruitment but is likely to produce more meaningful data. If this proves impossible, an alternative strategy would be to study women meeting diagnostic criteria for one sexual disorder who have subsyndromal levels of another sexual disorder. For the data to be meaningful, a clear specification of the population studied is necessary in order to ascertain if the findings are replicable. This requires that the criteria for the target disorder be operationalized as well as the criteria for non-target disorders or that the degree of impairment be quantifiable. As the literature concerning the relationship between physiological and subjective aspects of sexual arousal indicates that measures of these dimensions are often minimally related, it is suggested that both physiological and subjective measures of arousal be utilized. As mentioned above, there appears to be considerable co-morbidity among female sexual disorders, thus, it is imperative that subjects are assessed on all aspects of sexual function. To maximize the likelihood of finding a drug effect, the ideal patient should have an idiopathic disorder which is not secondary to a known medical or psychiatric etiology unless the
investigation concerns the treatment of a disorder which is secondary to pharmacotherapy (i.e. secondary to antidepressant or anti-psychotic drug therapy) or hormonal therapy (i.e. secondary to hormone replacement therapy or oral contraceptive use). The problem should also not be etiologically related to relationship discord as it is unlikely that any pharmacological preparation will reverse sexual dysfunction secondary to relationship discord. Another variable which should be considered is whether the sexual partner has a sexual problem [11].

Limiting research to women with acquired disorders is usually preferred in Phase II and III studies. The rationale for this is that women with acquired disorders have demonstrated the ability to respond sexually in the past. A common assumption among clinical investigators is that societal and cultural prohibitions are unlikely to be etiological factors if the woman was able to be sexually responsive at an earlier time in her life. This may not necessarily be true given the level of sexual trauma that can happen to adult women. Another suggestion is that the disorder be of moderate severity and of a medium duration. It may be extremely difficult to demonstrate efficacy in long standing severe problems. Conversely, patients with extremely mild problems should be avoided as there is minimal room for improvement. This may make it difficult to demonstrate a treatment effect. When feasible, it is preferable to select a group with a similar hormonal status, e.g. pre-menopausal, postmenopausal with hormone replacement, postmenopausal without hormone replacement.

Hormonal status remains a difficult issue since even exclusion and inclusion criteria vary across sites and lab assays. Related variables that need to be considered for patient selection include whether the patient had a natural or surgical menopause, years post-menopause, whether she is on hormone replacement, whether the hormone replacement is oral or transdermal, whether it is estrogen or estrogen plus testosterone. If oral contraception is used, the type of oral contraception should be listed.

Certain clinical populations may be especially suited for the study of hormonal interventions. For example, women who are post-oophorectomy may be excellent candidates in which to demonstrate the effects of testosterone or estrogen replacement therapy. An effect of testosterone on sexual responsivity may be much more straightforward to demonstrate in a population with clear hypogonadal androgen levels than in a population with androgen levels within the normal range. The safety issues (of potentially high levels of testosterone or estrogen) involved may also be easier in the hormone “replacement” model.

Other essential variables to measure include age, partner function and symptoms of depression and anxiety. Clearly, baseline function prior to the intervention needs to be carefully documented. It is recommended that the use of retrospective recall be avoided or used for brief time periods such as the past week [12]. Some investigators have utilized criterion levels of serum estradiol, serum hormone binding globulin (SHBG) and/or free testosterone as entry criteria [13]. It is unclear how advisable this is given the controversy about what constitutes threshold values of these compounds for normal sexual function. To build the database on hormonal levels as well as to increase the clarity of the characterization of the sample, it is probably advisable to include basic hormonal values (estradiol, total testosterone, SHBG, and perhaps DHEAs) as descriptive information in most studies, particularly those of post-menopausal women.

**DEFINING THE DISORDER OF THE PATIENT POPULATION**

**a) Inclusion criteria**

Phase II and III studies have included broad age ranges. In view of the still forming sexuality of adolescent women in western cultures, it may be wise to keep the lower age limit to 21. For Phase III studies, a stable monogamous relationship with a willing and informed partner is advisable. Increasingly, particularly with new privacy regulations enacted in the United States, the formal agreement, via informed consent, of the partner is becoming essential. The patient subject must identify the specific disorder and register personal distress about its effect on her. The duration of the problem can vary, excluding for the Phase II and III trials lifetime disorders, but should be relatively consistent for the past three months. The degree of severity may vary, depending on the agent being introduced. As yet there is no single way to assure a consistent measure of severity, though some have used clinical interview ratings combined with scored on the Female Sexual Function Inventory (FSFI) [14] or other scales. The difficulty with a cutoff score on the available scales is that there is not much evidence that this method alone will adequately capture a diagnostic group. At this time, the use of a sexual functioning scale should augment decisions about diagnosis but not be used without documented specific screening questions by interview.
b) Exclusion Criteria
Exclusion criteria are used to strictly define the study population and to guard against including patients who are at inherent high risk from study participation. Whereas erectile dysfunction, and to a lesser extent premature ejaculation, have contributed to clear exclusion criteria for men, the picture is less clearly defined for women.

IV. OUTCOME ASSESSMENTS
The outcome of clinical trials in treating women’s sexual dysfunctions should be assessed only by validated instruments. Historically, studies of women’s sexual dysfunctions have suffered from the following problems, which may have an impact on the validity of the results [12, 15].

MEASUREMENT ISSUES:
1. Outcomes are assessed by verbal interactions with the patient and not by a standardized, written questionnaire.
2. Sexual status and quality of life questionnaires are not used.
3. Partner information on sexual interactions is infrequently used.
4. Although many scales have been translated into a variety of languages, scales have not been validated with different racial/ethnic groups in the United States.
5. Age is not taken into account for menstrual validation and age-based norms are rarely provided.

DIAGNOSIS ISSUES:
1. Multiple sexual dysfunctions (e.g., hypoactive sexual desire, sexual arousal disorder, orgasmic disorder) are grouped into a single category, female sexual dysfunction (FSD), as if they were homogeneous, of common origin, and equally responsive to the same treatment.
2. There is lack of careful differential diagnosis, or missed accounting, for comorbidity of sexual disorders.

DESIGN ISSUES:
1. Follow-up periods are of short or indeterminate length.
2. Pre-treatment and post-treatment clinical status is poorly defined.

3. When outcomes are assessed by an interviewer, the interviewer is not blind to treatment condition.
4. Women of different hormonal statuses (e.g., premenopausal, post-menopausal, taking hormonal contraception) have been grouped into a single category.
5. Placebo controls are omitted.
6. The lowest effective does is often not clearly demonstrated.
7. Treatment effects after stopping active treatment are usually not studied.

For the effectiveness of a treatment to be measured and compared to other treatments, both pre-treatment and post-treatment assessments must be standardized.

Response variables are the outcomes or endpoints measured during the course of a clinical trial. Response variables should be few in number and should be identified before the clinical trial begins. When multiple response variables are used, statistical methods, such as multivariate techniques or Bonferroni corrections, should be used to correct for the number of statistical tests [16, 17]. Measures used in clinical trials of treatment for women’s sexual dysfunctions include physiological measures, patient self-report questionnaires or diary reports of sexual function, sexual distress, partner assessments, and measures of quality of life. Each of these measures has certain advantages and disadvantages compared with the others.

1. PHYSIOLOGIC MEASURES
Purported organic factors that affect sexual function include aging, menopause, medical conditions, medications, and neurological deficits [18-21]. Evaluation of female sexual response mechanisms is technically challenging and lacks standardized techniques. Many trials to date lack physiological, objective end points that directly correlate to subjective complaints. In this section we focus on current literature pertaining to clinical outcome measurements used in diagnosing organic causes of women’s SD. Specifically, we review data that supports the assessment of vasculogenic, neurologic and endocrinologic factors in outcome measurement. Physiological measures of sexuality in clinical laboratory settings are currently seen as insufficient endpoints by the FDA.

a) Vasculogenic Female Sexual Dysfunction
During female sexual arousal, afferent sensory
impulses activate the central nervous system and cause smooth muscle relaxation in the clitoris and vagina, as well as increased genital blood flow. These physiological sequences result in vaginal and clitoral lengthening and widening, vaginal wall engorgement and the production of vaginal lubrication from transudate [22]. Several techniques for measuring vascular physiological outcomes in the assessment of female sexual dysfunction have been studied. They include: vaginal plethysmography, Doppler ultrasonography, laser Doppler velocimetry, vaginal pH measurements, vaginal compliance measurements, vaginal oxygen tension measurements, magnetic resonance imaging (MRI), postmortem histological evaluation of urogenital tissues. Each of these methods has advantages and disadvantages.

Several human trials have attempted to quantify hemodynamic changes associated with female sexual arousal. To date, photoplethysmography has been one of the most frequently employed methods for this purpose. Sincathak and Geer were the first to introduce vaginal photoplethysmography to measure vaginal vasocongestion [23]. A tampon-shaped probe containing an incandescent light source and a photo-cell was placed into the vagina. The light source and photo cell were later modified by Hoon et al. to contain a more efficient infrared light emitting diode (LED) and phototransistor, in order to prevent artifact associated with blood oxygenation, hysteresis and light history effect (24). The light source illuminates the tissues, while the transistor responds to the light that is scattered back from the vaginal wall. The amount of light backscattered is dependent on the volume of blood present in the vaginal wall capillaries. Vaginal pulse amplitudes (VPA) are recorded using the alternating current (AC) signal and detect minute blood volume changes in the vaginal mucosa. Vaginal blood volumes (VBV) are recorded with the direct current (DC) signal and are capable of measuring changes in blood volume that are occurring slowly, representing the pooling of blood in the vaginal tissue [25].

Early studies using vaginal plethysmography focused on vascular responses to erotic stimuli during arousal versus basal states [26-31]. These studies recruited female volunteers and evaluated vasocongestive responses using VPA in combination with VBV [26-30], VBV alone [24] or VPA alone [31]. The five studies evaluating both VPA and VBV all noted increased vascular responses to erotic stimuli compared to baseline, dysphoric and/or neutral stimuli. Additionally, data from the five studies that included both VBV and VPA measurements reported that VPA is a more sensitive and reliable measurement in assessing blood volumes during sexual arousal.

Following this discovery, a later study evaluated the influence of erotic stimuli on the VPA response [31]. They noted a significant difference in the dynamic flow in women exposed to erotic stimuli compared to baseline. Similarly, Hoon et al. measured VBV alone and found an increased response to erotic stimulus compared to dysphoric or neutral stimuli [24]. However, these studies have been criticized based on several observations [32]. Two prior studies reported on the correlation between pulse amplitude and blood volume with conflicting results: Zingheim et al. reported no correlation between these variables while Heiman found significant correlations in normal women [33, 34]. A poor understanding of the mechanisms involved in vasocongestion during sexual arousal also complicates conclusions drawn on the findings from only one measurement. Although these findings appear to strengthen the argument for using both VBV and VPA as physiological outcome assessment measures in clinical trials, until the role of static and dynamic flow are better delineated, the repeated reports of lack of VBV stability and reliability do not support its use whereas VPA appears to have reasonable value in the appropriate designs. The concomitant use of subjective report of sexual response during VSS studies is essential.

Despite the promising future for photoplethysmography, these studies have several limitations. Firstly, the study groups were small samples of predominantly young women (age range 19-31). Additionally, studies rarely found a significant correlation between subjective sexual reports and objective vascular findings [33]. Lastly, no validated techniques were used to define female sexual arousal disorder in these subjects.

A limited number of studies have unveiled conflicting results for the use of vaginal plethysmography to compare sexually functional and dysfunctional women (Table 2-A). Wincze et al. evaluated 12 women to determine how asymptomatic women differ from symptomatic women in their physiological responsiveness during and shortly after an erotic stimulus [35]. Vaginal blood volume following a 7-minute erotic video was measured in six women who had previously sought sexual therapy for preorgasmic and orgasmic dysfunction and compared to results from six sexually functional controls. Study
Table 2-A. Photoplethysmography Studies with Clinical Samples

<table>
<thead>
<tr>
<th>Author</th>
<th>Method</th>
<th>Study Groups</th>
<th>Findings</th>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wincze et al., 1979 [35]</td>
<td>Compare responses to erotic video</td>
<td>8 normal sexual function</td>
<td>↑ VBV change scores in normal vs. clinical</td>
<td>Strengths</td>
<td>Validated questionnaire for arousal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 sexual dysfunction</td>
<td>Lower ratings of satisfaction in clinical</td>
<td></td>
<td>Small sample size</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No difference in arousal between the two study groups</td>
<td></td>
<td>Dysfunction diagnosis not standardized</td>
</tr>
<tr>
<td>Morokoff &amp; Heiman, 1980</td>
<td>Compare functional responses to erotic</td>
<td>11 normal sexual function, matched</td>
<td>VPA not different between groups for any stimulus</td>
<td>Strengths</td>
<td>Dysfunction diagnosis standardized</td>
</tr>
<tr>
<td></td>
<td>videotapes, audiotapes and fantasy</td>
<td>for age and years married</td>
<td>Subjective arousal ↓ in clinical</td>
<td></td>
<td>Validated questionnaire for arousal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11 low arousal and anorgasmia</td>
<td>Correlation between VPA and subjective arousal for both groups</td>
<td></td>
<td>Small sample size</td>
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<td>Heterogeneous sexual complaints</td>
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<td>VBV not measured</td>
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Table 2A. “Photoplethysmography Studies with Clinical Samples”

<table>
<thead>
<tr>
<th>Author</th>
<th>Objective</th>
<th>Study Groups</th>
<th>Findings</th>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
</table>
| Palace & Gorzaika, 1980 [36] | Compare responses to anxiety-eliciting and erotic video                    | 16 normal sexual function                        | • Anxiety ↑ genital arousal both groups VBV in clinical compared to control for both stimuli  
• Subjective arousal not different between groups  
• No correlation between VBV and subjective arousal for either group                                                                 | Dysfunction diagnosis standardized  
• ↓ questions to evaluate arousal                                                                                                           | Small sample size  
• Heterogeneous sexual complaints  
• VPA not measured                                                                                                                         |
| Palace & Gorzaika, 1992 [38] | Responses to erotic video  
• To identify flaws in previous study designs                                  | 16 normal sexual function, matched for age and years married  
• 16 sexual dysfunction                                                                                                                   | • ↓ VBV dysfunctional vs. functional for all stimuli  
• Subjective arousal ↓ in clinical  
• Correlation between VBV and subjective arousal in functional only  
• Standardized technique ↓ inconsistencies                                                                                               | Dysfunction diagnosis standardized  
• Validated questionnaire for arousal                                                                                                       | Small sample size  
• Heterogeneous sexual complaints  
• VPA not measured                                                                                                                         |
| Meston & Gorzaika, 1996 [41] | Responses to erotic video                                                  | 12 normal sexual function                        | • ↑ VBV and VPA only with SNS activation                                                                                                     | Dysfunction diagnosis standardized  
• Validated questionnaire for arousal                                                                                                       | Small sample size                                                                                                                  |
patients had significantly lower vaginal blood volume change scores when compared to controls. Similar to reports from other investigators, they found no significant differences in subjective accounts of sexual arousal between the two groups. The clinical group had lower ratings of sexual satisfaction rated on 7-point Likert scale.

Palace and Gorzalka found similar results in a study comparing the responses of sixteen women seeking treatment for various sexual dysfunctions and 16 non-clinical controls [36]. Sexual dysfunction was confirmed using the was The Sexual Functioning Index (SFI) and the Global Sexual Satisfaction Index (GSSI) of the Derogatis Sexual Functioning Inventory (DSFI) [39]. The goal of this investigation was to examine the effects of anxiety eliciting stimuli on sexual arousal and to compare functional and dysfunctional women’s physiological and subjective responses to erotic stimuli. They presented these women with two videotape conditions:

1) a neutral pre-exposure stimulus paired with a three-minute erotic stimulus; and

2) a 3-minute anxiety evoking stimulus paired with a three-minute erotic stimulus. VBV measurements were recorded using vaginal plethysmography and subjective data was obtained using a 33-item, self-report questionnaire, rated on a seven-point Likert scale. Sexual arousal was defined as deviations from baseline and subsequent stimuli were only applied after VBV readings returned to baseline. Additionally, data was collected at 4-second intervals and at the two 10-second time blocks with the greatest deviation from baseline as described by Wincze et al, and Morokoff and Heiman who reported on the use of plethysmography to evaluate women with sexual dysfunctions [35-37]. Physiological assessments were made using a vaginal photoplethysmograph [40]. Responses were recorded as deviations from baseline and subsequent stimuli were only applied after VBV readings returned to baseline. Additionally, data was collected at 4-second intervals and at the two 10-second time blocks with the greatest deviation from baseline as described by Wincze et al and Palace et al., vaginal plethysmography was performed using the AC current and recorded as VPA. No significant differences were found in physiological responses between these groups, despite a greater variety of stimuli which included a nine-minute erotic videotape, a six-minute erotic audiotape and self-generated sexual fantasy. Although the dysfunctional group rated their sexual arousal significantly lower than controls, no significant differences were found between these ratings and VPA during erotic stimulation. This study was unique in its use of a valid, reliable tool to measure sexual response.

In response to the contradictory findings of the above studies, Palace and Gorzalka attempted to provide data that could explain the inconsistencies [35-38]. They postulated that the disparities resulted from differences in study design and data collection, conservative measurements of subjective outcomes and women’s inhibitions, and sought to reconcile the discrepancies. Using separate newspaper and posted advertisements directed toward sexually functional and dysfunctional women, 32 heterosexual women aged 22-41, devoid of psychopathology and medical or organic conditions that may affect sexual function, were recruited to participate.

Patients were stratified based on their subjective complaints with a resultant 16 women with heterogenous complaints constituting the dysfunctional group and an additional 16 women who reported no history of treatment for sexual dysfunction and satisfaction with their sexual relationship serving as controls. Validated methods for diagnosing sexual dysfunction were employed using The Sexual Functioning Index (SFI) and the Global Sexual Satisfaction Index (GSSI) of the Derogatis Sexual Functioning Inventory (DSFI) [39]. Patients who met criteria for dysfunctional classification were matched by age and sexual experience to functional controls.

Three 3-minute erotic videotapes were prepared by editing original films obtained from previous authors who reported on the use of plethysmography to evaluate women with sexual dysfunctions [35-37]. Physiological assessments were made using a vaginal photoplethysmograph [40]. Responses were recorded as deviations from baseline and subsequent stimuli were only applied after VBV readings returned to baseline. Additionally, data was collected at 4-second intervals and at the two 10-second time blocks with the greatest deviation from baseline as described by Wincze et al, and Morokoff and Heiman to evaluate for methodological biases that may have contributed to contradictory results in those studies. Sexual arousal responses were obtained using a 10-item self-report rating scale that was noted to be a sensitive indicator of emotional reactions to erotic stimuli [37]. Dysfunctional women scored significantly lower on the SFI and GSSI than the functional group. Dysfunctional women also reported less sexual satisfaction, were significantly less interested
in sexual activity, and were less likely to achieve orgasm. In this group 44% reported low sexual desire and 94% reported infrequent orgasm. These findings validated the classification of dysfunctional in this group.

Functional subjects exhibited significant increases in VBV to all three stimuli, while the dysfunctional group experienced no significant VBV changes following any of the same stimulus conditions. Overall, dysfunctional women repeatedly demonstrated significantly less VBV than functional women exposed to the same stimuli. Positive correlations between physiological genital arousal and perception of sexual arousal were only significant for the functional women.

This investigation helped to clarify the contradictory findings of the previous studies comparing functional and dysfunctional women [35-37]. Specifically, they found that by standardizing the physiological and subjective methods of data collection, assessing the arousal eliciting capability of the stimuli and reducing social demand, they were able to explain the discordant findings in the literature. They were also able to demonstrate different patterns of sexual responses in functional and dysfunctional women.

This study is limited, however, in that VPA measurements which have been found to be more sensitive in the majority of studies [26-30], were not recorded in conjunction with VBV. In addition, the absent correlation between physiological and subjective findings in the clinical group may be confounded by their poorer understanding of the anatomy, physiology, and psychology of sexual behavior, more conservative sexual attitudes, negative assessments of physical appearance, and negative affects that they reported at baseline. All of the aforementioned studies evaluating sexual dysfunctions and vaginal blood flow responses are limited to comparisons of women with heterogeneous dysfunctions.

Meston and Gorzalka used vaginal plethysmography to measure sexual responsiveness in groups of women classified as functional, low desire or anorgasmic to correct for possible biases secondary to differences in etiology of dysfunction [41]. Sexual function was determined using two questionnaires, the Derogatis Sexual Functioning Inventory and the Orgasmic Functioning questionnaire [39-43]. Using this modality, they measured the VPA and VBV responses after activation of the sympathetic nervous system, induced via acute exercise, followed by an erotic stimulus (video). Responses were compared to non-exercise conditions prior to exposure to the erotic stimulus. Results showed that only in the presence of increased autonomic arousal did physiological sexual responses between orgasmic and anorgasmic women differ. These findings concur with previous studies of Morokoff and Heiman, who also found no differences in VPA measurements to an erotic film between controls and women with low sexual arousal and anorgasmia [37].

These data suggests that the measurement of VBV and VPA responses to erotic stimuli in conjunction with conditions of increased autonomic arousal may potentially provide a useful means of evaluating anorgasmic women. This lends more argument for simultaneous measurements of both VPA and VBV in Phase I and II clinical trials, until a better understanding of their independent relationships are regarding the various sexual dysfunctions. However the bulk of the evidence remains supportive of measuring VPA over VBV and if one measure is selected, it should be VPA.

Comparison between studies using vaginal plethysmography is difficult due to the small size of the studies, the variations in study design, lack of standardized definitions the of sexual dysfunctions, differences in erotic stimuli (video, audio, text) and differences in signals used for analysis (VPA or VBV). These studies are also hampered in that no method for quantifying blood flow has been established, and this necessitates within group subject designs. Additionally, all of the aforementioned studies evaluating sexual dysfunctions and vaginal blood flow responses are limited in that they compared women with heterogeneous dysfunctions and the groups did not evaluate older women, post-menopausal or homosexual women. Finally, the absence of a true baseline and the movement artifact, have all been described as technical drawbacks inherent to this method [40]—that are necessary to take into account in designing studies. Still, the current literature suggests that VPP has strong potential and value as one outcome measure for evaluating sexual dysfunctions in women.

Pulse waved Doppler ultrasonography is another technique for measuring blood flow changes in the vaginal and clitoral arteries [44]. Peak systolic velocities (PSV) and end diastolic velocity (EDV) blood flow can be measured. Similar to vaginal pulse amplitude and vaginal blood flow measurements obtained with photoplethysmography, PSV and EDV represent dynamic and static blood flow changes that occur with each heartbeat. This modality provides
continuous, real-time imaging for evaluating female pelvic anatomy and vaginal blood velocity, measured in centimeters per second (cm/s). This technology is currently under investigation for validity and standardization and is a promising technique in the evaluation of vaginal blood flow changes.

In a cohort study that evaluated 48 women with various sexual complaints, Berman et al. used duplex Doppler ultrasound to measure changes in blood velocity after combined stimulation with an erotic video and a vibrator [44]. Following 15 minutes of stimulation, they documented significant increases in the blood velocity to the vagina, urethra, clitoris, and labia after sexual arousal in all patients. Older women, defined as women between the ages of 55 and 67 years, had significantly lower baseline blood velocities (PSV and EDV) than younger women; however, this significance was lost following erotic stimulation. Although a higher baseline and post-stimulation blood velocities were reported in postmenopausal women taking hormone replacement therapy compared to untreated postmenopausal women, these differences were not significant. Conclusions from this data should be made with caution, since age cut-offs were made arbitrarily, normative data has not been established with this model, heterogeneous sexual dysfunctions were used and, as with previous studies, results from physiological outcomes and subjective sexual reports did not correlate.

Sarrel et al. reported using laser Doppler velocimetry to evaluate vaginal blood flow in postmenopausal women [45]. A monochromatic light is emitted from a laser Doppler and penetrates epithelial and mucosal surfaces to a depth of 1 mm. The flux of red blood cells is calculated by multiplying the percentage of deflected light by the mean velocity of the erythrocyte movement using a velocimeter and expressed as arbitrary units of output voltage. In one review article, Sarrel reported an increase in vulvar blood flow of almost 50% following estradiol treatment and decreases in flow following 8-10 days of progestin therapy. No additional information was provided regarding the study design or population evaluated. His second report from a clinical trial for which this outcome measure was used, indicated that vaginal blood flow was significantly increased following four weeks of treatment with conjugated equine estrogen plus methyltestosterone when compared to estrogen therapy alone [46]. These findings correlated with subjective reports on the menopause symptom and the sexual activity scales which showed an improvement in sexual desire, fantasy and response and decreased dyspareunia following androgen therapy. Doppler laser velocimetry in the assessment of vasocongestion during sexual arousal is not well documented in the literature. While it is advantageous in that it controls the depth of penetration and allows for vascular evaluation at multiple anatomical sites, its utility as an outcome measure of clinical trials is to date limited (Table 2b).

Determination of oxygen tension (pO2) at the vaginal surface during sexual stimulation has also been described as indirect measurements of vaginal blood flow. In the first report by Wagner et al., seven healthy females ages 24-33 years underwent placement of an electrode secured to a ring shaped suction device [47]. The electrode was covered by a oxygen-permeable, hydrophobic membrane and contained a platinum cathode and a silver anode and placed in the posterior vaginal wall 4-5 cm from the introitus and a little to the left. Current was generated by a polarizing voltage placed at the cathode that reduced oxygen. A special oxygen monitor (Radiometer TCM 1) was used to display pO2 values.

Recently, in another small pilot study that included 12 healthy volunteers, aged 20-25 yrs with normal sexual function, Sommner et al. re-described this simple technique [48]. They introduced a modified Clark oxygen electrode into the vagina, four centimeters from the introitus, on the right lateral wall and a second was placed on the right labia minor. In both studies, basal pO2 values were low; however, a smaller mean and range were noted in Sommner’s study as compared to Wagner’s original report (2-6 mmHg, mean 3.8±0.9 vs. 0-35 mmHg, mean of 9.3±10.7). These authors obtained measurements at baseline, during self-stimulation and after orgasm. Results form both studies showed an increase in transcutaneous pO2 immediately after stimulation began and continued to increase until peak levels were noted at orgasm. Following orgasm, a decrease in pO2 occurred gradually in the vagina, with return to baseline 10-30 minutes after climax. Sommner’s study also revealed that a more rapid return to baseline was noted in the labia minor. Additionally, simultaneous heart rate and blood pressure were obtained in their study and positively correlated with pO2 findings.

Sommner et al. concluded that increased oxygen tension was likely secondary to blood flow since other studies have shown an association between transcutaneous pO2 [49, 50]. They reported that the reliabi-
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<tr>
<th>Author</th>
<th>Method</th>
<th>Study Groups</th>
<th>Findings</th>
<th>Strengths</th>
<th>Weaknesses</th>
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<tbody>
<tr>
<td>Berman et al, 1999 [44]</td>
<td>Doppler Duplex</td>
<td>48 sexual dysfunctions</td>
<td>↑ blood velocity after sexual arousal</td>
<td>No control group used</td>
<td>No normative data</td>
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<td>NS ↑ in baseline and post-stimulation blood velocities in PMP women with and without HRT</td>
<td>Heterogenous sexual complaints</td>
<td>No validated technique to confirm dysfunction</td>
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<td>No correlation between physiological and subjective findings</td>
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<td>Sarrel et al, 1990 [45]</td>
<td>Laser Doppler</td>
<td>20 postmenopausal women</td>
<td>↑ vaginal blood flow after estrogen + methyltestosterone compared to estrogen alone</td>
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<td>Only published study on technique</td>
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<tr>
<td>Wagner et al, 1978 [47]</td>
<td>Oxygen Tension</td>
<td>7 healthy women</td>
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<td>Small sample size</td>
<td>No assessments of patients with SD</td>
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<td>Women with sexual dysfunctions not studied</td>
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Table 2-B. Other Studies Evaluating Vasculogenic Methods for Diagnosing Women’s Sexual Dysfunctions

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<th>Study Groups</th>
<th>Findings</th>
<th>Strengths</th>
<th>Weaknesses</th>
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<tr>
<td>Sommer et al, 2001 [48]</td>
<td>Oxygen Tension</td>
<td>12 normal sexual function</td>
<td>♦ transcutaneous pO2 immediately after stimulation until peak levels noted at orgasm</td>
<td></td>
<td>♦ Consistent with previous data deactivated ♦ Small sample size ♦ No assessments of patients with SD ♦ Indirect measures of pO2 ♦ No validated technique to confirm normal sexual function</td>
</tr>
<tr>
<td>Wagner et al, 1984 [52]</td>
<td>Vaginal pH</td>
<td>10 normal sexual function</td>
<td>♦ Unreliable tests with varying results among patients after stimulation</td>
<td></td>
<td>♦ Dysfunction diagnosis standardized ♦ Validated questionnaire for arousal</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>♦ Small sample size ♦ No assessments of patients with SD ♦ No validated technique to confirm normal sexual function ♦ Women with sexual dysfunctions not studied</td>
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<tr>
<td>Berman et al, 1999 [155]</td>
<td>Vaginal pH</td>
<td>48 sexual dysfunctions</td>
<td>Vaginal pH increases after sexual stimulation&lt;br&gt;Lower pH in PMP women with HRT than without</td>
<td>Weaknesses&lt;br&gt;- No controls&lt;br&gt;- Heterogeneous sexual complaints&lt;br&gt;- No validated technique to confirm normal dysfunction&lt;br&gt;- Conflicts with previous data</td>
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<td>Berman et al, 1999 [155]</td>
<td>Vaginal pressure-volume changes</td>
<td>48 sexual dysfunctions</td>
<td>Sexual stimulation increases compliance&lt;br&gt;Older women have lower compliance than younger women&lt;br&gt;PMP women with HRT have higher than those without</td>
<td>Weaknesses&lt;br&gt;- No controls&lt;br&gt;- Heterogeneous sexual complaints&lt;br&gt;- No validated technique to confirm normal dysfunction&lt;br&gt;- No other published studies on technique</td>
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<tr>
<td>Deliganis et al, 2002 [55]</td>
<td>Dynamic MRI</td>
<td>12 healthy women</td>
<td>Changes † in 7/10 subjects in clitoral glans and 8/10 in clitoral body after erotic stimulation&lt;br&gt;Changes not seen in the two control subjects&lt;br&gt;No differences were found between premenopausal and postmenopausal women</td>
<td>Strengths&lt;br&gt;- Subjective and objective findings correlate</td>
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<tr>
<td>Maravilla et al, 2003 [156]</td>
<td>Dynamic MRI</td>
<td>9 healthy women</td>
<td>Enhancement of genital structures after erotic video&lt;br&gt;Anatomic clitoral volume increased from baseline to arousal&lt;br&gt;Good intra-subject reliability&lt;br&gt;Clitoral volume analysis is more reliable clitoral analysis than signal intensity&lt;br&gt;Clitoral volume change † for premenopausal than postmenopausal women</td>
<td>Strengths&lt;br&gt;- Subjective and objective findings correlate</td>
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lity, reproducibility, ease of handling and the ability to collect data without a physician present in the room are factors that render this modality more advantageous than Doppler ultrasonography. Weaknesses include the extrapolation of results from indirect measurements of arterial pO2, the small number of subjects, the omission of validated techniques to confirm normal sexual function. In addition, they do not provide an explanation of why the labia minor and the lateral and posterior vaginal wall were chosen as sites of measuring pO2, given the later comment that previous studies showed inconsistent results based on the area of electrode placement. Although the differences in basal pO2 values may be the result of the newer techniques used, these differences should be further investigated to avoid the introduction of procedural biases. Future studies that include larger subject numbers, direct comparisons with findings from Doppler ultrasonography and a validated assessment of patients with sexual dysfunctions may be helpful in elucidating the usefulness of this modality in women’s sexuality. To date it is not appropriate for clinical trials due to the lack of adequately controlled studies on women with and without sexual dysfunction.

Masters was the first to report on the acidity of the vagina during sexual stimulation [51]. Sexual stimulation causes vasocongestion, which increases the hydrostatic pressure within the capillary walls of the vagina, causing a transudation from the vaginal epithelial cells. Normal vaginal pH ranges from 3.8-4.2, however, the vaginal pH can increase to 6.5-7.8 as a result of sexual arousal [44, 51]. Although vaginal pH testing is simple, results may be technically limited. Wagner et al. recruited 10 women aged 19-30 and measured vaginal pH at six sites of the vagina using a glass pH electrode [52]. The patients were instructed to perform clitoral stimulation to orgasm after which, the vaginal pH was re-measured in the 8 patients who were able to induce orgasm. They found that pH testing during sexual arousal is unreliable and showed varying results among individuals; they also found non-significant differences based on the site of measurement.

Berman et al. found consistent pre-stimulation and post-stimulation pH values [44]. Using a 1 cm probe, they found that vaginal pH increases significantly after sexual stimulation and that menopausal women taking hormone replacement therapy had lower pH values than those women who did not take this medication. Although the pre and post-stimulation pH’s were consistent, and relative changes were recorded, the baseline vaginal pH’s were much higher than expected for normal vaginal flora (mean = 5.68 ± 0.96 for all women in the study). Since vaginal pH measurement can be affected by vaginitis and atrophic changes, care must be taken to ensure that the vaginal flora is normal before relying on this test. Given the small number of patients sampled in both studies, the contrasting results obtained and the variety of sexual complaints, this outcome measure is not a currently acceptable measure of sexual function in women.

There is limited data regarding the use of vaginal pressure-volume (compliance) changes in the evaluation of the female sexual response. Sexual stimulation causes vaginal smooth muscle relaxation, resulting in an increased length and diameter of the vagina thereby decreasing pressure and increasing compliance (Compliance = Pressure/Volume) [22]. In the same 48 pre and post-menopausal women who underwent pH measurements and vaginal blood flow evaluations, Berman et al. measured vaginal changes with a compliance balloon [44]. Sexual stimulation resulted in significant increases in compliance compared to baseline. Berman et al. showed this response measuring vaginal changes with a compliance balloon. Sexual stimulation resulted in significant increases in compliance. They demonstrated that older women had lower compliance measurements than younger women and that menopausal women who did not take hormone replacement therapy had higher compliance values than those who were taking hormone therapy. These findings are consistent with data suggesting that aging and menopause with resultant decreases in circulating estrogen levels leads to genital atrophy, vaginal wall smooth muscle fibrosis, and collagen deposition [53]. This was the only study identified that evaluated vaginal compliance. Since it lacked a control group for comparisons, no conclusions can be made about the effects of abnormal sexual function on the results obtained from this measurement.

Another outcome study evaluated postmortem and surgically obtained human clitoral tissue in three different age groups (6months-15yrs, 44-54yrs, and 55-90 yrs) [54]. Results obtained revealed that increasing age is associated with a loss of corporal smooth muscle and replacement with fibrotic connective tissue. They also noted that clitoral smooth muscle content was lower in women with cardiovascular disease-related deaths. They concluded that age and chronic ischemic changes resulting from atherosclerosis, cause permanent changes in genital tis-
in elderly females. Although this study provides some insight into the physiological changes in the female genitalia that occur with age, correlation of these findings with patient symptomatology and pelvic vascular blood flow changes was not performed. Moreover, age grouping was randomly performed with no justification for the stratification methods. Also, the use of combined cadaveric and surgical specimens and the failure to report on time from death or surgery to fixation and staining of the samples, are confounding factors that may have affected the study results. Consequently, extrapolation of this data cannot be used to make conclusions regarding age or vascular blood flow as potential causes of sexual arousal dysfunction and, more importantly, do not make it appropriate for outcome measurement. Other means of investigating smooth muscle functioning might be of interest to pursue.

One of the newer modalities being evaluated for the assessment of female sexual dysfunction is dynamic MRI. Deliganis et al. sought to determine if dynamic MRI with delayed blood pooled contrast, MS-325, can illustrate sexual arousal at the perineum in healthy women in a phase 1 methodology study [55]. MS-325 was chosen over conventional media due to its slower extravasation into the interstitial space and the decreased signal intensity in the extracellular space which allowed for delayed pooling and maintains a higher level of contrast enhancement in the vascular space for a prolonged period. Twelve healthy volunteers were enrolled after undergoing a detailed sexual history about sexual behavior followed by a complete physical exam.

The contrast agent was given intravenously and patients watched a 21-minute videotape while being imaged the entire time. The video consisted of a 21-minute neutral segment, a 15-minute erotic segment, and then a 9-minute neutral segment. Two patients only saw a neutral video and served as controls. Patients answered self-assessment questionnaires at 3 minutes before the neutral portion of the video, just prior to erotic stimulation and immediately after viewing all videos. Two independent radiologists evaluated the results for quality of the results and depiction of the anatomy. Relative regional blood volume (rRBV) was estimated from time-versus-signal intensity curves for the vaginal wall and the clitoris, including the crura, clitoral body and the glans. The total volume was measured by summing all four sites in cubic centimeters at each time point by using a planimetric method. If distinction could not be made between the clitoris and the adjacent tissue, all enhancing tissues were included in the calculation.

Following contrast enhancement, image quality improved and rRBV changes were significantly increased in 7 of the 10 subjects in the glans of the clitoris and 8 of the 10 subjects in the clitoral body following erotic stimulation. Comparatively, these changes were not seen in the two subjects who were shown only neutral material. Overall, the mean rRBV increased in the study group at the glans clitoris (40% ± 10 SEM) and in the clitoral body (24% ± 10 SEM). Comparatively, these changes were -3% ± 5 SEM in the glans clitoris and 3% ± 8 SEM in the clitoral body for controls who had only neutral stimuli. No significant differences were found between premenopausal and postmenopausal women at these same sites. The quantitative measurements of clitoral volume revealed more exaggerated changes between the first neutral segment and the erotic segment, the mean volume change was 118% ± 73 SEM (range 51%- 280%). Again, no differences were found between premenopausal and postmenopausal women. The authors concluded that MR imaging may be a useful diagnostic tool for evaluating vasculogenic female sexual arousal disorder and potentially clinical changes in genital response. Although both measurements showed similar results, clitoral volume measurements may be more precise and reproducible and less susceptible to movement artifact.

Since this method has only been recently described, there are still a number of technical limitations to this model:

1) Gross estimations were made when a true distinction could not be made between the clitoris and adjacent tissue and may have resulted in an overestimation of the clitoral volume in this setting.

2) The 3 variable model, designed to express rRBV as a function of time may cause an underestimation of the true blood volume.

3) Most subjects continued to have contrast enhancement that did not correlate with erotic stimulation.

4) Since rRBV is estimated from averaging small regions of interests (ROI), potential errors may result.

In addition to potential technical errors, conflicting data was found in one control subject and review of images was not strictly blinded. For these reasons, utility of a model that evaluates vascular and anatomic dynamic relationships, has tremendous potential for evaluating sexual dysfunctions in women. Investigation into the true impact of the
women. Investigation into the true impact of the current limitations on study results and a detailed cost analysis should be performed before promoting this model. Currently it is not ready for use in clinical trials as it is limited to one set of investigators, has not fully compared FSD and non-FSD subtypes of women, and is limited to small samples.

b) Neurogenic Sexual Dysfunction Measurement

Female sexual arousal is a vasocongestive and neuromuscular event that is in part controlled by the autonomic nervous system. Originally, this series of events leading up to orgasm was thought to be primarily parasympathetically mediated, however, newer research implicates the sympathetic nervous system as a critical component [22, 41, 56, 57]. The preganglionic parasympathetic fibers that innervate the vagina and clitoris originate in the sacral parasympathetic nucleus in the spinal cord. Parasympathetic information is transmitted to peripheral tissues via the pelvic nerve. The sympathetic nerve fibers originate in the dorsal gray commissure and the intermediolateral column at the thoracolumbar level. Sympathetic responses are conveyed by the hypogastric nerve and the paravertebral chain. Sensory afferent information caused by stimulation of the genitalia is transmitted via the pudendal, hypogastric, pelvic, and vagus nerves to these spinal nuclei. Central control is maintained by descending projections from the cerebral cortex [58].

The sensations of touch, light pressure and vibration are conducted by large, myelinated fibers in peripheral nerves and by the dorsal column of the spinal cord. During genital stimulation, it is believed that recruitment of fibers in this pathway play a central role in the normal female sexual arousal mechanism [59]. The elaborate neurological pathways that include central, sympathetic, parasympathetic and somatic interconnections are paramount in normal female genital tissue functioning. Thus, pathological conditions that cause alterations in these nerve tracts, such as multiple sclerosis, spinal cord injury, herniated discs, lumbosacral plexus disorders or peripheral neuropathies could potentially lead to neurogenic FSD. This area of research has only recently been investigated in both human and animal models using both direct and indirect nerve stimulation methods. Below we will evaluate each of these systems and their role in female sexuality.

Only a few clinical studies to date have investigated sensory deficits as a cause of sexual dysfunctions in women. Most investigators have used the technique of quantitative sensory testing (QST) of the genitalia for this purpose. This modality is most commonly used in the assessment of peripheral neuropathies, however, some researchers have investigated its use for central disorders as well [59]. The most common stimuli that are evaluated using QST are sensations of pressure, vibration, or temperature. Typically, the method of limits is utilized in which a quantified stimulus (vibratory or temperature) is increased by a known amount until it is perceived by the patient. This method has been shown to be a valid, reproducible, descriptor of sensory function, although it has not been widely tested [59, 60].

Vardi et al. were first to use QST to determine normative values for female genital sensation [59]. A prospective evaluation was performed of 89 healthy women volunteers, between the ages of 18-78 years, reporting normal sexual function. Normal sexual function was confirmed using a questionnaire; however, no description of the validity of the questionnaire was available. Sixty-one patients, between the ages of 18 and 80 years were evaluated, however, no other information is provided for this subgroup. Sensory function was assessed measuring warm and cold thermal thresholds and ascending and descending vibratory thresholds on the anterior and posterior vagina and clitoris. They found that thermal measurement of and vibratory thresholds of both the vaginal and clitoral region are clinically feasible, valid and repeatable. They also noted that thermal clitoris and the warm threshold of the anterior vaginal wall sensations are less reliable and that ascending vibration has better repeatability than descending vibration or thermal sensations. Patients were stratified into two groups:

1) age \leq 30 years and

2) age < 50 years. Normograms were calculated for the warm and cold thresholds as well as from the ascending vibratory thresholds. Age dependency was noted for the thresholds of four of the six measurements; Cold thresholds of the clitoris and warm thresholds of the anterior vaginal wall were not affected by age.

Unfortunately, no clinical data is provided for one third of the patients (61/150), the questionnaire used to assess normal sexual function was not described and therefore cannot be assumed to be validated and no comparisons were made on people with sexual dysfunction. These factors limit interpretation of the study.

Romanzi et al. evaluated 37 women with a mean age of 48.7± 13.8 years [61]. Using Semmes-Weinstein
monofilaments applied to the clitoris and bilateral labia, neurological integrity was assessed. Five patients had multiple sclerosis (MS) and were excluded from the analysis comparing neurological sensation in patients with normal sexual function (n=18) and those with sexual dysfunction (n=14). Sexual function was confirmed using a validated questionnaire. A positive correlation was found between reduced vulvar sensitivity and sexual function.

The simple, non-invasive techniques required for QST are ideal for investigative purposes. These early efficacy trials suggest that QST can be used to further elucidate the relationship between peripheral nerve degeneration and sexual function. Larger studies are needed to correlate validated symptomatology and to evaluate for confounding variables. The limited data available to date precludes any generalizations about this outcome measure but it is promising for further study as an assessment of sensory functioning that might be important in women's sexual functioning.

The predominant research on central nervous system defects and women's sexual function has been reported in a series of studies conducted by Sipski et al [62-66]. Based on the theory that neurological impulses initiate the series of vascular changes associated with sexual function, Sipski et al used vaginal plethysmography as an indirect outcome measure of neurological integrity and its relationship to sexual function.

The first study that evaluated physiological outcome measures in patients with upper motor neuron (UMN) spinal cord injuries (SCI) compared 13 tetraplegic patients with injuries at T6 and above to 8 able-bodied controls (ABCs) using vaginal plethysmography in a laboratory based study. Previous assumptions in review articles and a case report, hypothesized that women with complete SCI can maintain reflexive but not psychogenic vasocongestion [66-68]. Based on this assumption, authors attempted to discern this relationship by comparing pure psychogenic responses to combined psychogenic and reflexive reactions between these two groups [62].

Comprehensive and standardized medical and neurological evaluations were performed. Inclusion criteria were normal menstrual history, no prior gynecological or neurological surgeries, absence of psychiatric disorders and medical stability. The mean age was 30 and 36 for patients with SCI and ABCs, respectively. The mean number of months post-injury ranged from 12 to 232 months. A validated spinal cord injury (SCI) sexual function questionnaire was developed specifically for this group and was used for subjective data collection. A 78 minute study protocol was divided as follows: 1) an initial 6 minute baseline period (B1), 12 minutes of audiovisual stimulation (V1), 6 minutes of baseline (B2), 12 minutes of audiovisual stimulation (V2), 6 minutes of baseline (B3), 12 minutes of audiovisual stimulation and manual stimulation (VM1), 6 minutes of baseline (B4), 12 minutes of audiovisual stimulation and manual stimulation (VM2) and 6 final minutes of baseline (B5). Monitoring of vaginal pulse amplitudes (VPA) during erotic video and self-stimulation was recorded intermittently. Clitoral stimulation was interrupted for two 45-second intervals to assess artifact. Verbal inquiry of subjective arousal on a scale of 1-10 was obtained at three-minute intervals throughout the study.

Women with complete SCI did not demonstrate increased vaginal blood flow in response to erotic audiovisual stimulation (pure psychogenic) even though subjective levels of arousal were significant. Conversely, the ABCs demonstrated an increase in both measurements following audiovisual stimulation. Similarly, in patients with SCI there was no change in blood volume following combined audiovisual and manual (psychogenic and reflexive) stimulation compared to audiovisual stimulation alone, whereas the ABCs had a significant increase in VPA. Overall, ABCs had significantly increased blood flow change scores than SCI patients for psychogenic stimulation when compared to baseline. Conversely, no differences were seen in blood flow change scores for psychogenic plus reflexive stimulation when compared to baseline or to psychogenic stimulation alone. Subjective arousal during pure psychogenic stimulation was similar between the two groups. However, with the addition of manual stimulation, the ABCs showed a significant increase in subjective arousal while the SCI patients did not. These findings provide supportive evidence that women with complete UMN SCI’s maintain reflex, but are not capable of psychogenic arousal.

This study assumes that blood flow directly correlates with neurological innervation, and therefore, has inherent flaws. Although stimulation of the pelvic nerve in rats and rabbits and the hypogastric nerves in dogs resulted in genital vasocongestion in the animal models, human studies have not substantiated these findings [69-72]. Another problem with this study is that the authors draw their conclusion
that reflexive arousal remains intact based on between group comparisons without regard for within group results. In this study, there was no difference in vaginal blood flow from audiovisual stimulation when compared to audiovisual plus manual stimulation in patients with SCI. These results conflict with the above findings since the SCI patients would be expected to increase their genital blood flow following manual stimulation if reflexive arousal were intact as proposed.

Although pure psychogenic stimulation was evaluated in the initial physiological study by Sipski et al., isolated reflexive stimulation was not assessed. In a follow up study of 10 patients with complete SCI and 10 ABCs matched by age and educational status, the authors sought to develop a model designed to evaluate reflexive arousal using the Stroop test, a distracting cognitive stimulus, combined with manual genital stimulation [63].

The original protocol was changed to 78 minutes and modified as follows: 6 minutes of baseline (B1), 12 minutes Stroop, 6 minutes of baseline (B2), 12 minutes Stroop with manual stimulation, 6 minutes of baseline (B3), 12 minutes Stroop with manual stimulation, 6 minutes of baseline (B4), 12 minutes masturbation, 6 minutes of baseline (B5). Data was collected using the techniques described above.

Results showed that VPA and subjective arousal were unchanged in patients with SCI when performing a distracting task in conjunction with manual stimulation versus performing a distracting task alone. This argues against the hypothesis that reflexive vasocongestion occurs in this population. The authors propose that these unexpected findings resulted from abnormal hand function that precluded adequate clitoral stimulation. Conversely, both blood flow and subjective arousal increase in ABC patients for the same comparisons suggesting that reflexive responses are active in this group. Higher change scores were also noted for ABC compared to SCI patients.

When masturbation was compared to Stroop plus manual stimulation, no significant change was noted in blood flow for ABCs, although the authors reported that there was a trend for the VPA to increase during masturbation alone. They concluded that a distracting task prevented maximal vasocongestion in ABCs; however, in the absence of statistical significance this generalization should not be made. It is possible that order bias may have played a role in the failure to achieve significance, since masturbation was always performed last in the testing sequence and further increases in vasocongestion may not have been possible. This concept is supported by the fact that cumulative excitation effect was noted for ABCs whereby blood flow was significantly higher in B3 to B5 vs. B1. Wincze et al. also found that higher initial levels of vaginal capillary engorgement were associated with less engorgement during erotic stimulation [35]. Larger studies should be performed to see if this trend materializes to significance.

Women with incomplete SCIs with and without the ability to perceive pinprick at spinal levels T11- L2 have also been studied [64]. Using a 78 minute protocol as previously described, photoplethysmography showed a significant increase in vaginal pulse amplitudes in response to audiovisual erotic stimuli and audiovisual stimuli with manual stimulation in ten women who had partial-normal pinprick sensation compared to seven women with no pinprick sensation at spinal levels T11- L2, who only responded to audiovisual stimulation in combination with manual stimulation. Compared to baseline, both groups showed an increase in subjective arousal following audiovisual stimulation, however, only the group with the intact T11-L2 pinprick sensation had further increases in their level of subjective arousal with additional manual stimulation. These observations supported the notion that women with UMN incomplete SCIs maintain the ability of reflex lubrication and may also maintain some psychogenic integrity. The presence or absence of pinprick sensation may help to distinguish between these two groups.

This concept was further explored with the use of Stroop, a distracting cognitive task previously described [65]. In patients with partial pinprick sensation, vaginal blood flow increases in response to Stroop plus manual stimulation compared to Stroop alone. No further increase in blood flow was noted when manual stimulation was compared to Stroop with manual stimulation. No vascular changes were noted in either setting in the group with absent pinprick sensation. This supports the presence of reflexive responses in patients with incomplete spinal cord injuries and suggests that the severity of the spinal cord injury dictates the extent to which this mechanism contributes to sexual arousal.

The current literature provided by Sipski et al. reporting vasocongestion as an indirect measurement suggests that neurological integrity may play a role in sexual dysfunctions. This hypothesis is supported by data from patients with incomplete
Sexual function in MS is assumed to occur as a result of the chronic nerve demyelination with associated degeneration. In one study that evaluated 41 subjects, (32 females and 9 males) with relapsing-remitting multiple sclerosis (MS), MRI was used to evaluate the association between severity of disease and sexual complaints [73]. A questionnaire was administered that assessed libido, excitement and orgasm of which loss of libido was the most frequently reported (26%). Overall, 50% of females reported at least one sexual disturbance. Anorgasmsia was found to correlate with brain stem and pyramidal abnormalities as well as the total area of brain lesions on MRI. The evidence from this study implies that sexual dysfunctions in MS may be related to organic lesions in the brain. Larger studies are warranted.

Using QST, Romanzi et al. evaluated 37 women as previously reported [61]. In their comparison of neurologically intact women (n=32) and MS patients (n=5) they found that patients with MS had significantly higher thresholds (worse neurological function) of the external genitalia when compared to controls. The small number of patients in the MS group do not allow for generalizations about this population.

Patients with temporal lobe epilepsy were found to have problems in hyposexuality in one study [74]. Some investigations have demonstrated that sexual function improves following temporal lobe surgery if the surgery was successful in controlling the seizure activity [75]. Extensive interconnections exist between the limbic system and the hypothalamus via the stria terminalis, the fornix and the median forebrain bundle [76]. Seizure activity in the hippocampus and other limbic areas had effects on neuroendocrinological function in limbic stimulation studies [77, 78].

In a small cohort study, Morrell et al. measured genital blood flow during sexual arousal in men and women with partial epilepsy of temporal origin (TLE) [79]. The group of women consisted of nine subjects with TLE and 12 normal controls. All subjects completed standardized inventories including the Beck Depression Inventory, the Sexual Behavior Inventory, the Sexual Arousalability Interview, and The Sexual Anxiety Interview. Genital blood flow (VPA) was measured using vaginal plethysmography subjects during presentation of alternating three-minute neutral and erotic video segments for 24 minutes. Women with TLE reported different imagined sexual activities as less arousing and more anxiety-producing compared to controls. They also had decreased genital blood flow in response to erotic stimuli compared to women without seizures. Subjective scores of arousal were similar for both groups.

This study demonstrates that patients with epilepsy may have predisposing factors for sexual dysfunction. The small sample size and lack of correlation to severity of disease (duration of condition, type of medications, frequency of seizures) limit the findings of this study. However, it lends some insight to the possibility of a true neurological etiology of sexual dysfunction.

### b) Hormones and Sexual Function Measurement

Sexual function is also dependent on the hormonal status of the woman. Estrogens have several important roles. They act as neurotrophic and psychotropic primers of the central nervous system [80], are responsible for primary and secondary sexual characteristics, and prime the sensory organs [81]. It is likely that endocrine levels are related to sexual functioning in a variety of ways and novel endocrine agents are being developed to address this. Currently there is significant controversy in the diagnoses relevant for hormonal treatment and the measures of estrogens and androgens in particular is considered problematic. Until there are validated standards of assay that are valid and reliable across laboratories, and until there is more agreement on normative values, recommendations for outcome measurement in clinical trials remain inconclusive [5, 82-96].

### SUMMARY POINTS:

Several studies have been performed that suggest that female sexual dysfunction is mediated by vasculogenic, neurologic and endocrinologic pathways that may occur naturally or as a pathological state. To date, vaginal plethysmography is the most widely studied method for evaluating both vasculogenic and neurogenic causes of sexual dysfunction. Doppler ultrasonography, laser Doppler velocimetry, vaginal pH measurements, vaginal compliance measu-
2. SELF-REPORT MEASURES OF SYMPTOMS AND DISTRESS

Self-report measures of women’s sexual functioning fall into three major categories: self-administered questionnaires, daily diaries, and structured interviews. These measures have the advantage of providing standardized and cost-effective assessment of past and current sexual functioning. Subject burden is low. Perhaps most importantly, a goal of treatment typically is improved sexual satisfaction, and self-report measures are most capable of capturing this important subjective aspect.

A good standardized instrument should measure multiple domains, include at least two items per domain, have internal consistency (α) of at least 0.70 for all domains, and demonstrate test-retest reliability at an interval of 2 to 4 weeks of at least 0.50 for items that should display stability over time. Typically daily diaries and structured interviews have not been subjected to these tests.

a) The Female Sexual Function Index (FSFI)

The Female Sexual Function Index (FSFI) is a 19-item self-report questionnaire that yields a total score as well as scores on 6 domains: desire, arousal, lubrication, orgasm, satisfaction, and pain [14]. Internal consistency and test-retest reliability are high for all domains. The FSFI discriminates between clinical and non-dysfunctional populations. The FSFI is recommended for use in clinical trials when a relatively brief, multidimensional self-report measure of women’s sexual functioning is needed. The FSFI is in Appendix A.

b) Brief Index of Sexual Functioning for Women (BISF-W)

The Brief Index of Sexual Functioning for Women (BISF-W) [97, 98] was developed for use in large-scale clinical trials and was patterned after the Brief Sexual Functioning Questionnaire for men (BSFQ) [99]. The 20-item scale yields an overall composite score and 7 domain scores: sexual thoughts/desires, arousal, frequency of sexual activity, receptivity/initiation, pleasure/orgasm, relationship satisfaction, and problems affecting sexual function. The instrument shows acceptable internal consistency for desire and pleasure/orgasm dimensions but low internal consistencies for the others; validity and sensitivity to change have been demonstrated [100, 101].

c) Sexual Function Questionnaire (SFQ)

This is a brief, multidimensional measure of women’s sexual functioning developed for clinical trials [102]. The 26 items assess seven domains of women’s sexual functioning: desire, physical arousal–sensation, physical arousal–lubrication, enjoyment, orgasm, pain, and partner relationship. The seven domains have been confirmed by factor analysis. Internal consistency of the subscales is excellent and test-retest reliability is moderate to good. The scale shows excellent discriminant validity and sensitivity to change. It has been developed and validated for 16 European languages and has been incorporated in clinical trials. The SFQ has been used in clinical trials of the efficacy of sildenafil with women [103], but otherwise has had limited use in clinical trials.

The SFQ is new and thus has limited use in clinical trials. Its psychometrics and multilingual forms make it an excellent questionnaire that would benefit from more use in clinical trials and comparison to the more widely used FSFI.

Occasionally other researcher-designed questionnaires appear in the literature and are called Sexual Functioning Questionnaire or SFQ [104-106], but are not the same as the SFQ discussed here.
d) Changes in Sexual Functioning Questionnaire (CSFQ)

This questionnaire is described by the authors as optimally administered in an interview [107, 108], and is therefore described below under interview measures. A self-administered questionnaire is available when interviews are not possible.

e) Derogatis Interview for Sexual Functioning (DISF/DISF-SR)

The Derogatis Interview for Sexual Functioning (DISF) is available in two formats: an interview format (reviewed below) and a self-report questionnaire format (DISF-SR) [109, 100]. The DISF-SR is available in male and female forms; originally written in English, it is also available in Danish, Dutch, French, German, Italian, Norwegian, and Spanish. Its 25 items assess 5 domains: sexual cognition and fantasy, sexual arousal, sexual behavior and experience, orgasm, and sex drive and relationship. Norms are available based on community samples. Test-retest and internal consistency reliabilities are strong. The DISF and DISF-SR are more recent versions of the older Derogatis Sexual Function Inventory (DSFI) [110], which contained 245 items and therefore was not suitable for clinical trials.

f) Index of Female Sexual Function (IFSF)

The IFSF was patterned after the widely accepted International Index of Erectile Function (IIEF) developed for men [111]. It contains nine items and yields a total score as well as scores in the following domains: quality of sexual intercourse, desire, sexual satisfaction, orgasm, lubrication, and sensation. Both domain scores and total scores show acceptable test-retest reliability.

g) Arizona Sexual Experience Scale (ASEX)

The ASEX was developed to be a very short (5-item) scale [112]. It includes one item each on drive, arousal, lubrication (female form), orgasm, and satisfaction with orgasm. It is therefore impossible to compute internal consistency reliability for each of these domains, although $\psi$ for the full scale is strong, 0.90. This scale may be a good choice if only a very brief instrument can be administered.

h) Female Sexual Distress Scale (FSDS)

The FSDS measures a slightly different outcome from other questionnaires reviewed here [113]. Specifically, it targets personal distress experienced by women related to sexual disorders. The 12-item scale shows strong internal consistency (0.93) and test-retest reliability (0.82) across 3 studies, and differentiates between sexually functional and sexually dysfunctional women [113]. Because subjective distress about sexual functioning is key to a diagnosis of sexual dysfunction, this measure is recommended for use in clinical trials in addition to the FSFI.

i) Female Intervention Efficacy Index (FIEI)

This 7-item scale, designed for use with trials of sildenafil, is unlike other questionnaires in that its goal is to measure very immediate effects of medical treatment [114]. Items are of the type: “After taking the pill, my vaginal lubrication...”. Internal consistency is strong. Face validity was established by a panel of experts (Table 3).

3. DAILY DIARY AND EVENT LOGS

Self-report questionnaires always, to some extent, tap retrospective accounts and therefore may be subject to memory errors or distortions [115]. Daily diaries or event logs attempt to overcome this limitation by asking the respondent to report on events close to the time that they happen. This method has been recommended by the U. S. Food and Drug Administration [116], although the emphasis on frequency of sexual activity is controversial [117]. Daily diaries typically ask subjects to report sexual activity daily, whereas event logs are completed only on days when sexual events have occurred.

The Female Sexual Encounter Profile (FSEP) was developed for this purpose [118]. It consists of a 7-item log completed for each sexual encounter, on which the subject records the type of sexual activity, desire, satisfaction with arousal, lubrication, orgasm, arousal, and appropriateness of conditions. Data on internal consistency, test-retest reliability, and validity are not available for this measure, as is typical for diaries and event logs. Moreover, diary measures are necessarily very brief because they must be completed repeatedly; therefore, they are highly restricted in the scope of measurement and do not provide the multidimensional assessment available with the best self-administered questionnaires.

Michelson et al. [119] used researcher-designed daily diaries in a clinical trial of mirtazapine, yohimbine, or olanzapine therapy for SSRI-induced sexual dysfunction in women. No data on reliability were reported. The diary measures did not detect differences between treatment and control groups. Similar findings were reported by Michelson et al. [120].
Table 3. Measurement Characteristics of Self-Report Inventories for Assessing Female Sexual Functioning

<table>
<thead>
<tr>
<th>Inventory</th>
<th># Items</th>
<th>Administration Time, Modality</th>
<th>Author, Year</th>
<th>Sample</th>
<th>Reliability</th>
<th>Validity</th>
<th>Domains Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Sexual Function Index (FSFI)</td>
<td>19</td>
<td>15-20 min questionnaire, women only</td>
<td>Rosen et al., 2000 [14]</td>
<td>• 131 normal women (21-68 years)</td>
<td>α = 0.82 for domains</td>
<td>Significant differences between FSAD and controls for all domains</td>
<td>Desire, arousal, lubrication, orgasm, satisfaction, pain</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• 128 women with FSAD (21-68 years)</td>
<td>r = 0.79 to 0.86 for test-retest</td>
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<tr>
<td>Berman et al., 2003 [148]</td>
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<td></td>
<td>• 31 women (mean age 38)</td>
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<td>Desire scale correlated with genital self-image</td>
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<td>Ferguson et al., 2003 [149]</td>
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<td></td>
<td>• 10 women with FSAD</td>
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<td>Sensitive to effects of treatment with Zestra</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• 10 women controls (31 to 57 years)</td>
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<tr>
<td>Meston, 2003 [150]</td>
<td></td>
<td></td>
<td></td>
<td>• 71 women with FOD—some also with FSAD or HSDD</td>
<td>α = 0.83 to 0.90 for controls</td>
<td>Discriminated between clinical and nonclinical samples on all domains</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 71 controls</td>
<td>r = 0.79 to 0.95 for FOD</td>
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<td></td>
<td></td>
<td>r = 0.58 to 0.94 for HSDD</td>
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<tr>
<td>Munarriz et al. (2002) [151]</td>
<td></td>
<td></td>
<td></td>
<td>• 113 women undergoing DHEA therapy</td>
<td></td>
<td>Sensitive to change from treatment</td>
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</table>
Table 3. Measurement Characteristics of Self-Report Inventories for Assessing Female Sexual Functioning

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<th>Reliability</th>
<th>Validity</th>
<th>Domains Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief Index of Sexual Functioning for Woman (BISF-W)</td>
<td>22</td>
<td>15-20 min questionnaire, women only</td>
<td>Taylor et al., 1994 [98]</td>
<td>269 normal women (20-73 years)</td>
<td>α=0.39, 0.83, 0.74 (interest, activity, satisfaction) r=0.68</td>
<td>Significant correlations with Derogatis</td>
<td>Interest, activity, satisfaction</td>
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<td></td>
<td></td>
<td></td>
<td>Nappi et al., 2003 (a) [153]</td>
<td>29 women with regular menstrual cycles</td>
<td></td>
<td>FSFI scores correlated with sex hormone levels</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Nappi et al., 2003 (a) [152]</td>
<td>29 women with sexual pain disorders</td>
<td></td>
<td>Sensitive to change from treatment with EST</td>
<td></td>
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<tr>
<td>Inventory</td>
<td># Items</td>
<td>Administration Time, Modality</td>
<td>Author, Year</td>
<td>Sample</td>
<td>Reliability</td>
<td>Validity</td>
<td>Domains Measured</td>
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</table>
| BISF-W, new scoring algorithm   | 15-20 min questionnaire | Mazor et al., 2000 [97]       | • 225 healthy women (20 to 55 years)  
• 104 women reporting decreased sexual dissatisfaction following hysterectomy and oophorectomy | α = 0.72, 0.39, 0.45, 0.72, 0.61, 0 (desire, frequency, receptivity, pleasure, satisfaction, problems (frequency based on 1 question, n = α) | Significant differences between healthy and clinical samples | Thoughts or desire; arousal; frequency; receptivity or initiation; pleasure or orgasm; relationship satisfaction; problems |
| Frohlich & Meston, 2002 [154]   |         |                               | 47 college women with elevated depressive symptoms (unmedicated)  
• 47 controls               | Detected differences between groups                               |
Table 3. Measurement Characteristics of Self-Report Inventories for Assessing Female Sexual Functioning

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<th>Domains Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual Function Questionnaire (SFQ)</td>
<td>26 for SFQ-V2</td>
<td>15-20 min. questionnaire</td>
<td>Quirk et al., 2002 [102]</td>
<td>• 781 women with FSD, 201 controls</td>
<td>α=0.66 to 0.91 r = 0.42 to 0.78</td>
<td>Significant differences between women with FSD and controls; Sensitive to change over clinical trial</td>
<td>Desire, sensation, lubrication, enjoyment, orgasm, pain, relationship</td>
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<td></td>
<td>Basson et al., 2002 [103]</td>
<td>• 577 estrogenized 18-55 years, 204 estrogen-deficient women 45-70 years, all with FSAD, some with other disorders</td>
<td>Did not detect differences between sildenafil-treated and placebo</td>
<td>Did not detect differences between sildenafil-treated and placebo</td>
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<tr>
<td>Changes in Sexual Functioning Questionnaire (CSFQ)</td>
<td>35</td>
<td>15-20 min interview or questionnaire, women and men</td>
<td>Clayton et al., 1997 [107]</td>
<td>• 122 medical students (68 men, 43 women) • 33 psychiatry residents (17 men, 16 women)</td>
<td>α=0.84 (except one scale with one item) r = 0.45 to 1.00 for items</td>
<td>Significant correlations with Derogatis</td>
<td>Desire, pleasure, frequency, arousal, orgasm</td>
</tr>
</tbody>
</table>

*Note: For each measure, the first study listed is the original standardization study.*
Table 3. Measurement Characteristics of Self-Report Inventories for Assessing Female Sexual Functioning

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</tr>
</thead>
<tbody>
<tr>
<td>Derogalis Interview for Sexual Functioning (DISF or DISF-SR)</td>
<td>25</td>
<td>10-15 min. interview (DISF) or questionnaire (DISF-SR), women and men</td>
<td>Derogalis, 1997 [109]</td>
<td>277 community women and men</td>
<td>α=0.74 to 0.80</td>
<td>r = 0.80 to 0.90</td>
<td>Cognition and fantasy, arousal, behavior, orgasm, drive and relationship</td>
</tr>
<tr>
<td>Index of Female Sexual Function (IFSF)</td>
<td>9</td>
<td>5 min questionnaire</td>
<td>Kaplan et al., 1999 [111]</td>
<td>33 postmenopausal women with sexual dysfunction</td>
<td>r = 0.70 for total score</td>
<td>Sensitive to changes with sildenafil therapy</td>
<td>Quality of intercourse, desire, satisfaction, orgasm, lubrication, clitoral sensation</td>
</tr>
<tr>
<td>Female Intervention Efficacy Index (FIEI)</td>
<td>5</td>
<td>&lt; 5 min. questionnaire</td>
<td>Berman et al., 2001 (b) [114]</td>
<td>26 women with FSAD, 11 controls</td>
<td>α=0.81</td>
<td>Sensitivity to change following treatment with sildenafil and EROS-CTD</td>
<td>1 item each on lubrication, sensation (amount and quality), satisfaction, orgasm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Berman et al., 2001 (a) [155]</td>
<td>35 women with sex dysfunction, 7 of them with unresolved CSA</td>
<td></td>
<td>Sensitive to change with sildenafil treatment, for those with no CSA history</td>
<td></td>
</tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Female Sexual Distress Scale (FSDS)</td>
<td>12</td>
<td>5 min. questionnaire</td>
<td>Derogatis et al., 2002 [113]</td>
<td>• Study I: 18 women with sex dysfunctions, 60 controls&lt;br&gt;• Study II: 174 women with FSAD; 145 women with HSDD, 102 controls</td>
<td>α = 0.93 to 0.97&lt;br&gt;r = 0.52 to 0.92</td>
<td>Detected differences between sexually functional and dysfunctional women; Sensitive to treatment effects</td>
<td>Single dimension of sexual distress</td>
</tr>
<tr>
<td>Ferguson et al., 2003 [149]</td>
<td></td>
<td></td>
<td></td>
<td>• 10 women with FSAD&lt;br&gt;• 10 controls (ages 31 to 57)</td>
<td></td>
<td>Sensitive to effects of treatment with Zustra</td>
<td></td>
</tr>
<tr>
<td>Munarriz et al., 2002 [151]</td>
<td></td>
<td></td>
<td></td>
<td>• 113 women undergoing DHEA therapy</td>
<td></td>
<td>Sensitive to change with treatment</td>
<td></td>
</tr>
<tr>
<td>Arizona Sexual Experience Scale (ASEX)</td>
<td>5</td>
<td>&lt; 5 min</td>
<td>McGahuey et al., 2000 [112]</td>
<td>• 35 women psychiatric patients, 22 women controls</td>
<td>α = .9055 for full scale&lt;br&gt;r = 0.80 to 0.88</td>
<td>Correlates with BISF-W, sensitive to sex dysfunction diagnosis based on clinical interview</td>
<td>1 item each on drive, arousal, lubrication, orgasm, orgasm satisfaction</td>
</tr>
</tbody>
</table>

*Note: For each measure, the first study listed is the original standardization study.*
4. STRUCTURED INTERVIEWS

Compared with self-report questionnaires, structured interviews provide the opportunity to develop rapport with the respondent. Interviews can potentially elicit further detail and clarification about symptoms, their primary or secondary nature, and the relationship between symptoms and satisfaction. Whether this format encourages more honest reporting of sexual events is debatable. One study found that the reporting of rape nearly doubled in face-to-face interviews compared with a telephone interview [121], but a study of risky sexual behavior among gay men found that risky behavior was more likely to be reported on the questionnaire than in the interview [122]. Many experts believe that the combination of a face-to-face interview to build rapport, with a written questionnaire to ensure anonymity, is optimal [123]. Given that most clinical trials involve clinical, face-to-face interviews that already have built rapport, questionnaires may then be best in promoting honest responding and efficiency.

Structured interviews are costly because of interviewer time. Therefore, they may not be appropriate for large-scale clinical trials.

a) Derogatis Interview for Sexual Functioning (DISF)

The DISF is the semi-structured interview version of the self-report questionnaire, DISF-SR, discussed above [109, 100]. It includes 25 questions tapping 6 domains: cognition/fantasy, arousal, sexual behavior, orgasm, and drive/relationship and takes 15 to 20 min. to administer in interview format. Norms are available. Reliability and validity are comparable to the DISF-SR. Inter-rater reliability for the interview form is high, 0.84 to 0.92 across the 5 domains.

b) Changes in Sexual Functioning Questionnaire (CSFQ)

The CSFQ comprises 35 items for women and is intended to be administered in interview format, requiring 15-20 min. [107]. It assesses sexual desire, pleasure, frequency, arousal, and orgasm. Test-retest and internal consistency reliabilities are acceptable, and the scale shows concurrent validity against the DISF-SR. Norms are available, by gender, for depressed patients, medical students, psychiatry residents, and nonpsychiatric outpatients [108].

c) Interviewer Rating of Sexual Function (IRSF)

This semi-structured interview involves standard opening questions followed by probe questions as necessary to allow the interviewer to rate the respon-

dent on a set of 10 items assessing sexual initiating, arousal, orgasm, anxiety, vaginal dryness, pain, and closeness to partner, as well as items tapping men’s sexual concerns [124, 126]. It has been used with women in clinical trials for treatment of antidepressant-associated sexual dysfunctions [120].

5. PARTNER ASSESSMENTS

Partner assessments of sexual functioning may be valuable in validating the patient’s self-assessment for items that should manifest couple agreement, such as frequency of intercourse, and are generally acceptable to regulatory agencies for inclusion in clinical trials. They cannot validate measures that may not be known about or agreed upon by both partners, such as frequency of masturbation or subjective sexual desire. Although partner adaptations of some measures of male sexual functioning have been developed [127]), no validated measures have been published for women’s sexual functioning, whether the partner is male or female. Assessments for partners of women with sexual dysfunction should be developed.

6. QUALITY OF LIFE AND TREATMENT SATISFACTION

Clinical trials may include measures of treatment satisfaction and broad measures of quality of life as secondary endpoints [128,129]. Most quality-of-life measures are disease-specific, e.g., living with diabetes, and are therefore inappropriate in assessing the effects of treatment for sexual dysfunctions. Recently several measures have been developed that are specific to sexual dysfunctions and measure sexual quality of life. Generic measures of quality of life are also available. Short measures of global sexual satisfaction are available as one of several dimensions assessed with the sexual functioning inventories reviewed earlier; for example, the FSFI contains a satisfaction subscale.

a) Index of Sexual Satisfaction (ISS)

The Index of Sexual Satisfaction (ISS) assesses satisfaction in the respondent’s sexual relationship with her partner [130, 131]. The 25-item questionnaire shows excellent internal consistency and discriminant validity. A clinical cutoff score of 30 or more indicates the presence of a clinically significant degree of sexual discord in the relationship.

b) Fugl-Meyer Life Satisfaction Scale

This 8-item life satisfaction questionnaire was deve-
d) Satisfaction with Life Scale (SWLS)

Among the generic measures of quality of life or life satisfaction is the Satisfaction with Life Scale (SWLS), a 5-item generic scale that assesses satisfaction with the respondent’s life as a whole [133]. It shows excellent internal consistency and test-retest reliability but has not yet been applied in clinical trials of treatments for sexual dysfunctions. The SWLS is recommended for use in clinical trials when a general measure of quality of life is desired.

d) Quality of Life Inventory (QOLI)

Another generic measure of quality of life scale is the Quality of Life Inventory (QOLI) [134-135]. The 16-item self-administered questionnaire assesses satisfaction or dissatisfaction in 16 domains of life (e.g., love, work). It shows strong internal consistency (0.77 to 0.89 in various samples) and test-retest reliability (0.80 to 0.91). It is used widely in assessment and treatment evaluation in managed care settings for disorders such as depression and chemical dependency [134].

Other generic measures [136] are too lengthy for practical use in clinical trials and assess many aspects — such as satisfaction with work — that are unlikely to be affected by a sexual dysfunction or its successful treatment.

Inclusion of quality of life measures raises methodological questions about how specific (narrow) or broad the endpoints should be in assessing the effectiveness of treatments. Certainly quality of life should be a secondary endpoint, not a primary endpoint. If a treatment improves global quality of life, the finding is impressive, but such a broad impact may not be realistic for most treatments.

7. ADVERSE EVENT MONITORING/SAFETY MONITORING

An important consideration in clinical trials of treatments for sexual dysfunctions is the monitoring and reporting of adverse outcomes and events. Methods for assessment include self-report symptom checklists, interviews and daily diary or event logs. A major advantage of symptom checklists is that they can be standardized and used across trials of different treatments; they are also cost-effective to administer. The advantage of interviews is that they can capture unanticipated adverse events and can probe for additional details. Because serious drug-related adverse events are rare, most clinical trials have insufficient statistical power to detect adverse events. Monitoring of adverse events is a crucial aspect of clinical trials.

The list of adverse events to be monitored will depend to some extent on the treatment and its anticipated side effects. For example, in one trial of transdermal testosterone, the following were monitored: hirsutism, acne, serum lipid concentrations, fasting serum glucose concentrations, serum insulin concentrations, blood counts, indicators of live function, and frequency of hot flashes [101]. Psychological monitoring should include depression and anxiety. Other adverse events that have been monitored include somnolence, insomnia, weight gain, and increased appetite [119]. Basic laboratory procedures such as, kidney and liver function, and vital signs need careful monitoring, as does ECG for some studies.

Standardized checklists should be developed for the monitoring of adverse events in the treatment of women with sexual dysfunction. These checklists should include a standardized core of adverse events that can be monitored across many potential treatments as well as a flexible section for events that may be anticipated for a specific treatment.

V. PROTOCOL DESIGN AND IMPLEMENTATION

A well-designed and carefully implemented study protocol serves as a written agreement between the investigator, the research participant and the scientific and regulatory community. It includes the goals and objectives of the trial, research design and methodology, plans for data analysis and overall organization of the trial. Each section should be described in detail with supplemental data or procedural information contained in a protocol appendix or manual of procedures. The protocol should be fully developed prior to the trial initiation and remain essential untagged except for minor updates or amendments during the course of the trial. The protocol should be agreed to in writing by each investigator and should be made available to all study personnel involved in the conduct of the trial. A copy of
the study protocol, investigator’s brochure and informed consent statement should be submitted to an Institutional Review Board for review and approval and appropriate regulatory agency prior to initiation of the trial.

The study protocol should be organized as follows:

1. **Table of Contents**

2. **List of Abbreviations and Acronyms**

3. **Synopsis of Protocol**

4. **Background of the Study**

   This section provides a concise overview of the epidemiology and clinical significance of the problem, alternative approaches to treatment, and the mechanisms or cite of action of the treatment under study. The need for a new therapeutic agent should be addressed, as well as the potential advantages or disadvantages of the study intervention. Also included in this section is a review of previous animal safety or toxicity studies in addition to any available pharmacokinetic and clinical data in humans.

5. **Study Objectives**

   Each of the study objectives should be stated clearly in advance. Primary and secondary objectives should be delineated, as well as the response variables to be measured in addressing each of these objectives. Any planned sub-group analyses should be specified in advance. The safety objectives of the study and adverse event monitoring plans should be described in this section. Although multiple objectives are possible, care should be taken not to overcomplicate the study design or conduct of the trial. This can result in excessive patient burden, diminished quality of data collection and speculative data analyses.

6. **Design of the Study**

   All aspects of the study design and procedures should be described in detail. This includes the type of design (crossover, parallel or mixed), blinding procedures, type of treatment control, number and sequencing of treatment periods, method of randomization, pre-treatment or baseline assessment, treatment interventions, and management of dropouts. Specific inclusion and exclusion criteria of patient selection should be included and study endpoints defined. Procedures for interim analysis and termination of the study should be specified. All study procedures and visits should be described in writing and listed in a flow-sheet or summary table.

   The *methods and procedures* section should provide detailed information for each study visit, specifying all study procedures to be performed, the response variables to be recorded at each visit, and the proper order or sequencing of study procedures and data collection. *Standardized laboratory procedures* (e.g. ECG, blood sampling) should be employed unless otherwise specified. Detailed instructions are especially important for in-clinic recording of genital responses (e.g., vaginal plethysmography/VSS protocols), in order to optimize the quality of recording and to ensure standardization of data collection across sites. These instructions may be contained in a protocol appendix or manual of procedures. The use of *concomitant medications* should be carefully monitored throughout the study and instruction provided for the recording and management of *adverse events* (e.g. serious vs. non-serious; treatment related vs. treatment unrelated). Clear criteria should be provided for *withdrawal* of patients from the study or for *study discontinuation*. Periodic reviews of the study by an *independent data safety monitoring board* (DSMB) are frequently used in other clinical trial areas (e.g. cancer, cardiovascular disease), although these are as yet uncommon in clinical trials of FSD. The role of the safety committee should be clearly specified, if relevant.

   Finally, this section of the protocol should contain a clear description of the *study materials*. The test article (e.g. drug tablet, solution) should be described in terms of its physical and chemical properties, formulation, and packaging. The *stability* of the formulation and specific requirements for *storage and handling* should be included. Information on *dosage and administration* of both active medication and control (e.g. placebo) is necessary, including unit dose, frequency of dosing, patient instructions, and labeling. The protocol should also specify the investigator’s responsibilities in recording the *receipt, dispensing, and return* of the study medications.

7. **Administrative Considerations**

   Issues related to the protection of subjects’ rights, monitoring and documentation of the study conduct, maintenance and retention of *study records*, and *publication policies* are all covered in detail in this section. A clear description should be provided of the level of *patient confidentiality* to be observed. Access to the study records by the sponsor, Institutional Review Board (IRB), DSMB, regulatory agen-
cy or others should be clearly specified. Also, the terms of confidentiality between the sponsor and the investigator should be defined.

A separate section should be addressed to the role of the IRB and the procedures to be followed in obtaining informed consent. A copy of the actual informed consent statement should be included as an appendix to the protocol.

**Summary Points:**

The study protocol is a written agreement between the investigator, the research subject, the regulators, and the scientific community. It includes the goals and objectives of the study, research design and methodology, plans for data analysis, and overall organization of the trial. The study protocol should be fully developed and agreed upon prior to initiation of the trial.

Essential features of the protocol include the background, study objectives, design and methods, and administrative considerations. Each of these sections should be completed in a clear and detailed fashion, with the entire protocol being reviewed by the sponsor, the Institutional Review Board, and the relevant regulatory agency.

Investigators should adhere to the study protocol as closely as possible throughout the conduct of the trial. Procedures should be specified in advance for monitoring of the trial, and for maintenance and retention of all study documents. Publication plans and policies should also be clearly specified.

### VI. DATA ANALYSIS AND REPORTING OF RESULTS

Although a detailed discussion of these methods is beyond the scope of this chapter, some general comments and recommendations can be made. To a large degree, the type of statistical model employed depends upon the nature of the research design (e.g., parallel, between-group vs. counterbalanced, crossover design) and the response variables being analyzed (e.g., continuous vs. dichotomous variables). Given the large number of statistical issues and data analysis considerations, it is essential that a qualified biostatistician be involved in the design and analysis of all clinical trials in FSD. In the data analysis phase, efforts should be made to ensure the statistician is either independent or blinded to the identification of treatment group assignments.

Sample power should be calculated in advance, using the best available estimates of the means and variances of the primary efficacy variables, and anticipated changes associated with treatment. Sample power for Phase III trials is traditionally based on estimates of efficacy, not safety. In this respect, studies usually are not adequately powered for detection of low-frequency safety problems. Standard formulae are available for the computation of sample power for a clinical trial.

**Sample size considerations for Phase II Studies.**

Phase II studies are normally designed according to the two stage designs of Simon [137, 138], which 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 have a small number of patients it is generally best to use exact statistical methods to analyze them: Examples are StatXact [139] and LogXact [140].

It is possible to design Phase II trials taking into account both toxicity and treatment response using methodology in Bryant and Day [141]. The sample sizes for the combination of treatment response and toxicity will be larger because you are taking two factors into consideration. Such designs have a mechanism for stopping the study should the toxicity prove to be too high even if the treatment response is adequate.

**Sample size considerations for Phase III Studies.**

Phase III studies are used to compare at least one treatment with a placebo control group or two or
more active treatment groups with each other. It is now common to see Phase III studies arranged in a two by two factorial design with the intention of investigating the interaction between two treatments but the classic study compares one new treatment with a placebo group. In FSD studies, there are no approved medications so that placebo control comparisons to new treatments are required in clinical trials. Assignment of patients to treatment group should be double blinded wherever possible and always randomized.

There are well-established statistical procedures for the design and analysis of Phase III studies and there is no excuse for an underpowered Phase III study without a clearly defined protocol and analysis plan. There are sample size formula for all of the common endpoints, measurements, repeated measures, proportions, and survival [142, 143]. Many trials are now designed to establish equivalence and these require special methods in the calculation of the power [144]. Many of these techniques are included in good sample size calculation software such as NQuery Advisor [145]. In the design of these studies it is important to use realistic values for the anticipated treatment effect and standard deviation of the response measure. Many studies turn out to be underpowered because the initial expectations about the treatment effects were much too optimistic.

All subjects randomized to treatment or control conditions should be included in an “intention-to-treat” analysis, in which data from dropouts or withdrawals are included in the final analysis of treatment outcome [146]. This general rule should not be applied to the assessment of adverse events, however, where it may be preferable to report the frequency of side effects only among those who actually received the treatment. Covariate adjustments of stratification techniques can be used to control for differences between the study groups in baseline levels of functioning or demographic characteristics (e.g. age, socioeconomic status, race/ethnicity, duration of illness), although covariance analysis should be performed only when specific statistical assumptions are met. A limited number of sub-group analyses may be conducted, paying careful attention to the potential lack of power and possibility of Type II errors associated with these analyses.

Assessing the magnitude of treatment effects is potentially difficult in FSD trials with so few Phase III studies having been done that test new agents. Effect size calculations can be used to provide a statistical estimate of the magnitude of treatment effects, although this approach is uncommon in FSD trials. Rather, it is more common to report the magnitude of treatment effects in terms of percentages of responders in the active compared to control groups. Such comparisons involve changes in scores on questionnaires, sub-scales of questionnaire, or selected questions from a daily diary. However, an alternative is simply comparing responses from baseline on standardized questionnaires, an approach that is necessary when defining a “responder” cannot easily be established. For example, in a multicenter trial of transdermal testosterone, the primary endpoints were the composite score on the BISF and the overall sexual frequency index from the telephone based daily diary, and secondary endpoints were BISF subscales and a general well-being index [101]. Changes from baseline were compared for placebo and control conditions.

Unfortunately, normative population data are lacking to establish response criteria for adequate sexual functioning at each age group. In the absence of such data, and until more of the complexities of diagnostic comorbidity or simply categorical overlap are further sorted out for FSD, continued disagreement on the definition of a treatment responder is likely. One approach to this problem is to report several measures of treatment efficacy, including both quantitative (e.g. number of satisfying sexual encounters) and qualitative (e.g. global satisfaction) indices. This allows for a more comprehensive assessment of the magnitude and consistency of treatment effects.

Several points should be closely attended to in the final report preparation and publication of all clinical trials. These are briefly as follows:

1. Authors should be selected for inclusion based solely on their contributions to the study design, conduct, analysis and write-up. Individuals who have not participated substantially in one or more of these aspects of the study should not be listed as authors on the final publication.

2. Full disclosure and acknowledgment should be made of the source of funding for the study. Additionally, potential conflicts of interest for each of the study authors or investigators should be clearly acknowledged.

3. A complete description of the study methods and procedures is essential, including a detailed description of the inclusion and exclusion criteria, patient selection and screening procedures, effica-
Patient rights and protections in clinical trials are specified in the International Ethical Guidelines for Biomedical Research Involving Human Subjects [147]. This declaration specifies that the health of the patient should be the primary concern of physicians doing clinical research. The purpose of biomedical research is to improve on clinical practice. Thus a physician or other healthcare investigator in clinical research would attempt to improve public health concerns without compromising the health of the individual and the potential benefits of a study have to be weighed against the risks to individual participating in the investigation. Ethical principles of the Declaration of Helsinki are particularly important in studies of compounds designed to improve the quality of life such as sexual dysfunction.

Specific issues of importance concern: informed consent, trial design, patient safety, and patient confidentiality. Informed consent is an ongoing process throughout the study and the investigator is responsible for making certain that the subject is fully informed and understands all aspects of the study and that the subject is always aware of the right to withdraw from the study at any time. In studies requiring partner participation in order to complete study endpoints, the sexual partner should also sign an informed consent. Minors and patients who are mentally incompetent are not suitable subjects. Also not suitable are individuals who are coerced into participating by family members. The subject should fully comprehend the nature of the medication and placebo condition; specifically, that the compound being tested is experimental and may or may not have a beneficial impact on the sexual complaint being studied.

Patient safety is partially assured by requiring that all studies be reviewed by an independent bio-ethical committee, such as an accredited institutional review board, in accordance with state and federal laws where the study is performed. There should always be a balance between the potential value of the study to the public and protection of individual patient safety. In quality of life studies, the risk to the patient should be very low.
Patient privacy and confidentiality must be respected and safeguarded at all times. There should always be protection of personal or health information that might identify an individual patient. Consent forms should explicitly state the extent and limitations of confidentiality and privacy.

Findings of clinical trials in FSD should be published in peer-review literature as well as being made publicly available following regulatory review. The ultimate objective of clinical trials, particularly in a new area of medical research like FSD diagnoses, is to impact the clinical care options of the patient. As such the design of the research protocols should have maximum relevance to the practicing clinician, with regard to clarity if not breadth of selection criteria and endpoints readily translated into clinically meaningful terms. Clinical research is a dynamic enterprise, requiring experimental testing and ongoing evaluation in the context of clinical practice. Clinical trials in FSD have not yet achieved this.

**Summary Points:**

Clinical trials in FSD should always be conducted in accordance with the highest ethical and clinical standards as specified in the Helsinki Declaration.

All clinical trials should be subject to the approval of an independent IRB, constituted according to the laws and regulations of the host country.

There must be a careful balance between the potential benefits and risks to the individual patient. Patients must be fully informed about the study, its risks and discomforts and its benefits. Consent should be freely given without compromising patient’s access to healthcare or further research involvement. Confidentiality must be protected to the fullest extent permitted by the law.

Findings from clinical research in FSD must be made available in a form that is practically and clinically useful.

Clinical trials in FSAD, HSDD require the use of the highest standards of trial designs, the best available outcome measures and careful statistical expertise. Based on the issues considered in the chapter, the following recommendations can be made:

1. Novel drugs or devices for the treatment of women’s sexual dysfunctions should be systematically evaluated through a comprehensive series of Phase I though IV clinical trials. The overall safety and efficacy of new agents must be carefully evaluated before regulatory approval is granted and the treatment enters widespread clinical use.

2. Generally, crossover designs are recommended in early phase Phase I or II studies. Parallel or combination parallel-crossover designs are preferred in Phase III and IV trials. It is possible that some agents are more subject to crossover effects and extra care should be taken when this is the case. Post treatment analyses should compare the active agent to the placebo (or comparison agent, if applicable) and to the baseline levels of functioning on a particular endpoint.

3. Study populations should be carefully defined, taking hormonal status, mood, and (for Phase III studies) relationship factors into account. Inclusion criteria should clearly define the condition under study, including duration and severity of the disorder, and a level of distress regarding the symptoms. Exclusion criteria should provide adequate safeguards against unnecessary risk of exposure in the study population. Special population studies are recommended to evaluate drug efficacy and safety in selected sub-populations (e.g., spinal cord injury, patients on anti-depressants).

4. Efficacy and safety endpoints are specified in advance. Recommended efficacy endpoints include self-report questionnaires (e.g., FSFI), patient and partner diaries (none currently validated), and objective measures of vasocongestive or neurogenic function (thus far more appropriate for Phase I and II trials).
satisfaction, quality of life measures, and partner reports on couple sexual activities are valuable information for Phase III and IV clinical trials.

5. Adverse events should be carefully monitored with symptom checklists or structured patient interviews. Adverse events should be classified according to severity and should be judged as treatment-related or treatment-unrelated by the investigator. Long term monitoring of adverse events, side effects and laboratory parameters is critically important in assessing the overall safety of new treatment agents.

6. A detailed study protocol should be developed and agreed upon by the sponsor, the investigator, the institutional review board, and the relevant regulatory agencies prior to initiation of the study. The study protocol should include a complete description of the background and study objectives, design and methods, plans for data analysis and overall organization of the trial. All aspects of the protocol should be strictly adhered to in the ongoing conduct of the study.

7. A qualified biostatistician, preferably independent to the study, should be involved in the design and analysis of all clinical trials in FSD. The definition of a treatment responder is only beginning to be identified for FSAD and FHSDD. At this time in the specification of treatment response variables, multiple data sources may be needed to measure changes in symptoms and satisfaction. Findings of clinical trials of FSD should be accurately reported, and investigators should make full disclosure regarding financial relationships with the study sponsor and sources of study funding.

8. All clinical trials should be conducted in accordance with standards of Good Clinical Practice and accordance with ethical principles concerning human subjects as specified in the Helsinki Declaration. All clinical trials should also be approved and monitored by an accredited independent human rights/ethics committee (IRB). Patients must be fully informed about the nature of the study, the potential for risks and hazards involved and the limits of confidentiality. Confidentiality should be protected to the fullest extent permitted by the law. The findings from clinical research should be disseminated in a form that is accurate and clinically useful to the physicians, health care providers, patients and society at large.
Glossary of Key Terms

Adverse Reaction: (Adverse Event.) An unwanted effect caused by the administration of drugs. Onset may be sudden or develop over time.

Approved Drugs: In the U.S., the Food and Drug Administration (FDA) must approve a substance as a drug before it can be marketed. The approval process involves several steps including pre-clinical laboratory and animal studies, clinical trials for safety and efficacy, filing of a New Drug Application by the manufacturer of the drug, FDA review of the application, and FDA approval/rejection of application.

Arm: Any of the treatment groups in a randomized trial. Most randomized trials have two “arms,” but some have three “arms,” or even more.

Baseline: 1. Information gathered at the beginning of a study from which variations found in the study are measured.
2. A known value or quantity with which an unknown is compared when measured or assessed.
3. The initial time point in a clinical trial, just before a participant starts to receive the experimental treatment which is being tested. At this reference point, measurable values such as CD4 count are recorded. Safety and efficacy of a drug are often determined by monitoring changes from the baseline values.

Bias: When a point of view prevents impartial judgment on issues relating to the subject of that point of view. In clinical studies, bias is controlled by blinding and randomization.

Blind: A randomized trial is “Blind” if the participant is not told which arm of the trial he is on. A clinical trial is “Blind” if participants are unaware on whether they are in the experimental or control arm of the study; also called masked.

Clinical: Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science.

Clinical Investigator: A medical researcher in charge of carrying out a clinical trial’s protocol.

Clinical Trial: A clinical trial is a research study to answer specific questions about vaccines or new therapies or new ways of using known treatments. Clinical trials (also called medical research and research studies) are used to determine whether new drugs or treatments are both safe and effective. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people. Trials are in four phases: Phase I tests a new drug or treatment in a small group; Phase II expands the study to a larger group of people; Phase III expands the study to an even larger group of people; and Phase IV takes place after the drug or treatment has been licensed and marketed.

Confidentiality Regarding Trial Participants: Refers to maintaining the confidentiality of trial participants including their personal identity and all personal medical information. The trial participants consent to the use of records for data verification purposes should be obtained prior to the trial and assurance must be given that confidentiality will be maintained.

Control: A control is the nature of the intervention control.

Control Group: The standard by which experimental observations are evaluated. In many clinical trials, one group of patients will be given an experimental drug or treatment, while the control group is given either a standard treatment for the illness or a placebo.

Controlled Trials: Control is a standard against which experimental observations may be evaluated. In clinical trials, one group of participants is given an experimental drug, while another group (i.e., the control group) is given either a standard treatment for the disease or a placebo.

Data Safety and Monitoring Board (DSMB): An independent committee, composed of community representatives and clinical research experts, that reviews data while a clinical trial is in progress to ensure that participants are not exposed to undue risk. A DSMB may recommend that a trial be stopped if there are safety concerns or if the trial objectives have been achieved.

Dose-Ranging Study: A clinical trial in which two or more doses of an agent (such as a drug) are tested against each other to determine which dose works best and is least harmful.

Double-Blind Study: A clinical trial design in which neither the participating individuals nor the study staff knows which participants are receiving the experimental drug and which are receiving a placebo (or another therapy). Double-blind trials are thought to produce objective results, since the expectations of the doctor and the participant about the experimental drug do not affect the outcome; also called double-masked study.

Efficacy: (of a drug or treatment). The maximum ability of a drug or treatment to produce a result regardless of dosage. A drug passes efficacy trials if it is effective at the dose tested and against the illness for which it is prescribed. In the procedure mandated by the FDA, Phase II clinical trials gauge efficacy, and Phase III trials confirm it.

Eligibility Criteria: Summary criteria for participant selection; includes Inclusion and Exclusion criteria.

Empirical: Based on experimental data, not on a theory.

Endpoint: Overall outcome that the protocol is designed to evaluate.

Experimental Drug: A drug that is not FDA licensed for use in humans, or as a treatment for a particular condition.

Food and Drug Administration (FDA): The U.S. Department of Health and Human Services agency responsible for ensuring the safety and effectiveness of all drugs, biologics, vaccines, and medical devices, including those used in the diagnosis, treatment, and prevention of HIV infection, AIDS, and AIDS-related opportunistic infections. The FDA also works with the blood banking industry to safeguard the nation’s blood supply.

Hypothesis: A supposition or assumption advanced as a
basis for reasoning or argument, or as a guide to experimental investigation.

**INCLUSION/EXCLUSION CRITERIA:** The medical or social standards determining whether a person may or may not be allowed to enter a clinical trial. These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions. It is important to note that inclusion and exclusion criteria are not used to reject people personally, but rather to identify appropriate participants and keep them safe.

**IND (INVESTIGATIONAL NEW DRUG):** A new drug, antibiotic drug, or biological drug that is used in a clinical investigation. It also includes a biological product used *in vitro* for diagnostic purposes.

**INFORMED CONSENT:** The process of learning the key facts about a clinical trial before deciding whether or not to participate. It is also a continuing process throughout the study to provide information for participants. To help someone decide whether or not to participate, the doctors and nurses involved in the trial explain the details of the study.

**INSTITUTIONAL REVIEW BOARD (IRB):** A committee of physicians, statisticians, researchers, community advocates, and others that ensures that a clinical trial is ethical and that the rights of study participants are protected. All clinical trials in the U.S. must be approved by an IRB before they begin. Every institution that conducts or supports biomedical or behavioral research involving human participants must, by federal regulation, have an IRB that initially approves and periodically reviews the research in order to protect the rights of human participants.

**INTENT TO TREAT:** Analysis of clinical trial results that includes all data from participants in the groups to which they were randomized even if they never received the treatment.

**NEW DRUG APPLICATION (NDA):** An application submitted by the manufacturer of a drug to the FDA - after clinical trials have been completed - for a license to market the drug for a specified indication.

**PEER REVIEW:** Review of a clinical trial by experts chosen by the study sponsor. These experts review the trials for scientific merit, participant safety, and ethical considerations.

**PHARMACOKINETICS:** The processes (in a living organism) of absorption, distribution, metabolism, and excretion of a drug or vaccine.

**PHASE I TRIALS:** Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients.

**PHASE II TRIALS:** Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.

**PHASE III TRIALS:** Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide adequate basis for physician labeling.

**PHASE IV TRIALS:** Post-marketing studies to delineate additional information including the drug’s risks, benefits, and optimal use.

**PLACEBO:** A placebo is an inactive pill, liquid, or powder that has no treatment value. In clinical trials, experimental treatments are often compared with placebos to assess the treatment’s effectiveness. In some studies, the participants in the control group will receive a placebo instead of an active drug or treatment. No sick participant receives a placebo if there is a known beneficial treatment.

**PLACEBO CONTROLLED STUDY:** A method of investigation of drugs in which an inactive substance (the placebo) is given to one group of participants, while the drug being tested is given to another group. The results obtained in the two groups are then compared to see if the investigational treatment is more effective in treating the condition.

**PLACEBO EFFECT:** A physical or emotional change, occurring after a substance is taken or administered, that is not the result of any special property of the substance. The change may be beneficial, reflecting the expectations of the participant and, often, the expectations of the person giving the substance.

**PRECLINICAL:** Refers to the testing of experimental drugs in the test tube or in animals - the testing that occurs before trials in humans may be carried out.

**PROTOCOL:** A study plan on which all clinical trials are based. The plan is carefully designed to safeguard the health of the participants as well as answer specific research questions. A protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study. While in a clinical trial, participants following a protocol are seen regularly by the research staff to monitor their health and to determine the safety and effectiveness of their treatment.

**QUALITY OF LIFE TRIALS (or Supportive Care trials):** Refers to trials that explore ways to improve comfort and quality of life for individuals with a chronic illness.

**RANDOMIZATION:** A method based on chance by which study participants are assigned to a treatment group. Randomization minimizes the differences among groups by equally distributing people with particular characteristics among all the trial arms. The researchers do not know which treatment is better. From what is known at the time, any one of the treatments chosen could be of benefit to the participant.

**RANDOMIZED TRIAL:** A study in which participants are randomly (i.e., by chance) assigned to one of two or more treatment arms of a clinical trial. Occasionally placebos are utilized.

**RISK-Benefit RATIO:** The risk to individual participants versus the potential benefits. The risk/benefit ratio may differ depending on the condition being treated.

**SIDE EFFECTS:** Any undesired actions or effects of a drug or treatment. Negative or adverse effects may include head-
ache, nausea, hair loss, skin irritation, or other physical problems. Experimental drugs must be evaluated for both immediate and long-term side effects.

**Single-Blind Study:** A study in which one party, either the investigator or participant, is unaware of what medication the participant is taking; also called single-masked study.

**Standard Treatment:** A treatment currently in wide use and approved by the FDA, considered to be effective in the treatment of a specific disease or condition.

**Standards of Care:** Treatment regimen or medical management based on state of the art participant care.

**Statistical Significance:** The probability that an event or difference occurred by chance alone. In clinical trials, the level of statistical significance depends on the number of participants studied and the observations made, as well as the magnitude of differences observed.

**Study Endpoint:** A primary or secondary outcome used to judge the effectiveness of a treatment.

**Study Type:** The primary investigative techniques used in an observational protocol; types are Purpose, Duration, Selection, and Timing.

**Toxicity:** An adverse effect produced by a drug that is detrimental to the participant’s health. The level of toxicity associated with a drug will vary depending on the condition which the drug is used to treat.

**Treatment IND:** IND stands for Investigational New Drug application, which is part of the process to get approval from the FDA for marketing a new prescription drug in the U.S. It makes promising new drugs available to desperately ill participants as early in the drug development process as possible. Treatment INDs are made available to participants before general marketing begins, typically during Phase III studies. To be considered for a treatment IND a participant cannot be eligible to be in the definitive clinical trial.

**Treatment Trials:** Refers to trials which test new treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.
APPENDIX A. THE FEMALE SEXUAL FUNCTION INDEX (FSFI)

Female Sexual Function Index (FSFI) ©

Subject Identifier ________________________________

Date __________________

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:

**Sexual activity** can include caressing, foreplay, masturbation and vaginal intercourse.

**Sexual intercourse** is defined as penile penetration (entry) of the vagina.

**Sexual stimulation** includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

**Sexual desire** or **interest** is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner’s sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?
   - 5 Almost always or always
   - 4 Most times (more than half the time)
   - 3 Sometimes (about half the time)
   - 2 A few times (less than half the time)
   - 1 Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?
   - 5 Very high
   - 4 High
   - 3 Moderate
   - 2 Low
   - 1 Very low or none at all

**Sexual arousal** is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how **often** did you feel sexually aroused (“turned on”) during sexual activity or intercourse?
   - 0 No sexual activity
   - 5 Almost always or always
   - 4 Most times (more than half the time)
   - 3 Sometimes (about half the time)
   - 2 A few times (less than half the time)
   - 1 Almost never or never
4. Over the past 4 weeks, how often would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?

| 0 | No sexual activity |
| 5 | Very high |
| 4 | High |
| 3 | Moderate |
| 2 | Low |
| 1 | Very low or none at all |

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

| 0 | No sexual activity |
| 5 | Very high confidence |
| 4 | High confidence |
| 3 | Moderate confidence |
| 2 | Low confidence |
| 1 | Very low or no confidence |

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

| 0 | No sexual activity |
| 5 | Almost always or always |
| 4 | Most times (more than half the time) |
| 3 | Sometimes (about half the time) |
| 2 | A few times (less than half the time) |
| 1 | Almost never or never |

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

| 0 | No sexual activity |
| 5 | Almost always or always |
| 4 | Most times (more than half the time) |
| 3 | Sometimes (about half the time) |
| 2 | A few times (less than half the time) |
| 1 | Almost never or never |

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

| 0 | No sexual activity |
| 1 | Extremely difficult or impossible |
| 2 | Very difficult |
| 3 | Difficult |
| 4 | Slightly difficult |
| 5 | Not difficult |

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

| 0 | No sexual activity |
| 5 | Almost always or always |
| 4 | Most times (more than half the time) |
3 Sometimes (about half the time)
2 A few times (less than half the time)
1 Almost never or never

10. Over the past 4 weeks, how difficult was it to maintain your lubrication (“wetness”) until completion of sexual activity or intercourse?

0 No sexual activity
1 Extremely difficult or impossible
2 Very difficult
3 Difficult
4 Slightly difficult
5 Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you reach orgasm (climax)?

0 No sexual activity
5 Almost always or always
4 Most times (more than half the time)
3 Sometimes (about half the time)
2 A few times (less than half the time)
1 Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how difficult was it for you to reach orgasm (climax)?

0 No sexual activity
1 Extremely difficult or impossible
2 Very difficult
3 Difficult
4 Slightly difficult
5 Not difficult

13. Over the past 4 weeks, how satisfied were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

0 No sexual activity
5 Very satisfied
4 Moderately satisfied
3 About equally satisfied and dissatisfied
2 Moderately dissatisfied
1 Very dissatisfied

14. Over the past 4 weeks, how satisfied have you been with the amount of emotional closeness during sexual activity between you and your partner?

0 No sexual activity
5 Very satisfied
4 Moderately satisfied
3 About equally satisfied and dissatisfied
2 Moderately dissatisfied
1 Very dissatisfied
15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

5  Very satisfied  
4  Moderately satisfied  
3  About equally satisfied and dissatisfied  
2  Moderately dissatisfied  
1  Very dissatisfied  

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

5  Very satisfied  
4  Moderately satisfied  
3  About equally satisfied and dissatisfied  
2  Moderately dissatisfied  
1  Very dissatisfied  

17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?

0  Did not attempt intercourse  
1  Almost always or always  
2  Most times (more than half the time)  
3  Sometimes (about half the time)  
4  A few times (less than half the time)  
5  Almost never or never  

18. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?

0  Did not attempt intercourse  
1  Almost always or always  
2  Most times (more than half the time)  
3  Sometimes (about half the time)  
4  A few times (less than half the time)  
5  Almost never or never  

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

0  Did not attempt intercourse  
1  Very high  
2  High  
3  Moderate  
4  Low  
5  Very low or none at all  

*Thank you for completing this questionnaire.*

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Outcome Assessments  

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Committee 7

Physiology of Female Sexual Function and Pathophysiology of Female Sexual Dysfunction

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The sexual response cycle in men and women includes the basic stages of sexual desire, arousal and orgasm. Understanding of the neurobiology and psychophysiology of these fundamental phases or aspects of sexual response has advanced dramatically since the early studies of Masters and Johnson (1966, 1970). A review of the early studies is beyond the scope of the present volume. This chapter will address recent studies of the physiological and pathophysiological processes in women’s sexual dysfunction; the corresponding mechanisms and physiological processes in men are described in Chapters XX, XX. Dramatic advances have occurred in our understanding of the neurochemical and hormonal mechanisms of sexual response. Many of these advances are based on animal models, although human studies are being reported with increasing frequency. The latter portion of the chapter includes an overview of these new and exciting areas of research. Following the principles of the International Consultation, criteria of evidence-based medicine were applied rigorously in the evaluation of all experimental literature in this new area of study. It is noteworthy that the committee identified over 600 references of relevance to the topic.

Scientific advances in women’s sexual health have lagged somewhat behind those of men’s sexual health. This is despite the fact that numerous epidemiologic studies show a higher prevalence of sexual complaints and problems in women than in men. Therapies for women with sexual dysfunction have not been developed in accordance with current physiologic understanding of women’s sexual function. This chapter addresses the contemporary evidence-based knowledge of the physiology of desire, arousal and orgasm in female sexual function and pathophysiology of disorders of desire, arousal and orgasm in female sexual dysfunction. The basic principles of evidence-based medicine were systematically applied in evaluating a large and growing body of research.

Due to ethical constraints and practical limitations, much of the current knowledge-base in sexual physiology is derived from studies in non-human species. These studies are reviewed first, prior to the studies in normal volunteers and clinical samples in the latter portion of the chapter.

While it is difficult to study the neurobiology of human sexual behavior experimentally, real progress in the past decade has been realized in understanding the neuroanatomical and neurochemical mechanisms that underlie sexual desire, and how sexual stimulation and reward impact on attractiveness and mate choice.

1. CONCEIVING OF COMMONALITIES

All organisms that engage in sexual behavior share a common set of principles and end-points that define
the behavior, along with particular neural mechanisms that make it successful. All organisms must be able to respond to hormonal and neurochemical changes that signal sexual desire and arousal. This ability underlies our moment-to-moment level of sexual arousability (as conceived by Whalen [1]), 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. All organisms 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 potential sex partners from those that are not sexually receptive, and to pursue sex partners 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 [2]. 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 [3].

With regard to models of human behavior, something performed 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 [4]. If the male is sluggish or non-responsive, 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 [5, 6]. Of course, such behavior would not be interpreted as sexual solicitation in most human cultures. However, solicitation in all species indicates a willingness or desire to copulate, and high levels of solicitation in females, or analogous courtship behaviors in males, suggest that the animals are highly motivated to copulate. At a strictly behavioral level of analysis, it does not matter whether the motivation to do so is driven by a primary desire for sexual gratification, offspring, conflict resolution, or other social rewards. Contrast solicitation with lordosis, the arching of the back characteristic of sexual receptivity in many mammalian females. There is no human counterpart to this behavior. Thus, solicitation in rats, and not necessarily lordosis, might be the most “analogous rat model” of sexual desire in women.

2. WHAT ANIMALS MAKE GOOD MODELS?

Any animal “system” in which the homology or analogy has predictive validity to human responses or physiological processes (and can be replicated) is a good model. Rats continue to be the most frequently-used animals in the study of sexual behavior, the most obvious reasons being that they are practical (e.g., small, easy to handle, and quite social) and they have a large literature associated with them. Rats also resemble humans in many analogous and homologous ways. Certain tissues and neuroendocrine systems in rats are strikingly similar to our own (e.g., the physiological control of erection or uterine tissue growth following estrogen treatment). As a social animal, rats have evolved a level of behavioral plasticity that allows them to adapt to a variety of ecological niches [7,8,9]. Like humans, their patterns of copulatory behavior can be described as “opportunistic”, and they will copulate in a variety of circumstances, in dyads, triads, or large groups [4,9-12]. Beach [10] noted that male and female rats will copulate in virtually any type of testing chamber. Rat sexual behavior has thus been examined experimentally in groups (4), in mate-choice paradigms (13, 14), and in traditional dyadic mating situations in a variety of unilevel or bilevel chambers (15-18). The use of different testing situations sometimes results in different patterns of copulatory behavior. Rather than such differences being considered an experimental annoyance, they stand as examples of the profound behavioral plasticity of rats in different circumstances, examples of the way that rats are able to alter their behavior to meet the demands of different contexts, much like humans do.

a) 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 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 neu-
ral “tone” or preparedness to respond to sexual incentives. This latter concept was defined as “arousability” by Whalen (1), 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).

b) Female sexual arousal

Physiological sexual arousal in women has received experimental attention. Drugs or stressful circumstances block vaginal and possibly clitoral blood volume in women. Clinical results with sildenafil in women with sexual arousal disorders have been inconclusive [19-21]. 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 [22-23]. For example, women are reported to experience cyclic fluctuations in arousability and desire, with peak incidents of female-initiated sexual activity coinciding with ovulation [24]. 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 [25]. The same pictures do not activate those ERP components during other phases of the menstrual cycle, or in women taking oral contraceptives [26]. 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 ovarioctomized rats by sequential administration of estrogen and progesterone [27].

In vivo experimental models of genital arousal in female New Zealand White rabbits have been developed by Traish, Goldstein, and their colleagues [28-33]. 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 intracavernosal pressure and blood flow, and decreased vaginal luminal pressure. Similar effects have been reported following pelvic nerve stimulation in female rats [34, 35]. 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 [36] 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 [37] 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.

c) Models of sexual desire

Desire has always been difficult to define [38-39]. In the DSM-IV-TR [40], the diagnosis of Hypoactive Sexual Desire Disorder 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 appears coherent but is circular. How does desire manifest itself?

Many clinicians and motivational theorists alike view desire as distinct from arousal in both animals and humans. This is apparent in the DSM’s categorization of arousal disorders 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” or “crave” sex (with wanting and craving defined here as in Robinson & Berridge, [41] for drugs of abuse). In practice, however, desire may well be informed or even confirmed by the presence of auto-
nomic 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 [19, 42]. When an individual expresses sexual desire behaviorally, it follows that attention and behavior focus on obtaining some form of positive sexual reinforcement.

Like people, animals manifest sexual excitement behaviorally. They will increase their motor output in anticipation of copulation and work for the opportunity to copulate or to obtain primary or secondary (conditioned) sexual rewards associated with copulation. Animals will also choose between two or more sexual incentives based on the strength of the incentive cues and the animal’s own internal drive state. What characterizes these behaviors is that they occur before copulation: Courtship, operant responses, conditioned locomotion in anticipation of sex, time spent near a particular sexual incentive, or choices made between two or more incentives, can all be considered analogies of anticipatory sexual desire. Simply put, animals with more “desire” will display more robust behavior than animals with less desire. Desire can also be inferred from certain appetitive behaviors that occur during copulation. A growing body of evidence indicates that these aspects of sexual behavior are altered in a relatively selective fashion by certain drugs that are known to alter desire in humans.

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, 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).

Bermant [43] and Bermant and Westbrook, (44) reported that female rats would bar-press for access to gonadally-intact, sexually active males. More recently, Matthews et al. [45] reported that access to intromissions from a male that were made contingent on poking a lever with the nose increased the incidence 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 [46-48] 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 [49].

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, scents, for certain types of clothing, even for fetish objects. 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. 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 [50, 51]. 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 features, 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 in animals seem instinctual and hard-wired by hormonal influences on the brain. For example, sexually receptive females spend more time near gonadally intact, sexually active males versus castrated, sexually inactive males [52]. However,
other preferences are conditioned by experience with sexual reward. Female rats find the ability to pace or control their copulatory contact with males rewarding [53], and will display conditioned place and partner preferences for cues associated with such reinforcement (see below). For example, in female rats, a neutral odor (almond) was paired with the ability of females to pace [54]. This is was done using a pacing chamber similar to that described by Erskine [15] and Paredes and Alonso [53] in which a Plexiglas divider is placed in the middle of the chamber. The bottom of the divider has one or more holes cut out that are small enough for the female to pass through, but too small for the male, thus the female can regulate her contact with the male simply by running from side to side. 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. 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 show a significant preference to stay with that male for their first ejaculation; females in the unpaired group did not show a conditioned ejaculatory preference. The selective copulation and mating behavior on the part of females in the paired group would be expected to assure paternity [55].

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 can be considered analogues of desire (and possibly subjective arousal). These measures can be recorded unambiguously in bilevel chambers, pacing chambers, mazes, or choice boxes [56]. 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, 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 [18]. 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 short, may increase desire in women. For example, ovariectomized female rats primed with estrogen and progesterone, or estrogen alone, and administered the melanocortin agonist PT-141, display a dramatic and selective increase in solicitations. Although in recent Phase I clinical trials, this drug was shown to increase vaginal arousal in women viewing a female-centric erotic film [57], it remains to be tested whether this drug will increase their desire for sex in appropriate circumstances, or as measured by paper-and-pencil tests of sexual arousal and desire. If so, then solicitation in female rats can be considered an analogue 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” [58]. More is known about the hormonal, neurochemical, and neuroanatomical control of lordosis than any other mammalian sexual behavior [59, 60]. 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 [58, 18]. Drugs that bind to D1 dopamine receptors, adrenergic receptors, oxytocin receptors, opioid receptors, or GABA receptors in certain hypothalamic brain regions can increase lordosis in ovariectomized rats primed with estrogen alone [61, 62]. These substances may work on neurochemical substrates normally activated by progesterone, or could work via cell-signaling cascades that activate progesterone receptors (e.g., as has been described by Mani et al. [63], 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 hypoactive sexual desire disorder.

d) Models of sexual reward

Like the expression of sexual desire, sexual reward has many faces and states of being. This alone makes it difficult to define what is and is not rewarding for any person or within a culture. Moreover, sexual behavior may occur for reasons that have nothing to do with sexual gratification per se. But sexual reward as a general concept has a more pervasive problem: its association in psychology with positive reinforcement. Positive reinforcers are traditionally considered events or stimuli that increase the probability of subsequent behavior [64]. Small food pellets to a hungry rat are positive reinforcers because they increase instrumental responding for them. Playing with one’s hair or sideways glances during a bout of flirting would also be considered positive reinforcers if they increase the degree of responding between the flirting pair [65].

All behaviors have a beginning, middle, and end, and satiety mechanisms place negative feedback on behavior by activating inhibitory neural pathways. Satiety mechanisms are absolutely critical for any regulatory behavior [66]. In the short term, consuming a large meal or copulating to sexual exhaustion decreases responding for food or sexual incentives. Fortunately, meals can be broken up into small bites that maintain operant responding for them. Sex partners cannot. This was the reason that Everitt et al. [67] used a stimulus light that predicted the arrival of a sex partner. The light acted as a conditioned reinforcer that could be presented for brief periods, and doing so supported relatively high rates of operant responding. If positive reinforcement equals reward, then satiety cannot be rewarding because it suppresses ongoing behavior. It is easy to see how theories of human sexual reward can be hindered by conflicting definitions of reward, reinforcement, and satiety: flirtations which are unambiguously rewarding if they lead to more behavioral output. However, orgasms would be rewarding only if they lead to more sexual activity; they could not be considered rewarding if they induce a period of sexual refractoriness.

In any motivational system, reward should be considered a dynamic function with an inverted U-shaped relationship to ongoing behavior: Low rewards do not sustain behavior, moderate to ideal rewards do, and high rewards induce the inhibitory feedback that characterizes satiety. 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. The reward value of satiety may also depend on the time frame. Although sexual satiety decreases sexual responding in the short term, the reward associated with it in female rats is necessary for the conditioning of sexual preferences in the long term.

1. Responding for sexual reinforcers

How do we infer sexual reward in animals? One 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’ [68] 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.

2. Reward in copulatory measures

Another way to infer sexual reward is based on copulatory activity. Indeed, solicitation and pacing in female 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.

3. Conditioned place preference

Contextual factors such as settings are important components of positive sexual experiences for women [69-73]. Salient cues in the environment may be associated with sexual reward in such a way that they increase arousal or desire directly in their presence. Accordingly, one way to infer sexual reward is to examine responses made toward contextual cues paired with sexual reward. With animals, this can be done using the conditioned place preference (CPP) paradigm. 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. CPP is said to have developed if the subject spends significantly more time in the reward-paired compartment than the other compartment. Stimuli or events that are capable of supporting CPP are referred to as “rewards” rather than “reinforcers”, because the subject has never been required to move into the paired compartment to experience them. Thus, CPP is not reinforced, per se, because it is displayed spontaneously on the final test. However, the increased time spent in the side paired with reward is clearly conditional upon the Pavlovian association of those contextual cues with the reward state.

CPPs have been demonstrated in female rats and hamsters. Oldenburger et al. [74] 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 [53] and Paredes and Vazquez [75] 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 the pacing chambers described above, in which a Plexiglas divider bisects the chamber. 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 [76], contextual cues associated with pacing elicit 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, Alfonso, Woehrling, and Pfaus [77] 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 [47] 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 interintromission 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. [45] (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.

In females, naloxone blocked the acquisition of a pacing-related CPP, suggesting that opioid systems in the brain of female rats are activated by sex-related cues [78]. Dopamine antagonists have not been reported to alter the development or expression of copulatory CPPs in female rats. In contrast, Meisel, Joppa, and Rowe [79] 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). (Figures 1 and 2)

e) Animal Models: A Synthesis

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. Females like to control the initiation and rate of sexual contact. Sexual behavior in females is strengthened with experience, making them less vulnerable to treatments that disrupt sexual responding. From an evolutionary perspective, sexual behavior appears to have similar processes and endpoints for all mammals, and perhaps for all species that engage in it.

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. It was 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. Control is an important aspect of sexual function in women, and problems with locus of control may form an important part of the etiology of different sexual disorders [80]. Female rats display proceptive 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 [24, 81]. 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.

Animal models will continue to be indispensable for studies of the neurobiology of sexual behavior. The knowledge that lesion and drug studies, neurochemical and neuroanatomical analyses and molecular approaches provided in animals guide our emerging work in the neuroanatomy of sexual responding in humans using functional magnetic resonance imaging or positron emission tomography. Animal models are needed to further understand the hormonal processes that lead to changes in sexual arousability (e.g., following hormone 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.

II. AROUSAL: PHYSIOLOGY OF GENITAL AROUSAL IN FEMALES

1. INNERVATION OF FEMALE GENITAL AROUSAL RESPONSE

The neural control regulating the female genital response is poorly investigated, and is therefore less understood than the male counterpart. The majority of investigations elucidating the neural control have been done in animal studies, primarily rodents, and only few human studies exist. The use of animal studies has clear advantages, as they are easily performed, but the obvious drawback is the lack of evidence of comparability between human and animal structures. As such, animal data primarily generate ideas for future human studies and conclusions from animal studies must be made with reservations.

Studies on regulation of genital arousal include those on regulation of vaginal blood flow, clitoral, labial and vestibular bulb engorgement, and vaginal smooth muscle wall. The role of contraction and relaxation of the vaginal smooth muscle wall in the genital arousal response is still debatable. Many in vitro studies have focused on vaginal tone and its regulation. Most likely this is because it is an easy end organ to study and exert basal smooth muscle properties,
Figure 1: TOP: Effects of the dopamine agonist apomorphine on solicitation and pacing behavior in ovariectomized female rats without hormone replacement (O), primed with estrogen alone (E+O), or primed with estrogen and progesterone (E+P). Data are means ± SEM. Tests were conducted in bilevel chambers. Apomorphine increased solicitations and decreased pacing in females primed with estrogen alone, but not without estrogen. Apomorphine did not affect solicitation or pacing in females primed with estrogen and progesterone. Females solicit sexual contact with males by orienting their heads toward the males, and then running away to another level. Pacing in bilevel chambers is defined as the number of level changes displayed by females prior to each mount by the male. Females with high sexual interest display a large number of solicitations and low number of level changes between mounts. This pattern of behavior increases their sexual contact with males.

BOTTOM: Dopamine release in the nucleus accumbens and dorsal striatum of sexually experienced female rats during sexual contact with males. Dopamine in extracellular fluid was extracted using microdialysis and analyzed by electrochemical detection after separation with HPLC. Samples were taken at 10-min intervals. To rule out general locomotion, females were first placed onto an elevated rotating drum for 20 min, followed by the drum rotating at a speed of 6 meters/min for another 20 min. Females were then placed into a clean testing chamber. This was followed by exposure to an increasing succession of stimulus intensities. First the bedding was replaced with clean bedding, then with bedding soiled by sexually active male rats. Then a male was placed behind a wire-mesh screen, after which the screen was removed to allow sexual contact for 20 min. The male was removed after this copulatory period. Nosepokes through the wire mesh were counted prior to copulation as a measure of the female’s precopulatory interest.
which may be comparable to that of the smooth muscles in the genital vasculature and clitoris.

a) Autonomic neurotransmitters in the female genital arousal response.

Adrenergic and cholinergic neurotransmitters have been identified in the postganglionic fibers to the vagina and the clitoris, primarily in animal models [82-88], as well as alpha-adrenergic receptors which have been demonstrated biochemically and functionally in the rabbit vagina [85, 86]. Little data exists on the presumed inhibitory effect of adrenergic stimulation on the female sexual genital response. In vitro experiments on the smooth musculature of the rat and rabbit vagina and rabbit clitoris show contractile response to adrenergic stimulation [89-91].

In a pilot study, oral phentolamine was administered to postmenopausal women with Female Sexual Arousal Disorder. The results indicated a moderate effect on subjective and objective parameters of sexual arousal. [92]. Unfortunately it was impossible to discriminate between preferential and central effects in the study. Meston and colleagues provided evidence for an excitatory role of peripheral adrenergic activation on sexual arousal in women. Ephedrine (50mg), an alpha and beta adrenergic agonist, facilitated vaginal photoplethysmograph measures of sexual arousal in a randomized controlled trial of 20 women [93].

Figure 2: Dose-response effects of the melanocortin agonist PT-141 on the sexual behavior of ovariectomized female rats primed with E+P. Data are means + SEM. Tests were conducted in unilevel pacing chambers bisected by a Plexiglas screen with four holes at the bottom small enough to allow the female, but not the male, free access from one side to the other. Females in these chambers pace their copulatory contact by running back and forth from the side containing the male. PT-141 increased solicitations, hops and darts, but did not affect pacing or lordosis. Interestingly, although PT-141 did not alter the latency to return to the side containing the male after an intromission, it increased the latency to return after an ejaculation. This pattern of data suggests that PT-141 increased the desire of female rats to initiate sexual contact, and further increased the intensity of stimulation received following ejaculation.
The role of noradrenaline in the control of clitoral erection is indirect and only elucidated by case reports on treatment of clitoral priapism with injection of adrenergic agonists [94, 95]. Despite the rich cholinergic innervation, the role of acetylcholine is uncertain. In the in vivo animal model described by Giuliano et al, intravenous injection of atropine only decreased the vaginal blood engorgement induced by stimulation of the pelvic nerve (PNS) slightly. In the same model, intravenous atropine decreased vaginal smooth muscle contractions also induced by PNS. In a small, uncontrolled study of six women, intravenous injection of atropine had no effect on the vaginal blood flow during masturbation [96].

**b) Non-adrenergic, non-cholinergic (NANC) neurotransmitters/ mediators:**

A great variety of NANC neurotransmitters/mediators have been identified in the female genital tract, mainly in animal models. In animal studies on the vagina and its vasculature, vasoactive intestinal polypeptide (VIP), nitric oxide synthase (NOS; producing nitric oxide, NO), neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP) substance P (SP), pituitary adenylate cyclase-activating polypeptide (PCAP), helospectine and peptide histidine methionine (PHM) have been demonstrated [84, 85, 88, 90, 97-104].

**In humans, nerves that contain** VIP, NPY, PACAP, NOS, and CGRP, **have been demonstrated** in the vagina [105-109]. Hoyle et al demonstrated a dense innervation of the vaginal vasculature (arteries, veins and subepithelial plexuses). Most abundant were NPY and VIP immunoreactive fibers, less abundant were NOS, CGRP and SP fibers [108]. Human studies are crucial, however the major drawback is that the tissue studied comes from women undergoing hysterectomy. This is tissue from the proximal part of the vagina, less innervated and of different embryological origin than the denser innervated distal part [110] that may be of more importance in the physiological sexual arousal response. An exception is the study of Jørgensen et al who demonstrated NPY-immunoreactivity in both the proximal and distal parts of the human vagina as plexuses of nerve fibers beneath the vaginal epithelium in relationship to the small vessels [107].

In the human clitoris, limited immunohistochemical studies have demonstrated that the clitoris is innervated by VIP, PHM, NPY, CGRP and substance P immunoreactive nerves [111]. **Signal transduction systems have also been investigated.** In cell cultures from human and rabbit vaginal smooth muscle, the signal transduction molecules cAMP and cGMP have been studied. In the vaginal smooth muscle cells cAMP was stimulated by PGE₁ and isoproterenol and cGMP by the NO donor; sodium nitroprusside, suggesting that these signal transduction pathways are of importance for regulation of vaginal smooth muscle tone. Furthermore, sildenafil enhanced the intracellular cGMP accumulation in the human and rabbit vaginal smooth muscle cells [112]. In the human vagina, PDE5 expression has been demonstrated in the anterosuperior vaginal wall [113].

**c) The role of NANC transmitters in the arousal response.**

Very little is known about the role of these neurotransmitters/mediators in the regulation of the genital arousal response in females. While their existence in the genital tract can be demonstrated, their functional role in the physiology and pathophysiology of genital arousal is unknown.

VIP has traditionally been considered to be the most important neurotransmitter in the regulation of human vaginal blood flow in the sexual arousal response. This assumption is based on 1) the high concentration of VIP in the tissue of the genital tract, 2) the close association of the genital vasculature and VIP containing nerve fibers, 3) the increase in the level of VIP in women from sexual arousal and 4) the increase of vaginal blood-flow in women from IV and subepithelial administration of VIP [109, 114-118]. This is only indirect evidence: further clinical studies must be performed in order to obtain more information. The role of VIP in the physiological arousal response needs to be investigated further.

During the last few years the role of NO in the arousal phase have been studied with more interest, partly based on the knowledge from males where NO is known to play a crucial role in the erectile response. New in vivo models on rats, rabbits and dogs have made it possible to investigate vaginal and clitoral blood flow, vaginal oxygen tension, vaginal temperature and vaginal luminal pressure as markers of sexual arousal. [31, 119-123].

In the in vivo animal models, pelvic nerve stimulation (PNS) increases vaginal blood flow and temperature as well as clitoral blood flow [34, 120, 122]. Stimulation of the pvvertebral sympathetic chain reverses the PNS induced effect in the rat [34]. In both the rabbit and the dog model, the PDE5-inhibitors sildenafil and vardenafil respectively enhanced the PNS induced vaginal and clitoral blood flow indicating that the NO/cGMP pathway is involved in
the physiological mechanism of female genital arousal [123, 124].

A role of the NO/cGMP system on clitoral erection is further indicated by in vitro animal experiments. In rabbit, clitoral corpus cavernosum inhibition of NOS dramatically abolishes electrically stimulated relaxation, whereas sildenafil augments the relaxation [89, 125, 126]. In human clitoral tissue, sildenafil has been demonstrated to inhibit PDE5 [127], and immunohistochemical studies have identified NOS immunoreactive nerve bundles within the glans and corpora cavernosa of the clitoris [128]. Clinically, sildenafil has been shown to enhance vaginal engorgement during erotic stimulus in healthy women without sexual dysfunction [129]. Several trials are being performed investigating sildenafil as a treatment for arousal disorders [130,131]. There are indications that the NO/cGMP system plays a role in the genital arousal response, but the exact role in the normal arousal response still needs to be investigated.

2. PATHOPHYSIOLOGICAL FACTORS THAT MAY INFLUENCE THE PHYSIOLOGICAL GENITAL AROUSAL RESPONSE

a) Diabetes

In rat models, diabetes mellitus (Type 1) induces vaginal fibrosis, measured as TGF-beta expression in collagen connective tissue, fibroblasts and smooth muscle fibers [132]. The nitrergic dependent relaxation of vaginal tissue is impaired during the diabetic state [90]. Park and colleagues also have demonstrated that type 1 diabetes mellitus in the in vivo rabbit model produces significant adverse effects on the hemodynamic mechanism of clitoral engorgement and leads to diffuse clitoral cavernous fibrosis [133].

b) Hypertension

In the rabbit, experimentally induced arteriosclerosis results in decreased PNS induced vaginal blood flow and vaginal wall pressure [31].

c) Conclusions and future directions.

The understanding of peripheral mechanisms and neurotransmitters regulating the female genital sexual arousal response is limited. Modulation of vaginal and clitoral engorgement, vasocongestion and vaginal lubrication may be antagonistic, regulated by parasympathetic and sympathetic components of the autonomic nervous system of the female genitalia. VIP and NO may be the primary facilitators with noradrenaline and NPY the primary inhibitors of the genital arousal response. There is a need to expand our current understanding of the physiological mechanisms responsible for the arousal response. Better understanding of the physiology and pathophysiology of genital arousal is necessary for improved clinical management of arousal disorders in women.

3. AROUSAL: NERVOUS SYSTEM IN GENITAL AROUSAL

Our knowledge regarding human female sexual function is at its initial stages, and many important unanswered questions in this area still need to be investigated. Most of the information available is derived from animal studies or drawn by analogy from studies in males. The female animal studies have been predominantly focused on behavioral studies and on the central nervous control of genital responses. Data regarding the peripheral nervous system and in particular the genital somatic sensory information pathways are very limited, especially vis-à-vis arousal and orgasmic functions. Neurogenic female sexual dysfunction can result from disease of the central or peripheral nervous system. The effects of specific spinal or peripheral neural injuries on female sexual response is under investigation and will hopefully lead to improved understanding of the neurophysiology of orgasm and arousal in normal as well as women with sexual difficulties.

a) Peripheral innervations involved in female genital response

Innervations of the pelvic organs have been previously reviewed by several authors [134, 135], but most of the information available today has been extensively studied in the rat. [136, 137]. In general, innervations of the genitals are comparable between human males and females. Sexual arousal is a vascular and neuromuscular event controlled by facilitatory parasympathetic and inhibitory sympathetic inputs. Autonomic preganglionic parasympathetic fibers to the vagina and clitoris originate in the sacral parasympathetic nucleus at the spinal cord, and the sympathetic fibers at the thoracolumbar level. Parasympathetic fibers are conveyed by the pelvic nerve, sympathetic fibers by the hypogastric nerve and the paravertebral sympathetic chain. In addition, both the somatic pudendal nerve and, very likely, the afferent and efferent fibers of the vagus nerve contribute to the genital sexual response.

b) Autonomic innervation

Both the hypogastric (sympathetic) and pelvic (para-
sympathetic) nerves innervate the pelvic ganglion. Postganglionic fibers innervate the pelvic organs, including the bladder, urethra, accessory sex glands, vagina, uterus and clitoris. The cavernous nerve provides the vasodilatatory innervation to the clitoris.[138] Identification of nerve fibers in the human vagina showed that there are significantly more fibers in the more distal part than in the proximal area. Moreover, the anterior vaginal wall that probably is the most sensitive part of the vagina displays a denser innervation than the posterior one [139]. The sacral parasympathetic nucleus neurons represent the main parasympathetic outflow to the genitalia in females. Preganglionic neurons of the hypogastric nerve emerge from the T12-L3 spinal segments from two separate nuclei, the dorsal gray commissure and the intermediolateral cell column, and represent the sympathetic outflow to the genital tract [140-142].

c) Somatic innervation

Anatomical studies show sensory fibers from the pudendal, pelvic and hypogastric nerves innervate the female pelvic organs. The pudendal nerve, which originates from the pelvic splanchnic branches of the sacral plexus, provides sensory innervation to the perineum, clitoris, and urethra. The motor axons originate in the spinal cord from two motor-neuron nuclei in the L5 segment of the spinal cord (dorsolateral and dorsomedial nuclei) [143]. Moreover, the motor innervation to the perineal striated muscle may be involved in the female sexual response, through voluntary contraction of the perineal muscle that can enhance arousal and play a role in the feeling of pleasure during intercourse [144].

Pelvic nerve sensory fibers innervate the vagina, cervix, and body of the uterus, with the greatest concentration in the fornix of the vagina [138]. The hypogastric nerve contains relatively few axons of afferent neurons, however, these neurons are important for conveying pain sensation from the uterus [142]. There is also some evidence that vagal fibers may convey sensory information from the female pelvic organs. This pathway remains functional after spinal cord transection and may account for the menstrual cramping and orgasm reported in women with complete spinal cord injury. [145, 146].

d) Spinal reflexes

Sexual arousal responses are mainly the product of spinal reflex mechanisms, and are under descending excitatory and inhibitory control from supraspinal sites. The afferent arm is primarily through the pudendal nerve. The efferent arm consists of coordinated somatic and autonomic activity. One spinal sexual reflex is the bulbocavernous reflex involving sacral cord segments S2-S4. Another reflex involves vaginal and clitoral cavernosal autonomic nerve stimulation, resulting in clitoral, labial and vaginal engorgement. [147].

The control of sexual function is based upon spinal mechanisms. The spinal cord provides the autonomic and somatic innervation of the sexual organs. Sensory information from the sexual organs project to interneurons in the lower spinal cord. These interneurons likely generate the coordinated activity of sexual responses.

III. AROUSAL: ROLE OF SEX STEROIDS MODULATING PHYSIOLOGY OF GENITAL AROUSAL IN FEMALES

1. STEROID BIOSYNTHESIS AND METABOLISM IN WOMEN

Androgen hormones are a class of C-19 steroids, produced by the gonads and the adrenals [148, 149]. Steroids with androgenic activity include testosterone (T), α-dihydrotestosterone (5 DHT), ∆4-androstenedione, ∆5-androstenediol, 5α-androstane 3β-17β diol, dehydroepiandrosterone (DHEA) and 3 α-hydroxy androsterone (Figure 3).

a) Physiology of Androgen Hormones in Women

Androgens modulate the function of many organs and tissues in women including the pituitary, bone, adipose tissue, kidney, skeletal muscle, blood, ovaries, uterus, vagina, oviduct, clitoris and mammary gland and regulate secondary sex characteristics [150]. Androgens are not only essential for the development of reproductive function in women and hormonal homeostasis, but also represent the immediate precursors for the biosynthesis of estrogens. Androgens affect sexual desire, bone density, adipose tissue distribution, mood, energy and well-being. Consequently, imbalance in androgen biosynthesis or metabolism in women may have undesirable effects on female general health as well as sexual and reproductive functions [151].

b) Biosynthesis of Androgens in Women

Approximately 25% of androgen biosynthesis takes place in the ovaries, 25% is produced by the adrenal gland and the remaining is produced in the periphery [148, 149, 152]. In women, essentially all of the
androgens detected in the urine are of adrenal origin [150]. In Addison’s disease, the output of urine androgens in the female approaches zero.

In the ovaries, cholesterol is metabolized to pregnenolone, which serves as the precursor for the synthesis of sex steroids. Biosynthesis of testosterone from pregnenolone proceeds via participation of several key enzymes in two interrelated pathways (i.e. $\Delta_5$ or $\Delta_4$ pathways). In the $\Delta_5$ pathway, hydroxylation of pregnenolone by $17\alpha$-hydroxylase and subsequent cleavage of the C-17,20 side chain by the C-17,20-lyase produces dehydroepiandrosterone (DHEA). The latter is converted to $\Delta_5$-androstenediol via $17\beta$-hydroxysteroid dehydrogenase (17$\beta$HSD). This derivative is converted into testosterone by the enzyme complex, $3\beta$-hydroxy $\Delta_5$ steroid dehydrogenase (3$\beta$HSD), $\Delta_4,5$ isomerase. In the $\Delta_4$ pathway, pregnenolone is converted first into progesterone by $3\beta$HSD, $\Delta_4,5$ isomerase. Progesterone is then hydroxylated at the C17 position by the $17\alpha$-hydroxylase and becomes the substrate for the C-17,20-lyase, which converts $17\alpha$-hydroxyprogesterone to $\Delta_4$ androstenedione. The latter product is metabolized to testosterone by the action of the 17$\beta$HSD.

Synthesis of estrogen from androgens in the ovary is believed to involve both the thecal layer and the granulosa. The theca cells have a rich blood supply and steroids synthesized in the theca can readily pass into the circulation. In contrast, the granulosa cell layer is relatively avascular and steroids formed in these cells cross into the theca interna in order to enter the circulation. Both the theca and the granulosa express the aromatase enzyme systems for synthesis of estrogens. In the theca cells androstenedione and estradiol are derived from 17-hydroxypregnenolone ($\Delta_5$ pathway). In the granulosa, pregnenolone is readily converted into progesterone suggesting a $\Delta_4$ pathway. Estradiol is the major steroid detected in ovarian venous blood. The estrogen yield is approximately 10 fold greater from 4-androstenedione than from testosterone.

The synthesis of estrogens from androgens is regulated by gonadotropic hormones, LH and FSH. FSH acts mainly on the granulosa cells while LH acts on multiple sites including the theca, stroma, luteal and granulosa. The theca interna expresses LH receptors which regulate androgen biosynthesis, mainly androstenedione and testosterone. Androgens ($\Delta_4$-androstenedione and testosterone) produced by the thecal compartment diffuse into the follicular fluid where they are converted into estrogens by the granulosa cells or released into the ovarian vein. The granulosa cells express FSH receptors and increased FSH levels increase the number of FSH receptors.

Figure 3: Structures of some C19 steroids that possess androgenic activity.
due to increased granulosa cell number. Furthermore, FSH upregulates the aromatase activity in the granulosa increasing the conversion of androgens to estrogens. Estradiol via autocrine or paracrine mechanisms increases the mitogenic activity, independent of that of FSH. Estradiol augments the activity of FSH in increasing aromatase activity and increasing the conversion of androgens to estrogens.

c) Androgen Biosynthesis in the Adrenal Gland

In the adrenal gland, cholesterol is metabolized to pregnenolone, which serves as the precursor for the synthesis of glucocorticoids and androgens. Biosynthesis of androstenedione from pregnenolone proceeds via participation of several key enzymes. Hydroxylation of pregnenolone by 17α-hydroxylase and subsequent cleavage of the C-17,20 side chain by the C-17,20-lyase produces dehydroepiandrosterone (DHEA). The latter is converted to Δ4- androstenedione via the enzyme complex, 3β-hydroxy Δ5 steroid dehydrogenase (3βHSD), Δ4,5 isomerase. The latter product is metabolized to testosterone by the action of the 17βHSD (Figure 4).

d) Peripheral Conversion of Androgens in Target Tissues

Conversion of precursor steroids, derived from adrenal or ovarian origin, into active androgens in peripheral tissues is an important pathway of androgen metabolism [149, 153]. Thus, DHEA and Δ4-androstenedione may be converted locally into estradiol and 5α-DHT in target tissues [149, 150, 152]. Labrie and his colleagues [153] suggested that in post-menopausal women almost 100% of active sex hormones are derived from peripheral conversion of the steroid precursor DHEA and DHEA-S into active estrogens and androgen hormones. This concept suggests that active androgen hormones could be made on demand by the target tissues from precursors of ovarian or adrenal origin. This would also suggest that in many tissues conversion of DHEA and Δ4-androstenedione from adrenal or ovarian origin to testosterone and estradiol may take place.

The conversion of DHEA and Δ4-androstenedione into specific metabolites in the peripheral target tissues is catalyzed by tissue-specific, unidirectional 17β-HSDs [152]. A family of several enzymes have been cloned and characterized to date. These enzymes may play an important role in providing target tissues with active sex steroid hormones, via a well-controlled intracellular pathway. Thus, local conversion of DHEA or DHEA-S into 4-androstenediol (via 3β-HSD) or Δ5 androstenediol (via 17β-HSD) leads to production of testosterone. Testosterone may be converted locally into 5α-DHT (via 5α-reductase) or into estradiol (via the aromatase). Δ4-androstenedione may be converted locally into estrogen via the aromatase and into estradiol via 17β-HSD [152]. Since specific target tissues express specific and selective isoforms of 17β-HSD, it is likely that conversion of the adrenal androgen precursor into active androgen derivative is regulated by the tissues’ specific physiological requirements.

e) Alterations in Ovarian or Adrenal Androgen Biosynthesis and Metabolism may lead to Androgen Insufficiency in Women

The concept of androgen insufficiency in women, in particular in pre-menopausal women, is controversial. Nevertheless, potential metabolic alteration in steroid biosynthesis in the ovaries or the adrenal may lead to reduced synthesis of androgens. In the ovaries, conversion of Δ4-androstenedione into estradiol is the predominant pathway.

It is possible that under certain pathophysiological conditions the ovaries continue to produce Δ4-androstenedione as an androgen precursor for estrogen biosynthesis but an inadequate production of androgen results, due to shunting of the Δ4-androstenedione to the aromatase or lack of 17β-HSD. Thus, in pre-menopausal women, sufficient estrogen levels may be reached with concomitant reduced levels of androgens. In addition, if reduced output of androgens from the adrenal due to other pathophysiological conditions is coupled with inadequate synthesis of androgen in the ovaries, then it is expected that the pre-menopausal woman would continue to have a menstrual cycle but with androgen insufficiency.

Data on serum androgen levels in healthy, pre-menopausal women without any symptoms of androgen insufficiency is lacking. It is necessary to establish normal and low serum androgen values in healthy subjects. Methodological differences in measurements of serum androgen levels further contribute to the difficulty in defining reduced levels of serum androgens in women. The fact that androgens are derived from multiple endocrine (ovaries and adrenals) and non-endocrine (peripheral) sources contributes further to the difficulty in defining the pathophysiology of androgen insufficiency in women. Testosterone and Δ4-androstenedione synthesized by the ovaries are utilized as substrates by the aromatase in the theca and granulosa cells. Thus, diffusion, compartmentalization, and expression of target-specific enzymes involved in the metabolism of andro-
Figure 4: iogenesis of testosterone from pregnenolone.
f) Effects of Plasma Binding Proteins on Availability of Bioactive Androgens

Sex hormone binding globulin (SHBG) binds testosterone and estradiol with high affinity but does not bind androstenedione or estrone. The concentrations of SHBG increase in response to estrogens, and during pregnancy increase five fold. SHBG synthesis is influenced not only by estrogens but also by thyroid hormones.

It is presumed that the free fraction of sex steroid hormone that enters the cells elicits the biological response. Thus the availability of bioactive hormone is dependent on the level of plasma binding proteins and the affinity of these steroids for the protein. Since the free hormone also acts on the pituitary to regulate further synthesis of steroids, and the free hormone is preferentially inactivated by the hepatic metabolism, one would suggest that plasma proteins play an important role in regulating the bioavailable steroids in the plasma. It is unclear, however, what role the plasma binding proteins play in physiological response. Thus, plasma sex steroid binding proteins may act as depot storage and transportation of sex steroids from the site of synthesis to the target tissue. It is difficult to speculate that changes in the levels of SHBG may contribute to androgen insufficiency in women. This needs further investigation.

2. Modulation of Female Genital Sexual Arousal by Sex Steroid Hormones

Pre-clinical and clinical studies suggest that estrogens modulate genital hemodynamics and are critical for maintaining structural and functional integrity of vaginal tissues [29, 155-157]. Estrogen-depletion resulted in a significant reduction in vaginal blood flow following pelvic nerve stimulation, when compared to controls. Estrogen replacement increased genital blood flow and lubrication [29, 157, 158]. Evidence suggests that estrogens may modulate blood flow by regulating the activity of neural and endothelial NO synthase and VIP in the vagina [104, 159-162]. In estrogen-deprived animals, vaginal lubrication was markedly decreased compared to controls and was restored by estrogen treatment [29]. Vaginal mucification was reduced by estrogen administration in ovariectomized animals [163]. There are limited studies examining the effects of estrogens on vaginal smooth muscle contractility. Recently, Kim et al. [164] demonstrated that electric field stimulation and VIP caused frequency- and dose-dependent relaxation of vaginal tissue strips. These responses were slightly attenuated in ovariectomized animals and significantly inhibited in estrogen treated animals.

Although clinical studies have indicated that androgens modulate sexual arousal responses [165-170], no investigations have addressed the mechanism by which androgens facilitate such responses. Preliminary studies from our laboratory have shown that androgen treatment of ovariectomized animals enhanced vaginal smooth muscle relaxation in response to electrical field stimulation [164]. In addition, androgen treatment normalized VIP-induced smooth muscle relaxation, suggesting that androgens modulate neurotransmitter function. Kennedy and Armstrong [171,172] have shown that androgens increase vaginal mucification in the rat. Treatment of ovariectomized rats with topical DHEA resulted in complete reversal of vaginal atrophy and stimulated proliferation and mucification of the vaginal epithelium [149]. Furthermore, preliminary data from work by Traish and Kim suggests that androgens maintain vaginal mucification in rabbits. Recent work has suggested that progesterone is an important signaling molecule in peripheral nerves, where it promotes myelin sheath formation by activating expression of specific hormone sensitive genes [173]. However, the role of progesterone on peripheral vaginal arousal is poorly understood. In the following section is a brief discussion of the experimental data on sex steroid hormones in modulating the physiological process of arousal. Specifically discussed is the role of steroid hormones in modulation of i) blood flow, ii) lubrication, iii) neurotransmitter function, iv) smooth muscle contractility, v) mucification, and vi) sex steroid receptor expression in genital tissues.

a) Modulation of Genital Blood Flow by Estrogens and Androgens

Although sexual receptivity in the female of lower animals is controlled by estrogens, sex drive in women is not stimulated by estrogen, as experienced in clinical studies. However, administration of androgens in females intensifies sexual interest
The role of NOS/cGMP pathway in regulating genital and Androgens

c) Regulation of Vaginal NOS Activity by Estrogens

To restore vaginal lubrication and health. Shed vaginal lubrication and genital atrophy may result in diminished blood flow, secondary to estrogen deprivation, may lead to decreased pelvic blood flow resulting in diminished vaginal lubrication, clitoral fibrosis, thinning of the vaginal wall and decreased vaginal submucosal vasculature [155]. In addition, estrogen deficiency leads to involution and atrophy of the genital organs, adversely affecting cervical, endocervical, and glandular mucin production. In contrast, estrogen therapy in post-menopausal women increases pelvic blood flow, re-establishing vaginal integrity and lubrication.

The effects of ovariectomy and estrogen replacement on vaginal lubrication were investigated in an animal model. Ovariectomy markedly diminished vaginal lubrication, suggesting that genital atrophy and diminished genital blood flow, secondary to estrogen deprivation, may bring about structural and functional changes in the genital tissues that negatively affect lubrication. Treatment of ovariectomized animals with estradiol significantly increased vaginal lubrication. Interestingly, treatment with testosterone alone did not improve vaginal lubrication [29]. The data in this study demonstrate that estrogen replacement in ovariectomized animals normalized vaginal lubrication to levels observed in control animals. These observations suggest that estrogen therapy in post-menopausal women with complaints of diminished vaginal lubrication and genital atrophy may restore vaginal lubrication and health.

c) Regulation of Vaginal NOS Activity by Estrogens and Androgens

The role of NOS/cGMP pathway in regulating genital blood flow has been under investigation. Traish et al and others have demonstrated the expression of phosphodiesterase type 5 in the vagina [112, 113], suggesting a role for this enzyme in regulating the second messenger cGMP. Cellek and Moncada [89] have shown that the clitoral corpus cavernosum relaxes in response to NO and that this response is facilitated by PDE type 5 inhibitors. Kim et al. reported that NOS plays an important role in stimulating blood flow in an animal model [28] and that inhibition of NOS by administration of LNAME resulted in reduced vaginal blood flow. The effects of androgen and estrogen deprivation and replacement on the expression and activity of NOS in rabbit vaginal tissue were investigated [175]. Androgens enhanced and estradiol downregulated NOS activity and protein in the vagina of ovariectomized rabbits.

Observations were in agreement with those reported by Batra and his colleagues with estrogen and progesterone in the rabbit model [104, 159-161, 175, 176]. The significance of down-regulation of NOS by estrogens and its up-regulation by androgens on vaginal hemodynamic parameters remains to be determined. Several clinical studies with sildenafil in women produced contradictory results [130-132, 177, 178]. It remains to be determined, however, if the endocrine status of the patient may play an important role in determining whether PDE type 5 inhibitor will be effective in facilitating genital arousal response.

d) Effects of androgens and estrogens on vaginal smooth muscle contractility

In the female animal model, pelvic nerve stimulation induces a coordinated peripheral genital swelling and lubrication response, increased clitoral and vaginal blood flow, increased length and diameter of the vaginal canal and clitoral corpus cavernosum, increased tissue pressure and engorgement of the vaginal wall and clitoris, and development of a transudate of lubricating fluid from the vaginal vasculature.

The changes in the tissue properties of the vaginal canal are in part regulated by smooth muscle contractility. It has been demonstrated that ovariectomy reduces smooth muscle relaxation to electric field stimulation and to VIP in organ bath studies [164]. Estrogen treatment of ovariectomized animals reduced the relaxation response. In contrast, androgen treatment facilitated VIP-induced relaxation. These observations suggest that androgens facilitate vaginal smooth muscle relaxation while estrogens attenuate this response [164].
e) Effects of ovariectomy and estrogen replacement on vaginal sialic acid content (mucification)

It has been suggested that mucin production in the vagina is stimulated by low doses of estrogen and is reduced by high doses of estrogen [163, 179, 180]. The effects of estradiol on production of sialic acid in the rabbit vagina were investigated by Traish and Kim (unpublished data). One group of animals remained intact and four groups underwent bilateral ovariectomy. Two weeks post-ovariectomy, animals were treated with vehicle, estradiol or testosterone. The ovariectomized, vehicle treated group showed a significant decrease in vaginal sialic acid concentration compared to the control group. Animals treated with estradiol demonstrated further decreases in vaginal sialic acid concentration, whereas no changes were observed with testosterone treatment, relative to the vehicle treated group. These observations suggest that estrogens regulate mucin production in the vagina, as demonstrated by reduced sialic acid content.

f) Effects of steroid hormones on estrogen and androgen receptors in the vagina

The vagina is a target tissue for sex steroid hormones. Several studies have shown the presence of steroid receptors by biochemical and immunochemical assays [181-188]. While the effects of steroid hormones on regulation of estrogen and progesterone receptor in reproductive organs have been extensively investigated [189], there are limited studies on the regulation of expression of sex steroid hormone receptors in the vagina. Steroid receptors are regulated differentially in different target tissues by sex steroid hormones. For example, estrogens increase expression of estrogen and progesterone receptors in uterine tissue [190]. However, in preliminary studies, we have observed that ovariectomy increased vaginal tissue content of ER alpha (Kim et al., unpublished observation). Further, estrogen treatment of ovariectomized animals reduced ER alpha expression in the vagina, as assessed by ligand binding studies and western blot analyses, suggesting tissue specific regulation of ER isoforms by estradiol. Androgen receptor expression is decreased by ovariectomy and was increased by estradiol or estradiol plus testosterone treatment, suggesting cross-regulation of AR by estrogens.

It has recently been reported that ERα expression is diminished or lost in the vagina of postmenopausal women, suggesting loss of physiological response mediated by this receptor isoform [188].

Since hormone therapy is utilized for management of post-menopausal women, it would be important to determine how sex steroids regulate the expression of vaginal steroid hormone receptors. Moreover, these studies will be invaluable to correlate the changes in receptor expression with changes in neurotransmitter function in modulating the physiological parameters of vaginal arousal (vaginal blood flow, lubrication, mucification and smooth muscle contractility).

3. SUMMARY

The important role sex steroids play in modulating sexual function in women has been recognized for many years. Receptors for sex steroid hormones (estrogens, progestins and androgens) are widely expressed in the brain and genital tissues suggesting that steroid hormones may modulate sexual function at the central level (desire and arousal) as well as the peripheral level (genital, arousal.). Sex steroid hormones are critical in maintaining structural and functional activity of genital tissue and therefore may be critical for genital arousal physiology (genital blood flow, lubrication, mucification, and sensation). (Figure 5) While the effect of androgens on sexual desire is fairly established, the role of sex steroid hormones on genital sexual arousal is not well understood. Sex steroid hormones’ modulation of genital tissue hemodynamics and genital arousal responses is an area that has received limited attention. Decreased circulating levels of estrogen following bilateral oophorectomy in the rabbit altered nerve-mediated vaginal blood flow and vaginal structure [157] and lubrication [158]. Administration of estrogen to ovariectomized animals increased genital blood flow [157, 158] and restored vaginal lubrication [29, 158]. Nevertheless, the cellular and molecular mechanisms by which estrogens regulate vaginal blood flow and lubrication remains poorly defined. Frequency- and dose-dependent relaxation of vaginal tissue strips caused by electric field stimulation and VIP were attenuated in ovariectomized animals, enhanced by androgen treatment and significantly inhibited in estrogen treated animals [164]. Androgens increase vaginal mucification in the rat [171, 172]. Estrogens reduced vaginal mucification [163].
1. Animal Models of Female Sexual Function

Few animal models have attempted to mimic the physiological changes that occur during orgasm in women since one cannot determine whether an animal ‘experiences orgasm’, unlike men where orgasm and ejaculation are related and relatively easily measured. Therefore, an appropriate model for orgasm in females has to rely on mimicking the physiological changes that occur during orgasm. Models developed to date to study female sexual function include lordosis, a hormone dependant behavior that examines the receptivity of the females [191, 192], pacing and proceptive behavior [15, 193], vaginocervical stimulation [194-197], and urethrogenital reflex [198, 199]. Other researchers have measured changes in vaginal and clitoral blood flow, temperature and secretions [34, 123, 126]. Due to delayed development of an appropriate model for female orgasmic reflexes and its implications, most studies to date have been performed in males with only a few studies in the last decade in females.

a) Urethrogenital reflex – a model of ‘climax’

The urethrogenital (UG) reflex model mimics the genital changes seen during ‘climactic’ responses. The UG reflex is a sexual response generated by a multisegmental spinal pattern generator involving the coordination of sympathetic, parasympathetic and somatic efferents innervating the genital organs. The neural responses are similar in males and females; the reflex is a spinal reflex, similar to the
orgasmic reflex described in spinal cord injured patients [200, 201]. In the acutely spinalized female rat, genital stimulation evoking the UG reflex results in rhythmic contractions of the striated perineal muscles as well as vaginal, anal and uterine contractions [198, 202]. Recordings in women during orgasm have shown coordinated rhythmic contractions of the vagina and anal sphincter that are virtually identical to recordings obtained during the UG reflex in the female rat [198, 199, 203, 204]. The UG reflex model has been used to examine the CNS control of genital reflexes (Figures 6 and 7).

b) Peripheral regulation of orgasmic reflexes

Orgasmic reflexes are regulated by both the somatic and autonomic nervous systems. The pudendal (somatic) nerve relays sensory stimuli from the external genitals, the perineum, clitoris and urethra, and the pelvic floor musculature. These sensory signals are essential for the urethrogenital (UG) reflex, [198, 205] and lordosis behavior [192]. The pelvic and hypogastric nerves mediate sensory information from the internal pelvic organs. Light touch, noxious or chemical stimuli of the vagina, cervix, and uterus are primarily mediated via the pelvic nerve [206-208]. The pelvic nerve is also vital for pregnancy or pseudopregnancy induced by mating or cervical stimulation [209-211]. The hypogastric nerve afferents that innervate the uterus, cervix, and ovaries may be important in the transmission of noxious stimuli from the uterus and genital vasocongestion [200, 201, 212-214].

While the pelvic and hypogastric afferents are not essential for evoking the UG reflex, their role in mediation of other sensory inputs during orgasm is unknown. Neural activity in the pelvic, pudendal and hypogastric nerve afferents are sensitive to the level of gonadal steroid hormones [206, 212, 213, 215-217], therefore these nerves may be important in hormone sensitive reflexes.

c) Non-spinal pathway (vagus nerve)

Evidence suggests that the vagus nerve conveys sensory information from female pelvic organs to nuclei in the brainstem [145, 218-220]. The vagal pathway appears to remain functional after spinal cord transection and has been implicated in menstrual cramping, analgesia, and the psychological feeling of orgasm in women with complete spinal cord transection. Electrophysiological studies in the rat support the idea of a vagal-genital pathway, but clear evidence for a direct pathway involved in genital organ responses remains to be clarified. Recordings of neurons in the nucleus tractus solitarius respond to mechanical stimulation of the vagina, uterine horn and cervix [221]. These responses were eliminated by spinal cord transection suggesting an essential spinal pathway. However, evidence for a direct link between the nucleus tractus solitarius and uterus was also provided. These authors concluded that the vagal nerve may act in a facilitatory role supplemental to the spinal pathways. The UG reflex is not abolished by vagal nerve cuts in the acutely spinalized, anesthetized female rat [222] and therefore is not dependant on vagal pathways. It is unclear whether the vagal pathway is supplemental to the spinal systems, or whether this pathway is activated after spinal damage. Further animal studies and verification of this hypothesis in clinical studies is required.
d) Peripheral nerve inputs to the spinal cord
Animal studies (primarily performed in rats) have examined the neuroanatomical pathways of the nerves involved in sexual function. The pudendal nerve afferents enter the spinal cord through the superficial dorsal horn of segments L6-S1 (human - S2-S4) and travel through the spinal cord to the medullary gray commissure, which is located in the lumbar spinal cord [143, 223, 224]. Pelvic afferents terminate primarily in spinal segments L6-S1 (sacral cord in humans). The fibers course through the lateral dorsal horn and enter the spinal gray [140, 225, 226]. The hypogastric nerve afferents terminate in the lumbar spinal cord and medullary gray of spinal segments T13-L3 [227].

e) Ascending and Descending Spinal Pathways
The spinothalamic and spinoreticular pathways relay sensory information to the brain. Primarily these pathways travel in the dorsal columns and dorsal lateral quadrant and consist of fast myelinated fibers which terminate in the thalamus [228-230]. Most of the spinoreticular fibers cross to the opposite side of the cord (below T8) and travel in the lateral spinal columns terminating in brainstem reticulolateral formation [230]. Descending information from the brain also passes through the dorsal and dorsolateral white matter before entering the spinal gray; the majority of the fibers of these pathways are crossed.

Recent studies in the rat have identified a group of spinocerebellar neurons that may be involved in ejaculation [231, 232]. These neurons, located in the lumbar cord, contain galanin, cholecystokinin and enkephalin [231-233]. C-fos is an immediate early gene that can be visualized in activated CNS neurons using immunocytochemistry [234, 235]. Using double labeling of fos and galanin, it was reported that galanin containing cells in L3-L4 of the spinal cord were activated with ejaculation and the UG reflex in the male but were not activated with vaginocervical stimulation in the female. Further studies examining the role of these neurons are required to clarify whether or not they have a role in female orgasmic responses.

2. EFERRENTS MEDIATING GENITAL RESPONSES
Orgasmic responses of the genital organs are mediated through autonomic and somatic efferents. These responses are regulated in a coordinated fashion. The efferent fibers of the pudendal nerve provide innervation of the pelvic floor and anal and urethral sphincters [143, 236]. 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 [143, 237]. Application of neuroanatomical tracers to the rat pelvic nerve resulted in labeling of the parasympathetic preganglionic neurons (the sacral parasympathetic nucleus), primarily in the lumbosacral spinal cord [226, 238]. Application of tracers to the hypogastric nerve resulted in labeling of the sympathetic preganglionic neurons in the upper lumbar spinal cord [141, 238, 239]. The preganglionic neurons were found in the medial gray and intermediolateral cell column.

a) Spinal Interneurons/ spinal pattern generator
The genital afferent input to the spinal cord relays through spinal interneurons, which eventually send signals to the efferent neurons that control the pelvic organs. The sensory information is also sent to other spinal segments and to the brain. Sexual reflexes occur in a coordinated fashion, therefore important spinal interneurons that transverse multiple spinal segments must regulate this coordination. A number of electrophysiological, anatomical, and functional studies have provided some information concerning the location of these spinal interneurons.

Anatomical transneuronal tracing studies using the neurotrophic virus, pseudorabies virus (PRV), have demonstrated the spinal neurons that innervate the pelvic organs. PRV was injected into the clitoris and uterus of female rats [142, 240, 241]. Postganglionic neurons were found in the major pelvic ganglia. Sympathetic and parasympathetic preganglionic neurons 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 sexual function course through the lower thoracic lumbosacral cord in the lateral and medial gray. These cells may be important in the integration of pelvic responses seen during sexual behavior.

Electrophysiological recordings in the cat have also suggested that interneurons in the medial gray are important in mediation of pelvic visceral and perineal stimulation [242-244]. Activation of c-fos, an immediate early gene, has been used to identify spinal and brain neurons that are activated during sexual function [202, 245-247]. Activation of the UG reflex led to increased activity
in spinal circuits that span multiple 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, fos positive nuclei were found throughout 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. Local interneurons in the lateral, intermediate and medial gray were associated with the preganglionic neurons [202]. These cells may represent components of the spinal pattern generator that regulates the UG reflex.

3. PHARMACOLOGICAL CONTROL OF ORGASM

Little is known about the pharmacological control of orgasmic reflexes in females. Similar pharmacological control in males and females is suggested due to the similar orgasmic dysfunctions in both sexes with the same class of drugs (e.g. SSRI, antihypertensives). While some information is known about the local neurotransmitters subserving blood flow to the penis and clitoris (e.g. NO, adrenergic etc) there is little known about the CNS neurotransmitters involved in mediating sensory and motor output during orgasm (see below). In male rats some evidence for a role for acetylcholine in erections, ejaculation and the UG reflex has been suggested [248, 249]. Since preganglionic and pudendal motor neurons contain acetylcholine, both spinal and peripheral mechanisms are possible. However, no studies have been done in females.

a) Supraspinal control: Inhibitory Control

The brain exerts an inhibitory and facilitatory influence on the spinal cord pathways involved in orgasmic reflexes. The nucleus paragigantocellularis (nPGi) exerts an inhibition of spinal sexual reflexes in males and females [250, Marson personal communication]. Bilateral lesions of this nucleus release galanin into the MPOA facilitates some female orgasmic reflexes such as the raphe magnus, Bar- 

b) Supraspinal control: Facilitatory control

Brain regions also facilitate sexual behavior. This is evident from psychogenic and nocturnal erections and arousal. It is well established that the medial preoptic area (MPOA) plays an important role in sexual behavior, especially in males. Lesions of this region severely attenuate or abolish male copulatory behavior in multiple species [68]. The MPOA does not appear to specifically regulate erections or sexual motivation, since medial preoptic lesions do not abolish erections caused by exposure to volatile odors from estrus females and masturbation [266-268]. However, stimulation of the MPOA induces the UG reflex and vaginal vasocongestion, and injection of galanin into the MPOA facilitates some female sexual behaviors [34, 269-272]. The MPOA does not directly innervate spinal circuits involved in sexual reflexes, therefore neurons in this region may relay various aspects of sexual behavior through other hypothalamic or brainstem nuclei [273-275]. Cells are activated in response to female sexual behavior in the MPOA [276-278]. Dopaminergic mechanism in the forebrain mediate some aspects of male and female sexual behavior [279-281], but the role of dopamine in orgasmic function in the female has not been studied.

The ventromedial nucleus of the hypothalamus is critical for the expression of lordosis behavior and neurons in this region are labeled following virus injection into the uterus and vagina [192, 241, Marson personal communication]. However, the relevance of lordosis to human sexual behavior has not been ascertained. Other brain regions may be involved in orgasmic reflexes such as the raphe magnus, Barrington’s nucleus, periaqueductal gray, ventral tegn-
mental area, paraventricular nucleus, medial amygdala, bed nucleus of the stria terminalis and the cerebral cortex. Most of these regions are labeled after transneuronal tracing of the genital organs and/or are activated with sexual behavior or project to the lumbo-sacral spinal circuits mediating orgasmic reflexes [142, 191 196, 241, 253, 254, 277, 278, 282-285], however their specific contribution to female orgasmic responses has yet to be determined.

**C. HUMAN PHYSIOLOGY**

### I. AROUSAL

Arousal: Evidence-based data on genital blood flow and sexual arousal in women

Sex steroids play a crucial role in maintaining the anatomical and functional integrity of all the structures involved in women’s sexual function [286, 287]. However, given the variety of physical, emotional and cognitive issues influencing women’s sexual health [288-290], direct involvement of sex steroids in female sexual dysfunction (FSD) remains controversial. FSD may appear in all stages of the reproductive life cycle even though an age-dependent decline, which is particularly evident at the time of menopause, is highly present [291, 292]. Reproductive-related events (menstrual cycle alterations, infertility, pregnancy and lactation, etc.) and hormonal manipulations (hormonal contraception, use of antiandrogens and ovariostatic treatments such as GnRH analogues, exogenous oral estrogens, etc.) are associated with consistent changes in desire, arousal and orgasm in women [293]. Menopause may be considered a good clinical paradigm for studying the effects of sex steroid deprivation on women’s sexual function [294, 295].

#### 1. SEX STEROIDS AND WOMEN’S SEXUAL FUNCTION

Sex steroids exert both organizational and activational effects which are relevant to sexual function, and their actions are mediated by nongenomic as well as direct and indirect genomic pathways [296-297]. Androgens are essential for the development of reproductive function and the growth and maintenance of secondary sex characteristics directly or through their conversion to estrogens [298]. Estrogens, as well, play a critical role in maintaining the physiological function of many tissues, including the central nervous system, the genital apparatus, and organs relevant to general health [299]. Sex steroids modulate cortical coordinating and controlling centers interpreting what sensations are to be perceived as sexual, and issue appropriate commands to the rest of the nervous system. In addition, sex steroids affect the sensitivity of both genital organs and hypothalamic-limbic structures where they elicit conscious perception and pleasurable reactions by influencing the release of specific neurotransmitters and neuromodulators [300]. Therefore sex steroids influence desire, arousal and orgasm throughout neuroendocrine and trophic actions in women.

**a) Estrogens and women’s sexual function**

The importance of adequate estrogen levels in preserving vaginal receptivity and preventing dyspareunia has long been established. At a level of estradiol (E2) less than 50 pg/ml, women reported vaginal dryness, increased frequency and intensity of dyspareunia, pain with penetration and deep insertion, and burning [301]. Women with higher E2 levels had no complaints related to sexual desire, response or satisfaction. Indeed, E2 levels below 35 pg/ml are associated with reduced coital frequency [302] and decline in estradiol is related to a decline in sexual functioning [303]. Vaginal dryness has been confirmed as the most important later consequence of hormonal changes during menopause [304], but pain during sexual intercourse seemed to reflect sexual arousal problems rather than be a pure consequence of vaginal atrophy [305]. Coitally active post-menopausal women were noted to have less genital atrophy in comparison to abstinent women and pre-menopausal sexual satisfaction was significantly associated with coital activity in elderly women [294]. The positive effect of E2 on mental well-being [306] may highly contribute to the maintenance of an active sexual life throughout the aging process.

**b) Androgens in women**

The major androgens in women include dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione (A), testosterone (T) and dihydrotestosterone (DHT). However, DHEAS, DHEA and androstenedione are considered as pro-androgens because they require conversion to testosterone to express their effects. Androgen biosynthesis occurs both in the ovary and the adrenal under the stimulation by LH and ACTH, respectively, together with intraglandular paracrine and auto-
c) Androgens and women's sexual function

While the androgen influence over women's sexual function has been hypothesized for a long time, it is only in recent years that basic research in laboratory animals and clinical trials with androgenic compounds are contributing to the understanding of the role of androgens on libido and sexual arousal [287]. Studies conducted in women of fertile age found an increase in the establishment of interpersonal relationships and exchange of sexual pleasure during the periovulatory period, corresponding to the plasma androgenic peak, even though no clear correlation has been reported between plasma androgen levels and sexual response [319, 320]. The strong motivation for sexual activity at the time of ovulation may be due to the peak of estradiol.

Some authors have reported that serum testosterone levels are related to genital response and to subjective physical sensation (lubrication and breast sensitivity) in response to visual erotic stimulation both in pre-menopause and post-menopause [321]. Moreover, anti-androgen administration has been associated with low libido in females [322]. Further evidence suggests that circulating free testosterone relates to sexual desire and masturbation in young women [323], while decreased free testosterone and DHEA-S were found in the majority of pre- and post-menopausal women complaining of decreased sexual desire [324]. While oral contraception seems to interfere with the spontaneous expression of sexual desire, the effects of the pill on mental well-being may play a role in sexual motivation [325, 326]. The relationship between sexual function and sex steroid changes from the use of oral contraceptives remains to be established, since women on the pill with lower androgen levels are those who declare a higher degree of sexual satisfaction [327]. No correlation has been established between the average levels of testosterone and sexual desire, sexual interactions, or autoeroticism among contraceptive users, with only non-users reporting a decrease in levels of sexual
desire during the peri-menstrual period associated with the changes in free testosterone over the menstrual cycle [328]. By contrast, during the pill-free week, when testosterone levels were found more elevated in contraceptive users, many women reported an increase in sexual motivation [329]. Finally, 5α-reductase activity is significantly impaired in target tissues in those women reporting low libido following menopause [330], while a significant correlation has been found between high levels of circulating testosterone and androstenedione and a lower index of vaginal atrophy [331].

d) Androgen insufficiency syndrome

Surgical menopause is associated with the androgen insufficiency syndrome, an increasingly accepted clinical entity comprising specific symptoms [332]. The fact that androgens serve as precursors for synthesis of estrogens in women, and therefore serum levels of androgen are expected to be greater than estrogen plasma levels, suggest that androgen insufficiency may exist in pre-menopausal as well as post-menopausal women. Androgen insufficiency in both pre-menopausal and post-menopausal women is a valid clinical diagnosis, under specific conditions.

Clinical symptoms of androgen insufficiency include diminished well-being, lethargy, loss of sex drive and interest, unexplainable fatigue and blunted motivation. Other signs of androgen insufficiency include reduced pubic hair, bone mass, muscle mass, poor quality of life, and more frequent vasomotor symptoms, insomnia, depression and headache [333]. Androgen insufficiency occurs in a number of circumstances, including normal aging (physiological menopause without estrogen therapy and pre-menopausal women reporting low libido and with circulating free T levels at lower limits of detection), ovarian insufficiency (unilateral oophorectomy, hysterec- tomy, spontaneous premature ovarian failure, after chemotherapy, after radiotherapy, hypothalamic amenorrhea), adrenal insufficiency (adrenal failure or surgery), in combination (hypopituitarism, auto-immune adrenal and ovarian failure), iatrogenic (treatment with exogenous oral estrogens, anti-androgen therapy, oral contraceptives, GnRH agonist therapy or chronic exogenous corticosteroid administration) [334].

Despite the growing interest in treatment of sexual dysfunction with androgens in the clinical practice, no normal range of testosterone has been agreed upon. This lack of consensus of definition is due in part to the difficulties with the sensitivity of assays for total and free testosterone in women and the fluctuations during the menstrual cycle and menopausal status [333]. At present it is considered reasonable to use values at or below the lowest quartile of the normal range for women in their reproductive years to support the diagnosis of androgen insufficiency syndrome. The biologically active androgen is testosterone, which circulates bound tightly to sex-hormone-binding globulin (SHBG) and loosely to albumin and transcortin. The fraction of testosterone which remains unbound to SHBG is deemed bioavailable. Thus plasma levels of total testosterone and free testosterone as well as SHBG need to be determined clinically. Treatments include estrogen therapy to restore adequate plasma estradiol levels in order to secure the vaginal environment, and after excluding other organic issues, androgen therapy to normalise androgen levels. Despite the lack of sensitivity of the assays and limited controlled clinical studies, an increasing body of evidence is emerging suggesting that women with signs and symptoms of androgen insufficiency respond well to androgen therapy without significant side-effects.

e) Estrogen and estrogen/progestin therapy

A recent systematic review including all randomized and placebo-controlled trials of treatment for FSD in postmenopausal women concluded that many treatments that are used in practice are not supported by adequate evidence [334]. Dyspareunia due to vaginal dryness appears to be most responsive to estrogen therapy (ET) via restoration of vaginal cells, pH, and blood flow [301]. Progestins can oppose these changes and lead to a recurrence of dryness and dyspareunia depending on their biochemical properties [336, 168]. However, even though estrogen therapy and estrogen/progestin therapy may be effective treatments for vaginal atrophy, increasing vaginal lubrication, they have not been shown to consistently increase sexual desire or activity and many women with FSD remain unresponsive [337]. There is a significant subgroup of women whose sexual difficulties respond initially to estrogen therapy but who subsequently revert to their initial problems, especially when that problem was loss of libido [338]. Studies conducted in the 1970’s reported that vaginal dryness was significantly decreased with estrogen therapy but women did not find any changes in masturbation, orgasm, frequency of intercourse or coital satisfaction [339]. Other reports in surgically and naturally menopausal women treated with oral conjugated estrogens failed to demonstrate positive effects on libido [340, 341], while a signifi-
cant benefit of estrogen therapy on libido, sexual activity, satisfaction, sexual function and capacity for orgasm was found in Swedish post-menopausal women [342]. A randomized, double-blind, placebo-controlled, crossover trial of estrogen and progesterone, alone and in combination, found beneficial effect of estrogen and estrogen/progestin therapy on sexual desire, enjoyment, orgasmic frequency and vaginal lubrication, with no difference in coital frequency on a short-term basis [343]. A recent study with transdermal estrogen therapy in postmenopausal women showed an improvement in satisfaction with frequency of sexual activity, sexual fantasies, vaginal lubrication and lack of pain during intercourse, without any effect on sexual arousal and frequency of orgasm [344]. Collectively, these data underline the evidence that estrogen and estrogen/progestin therapies are not univocally efficacious in treating female sexual dysfunction and the addition of androgen has proved helpful. However, it is necessary to investigate the differences, mainly on plasma sex steroid and SHBG levels, among various schemes of conventional hormone therapies in terms of type of molecule, route of administration, mechanism of action and metabolism.

f) **Estrogen/androgen therapy**

The most interesting findings on positive sexual effects of sex steroids at menopause come from studies with oral and transdermal combination of estrogens and exogenous testosterone. In the past, testosterone propionate administered twice weekly at a dose of 25 mg, starting on the 12th day of the menstrual cycle, and at a maintenance dose of 10 mg monthly thereafter, was effective in relieving menopausal symptoms in those women who did not have complete benefit with estrogen therapy [345]. While relieving hot flushes, estrogen/androgen therapy improved well-being and libido and produced a “smoother transition” [346]. In a series of surgically menopausal women treated with estrogen/androgen therapy, sexual arousal, desire and fantasies increased in comparison with estrogen therapy alone, and a positive effect on frequency of coitus and orgasm was particularly evident during the first 2 post-injection weeks [167]. In a pilot case series of non-responders to oral estrogen therapy, androgen therapy by implants was added with a significant improvement in libido, enjoyment of sex, ability to reach orgasm and initiation of sex [347]. Similarly, women on estrogen therapy complaining of loss of desire and reduced enjoyment of sex who were treated with estrogen/androgen therapy implants showed significant improvement with a marked change in orgasmic capability and initiation of sex when androgen therapy was added [169]. When post-menopausal women unhappy with their estrogen therapy regimen were randomized to receive either esterified estrogens or esterified estrogens with methyltestosterone for 8 weeks, a significant improvement of sexual sensation and desire was evident with a clear increase in vaginal blood flow measured by laser Doppler velocimetry [348]. Sexual function improved with estrogen/androgen therapy, even though circulating estradiol levels were lower than those measured during previous estrogen therapy, leading to the conclusion that androgens play a pivotal role in sexual function while estrogens do not have a significant impact on sexual drive and enjoyment [337]. The addition of testosterone undecanoate improved specific aspects of sexual function such as enjoyment of sex, satisfaction with frequency of sexual activity and interest in sex more than estrogen alone in ovariectomized women [349]. A reproducible result was obtained treating women with surgical menopause on estrogen therapy with two doses of transdermal testosterone (150 ug/ and 300 ug/d) versus placebo. A significant improvement in sexual function with a further increase in scores for frequency of sexual activity and orgasm when women were taking the higher dose was reported [350]. In this study, however, there was an extremely strong response in sexual function in women on placebo and 24% of study participants withdrew from the trial because of androgen-related adverse effects [350]. Therefore, the use of androgens in the clinical management of menopause needs a certain degree of caution, in particular because the long-term effects of such medications on women’s general health are still unknown. The type and route of androgen therapy seem crucial given the evidence that oral methyltestosterone, and not transdermal testosterone, decreases SHBG production and affects bioavailable plasma sex steroid levels differently when combined with different types of estrogen therapy [348,350]. There is, however, no doubt that estrogen/androgen therapy is efficacious in treating FSD at menopause and should be used in clinical practice to improve sexual symptoms at menopause.

g) **Other hormonal agents**

Estrogen/androgen therapies are still unavailable in several countries. In Europe long-term experience with treating climacteric symptoms, depressed mood and libido is available with tibolone, a synthetic ste-
roid with tissue-specific estrogenic, progestagenic and androgenic properties [351, 352]. Apart from the direct effects of its metabolites in the vagina and brain areas relevant to well-being [353, 354], tibolone lowers SHBG, thus increasing free estradiol, testosterone and DHEA-S levels [355]. In randomized studies against placebo or estradiol/NETA, tibolone treatment alleviates vaginal dryness and dyspareunia, ameliorating issues with libido, arousal and sexual satisfaction in post-menopausal women to a greater extent [356, 357]. Moreover, tibolone shows a positive effect on sexuality which is reproducible with that observed with estro-androgenic preparations [358]. This data, together with the recent observation that tibolone significantly increases vaginal pulse amplitude at baseline and following erotic stimulation against placebo [359], further supports the notion that such a tissue-specific compound is a good therapeutic option to relieve decreased libido, arousal and lubrication at menopause because of its estrogenic and androgenic properties.

Concomitant administration of raloxifene, a selective estrogen receptor modulator (SERM), used in the prevention of menopausal osteoporosis, did not alter the effects of the 17β-estradiol ring on symptoms of genitourinary atrophy [360] and did not counteract the improvement of vaginal atrophy observed by use of either low-dose conjugated estrogen cream or non-hormonal moisturizer in post-menopausal women [361]. DHEA, as a precursor of estradiol and testosterone, has been proposed as the treatment for decreased libido in both pre- and post-menopausal women, with encouraging results [362, 363]. Studies conducted in elderly women have shown a positive effect of DHEA on mental well-being and on motivational aspects of sexuality with a mild relief of climacteric symptoms [364].

**h) Conclusion**

Better understanding of the role of sex steroid hormones in modulating female sexual function requires investigation of the biochemical, cellular and physiological mechanisms by which sex steroid hormones modulate sexual function in general and genital sexual arousal in particular in experimental models. With the emerging consensus on female sexual dysfunction and sex steroid insufficiency together with establishment of a host of experimental models and the advancement in biochemical and molecular biology approaches for pre-clinical research, it is anticipated that the coming years will bring advancement in knowledge resulting in better management of female sexual dysfunction by sex steroid hormones.

Further studies are needed to clarify the relevance of sex steroids to women’s sexual function and the impact of hormonal treatments on the clinical expression of sexual symptoms. Well-defined endpoints and outcomes and a general consensus on the diagnostic framework for assessment and treatment of FSD are important goals for the future of sexual health and well-being. Even from a hormonal perspective, FSD must involve a multidisciplinary approach to avoid dangerous body-mind separations.

**Short-summary:** Sex steroids are essential in women’s sexual function, but their direct involvement in sexual dysfunction is controversial, due to the multidimensionality of women’s sexual health. Both estrogens and androgens contribute to preserve libido, arousal and orgasm. Menopause, particularly when it occurs following surgery, is a good clinical paradigm for studying the effects of sex steroid deprivation on women’s sexual function. Several estrogen therapy and androgen therapy protocols have been proposed to treat female sexual dysfunction (FSD); the combination of the two seemed the most effective in restoring sexual function. Other hormonal agents, such as tibolone and DHEA have been proposed with promising effects, however, a better understanding of the role of endogenous and exogenous hormones on women’s sexual function is mandatory.

**2. SEXUAL AROUSAL IN WOMEN**

**a) Vaginal lubrication, basal and during sexual arousal**

During sexual quiescence the human vagina is a potential space with an H-shaped transverse cross-section and an elongated S-shaped longitudinal section. The anterior and posterior walls of the vagina are collapsed and touching each other. Nevertheless they do not adhere as they are covered with a thin layer of fluid allowing them to separate easily. No glandular elements have ever been identified in the normal human vagina. The fluid is mainly a vaginal plasma transudate mixed with desquamated cervical and vaginal cells and cervical secretion [365, 366] for review. The vaginal fluid is transudate from the circulating blood through the vessels underlying the vaginal epithelium. A plasma-filtrate from the blood leaks out of the capillaries into the interstitial tissue space. In the vagina the fluid then passes through the epithelium. In the sexually unstimulated state, the vaginal fluid has a higher K+ and lower NA+ concentration compared to plasma throughout the phases of the menstrual cycle [367, 368]. The basal transudate that percolates through the epithelium is
modified by the cells’ capacity to reabsorb Na+ ions. During non-sexual stimulation the slow passage through the epithelium results in sufficient contact time, making the cells capable of reabsorbing Na+ by the vaginal epithelium and acting as the main determinant of reabsorption of vaginal fluid through the mechanism of ionic driving force. This leads to a basal condition where the vagina is moist, but not lubricated enough to have penetration without pain.

During sexual arousal the blood supply to the vaginal epithelium is rapidly increased as a consequence of neural innervation via the sacral anterior nerves (S2-S4) [369, 370]. The increased blood flow results in increased ultrafiltrate through the vaginal epithelium and thus a saturation of the limited reabsorptive Na+ transfer capacity of the cells. As a consequence of this, the liquid accumulates at the vaginal surface as clear, slippery and smooth lubricant, moistening the vagina so painless penile penetration and thrusting is possible. In addition to the increased blood flow, the venous drainage is most probably reduced, resulting in vasocongestion and genital engorgement, clitoral erection and increased genital sensitivity [366].

b) DSM-IV

In the current DSM-IV classification system, female sexual arousal is described entirely in terms of genital indices of a sexual response as the “lubrication-swelling response” [371]. The definition of female sexual arousal disorder (FSAD) is consistent with this definition. This is in sharp contrast with clinical practice where it is often the lack of subjective arousal that leads women to seek treatment. Women are, in contrast to men, relatively unaware of whether they are lubricating adequately or not and tend to define sexual arousal in terms of their subjective feeling state [372]. Lack of a physical sexual response usually leads to complaints of discomfort and pain and it is rarely presented in terms of a perceived incomplete or absent lubrication and/or swelling. Moreover, the problem in diagnosing female arousal disorder is related to the lack of specificity as to what exactly constitutes a ‘normal sexual arousal phase’. Women vary greatly in the ease and latency of sexual arousal, and in what kind of sexual stimulation is adequate for sexual arousal to occur [373].

Although the DSM-IV classification system is widely accepted, it lacks objective, empirically grounded criteria. Actual clinical practice confronts us with a large comorbidity of sexual dysfunctions in women. Difficulties in differential discriminating between disorders may have to do with the lack of adequate physical markers for most of the disorders, inadequate theory, and the lack of normative data as to what is ‘functional’ and what is ‘dysfunctional’. Lack of sexual arousal may well be the underlying mechanism for many different sexual complaints. Lack of sexual arousal is often related to inadequate sexual stimulation due to contextual and relational variables rather than to somatic causes.

c) Objective Measures of genital sexual responses

Physiological measures for the assessment of sexual arousal in women have a relatively short history in sexology [23, 374]. Prior to the development of genital measures, research on the psychophysiology of sexual response was only possible by the use of extragenital measures such as heart rate, respiration, blood pressure, sweat production, and body temperature to index sexual arousal. With the work of Masters and Johnson, genital changes during sexual arousal started to be observed. For instance, they described the engorgement of the labia minora with a two to three fold increase in diameter [375]. As a result of this engorgement the labia become everted, exposing their non-squamous epithelium [300]. Labial temperature has been used to measure these changes [376, 377], whereas vaginal temperature measured by means of a thermistor probe was shown by Fisher to reflect core temperature and was relatively insensitive to changes in arousal [378]. Recently Sommer et all introduced a method to measure significant intra-subject changes in partial oxygen pressure in the vaginal wall and the minor labia during sexual arousal by means of a modified Clark oxygen electrode [379].

The erectile tissue of the clitoris, composed of the clitoral shaft with two corpora cavernosa and the corpus spongiosum, the crura and the clitoral glans, shows vasocongestion during sexual arousal in much the same way as does the penis. Only recently methods such as color Doppler ultrasonography measurements of clitoral blood flow have become available to visualize these clitoral changes [380]. Data to discriminate between normal and abnormal patterns in clitoral blood flow during sexual arousal start to appear in the literature [381] but the clinical relevance of these data is still under discussion. Duplex ultrasonography is used for measuring vaginal blood flow as well. The probe is usually tampon-shaped or fitted into a vaginal speculum [380, 382]. The challenge is to develop experimental conditions where the transducer can be comfortably attached to the measurement site, allowing for continuous mea-
surement, without requiring the presence of another person in the same room. A recent study on the effects of training with the EROS device showed not only significant increases in clitoral and corpus spongiosum peak systolic and end-diastolic velocity values but in clitoral and corpus spongiosum diameter as well [383]. Magnetic Resonance Imaging (MRI) is another promising method to monitor sexual response [384]. Using rapid dynamic serial high-resolution MRI Maravilla et al described the genital changes during sexual arousal in a small group of healthy women [384]. Non-invasive BOLD-fMRI was used by Park et al for the first time to visualize those parts of the brain that are activated during cognitive sexual arousal [385].

Most of the advances of the past two decades are in the methods used to monitor changes in vaginal vasocongestion. These methods vary in terms of validity, specificity, and practical applicability. The two most widely used techniques to measure vaginal vasocongestion are vaginal photoplethysmography, first introduced in 1975 by Sinchak and Geer [386], and the oxygenation-temperature method developed by Levin and Wagner in 1977 [387]. Levin and Wagner’s device consists of a heated oxygen electrode fitted into a suction cup that is attached to the vaginal wall. The electrode is heated by an electric current to a set temperature. 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 heat loss and increased power will therefore be needed to maintain the electrode at the set temperature. The change in power in milliwatts is an indirect measure of the change 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 vaginal photoplethysmograph is a menstrual tampon-sized device, easy to insert and sterilize, containing incandescent light, or an infrared or visible red light-emitting diode as a light source, and a light sensor. The light source illuminates the blood vessel plexus under the epithelium of the vaginal wall, and the light sensor picks up the light that is backscattered from the illuminated area [388]. Two signals are usually obtained from the light sensor. When the signal is coupled to a DC amplifier, slowly developing changes in vaginal blood volume (VBV) are observed, which are thought to reflect pooling of blood in the vaginal tissue. With AC coupling, a measure of vaginal pulse amplitude (VPA) is obtained, reflecting phasic changes in vaginal engorgement with each heart beat. The greater the blood content of the vaginal tissue, the greater the signal’s amplitude. VPA has been shown to have excellent divergent and convergent validity and is a more sensitive and reliable measure than VBV [371].

Each technique has its advantages and limitations [389]. For instance, the oxygenation-temperature measure can be calibrated in terms of absolute blood flow and is relatively free of movement artifacts. The reliability of the signal does not seem to be compromised by masturbation, clitoral vibration, or orgasm. Disadvantages are its expense, the fact that the electrode should not be applied for long periods of recording to protect the vagina from heat damage, and the device needs to be attached by the researcher. The vaginal photoplethysmograph does not determine absolute levels of blood flow and is not reliable during and after orgasm [388], but surpasses the other measure with respect to practical applicability. It can be inserted by the subject herself and is well tolerated, thus diminishing the intrusiveness of the measure and allowing for long recording periods. With the right statistical design, that is a one-session within-subjects design or a placebo-controlled crossover design in the case of pharmacological studies, and the data obtained from vaginal photoplethysmography can be readily interpreted.

Practical applicability is not a trivial issue. Studies measuring sexual responses in the vagina are limited as it is, with the restriction to solo sexual activities and their contrived context [374, 390]. It therefore seems crucial to use a measure and a procedure that most women would be willing to undergo, respecting a woman’s privacy, and allowing her to become sexually aroused in the laboratory. Balancing validity and applicability concerns, at present, vaginal photoplethysmography seems to be the method of choice.

3. EVIDENCE OF ORGANIC AND STIMULUS RELATED FACTORS CONTRIBUTING TO FSAD

Recently, investigators interested in the pathophysiology of female sexual dysfunction have proposed that in some women, female sexual arousal problems are associated with vascular and clitoral erectile insufficiency [31]. These authors suggest that future management strategies for women with sexual arou-
sexual problems should be aimed at assessing vasculogenic sexual dysfunction, especially if these women are post-menopausal. It is highly unlikely that organic factors in female sexual dysfunction are absent. Nevertheless, the finding of a vascular irregularity does not necessarily mean that it is the organic factor causing the sexual difficulties. Psychophysiological assessment therefore should be more routinely implemented as a diagnostic tool to answer the question whether or not an adequate genital sexual response is possible in the presence of possible organic abnormalities.

Another important question is how well the available vaginal vasocongestion measures differentiate between women with and without sexual problems. Only a small number of studies exist to date that assessed differences in vaginal response between women with and without sexual problems, all using vaginal photoplethysmography. Some of these studies examined sexual responses to erotic stimulus materials in low arousal or non-orgasmic women [391-393], other studies combined women with different sexual dysfunctions into one group [22, 394], one studied low desire and anorgasmic women [395], one study examined sexual responses of women with dyspareunia to oral sex and intercourse scenes [396] and one study compared sexual responses of women with and without FSAD [397]. It is difficult to compare these studies and interpret the different findings, because the nature of the sexual problems varied between and even within studies, different erotic stimuli were used, and studies differed with respect to the way vaginal responses were measured (using either VPA or VBV or both) and analysed.

The Meston and Gorzalka [395] study was the first to compare different diagnostic categories, thus making the important step toward differentiating patterns according to the presenting sexual problem. Wouda et al [396] were the first to study vaginal responses of women with sexual problems to sexual stimuli differing in content. Eighteen women with dyspareunia participated. In this study an erotic scene depicting fellatio and cunnilingus followed a neutral baseline period. Then the women were subjected to a return-to-baseline period followed by a cunnilingus scene and an intercourse scene. There were no differences in VPA between the women with dyspareunia and a control group of women without sexual problems in the first four phases of the experiment. But during the intercourse scene, responses of the control group further increased while in the dyspareunia group responses declined. There were no differences in subjectively reported sexual arousal to the last scene. These results suggest a number of things. First, differences in vaginal vasocongestion response may be highly situation- or stimulus specific. Only during the intercourse scene VPA was significantly lower in the clinical group. Second, genital measures and subjective feelings did not correspond.

A large number of studies have addressed this issue of correlation between psychophysiological measurements and subjective feelings of arousal. In a few studies positive correlation between VPA or VBV and subjective feelings of sexual arousal were reported, but the majority failed to find a relationship between genital and subjective sexual arousal [23, 398]. This finding, confirmed in an MRI study [384], seems to be unique for women. In men without sexual problems, correlation between penile circumference change and subjective report are usually fairly high [23].

Laan et al consistently found VPA to occur automatically in response to an explicit erotic stimulus such as erotic film [398]. That is, vaginal vasocongestion increases within seconds after the onset of the stimulus, without most women being aware of this happening, even when the stimulus is negatively evaluated or induces little or no feelings of sexual arousal. Women simply do not attend to genital changes when assessing their subjective feeling state. Their subjective experience of sexual arousal is determined less by feedback from their genitals (which becomes more important as genital arousal increases) than by the intensity and appraisal of the sexual stimulus. Therefore, genital measures should always be used concurrently with subjective measures of sexual arousal.

These findings suggest an important role for the sexual stimulus in psychophysiological studies. In order to meaningfully compare clinical groups within and between labs, some level of standardization with respect to the type of erotic stimulus seems essential [305]. Finally, measuring vaginal vasocongestion in the absence of a sexual stimulus may lead to false conclusions. For instance, a recent study demonstrated an estrogen related difference in VPA between pre-menopausal and untreated post-menopausal women during initial baseline, before any erotic stimulation had taken place [305]. During subsequent erotic stimulation, however, this difference in VPA between groups disappeared, suggesting that inadequate erotic stimulation may be more important in sexual arousal disorders than a vasculogenic dysfunction related to menopause [397]. This study thus
demonstrates that when measuring VPA without adequate sexual stimulation, one could wrongfully determine organic factors contribute to arousal problems, while in fact with adequate stimulation there is an adequate lubrication-swelling response.

The findings of this study were replicated in a recent study where genital responses of four groups of women were compared: medically healthy pre- and post-menopausal women with and without FSAD [397]. In selecting the groups with FSAD the criteria of DSM-IV were strictly adhered to, meaning that the main complaint had to be a diminished or absent lubrication-swelling response, that there was marked distress as a result of the sexual dysfunction and no comorbidity of medication, medical condition and/or psychopathology. The only significant difference that was found was a difference in VPA between pre- and post-menopausal women in a non-sexually stimulated baseline condition. During visual sexual stimulation no differences in VPA between the four groups could be observed. The sexual problems of the pre- and post-menopausal women with FSAD are therefore not related to their potential to become genitally aroused. During the visual sexual stimulation the women with FSAD, however, reported weaker sexual arousal and genital sensations, less positive affect, and more negative feelings. Contextual and relational variables resulting in a lack of adequate sexual stimulation are therefore most likely the underlying cause for their sexual arousal problems. In a recent MRI study no differences were found between pre- and post-menopausal women in changes during sexual arousal of the vaginal wall, vaginal mucosa, clitoris, femoral vein signal intensity, relative regional blood volume, and clitoral volume [384].

In medically healthy women, impaired genital responsiveness is not a valid diagnostic criterion. The current DSM-IV FSAD definition therefore is in need of revision. The only studies showing significant impairment of psychophysiological genital responses are studies of women with FSAD who have a medical condition that is known to have a potential negative impact on genital neuro-vascular and/or neuro-endocrine functions [399-401].

In assessing sexual arousal in women there is a need for simultaneous measurements of both the cognitive and physical aspects of arousal. Subjective arousal estimates are necessary to answer the question whether or not the women is able to experience feelings of sexual arousal under different stimulus conditions. In assessment of the physical aspects of arousal the main question to be answered is whether or not with adequate stimulation by means of audiovisual, cognitive (fantasy) and/or vibrotactile stimuli a sufficient lubrication-swelling response is possible. If such a 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.

Although psychophysiological testing has not been a routine assessment [402], it can be useful both in the diagnostic phase and in assessment of the effects of medical and/or pharmacological interventions [403].

II. ORGASM: PHYSIOLOGY OF ORGASM IN FEMALES

Mah and Binik have recently written about human orgasm: “Despite numerous efforts, orgasm remains the most poorly understood of the sexual responses, and attempts to propose a universally accepted definition of orgasm have met with little success”. [23, 300, 404,]. The most accurate definitions of human orgasm are probably those integrating bio-psychological perspectives which thus describe both the complex of genital and systemic changes and modifications and the emotional and mental components of the acme of sexual pleasure [300, 404-406]. A so-called “orgasmic platform”, potentially responsible of either the genital pleasure at the acme and one possible biological basis for the greater capacity for multiple orgasm, has been suggested in women as the result of genital sexual arousal [375, 389, 404]. Sensory trigger points have been advocated at the orgasmic platform level, including the clitoris and vagina, clitoral and periurethral glans, cervix, uterus, anal mucosa, and proprioceptive stimuli from the levator ani and perivaginal muscles [407]. Non genital trigger points are, for instance, the breast and nipples, skin and sensory organs [366, 404]. At least two major situations have been described anatomically: clitoral versus vaginal orgasm [375, 404, 407]. Clitoral stimulation is the main source of sensory input for eliciting orgasm. A large majority of women report that clitoral stimulation is important for achieving orgasm; furthermore, several authors suggest that clitoral stimulation, either during coitus or during non-coital sexual activities (i.e. self-masturbation or hetero-masturbation and petting), is fundamental for obtaining the orgasmic phase in most women [375, 389, 404, 407-410]. Orgasm attained with clitoral stimulation tends to be more localized and intense, sharper and physically more satisfying.
On the other hand, coital orgasm is generally described as more diffuse throughout the whole-body, with throbbing feelings and stronger, longer lasting and more psychologically satisfying [404, 408, 411-414]. Singer previously suggested also other types of women’s orgasm, including the vulva’s orgasm identified by orgasmic platform contractions and induced by both coital or non coital sexual activity as well as the uterus’ orgasm as produced by cervical jostling from deep coital thrusting, with the potentiality to obtain a so-called blended orgasm with elements of both [415]. Both anatomic and functional biologic modifications of these triggers points and areas can significantly affect the women’s orgasmic phase.

Orgasmic responses cannot be totally separated from arousal responses since there is an overlap and a continuum in the physiological and psychological changes that occur during sexual activity. In addition, certain changes that occur during arousal are necessary to achieve orgasm. However, there are a number of physiological changes that accompany orgasm.

1. PHYSIOLOGICAL CHANGES THAT ACCOMPANY ORGASM

The physiological changes that occur with orgasm in women include changes in the balance of autonomic function, and muscular contractions. In addition, circulating levels of several hormones increase in concentration. Specifically, rhythmic contractions of the vagina, uterus, and anal sphincter and changes in vaginal and clitoral blood flow, [71, 203, 204, 375, 388, 416-421] have been reported. Increases in heart rate, blood pressure and respiration also occur during orgasm [375, 421, 423-425]. Circulating levels of prolactin, vasopressin, oxytocin, adrenaline and vasointestinal polypeptide have been reported to increase with orgasm [416, 426-429]. Prolactin in particular increased with orgasm and was maintained for approximately 60 minutes after orgasm [428-430], and thus may be a useful measurement of orgasm in future studies.

Similar physiological changes occur during orgasm in men and women. In men orgasm is generally associated with ejaculation. In some women reports of secretions from the periurethral glands have been reported during orgasm, although it is unclear whether ejaculation in women consistently occurs and if these secretions differ from urine, or whether it is always associated with orgasm [425, 431-435].

Cardiovascular changes and increase in heart rate, respiration and blood pressure that occur with orgasm are common responses seen during various types of exercise, therefore monitoring cardiovascular changes independently of specific genital changes is not a good marker for orgasm. Changes in circulating hormonal levels, such as prolactin, may be reliable indices of orgasm; however these values cannot be measured in real time and may vary between assays and individual. The most reliable index of orgasm appears to be monitoring genital changes.

2. ORGASM IS A SPINAL REFLEX

Evidence based on human and animal studies indicate that sexual climax (orgasm) is a reflex mediated by the spinal cord which may involve a spinal pattern generator [436-439]. Studies in men and women have reported that orgasmic reflexes are still present after spinal cord injury [200, 201, 440]. By classifying women based on sensory preservation of their dermatomes, Sipski and colleagues showed that differences in genital responses to audio-visual erotic stimulation were based on the degree of sensory damage in the T12-L3 dermatomes. In contrast, women with injury of the lower motor neurons and S2-S5 dermatomes are less likely to reach orgasm through direct genital stimulation compared to women with injury at or above T11 [200, 440]. These data suggest that orgasmic responses require intact reflexes that relay in the sacral spinal cord.

a) Neurobiology- CNS pathways

Female genital structures need to be altered from their basal, unexcited state into active, sensitized areas for pleasure. The major genital sites where sexual arousal/pleasure is generated include labia minora/introitus, the clitoral shaft, glans, and bulbs; periurethral glans; the urethra; Halban’s fascia; the G-spot and the anterior fornix erogenous zone. Breasts, nipples, and inside of thighs are the other female erogenous sites (xxx). Spinal cord reflexes are mainly responsible for the sexual arousal responses of these multiple genital and non-genital peripheral anatomic structures. The afferent reflex arm is primarily through the pudendal nerve. The efferent arm consists of coordinated somatic and autonomic activity. The bulbocavernous reflex involving sacral cord segments S2, S4 and S4 is the one spinal reflex in which pudendal nerve stimulation results in pelvic floor muscle contraction. Vaginal and clitoral cavernosal autonomic nerve stimulation is another spinal sexual reflex resulting in clitoral, labial and vaginal engorgement [147]. Masters and Johnson noted that the anterior third of the vagina becomes vasoconges-
ted during arousal to form the orgasmic platform [375]. After adequate sensory stimulation, central neurotransmitter discharge during orgasm results in repeated 1-second motor contractions of the pelvic floor (three to eight per orgasm) followed in 2 to 4 seconds by repeated uterine and vaginal smooth muscle contraction [147].

A number of spinal sites control descending these spinal reflex circuits by inhibitory and excitatory means. The lumbosacral spinal cord receives sensory input from pelvic, hypogastric and pudendal nerves, which relay information to the dorsal horn, the medial, central and lateral gray matter of the lumbosacral spinal cord [143, 224, 225]. (Figure 8) This sensory information is relayed to supraspinal sites via the spinothalamic and spinoreticular pathways [407]. The fast myelinated fibers of the spinothalamic pathway terminate in the posterolateral nucleus of the thalamus and are then relayed to the medial thalamus. The spinoreticular fibers are slower and terminate in brain stem reticular formation.

b) Modulatory input

Modulatory input regarding female sexual function is carried out by higher centers of the central nervous system. In the brainstem, several nuclei, including the nucleus paragigantocellularis, the raphe nuclei pallidus, and locus ceruleus project to pelvic efferent neurons and interneurons in the lumbosacral spinal cord, most likely role to modulate lumbosacral spinal cord reflexes [142, 442-444]. The periaqueductual gray matter of the midbrain is heavily interconnected with the brainstem and hypothalamic sites related to sexual behavior, seemingly serving as a relay center [445]. Within the hypothalamus, the medial preoptic area, nucleus paraventricularis, and ventromedial nucleus, are believed to have major roles in female sexual function [416]. Serotonin, dopamine, epinephrine, histamine, opioids and gamma-aminobutyric acid are neurotransmitters and neuropeptides modulating female sexual function.

Serotonin applied to the spinal cord inhibits spinal sexual reflexes. Orgasmic dysfunction has been reported by the use of selective serotonin reuptake inhibitor anti-depressants, which elevate the level of serotonin in the brain [446, 447]. Cyproheptadine, a serotonin2 antagonist, has been effective in alleviating anti-depressant induced anorgasmia [448].

Oxytocin may work synergistically with sex hormones to facilitate muscle contractions during orgasm. Oxytocin from the paraventricular nucleus of the hypothalamus is secreted into the blood stream during arousal and orgasm. Using a continuous blood sampling technique and anal electromyography, Carmichael et al reported a positive correlation between oxytocin levels and the intensity, but not duration, of orgasmic contractions in females and males. For multi-orgasmic women, the amount of oxytocin increase also correlated positively with subjective ratings of orgasmic intensity [416].

Although 30% to 40% of women cannot achieve orgasm without concurrent clitoral stimulation or through coitus alone, only 5% to 8% of women are totally unable to achieve orgasm with any type of stimulation [449, 450].

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D. CLINICAL PATHOPHYSIOLOGIES OF SEXUAL DESIRE, AROUSAL AND ORGASMIC DYSFUNCTION IN WOMEN

Sexual dysfunction in women 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 an impact on the quality of life. The aim of this section is to try and distinguish among several of the most
frequent clinical pathophysiological mechanisms of women’s desire, arousal and orgasmic dysfunctions, aiming to correlate with several modifiable and unmodifiable risk factors. As most of the research on female sexuality has focused on psychological and relationship aspects of this issue, there are a limited number of evidence based studies about female sexual function and very few for orgasmic disorders.

I. NEUROLOGIC PATHOPHYSIOLOGY

Female sexual dysfunction due to neurologic causes is currently unexplored and probably under-diagnosed. The same neurogenic disorders that cause erectile dysfunction in men can cause sexual dysfunction in women. Many neurological disorders such as multiple sclerosis, peripheral neuropathy and lumbar radiculopathy can cause abnormal innervation to the female genital organs.

It is assumed that any neural lesion, central or peripheral, which causes sexual dysfunction, should have sensory deficit as its mainstay. Therefore, the need to quantitatively measure the sensory function of the vagina and clitoris is becoming obvious.

1. MEASUREMENT OF SENSORY FUNCTION OF THE GENITALIA

Quantitative sensory testing is used in assessment of sensory function for diagnosis of neural disorders. It is most commonly used for assessment of neuropathies and other peripheral disorders [451]. These tests are based on administration of quantified stimuli, usually of pressure, vibration or temperature, in a controlled way. Most commonly, the subject defines the sensory threshold by indicating the onset of perceived sensation either verbally or by button-press.

a) Nerve Fibers

Nerves consist of fibers of variable diameter with the thicker fibers having a faster conduction velocity. Three types of fibers are generally recognized in the sensory subclass of nerve fibers: A-beta fibers, the largest fibers, mediate touch, mild pressure, sensation of joint position and vibration. A-delta fibers, smaller than A-beta fibers, mediate sensation of cold and early components of pain sensation. C fibers, the slowest and smallest, mediate sensation of warmth, the main component of pain sensation and subserve most autonomic peripheral functions. The thermal senses, warm and cold, are served by small nerve fibers, and are probably less relevant for sexual function. Nevertheless, a complete assessment of sensory function should include modalities of all types. At the peripheral level, the same class of fibers that subserve autonomic function subserve thermal senses. Disorders that affect these fibers, such as diabetic neuropathy, affect both sensory and autonomic fibers [451]. Measurement of small fiber sensory function can therefore give indirect insight regarding the function of the as yet unexplored autonomic system in these organs.

b) Methodology

A system and methodology for quantitative assessment of genital sensory functions with age-corrected normograms for thresholds of vibratory and thermal sensations for the clitoris and vagina is available [452]. Age dependency of the genital vibratory threshold is impressively similar to its age dependency for the skin of limbs [453], supporting the validity of this test in the genital area. Clitoral measurement was found to have a smaller age effect, perhaps due to the richer innervation of the clitoris, rendering the age effect less significant. Quantitative sensory testing is often criticized or even dismissed because of its subjective nature [454]. However, some authors have shown that results are repeatable and, therefore, can be used as a valid descriptor of the sensory state [455, 456].

2. SPECIFIC DISORDERS AFFECTING SEXUAL DYSFUNCTION

Central and peripheral neurologic disorders may cause sexual dysfunction and could induce both autonomic motor and sensory disorders. It is expected that patients with multiple sclerosis, spinal cord injuries, herniated disc disorders, lumbosacral plexus disorders, and peripheral neuropathies will have impaired sensory function, which will be expressed as sensory threshold increases.

a) Neuropathy

It has been shown that sensory testing of the genitalia in 36 neurogenic females with sexual dysfunction (15 with diabetes, 14 with Multiple Sclerosis and 7 with lumbar discopathy) can be a useful tool in diagnosing female sexual dysfunction of neurogenic origin, (most strongly the assessment of clitoral vibratory stimuli) [457]. Although perineal trauma occurs in both genders, data supporting the association between sexual dysfunction and blunt perineal trauma in women is lacking. A study that looked at the patient characteristics of women with sexual dysfunction that had undergone blunt perineal trauma
implicated a neurogenic form of sexual dysfunction, with primary complaints of organic disorders and abnormalities on genital sensory testing [458]. In another publication the same authors reported three cases of post-traumatic clitoral neuropathy and neuralgia resulting from trauma to the genitalia. The consequent numbness, pain and dysautonomia have led to sexual dysfunction in all three women [459].

b) Conclusion

Although there are significant anatomic and embryologic parallels between men and women, the multifactorial nature of female sexual dysfunction is clearly distinct from that of the male. There is considerably more research on these issues in males. From a clinical point of view, deficits in genital sensation are probably responsible for many cases of female sexual dysfunction. To date, there are only sparse data on the effect of neurological diseases affecting the peripheral nervous system or various surgical techniques (in particular hysterectomy) on sexual arousal and orgasm. Development of new diagnostic tests and surgical techniques, which spare the genital nerve, will be mandatory. There is a tremendous need for more research in this area.

3. NEUROLOGICAL DISORDERS

The knowledge obtained from the studies about the effect of neurological disorders on female orgasm leads to better understanding of the neurological pathways that control sexual response in normal women. There are limited number of well designed, controlled studies dealing with neurological organic dysfunction. The majority of these studies examined the effect of spinal cord injuries on female sexual responses.

a) Spinal cord injury

There is little available literature about sexual dysfunction in women with spinal cord injury (SCI) [200, 201, 220, 460-467]. Women’s desire for sexuality and sexual activities seems to decrease after injury [465]. Charlifue et al [468] reported that sex was less important after injury in their series of 231 SCI women; other authors found a significantly higher level of hypoactive sexual desire after injury as compared with their sexual drive prior to injury itself [469]. A decrease in frequency of self-masturbation in these women has been reported [470] with preferred sexual activities after SCI reported to be kissing, hugging and touching [468].

The influence of SCI on sexual response depends on the degree and location of injury in the spinal cord. Among women with spinal cord injury, 7% to 23% are unable to achieve orgasm [471]. Most of the data available about women’s sexual dysfunction after SCI comes from laboratory-based research [200, 201, 220, , 464-466]. Pathophysiology of orgasmic phase in women with SCI’s has been studied in laboratory settings [200, 201]. In a study of 25 women with SCI at and above the level of T6 and 10 able-bodied control subjects, the ability to achieve orgasm were documented [200]. Subjects underwent a 75 minute protocol in the laboratory, designed to obtain information on the physiological events accompanying orgasm. Data were analyzed both within and across neurological groups: complete SCI, incomplete SCI, and able-bodied controls. Fifty two percent of subjects with SCI achieved orgasm. The capacity to achieve orgasm was shown to be unrelated to level or completeness of injury in women at levels of injury T6 and above.

Sipski et al reported the results of a study enrolling 12 women with a lower motor neuron (LMN) injury affecting the S2-S5 spinal reflex arc and 50 SCI women with UMN injuries [201]. Ability to achieve orgasm was assessed historically and in the laboratory. Historically, only 55% of SCI women were able to reach the orgasm post-SCI, whereas 44% were orgasmic in the laboratory [200, 201]. These authors demonstrated that in each condition, SCI subjects were significantly less likely to achieve orgasm than controls, and orgasm was less likely if a woman had a complete LMN injury affecting the sacral segments than any other level and degree of injury [200]. Latency to orgasm was greater in women with SCI’s compared to normal subjects. Sipski showed a significant difference in average latency to orgasm when able-bodied subjects were compared to SCI subjects [201]. On the other hand, the so-called systemic modifications that usually accompany the orgasmic phase, such as blood pressure, heart rate and respiratory rate fluctuations, were generally similar between women with and without SCI.

In women with complete upper motor neuron (UMN) injuries affecting the sacral segments, the ability for reflex without psychogenic lubrication of the vagina should be maintained [462,466,468]. The presence of psychogenic arousal in the absence of arousal induced by genital stimulation was documented in women with complete SCIs at and above the level of T6 [466]. In contrast, in women with incomplete UMN injuries affecting the sacral segments data seem to demonstrate an ability to main-
tain both the capacity for reflex and psychogenic lubrication. Sipski et al also reported that those women with higher ability to perceive a combination of light touch and pinprick sensation in the T11-L2 dermatomes have a greater likelihood of achieving psychogenic lubrication [201]. With all levels and degrees of SCIs, the ability to achieve psychogenic arousal depends on the degree of sensory preservation in the T11-L2 dermatomes but not on the degree of sensory preservation at T6-9 or S2-5 levels [201]. Moreover, psychogenic control of female genital vasocongestion is dependent on sympathetic stimulation [468, 469]. Therefore, preservation of sensory function in T11-L2 is a precondition for the ability of SCI women to have psychogenic arousal.

Orgasm has also been studied in SCI women showing that approximately 50% have the ability to achieve orgasm [470]. In women with T6 injury and above the capacity to achieve orgasm is unrelated to the level of the injury [200]. A significant difference was noted in the ability of women with complete lower motor neuron injuries, affecting S2-5, to achieve orgasm as compared to other types of injuries[466]. The authors concluded that an intact sacral reflex arc is needed to achieve orgasm and that orgasm may be a reflex response of the autonomic nervous system [200, 472, 473]. Furthermore, Sipski et al [200] also proposed that the orgasmic sensory experience may be partially derived from afferent autonomic innervation, which remains after complete SCI. Whipple et al, however, suggested that the vagus nerve can provide innervation to the cervix and is the source of cerebral transmission of orgasmic sensation in women [220].

b) Multiple sclerosis

Current prevalence rates for multiple sclerosis (MS) are 1/1000 Americans and 2/1000 Northern Europeans [473]. A disorder affecting both the brain and the spinal cord, multiple sclerosis can cause difficulties in achieving orgasm. Sexual dysfunction is common among multiple sclerosis (MS) patients and has a reported prevalence of 46%-80% [472, 474-478]. Sexual activity ceases or is significantly unsatisfactory in 39% of MS women [472]. Symptoms reported included fatigue in 68%, reduced sensation in 48%, reduced vaginal lubrication and difficulty with arousal in 35%, difficulty reaching orgasm or anorgasmia in 72%, and dyspareunia and other sexual pain disorders Villeroy [472, 474-477, 479].

In a case-control study, Zorzon et al [480] reported data concerning sexuality in a series of 70 consecutive women suffering from MS as compared to a control group of age-matched women with chronic disease (rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis and ankylosing spondylitis) and another of healthy subjects. The number of MS patients who reported a reduction in sexual desire was higher than in both patients suffering from a chronic disease and normal subjects. The same authors found a significant difference in sexual desire between patients and healthy controls. In this series MS women had decreased vaginal lubrication compared to healthy controls while the difference from chronic disease controls was not statistically significant. Changes in vaginal sensation, while very common, were more common in MS cases than in both chronic disease controls and healthy subjects. Overall, more than one-third of women experienced a decrease in vaginal lubrication and libido.

Similar frequencies in modifications of vaginal lubrication and vaginal sensation, orgasmic capacity and diminished sexual desire have also been previously reported by other researchers [477,481-484]. Problems with sexual function were reported significantly more often by women with physical disability due to the disease, (expressed by lower Expanded Disability Status Scale (EDSS scores) [485]. In 47 women with advanced multiple sclerosis, 38.3% reported diminished orgasmic capacity and 12.8% anorgasmia. The changes in sexual function correlated with neurological symptoms from the sacral segments, such as weakness of the pelvic floor and bladder and bowel dysfunction [486]. Zorzon et al also reported data concerning a correlation analysis in the same cohort of women with MS [486]. Spearman correlation analyses between symptoms of sexual dysfunction and characteristics of both patients and clinical type of MS was performed. Sexual dysfunction significantly correlated with relapsing-remitting MS but not with either the primary-progressive or the secondary progressive type. A close correlation was also found between sexual dysfunction and age at onset of symptoms and the current age of the woman but not with the duration of the neurological disease itself. Similarly, a significant correlation was found between sexual and physical disorders, sphincteric and bladder dysfunction, fatigue score and both cognitive deterioration, as assessed by the Mini Mental State Examination [487] and the neurological impairment, as assessed by the EDSS [488]. Other studies have shown a correlation between sexual and bladder dysfunction in MS patients [489, 490]. Nortvedt et al also reported a significant reduc-
A similar correlation was demonstrated between sexual dysfunction and low educational level and a high value for either depression, as assessed by the Hamilton Depression Rating Scale (HDRS) [491], or anxiety [492], as assessed by the Hamilton Anxiety Rating Scale (HARS) [491]. After a 2-year follow-up, the percentage of patients with at least one sexual disorder remained stable at more than 70% [493]. Although men reported at least one sexual dysfunction more frequently than women, when both men and women were considered altogether, in a univariate analysis, changes in sexual function throughout time correlated with modifications in bladder function and EDSS score. After removing the effect of psychological aspects, only changes in bladder function maintained a significant correlation with fluctuations in sexual function. When comparing women suffering from chronic diseases and healthy subjects, Zorzon et al reported that anorgasmia and hyporgasmia were the more commonly reported sexual dysfunction in MS patients, followed by decreased vaginal lubrication and reduced libido [480]. Fewer women with MS were able to achieve orgasm than their peers (chronic disease controls and healthy controls) [480]. More than one-third of women reported greater difficulty or inability to achieve orgasm than before the disease, with a statistically significant difference as compared with chronic disease controls. Anorgasmia or hyporgasmia was reported more frequently with a statistically significant difference in comparison with healthy controls. Interestingly, Hennessey et al reported the results of a survey on urinary, fecal and sexual dysfunction in 68 men and 106 MS women [494] and found that although sexual problems occurred in 52% of MS women enrolled, 61% were satisfied with their sexual activity.

Yang et al performed pudendal somatosensory evoked potential testing on 14 women with MS. The most common complaint among these patients was difficulty with orgasm. An abnormal or absent pudendal somatosensory evoked potential was highly associated with lack of or difficulty achieving orgasm [495].

It is probable that primary sexual disorders in some neurogenic MS patient result from the demyelination process that interrupts the continuity of the neural pathways, altering the neural function that is essential for normal sexual performance. Clearly, the neuropathy caused by autoimmune-induced damage to the myelin sheath is the main reason for the classic neural symptoms of the disease. Moreover, electro-diagnostic data imply that pudendal somatosensory innervation is necessary for normal female orgasmic function [495]. Clinical use of sensory testing in MS patients was reported in a group of 24 females, showing that sensory testing of the genitalia in MS patients, most strongly the assessment of clitoral vibratory stimuli, can be a useful tool in diagnosing female sexual dysfunction of neurogenic origin [496].

4. DEPRESSION AND ANTIDEPRESSANTS

The incidence of depression in women varies during the life span. The peak incidence during childbearing years appears to be associated with cyclic hormonal changes. Women also present with reproductive-specific mood disorders: pre-menstrual dysphoric disorder (PMDD), depression in pregnancy, post-partum mood disorder (PDD) and peri-menopausal depressive disorder [497-500]. The fluctuation of ovarian steroids during specific phases of the reproductive cycle may bear some relationship to the particular vulnerability of women for mood disorders. The ovarian hormones could exert their effects on mood directly or indirectly by their effects on neurotransmitter, neuroendocrine, or circadian systems. Hormonal changes associated with the reproductive cycle may provoke affective changes in predisposed individuals. Moreover, there are a variety of disturbances in biological rhythms observed in mood disorders. An example is depression associated with the luteal phase of the menstrual cycle [501-503]. Major depression is frequently related to women's sexual dysfunction (over 70% of patients) [503-505]. Changes in sexual interest/satisfaction and loss of libido are frequently and consistently related to major depression [506-508]. Nevertheless, a good quality sex life is regarded by 70% of the general population and by as many as 75% of depressed patients as a fundamental part of quality of life [509-510].

Antidepressant medications can exacerbate pre-existing sexual dysfunction or induce new sexual disorders [500, 506-526]. Sexual dysfunction has been reported to be associated with all classes of antidepressants (MAOIs, TCAs, SSRIs, SNRIs and new generation antidepressants) in patients with depression and various anxiety disorders [520]. The clinical assessment of depressed women requires a comprehensive evaluation of sexual function prior to the
affective disorder, disturbances associated with the onset of depression and changes or dysfunctions associated with antidepressant treatment. Other factors to be included in evaluating sexual dysfunction include inquiry about concurrent medical conditions, somatic treatments, lifestyle risk factors, and response to antidepressants [516]. Absent or delayed orgasms are the sexual side effects most commonly associated with selective serotonin reuptake inhibitors (SSRI’s) [519], with desire and arousal disorders also frequently reported [516, 517]. The negative effects of SSRIs on sexual function appear strongly dose-related and can vary among group according to serotonin and dopamine reuptake mechanisms, induction of prolactin release, anticholinergic effects, inhibition of nitric oxide synthase and pharmacokinetics [516]. While men taking SSRIs report higher rates of sexual side effects, women seem to experience more severe sexual dysfunction [521]. Sexual dysfunctions which last during long-term administration of antidepressants may result in treatment discontinuation [515, 516, 522]. This places patients at increased risk for recurrence, relapse, chronic illness, and mortality (e.g., suicide). Recently; Zajecka et al reported that in a series of 681 outpatients with chronic forms of DSM-IV [371] major depressive disorders, sexual dysfunction was reported by 48% of women before any antidepressant treatment [511]. After a 12 week treatment course with nefazodone or Cognitive Behavioral Analysis System (CBASP) or a combination of both nefazodone and CBASP, a statistically significant linear improvement in sexual function was noted in all 3 treatment groups. Improvement in depressive symptoms was associated with improved sexual interest and satisfaction.

Similar results have also been reported by Bobes et al [523]. Using the Changes in Sexual Functioning Questionnaire (CSFQ) [524], sexual desire/interest showed a substantial baseline effect (30% of patients indicated a maximum score) for depressed women treated with nefazodone at baseline and treated with paroxetine at final visit. As compared to the baseline, nefazodone treatment was able to promote significant improvement in depressed women in terms of sexual desire/frequency, pleasure, sexual arousal and orgasm [523]. Michelson et al underlined similar results, even accounting for the decreased sexual function (most pronounced with orgasm) that occurred during continued treatment for increased depressive symptoms [525]. Sexual function was assessed in depressed patients participating in a multi-center trial of acute and chronic fluoxetine therapy. Patients were evaluated at study entry (baseline), after 13 weeks of fluoxetine 20 mg daily, and during 25 weeks of chronic therapy with fluoxetine 20 mg daily, fluoxetine 90 mg weekly, or placebo. In a 13-week open-label trial among 501 patients who met DSM-IV criteria for depression, 51.6% of women reported improvement, 35.0% reported no change, and 13.4% of women and 17.4% reported worsening of overall sexual function. During double-blind chronic therapy there were no statistically significant differences in change in sexual function between treatments [525].

Nappi et al demonstrated that depression may be bimodally related to women’s sexual dysfunction [526]. In a cross-sectional study, frequency of self-reported sexual symptoms in 355 women attending menopause clinics was investigated and related to other vasomotor, psychological, physical, and genital complaints. As expected, pain during sexual intercourse and low libido/lack of arousal were significantly more frequent with age and years since menopause. Reduction of sexual pleasure/satisfaction (45.9%) was common with age, but was more frequent the longer the time since the menopause. However, examining the intensity of sexual symptoms in relation to the presence of other complaints, Nappi and co-workers found that physical, psychological and genital well-being significantly affects the components of sexual response after the menopause and depressive symptoms were more common in women with sexual complaints [526]. Thus, depression is an important co-factor in many diseases that are potentially associated with sexual dysfunction in women. Some authors underlined the role of depression in worsening the quality of life and sexual function in MS patients [527-528]. Janardhan et al demonstrated that depression and fatigue were independently associated with impaired quality of life in MS, after accounting for physical disability, suggesting that their recognition and treatment can potentially improve quality of life [527].

Zorzon et al examined 62 men and women with MS using MRI of the brain [528]. When comparing patients with and without sexual dysfunction, the only significant difference was in the pontine brain parenchymal fraction (BPF). When a linear multiple regression analysis was performed, sexual disorders were associated with depression and, after adjusting for depression and anxiety, with bladder dysfunction and pontine BPF. This relationship between sexual dysfunction and pontine atrophy confirmed the correlation of sexual dysfunction with bladder dysfunc-
tion and highlighted the role of depression in determining sexual dysfunction even in this particular subgroup of women. To confirm the significant role of depression as a co-factor of sexual dysfunction, Salonia et al recently reported data about sexual dysfunction in 30 women suffering from coronary artery occlusive disease (CAD) [529]. Sexual dysfunction was reported by 9 of 30 women, 7 of whom had this complaint prior to symptoms of ischemic heart disease. According to the results of the Female Sexual Function Index (FSFI) [530], 77.8% of these women reported hypoactive sexual desire disorder (HSDD), 77.8% sexual arousal dysfunction, 100% orgasmic disorder, and 67% a combination of hypoactive sexual desire, arousal, orgasmic and sexual pain disorders. Fifty-seven percent of the enrolled women showed depressive symptoms, as determined by the BDI [531], which significantly correlated with the Female Sexual Distress Scale (FSDS) [532] and with each one of the FSFI domains.

5. ENDOCRINE ALTERATIONS

a) Thyroid disease

While peer review literature reports some contributions of thyroid disease to men’s sexual dysfunction [533-538], there were no papers found evaluating sexual function and dysfunction in women complaining of either hypothyroidism or hyperthyroidism. Preliminary data has recently been reported regarding sexual function and dysfunction in 48 women with thyroid disease (30 hypothyroidal women, and 18 hyperthyroidal subjects) [533]. All patients underwent a detailed evaluation and the results of their FSFI scores were compared with those of a control group of healthy age-matched women. Women complaining of thyroid problems had lower scores for both the lubrication and the orgasm domain of the FSFI as compared with the control group, and dysthyroidal women reported significantly higher genital pain during both coital and non-coital sexual activity than controls. When co-morbidities were evaluated, a high rate of depression was found in the women with thyroid disease; the BDI score correlated significantly with the desire, arousal and satisfaction domains of the FSFI. A higher rate of depression also correlated with a higher rate of sexual distress, as determined by the Spearman correlation analysis between the BDI and the FSFI. When the FSDS was correlated with the different FSFI domains, a significant correlation was found between women’s sexual distress and overall sexual satisfaction.

b) Hyperprolactinemia

Hyperprolactinemia is the most common endocrine disorder of the hypothalamic-pituitary axis [539], occurring more commonly in women. It is associated with pronounced reductions of both sexual motivation and function. Elevated levels of prolactin (PRL) inhibit GnRH pulsatility [540, 541]. Although some experimental evidence suggests that hyperprolactinemia suppresses physiologic reproductive functions while maintaining sexual drive, other studies clearly indicate that chronic PRL elevation negatively impacts sexual libido [542, 543]. Hulter et al assessed sexual function and sexual appreciation in a comprehensive interview of 48 women with well-defined hypothalamic-pituitary disorders [544]. A total of 79.2% of the women had developed a lack of or a considerable decrease in sexual desire, while problems with lubrication and orgasm were reported in 64.6% and 68.7% of the women, respectively. In this series, normal menstrual pattern, young age and intra-sellar tumor growth correlated better with normal sexual desire and sexual function than did normal prolactin levels and normal testosterone levels. In a previous study [545], the same authors investigated sexuality in 109 women with morphologically verified hypothalamic-pituitary disorders, finding that 62.4% had noticed a decrease in sexual desire. This problem was shown for 84.1% of the women in this group with hyperprolactinemia, but only in 32.6% of the women with normal serum prolactin.

A correlation between hyperprolactinemia and sexual disturbances among uremic women on hemodialysis have been reported [546, 547]. Mastrogiacomo et al reported that among 99 women on maintenance hemodialysis, the rate of sexual intercourse and the ability to reach orgasm were significantly lower than in age-matched controls [546]. Eighty percent declared a reduction in their sexual desire, and the frequency of intercourse decreased after dialysis. Aging, an unmodifiable risk factor, decreased the sexual activity in both the sick and healthy populations, but in uremic patients sexual activity ended at an earlier age. Patients with hyperprolactinemia reported lower frequency of intercourse as well as lower percentage of orgasm than women with normal prolactin levels.

Recently a correlation has been made between hyperprolactinemia and antidepressive, antipsychotic and neuroleptic drugs. Several drugs are known to affect sexual function negatively, including psychoactive drugs (opiates), hypotensive drugs and antihistamines [406, 540]. Antipsychotic and neuro-
leptic drugs reduce sexual drive, in part related to
drug-induced of hyperprolactinemia. Neuroleptics
typically elevate plasma prolactin, associated with
both loss of libido and anorgasmia [406, 540, 548-
555]. Antidepressant agents such as SSRI’s may
induce hyperprolactinemia [556-559], although no
research has been found which accurately reports
prevalence and characteristics of this phenomenon.
In women this secondary hyperprolactinemia
induces symptoms from decreased sexual drive to
orgasmic disturbances such as anorgasmia and
delayed orgasm [512, 556-559].

**c) Diabetes mellitus**

Few studies have investigated the significance of
diabetes in causing women’s sexual dysfunction
[401, 570-579]. Neuropathy, vascular impairment
and psychological problems have been correlated
with decreased libido, spontaneity of arousal, vagi-
nal lubrication and orgasmic function and dyspareu-
nia in women complaining of diabetes mellitus. The
most common sexual dysfunction in women with
diabetes is decreased sexual arousal with slow and/or
inadequate lubrication. Women with diabetes may
also experience a decrease in sexual desire and
increase in dyspareunia, whereas problems with
orgasm are not more frequent.

Jensen et al reported that diabetic spouses of diabetic
men had more problems with arousal than healthy
spouses [567]. Although the mechanism is unclear,
the rate of sexual dysfunction among women with
type-II diabetes was significant, while type-I did not
demonstrate any significant change [575, 578]. In
1998 Enzlin et al wrote a review of the literature on
this topic [582]. Enzlin showed that diabetes slightly
increased the risk of women’s sexual disorders.
Schiel et al [583] studied 127 type-I diabetics, 36% of
whom were women and 117 type-II diabetics, 54% of
whom were women. He showed that overall
prevalence of sexual dysfunction in women was 18%
among type-I diabetic patients and 42% among type-
II diabetic subjects.

Enzlin et al reported on prevalence and characteristics
of sexual dysfunction in 120 women with type-I dia-
betes mellitus as compared with 180 age-matched
healthy controls [584]. With a response rate of 80.8%,
Enzlin showed that significantly more women with
diabetes (27%) than age-matched controls (15%) reported sexual dysfunction. Diabetic women presen-
ted a higher prevalence of arousal dysfunction than
healthy women, however there was no significant dif-
ference in decrease of desire. There was no significant
difference in orgasmic disorders or sexual pain disor-
ders between the women with and without diabetic
complications. A significant difference was found for
decreased lubrication, although often 2 and 3 sexual
problems were reported.

Patients complaining of sexual disorders were not
significantly different in age, BMI, length of disease
or HbA1c values as compared with those without
sexual complaints. A significant association was
found between the number of complications and the
number of sexual complaints, although this analysis
did not show any statistically significant correlation
between sexual complaints and peripheral neuropa-
thy, autonomic neuropathy, nephropathy and retino-
pathy, menopausal status, use of hormone therapy or
use of oral the contraceptive pill. Based on BDI
score, twice as many diabetic women were depressed
than controls.

Erol et al published data on the prevalence of sexual
dysfunction in 72 women with type-II diabetes melli-
tus without other systemic co-morbidities and 60 age-
matched healthy subjects [585]. Mean FSFI scores of
patients was 29.3 compared to 37.7 for controls, with
the main complaints of the diabetic women being
reduced libido (77%), diminished clitoral sensation
(62.5%), complained of vaginal dryness (37.5%) vagi-
nal discomfort (41.6%) and orgasmic dysfunctions
(49%). The authors concluded that the higher rate of
sexual disorders among diabetic patients was respon-
sible for lowering their quality of life.

In order to evaluate the prevalence and predictors of
sexual dysfunction in women with both type-I and
type-II diabetes mellitus, 72 diabetic women, 42
type-I and 30 type-II were compared with healthy
age-matched controls [586]. Women complaining of
diabetes mellitus had worse FSFI scores for the desi-
re, lubrication and orgasm domains as compared
with the control group, and significantly higher
sexual pain at the genitalia level (both coital and
non-coital sexual activity) than controls. The BDI
score, 48% in diabetic women, was significantly cor-
related with the arousal, orgasm and satisfaction
domains of the FSFI. The Spearman correlation ana-
lysis was also statistically significant between BDI
and FSDS score. A significant correlation was also
found between aging and reduced desire and be-
tween aging and lubrication.

Sexual dysfunction is highly prevalent in diabetic
women and these patients are clearly at higher risk of
developing sexual desire, arousal and orgasm disor-
ders than age-matched controls. More investigation
is needed to better understand the contributions of

725
the psychological and diabetes-related somatic factors to sexual dysfunction in women with diabetes mellitus.

6. PELVIC SURGERY

a) Pelvic surgery for rectal cancer

When a conventional low anterior and abdomino-perineal resection with extended lymphadenectomy is performed for advanced lower rectal cancer, sexual and bladder function are often sacrificed [587-589], reported to be between 10% and 60% [589]. Extended circumferential margins are required for a complete resection, or multimodality treatment is utilized, including preoperative external beam radiation therapy, radical surgery and intraoperative radiotherapy, to improve the cure rate of both the presentations of rectal cancer [589-594]. Sexual and bladder dysfunctions are usually caused by a non-nerve-sparing surgical approach during the procedure, with the surgical damage of one or more of the autonomic nerves consisting of the paired sympathetic hypogastric nerve, sacral splanchnic nerves and the pelvic autonomic nerve plexus. Several kinds of nerve-sparing surgery (NSS) for organ-confined or advanced rectal cancer have been developed aiming at both preserving sexual and genitourinary function and extending the surgical margins [587, 594-606]. Enker et al reported that in patients undergoing abdomino-perineal resection for primary cancer of the rectum, performed in accordance with the principles of total mesorectal excision (TME) and autonomic nerve preservation (ANP), sexual function was preserved in approximately 57% of patients undergoing APR versus 85% of patients undergoing sphincter preservation [607].

Data on this topic in women are very rare and conflicting. A few papers reported the results of both prospective and retrospective studies aiming at evaluating urinary, bowel and sexual function in both men and women, but without any standardized method from the woman’s point of view. In addition, most of the outcome studies enrolling both men and women paid attention only to the male hemisphere.

Recently, Pocard et al studied prospectively the pre-and post-operative urinary and sexual function in 7 women who underwent a sphincter-preserving operation for rectal carcinoma by means of a curative TME with ANP, without preoperative irradiation, with complete surgical identification and subsequent preservation of both hypogastric and sacral splanchnic nerves [608]. Four out of the 7 women were sexually active before undergoing the surgical procedure. Sexual activity and ability to achieve orgasm was unchanged in these women and no incidence of dyspareunia was reported. Chorost et al reported similar results in a retrospective review on the medical records of 52 consecutive patients who underwent potentially curative procedures for rectal cancer [609]. Pre-surgical discussion about the potential risk of sexual dysfunction was not documented in the pre-operative consent in 37 of 52 patients, however, only 1 out of the 16 women reported post-therapy sexual dysfunction.

Multimodality treatment can increase the chances of damaging the urogenital nerves and organs which could result in voiding and sexual disorders [587, 593, 602]. There is a paucity of literature devoted to the impact of surgery alone or multimodality treatment on women’s sexual function. Mannaerts et al reported the sexual outcome results of a population of both men and women suffering from locally advanced primary and locally recurrent rectal cancer [594]. Using questionnaires, sexual function was evaluated during the 6 months prior to aggressive multi-modality therapy as well as during follow-up (median 14-months, range 4-60 months) to assess clinical outcome. Interest in sexual activity and ability to achieve orgasm decreased in women after the treatments. Among the study population, the mean quality of orgasm was reduced from in both the primary rectal cancer group and the locally recurrent rectal cancer group. Age greater than 60 years significantly reduced the ability to have post-operative orgasm as well as the ability to have sexual intercourse [594]. The same authors, reporting the long-term functional outcome after a multi-modality treatment for locally advanced primary and locally recurrent rectal cancer, found that 56% of respondents complained of sexual inactivity [610]. In a retrospective small survey of 43 patients with low rectal cancer who underwent low anterior resection with or without neoadjuvant or adjuvant radiotherapy, Chatwin found that sexual dysfunction was reported 2 of the 11 sexually active women [611]. Despite their reported fecal, urinary and sexual dysfunction, most patients were satisfied with their quality of life.

Recently Quah et al reported the results of a retrospective analysis of pre-operative and post-operative bladder and sexual function in patients who underwent laparoscopically-assisted and conventional open mesorectal resection for cancer [612]. No significant difference in sexual function was found in women.
b) Radical cystectomy for urologic malignancies

No paper was identified dedicated to the evaluation of sexual function in women after surgery for bladder cancer [613-619]. Genitourinary (GU) cancers are commonly associated with treatment-related sexual dysfunction varying from mild to severe. Sexual dysfunction may occur as a result of cancer and its treatment. Sexual function is sensitive to the effects of both physical and emotional trauma, particularly when the cancer affects the genital organs.

Marshall et al described anterior exenteration in women performed accurately with a disciplined anatomic approach [615]. Women undergoing cystectomy with the simultaneous removal of uterus, ovaries, and parts of the vaginal wall face had issues regarding their femininity as well as concerns regarding future sexual function. Excision of the uterus, a portion of the vagina and the urethra seems to reduce the potential for pelvic recurrence but a vaginal reconstruction and continent urinary diversion provide a better quality of life with maintenance of sexual function and urinary continence.

Bjerre et al conducted a study aimed at evaluating the sexual profile in women after urinary diversion by either radical cystectomy with continent Kock reservoir or ileal conduit diversion [616]. No significant differences were found among the 37 patients who completed the questionnaire. Among whose sexual activity decreased, almost one-third gave physical problems or decreased desire as the reason and 30% felt less sexually attractive, with cystectomized patients reporting a higher percentage than the others. A higher frequency of dyspareunia among patients with a continent reservoir was an unexpected finding.

Nordstrom et al described the sexual function outcome of 66 men and women who underwent an ileal conduit urinary diversion because of bladder cancer or incontinence/bladder dysfunction [617]. Five of the 6 women treated by cystectomy, who had been sexually active pre-operatively, reported either a decrease or cessation of coital activity post-operatively, due mainly to a decrease in sexual desire, dyspareunia and vaginal dryness. One woman reported the inability to experience orgasm after surgery. Compared with women with bladder cancer, those with incontinence/bladder dysfunction were more likely to have an active sexual life after urostomy surgery. A post-operative increase in activity was shown by 7 women in this group, 4 of whom had been sexually inactive before surgery, because the surgery eliminated the need for incontinence pads or indwelling catheters. Hautmann et al presented data about a nerve sparing cystectomy with orthotopic bladder replacement in women [618], but neglected to make observations regarding sexual function.

Horenblas et al have reported preliminary results of a modified cystectomy, called sexuality preserving cystectomy and neobladder, the intent of the surgical technique being to achieve maximal tissue conservation, potentially preserving normal sexual function and satisfactory urinary tract reconstruction [619]. The surgery consists of pelvic lymph node dissection followed by cystectomy with preservation of all internal genitalia. An ileal neobladder was then anastomosed to the urethra. This type of surgical approach was suggested for women suffering from bladder cancer stages T1-T3 with absent tumor growth in the bladder neck and absent invasive tumor in the bladder trigone. Three women aged 38 to 71 years old were enrolled in this protocol and all reported normal vaginal lubrication during sexual activity.

c) Hysterectomy and sexual function

Reports of deterioration of sexual function after hysterectomy is estimated to be between 13% and 37%, which may be through one or more mechanisms [620-625]. Quality of sexual life after hysterectomy may be influenced by several situations resulting in conflicting suggestions [626-632]. Many of the studies exploring sexuality after hysterectomy have methodological flaws, including vague measures of sexual satisfaction and potential for recall bias [633]. In a comprehensive review article, Carlson reported that in women undergoing hysterectomy for non-malignant conditions there is a marked improvement in symptoms and quality of life during the early years after surgery [626]. Hysterectomy did not seem to cause long-term psychiatric morbidity and psychological status generally improved after surgery itself. Rhodes et al [625] recently published the results of a 2-year prospective study which examined measures of sexual function prior to hysterectomy and at 6, 12, 18 and 24-month follow-up after surgery. A total amount of 1101 women completed the study. These authors showed that both sexual desire and frequency of sexual relations significantly increased after hysterectomy and throughout the follow-up period. Frequency and strength of orgasm also increased significantly after surgery. Lack of orgasm pre-operatively was most significantly associated with absence of orgasm after surgery; possibly influenced by aging. Women also reported vaginal dryness improved after hysterectomy.
In contrast, several papers reported a decrease in quality and frequency of sexual activity after hysterectomy. Rako [627, 628] emphasized the importance of the ovaries as a critical source of testosterone as well as estrogen; thus, removal of the uterus, even after ovary-sparing procedures, can jeopardize their function. Loss of a physiologic level of testosterone in women after hysterectomy can decrease quality of life in terms of libido, sexual pleasure, and sense of well-being. An analysis by Cutler et al correlated the impact of hormonal deficit on sexuality and overall quality of life in hysterectomized women [629]. In the US more than half a million women per year undergo hysterectomy as treatment for chronic benign gynecologic conditions [634], a rate 5 times higher than that of the European countries. Estrogen, progesterone, and androgen levels all tend to be altered by hysterectomy. Furthermore, all these sex hormones affect physiologic systems including the cardiovascular system, bone metabolism, cognitive function, sexual response and sexual attractiveness [629].

These conditions are made worse when hysterectomy is accompanied by bilateral oophorectomy. Since the ovaries provide approximately half of the circulating testosterone in pre-menopausal subjects, after surgery many women report impaired sexual function despite estrogen replacement. Shifren et al [350, 635] reported that in women with impaired sexual function after surgically induced menopause high dose transdermal testosterone may be useful, increasing the Brief Index of Sexual Functioning for Women (BISFW) [636] scores for frequency of sexual activity and pleasure-orgasm. In the same group of surgically menopausal women, the percentages of those who had sexual fantasies, masturbated or engaged in sexual intercourse at least once a week increased two to three times from baseline. This issue is actually strongly debated [350, 637, 638].

The estrogen deficiency which results from pre-menopausal hysterectomy with bilateral oophorectomy is associated with vaginal dryness [625, 639], although several reports also demonstrate vaginal dryness after pre-menopausal simple hysterectomy due to potential ovarian damage and failure subsequent to the surgery itself [640-642]. The vaginal orgasm, consequent to the stimulation of nerve endings in the uterovaginal plexus, should be hindered by hysterectomy with cervix removal, but theoretically clitoral orgasm should not be damaged [643]. However, surgical damage to the pelvic autonomic nerves during radical hysterectomy is thought to be responsible for considerable morbidity, including sexual dysfunction.

Surgical preservation of the pelvic autonomic nerves in both laparoscopic and traditional radical hysterectomy deserves consideration in an attempt to improve both cure and quality of life in cervical cancer patients as well as chronic benign conditions [632, 644-665]. Well-designed prospective studies are needed to evaluate the impact of this common surgery on overall sexual function in both pre- and post-menopausal women.

7. CEREBROVASCULAR ACCIDENTS-ORGASMIC DYSFUNCTION

The most common sexual problems in women that have been identified after stroke include decline in libido, coital frequency, vaginal lubrication and orgasm. A number of studies have examined the impact of stroke on female sexual dysfunction but there are few prospective studies. In a prospective 6-month follow-up study, Korpelainen et al assessed the impact of stroke on libido, sexual arousal, coital frequency and satisfaction with sexual life in 38 men and 12 women, 32 to 65 years old [666]. Only married patients with an active sexual life before the stroke and without other peripheral or central nervous system conditions known to affect the autonomic nervous system, severe aphasia or psychiatric illnesses or diseases affecting daily activity were included in the study. The women, all of whom were able to attain orgasm prior to their strokes, reported decreased vaginal lubrication and ability to reach orgasm, with 30% and 20% anorgasmic at 2 and 6 months respectively.

Animal models will continue to be indispensable for studies of the neurobiology of sexual behavior. This includes understanding the neuroanatomical and neurochemical mechanisms that underlie sexual desire, viewed by many clinicians and motivational theorists as distinct from arousal in both animals and humans. Lesion and drug studies, neurochemical and neuroanatomical analyses and molecular approaches provided by animal studies guide our emerging work in the neuroanatomy of sexual response in humans, using functional magnetic resonance imaging or positron emission tomography. Animal models are needed to further understand the hormonal processes
that lead to changes in sexual arousal, as invasive and direct studies of brain or organ function possible in animals cannot be conducted in human subjects.

The understanding of peripheral mechanisms and neurotransmitters regulating the female genital sexual arousal response is limited. Modulation of vaginal and clitoral engorgement, vasocongestion and vaginal lubrication may be antagonistic, regulated by parasympathetic and sympathetic components of the autonomic nervous system of the female genitalia. VIP and NO may be the primary facilitators with noradrenaline and NPY the primary inhibitors of the genital arousal response. There is a need to expand current understanding of the physiological mechanisms responsible for the arousal response in order to improve clinical management of arousal disorders in women.

In assessing sexual arousal in women there is a need for simultaneous measurements of both the cognitive and physical aspects of arousal. Subjective arousal estimates are necessary to answer the question whether or not the woman is able to experience feelings of sexual arousal under different stimulus conditions. In assessment of the physical aspects of arousal the main question to be answered is whether or not, with adequate stimulation by means of audiovisual, cognitive (fantasy) and/or vibrotactile stimuli, a sufficient lubrication-swelling response is possible. If such a response is possible, an organic contribution to the arousal problem of the individual women is clinically irrelevant.

Sex steroids are essential in women's sexual function, but their direct involvement in sexual dysfunction is controversial, due to the multidimensionality of women's sexual health. Both estrogens and androgens contribute to preserve libido, arousal and orgasm, and menopause in particular, when it occurs following surgery, is a good clinical paradigm for studying the effects of sex steroid deprivation on women's sexual function. The fact that androgens serve as precursors for synthesis of estrogens in women and therefore serum levels of androgen are expected to be greater than estrogen plasma levels in women suggests that androgen insufficiency may exist in pre-menopausal as well as post-menopausal women. Although androgen insufficiency may result from a number of circumstances, the diagnosis is difficult because of the lack of precise definitions as well as sensitive assays for free testosterone. Plasma levels of total T, free T and SHBG need to be determined clinically. An increasing body of evidence suggests that women with signs and symptoms of androgen insufficiency respond well to androgen therapy without significant side-effects. Several estrogen therapy and androgen therapy protocols have been proposed to treat female sexual dysfunction, however, a better understanding of the role of endogenous and exogenous hormones on women's sexual function is mandatory. This requires investigation of the biochemical, cellular and physiological mechanisms by which sex steroid hormones modulate sexual function in general, and genital sexual arousal in particular, in experimental models.

The control of sexual function is based upon spinal mechanisms. The spinal cord provides the autonomic and somatic innervation of the sexual organs. Sensory information from the sexual organs project to interneurons in the lower spinal cord. These interneurons likely generate the coordinated activity of sexual responses. Evidence based on human and animal studies indicate that sexual climax (orgasm) is a reflex mediated by the spinal cord, which may involve a spinal pattern generator. Human studies have reported that orgasmic reflexes are still present after spinal cord injury. By classifying women based on sensory preservation of their dermatomes, orgasmic responses have been shown to require intact reflexes that relay in the sacral spinal cord. From a clinical point of view, deficits in genital sensation such as from spinal cord injury and multiple sclerosis are probably responsible for many cases of female sexual dysfunction. Data on the effect of neurologic diseases affecting the peripheral nervous system or various surgical techniques (in particular hysterectomy) on sexual arousal and orgasm are limited. Development of new diagnostic tests, and surgical techniques which spare the genital nerve, are mandatory. There is a tremendous need for more research in this area.

CONCLUSION

Sexual problems in women are highly prevalent, frequently distressing, and poorly understood at present. There has been a long history of neglect of sexual problems generally in medicine, but especially in women. The causes and treatments of sexual dysfunction in women have been of academic concern for more than half a century, but there are limited integrative (psychologic and biologic) research efforts at understanding physiology and pathophysiology of women's sexual health issues.
There is emerging knowledge on women’s sexual dysfunction from the establishment of a host of experimental models, from advances in psychological, biochemical and molecular biologic approaches and the development of new diagnostic tests. Well-defined end-points and outcomes and a general consensus on the diagnostic framework for assessment and treatment of FSD are important goals for the future of sexual health and well-being involving both mind and body. It is anticipated that the coming years will bring new knowledge and improved clinical care in the management of women’s sexual dysfunction.

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CHAPTER 2

Committee 1

Definitions, Classification, and Epidemiology of Sexual Dysfunction

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I. GENERAL INTRODUCTION

II. INTRODUCTION TO DEFINITIONS OF SEXUAL DYSFUNCTIONS

III. DEFINITIONS OF SEXUAL DYSFUNCTION FROM THIS CONSULTATION

IV. DESCRIPTIVE EPIDEMIOLOGY

V. ANALYTICAL EPIDEMIOLOGY

VI. CONCLUSIONS

VII. RECOMMENDATIONS

REFERENCES
Definitions, Classification, and Epidemiology of Sexual Dysfunction


I. GENERAL INTRODUCTION

As a first order of business for this committee, definitions for the various conditions to which this consultation is directed were required. The committee and the entire consultation struggled with this. Whether to use the word dysfunction consistently for sexual problems for men and women was discussed in detail. There were some who felt that there should be some consistency of terms, others who felt that disorder was a better word particularly for those problems with sexual function experienced by women. Other definitions did not require a specific term such as disability, dysfunction, disorder, or incapacity (all discussed by this committee as a possible common unifying term) as you will see below, for example dyspareunia, vaginismus, or early ejaculation. It can be argued, quite rationally, that many of these conditions are symptoms, such as erectile dysfunction, and therefore may represent various etiologic categories or manifestations of other diseases such as diabetes mellitus. For many conditions affecting the sexual activity of women, it was thought that a definition should include an element of bother or distress. This committee has chosen for epidemiological reasons to present a per se definition and add bother and distress as descriptors that can certainly enhance clinical use. For instance, in the previous consultation on erectile dysfunction, the word “satisfactory” appeared in the definition of that disorder. This committee wondered “satisfactory” for whom, the man, and/or his partner, in one situation or another. The committee felt that the word warranted further description when used and chose to leave it out of the new definition that appears below.

Epidemiological data are the basis for assessing the overall impact of a condition on a given society. The two components of epidemiology, descriptive epidemiology (incidence and prevalence by persons, place and time- usually focusing on nationally and regionally representative samples) 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. 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. In the 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 from different investigations. Different methodological rationales, such as the time period studied (3 months, 6 months, 1 year, life-long), different age strata included and (self-) selection biases are other problems in comparative analysis. Some reports include only one particular sexual disorder, most prominently for studies for erectile dysfunction, while some include different conditions in both genders, making it possible to perform cross-gender epidemiological calculations.

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

A major thrust of this particular consultation was to use evidence-based medicine standards for inclusion
of material analyzed and cited [1]. This committee has, concerning descriptive epidemiology, adhered to the classification of epidemiological validity described by Prins et al [2], who identified 15 dichotomizable (yes/no) points for being recognized as valid from the prevalence or incidence point of view. (Table 1). In this chapter only nationally or regionally representative studies published in peer-reviewed journals 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 also scored Ib or higher using the evidence-based criteria. [1].

Table 1. Criteria for the methodological quality assessment of prevalence studies- one point for yes to lower case query

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<tr>
<th>External validity</th>
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<td><strong>Source population</strong></td>
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<td>a) Does the method to select and invite participants result in a study population that covers the complete population or a random sample?</td>
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<tr>
<td><strong>Description of the eligibility criteria</strong></td>
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<td>b) Is the age range specified?</td>
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<td>c) Are inclusion and exclusion criteria specified?</td>
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<td><strong>Participants and nonresponders</strong></td>
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<td>d) Is the response rate &gt; 70%, or is the information on nonresponders sufficient to make inference on the representativeness of the study population?</td>
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<td><strong>Description of the study period</strong></td>
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<td>e) Is the study period specified?</td>
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<td><strong>Description of the study population</strong></td>
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<td>f) Are important population characteristics specified?</td>
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<th>Internal validity</th>
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<td><strong>Data collection</strong></td>
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<td>g) Are the data prospectively collected?</td>
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<td><strong>Measurement instrument (questionnaire, interview, additional)</strong></td>
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<td>h) Is the measurement instrument validated?</td>
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<td>i) Is the period covered by the measurement instrument specified?</td>
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<td><strong>Definition of diseases</strong></td>
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<td>j) Is a definition of the disease stated?</td>
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<td><strong>Reported prevalences</strong></td>
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<td>k) Are age-specific and gender-specific prevalences reported?</td>
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<td>l) Are possible correlates of disease reported?</td>
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<td><strong>Informativity</strong></td>
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<td>m) Is the method of data collection properly described (interview, questionnaire, additional measurement)?</td>
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<td>n) Are the questions and answer possibilities stated?</td>
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<td>o) Are the reported prevalence rates reproducible?</td>
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At present, the two most widely used sets of definitions of sexual dysfunctions are those given by the World Health Organization (WHO), 1992 [3] in the ICD-10, and by the American Psychiatric Association, (DSM-IV), in 1994 [4]. In sexual medicine, the ICD-10 has mainly been used within somatic care and the DSM-IV within psychological/psychiatric settings. Both sets of definitions are basically built upon the mainly physiological model of genital responses and symptoms disturbing coital intercourse first described by Masters and Johnson [5]; later modified by Kaplan [6]. Both sets add to the sexual response “cycle” sexual pain definitions 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 mainly described in terms of vaginal physiological response; while for the men, satisfactory intercourse 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 definatory (A and B) categories describing psychogenically based disorders: The A category focuses on defining sexual disorders per se. The common denominator of all is: “persistent or recurrent”. It is explicitly pointed out that each disorder must be a 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 are 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 enables distinguishing a dysfunction per se from its emotional impact (but only if marked) – intra- as well as interpersonal-ly. The B category does not leave a possibility for inclusion of mild or sporadically occurring distress.

Some years ago a consensus panel recommended a new diagnostic and classification system for women’s sexual dysfunctions incorporating both physiological and psychological pathophysologies and personal distress. The consensus panel [7] recommended a set of definitions which includes a personal distress dimension for most of the dysfunctions. An important feature of the DSM-IV (A and B categories) and the Basson et al [7] 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 several different situations) vs situational (certain situations). It is underlined that the clinical evaluation should include etiological factors. An example of such classifications is that given in 1999 by Lizza and Rosen. [8] (Table 2).

Table 2. Classification for Male Erectile Dysfunction

<table>
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<tr>
<td>1. Vasculogenic</td>
<td>Arteriogenic Cavernosal Mixed</td>
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<td>2. Neurogenic</td>
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<td>3. Anatomic</td>
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<td>4. Endocrinologic</td>
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Psychogenic

1 Generalized Type

a) Generalized unresponsiveness
   i. Primary lack of sexual arousability
   ii. Aging-related decline in sexual arousability

b) Generalized inhibition
   i. Chronic disorder of sexual intimacy

2. Situational Type

a) Partner related
   i. Lack of arousability in specific relationship
   ii. Lack of arousability due to sexual object preference
   iii. High central inhibition due to partner conflict or treatment

b) Performance related
   i. Associated with other sexual dysfunction/s
   ii. Situational performance anxiety

c) Psychological distress or adjustment related
   i. Associated with negative mood state or life stress

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

The definitions of sexual dysfunctions for women came primarily from deliberations by the work of an international group of experts [16], supported by the American Foundation for Urological Disease and the members of chapter 16 of this book.

Sexual interest/desire dysfunctions are diminished or absent 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. This same definition for this disorder applies to men as well (see below).
The area of sexual arousal disorders is divided into three subtypes. *Genital sexual arousal dysfunctions* are absent or impaired genital sexual arousal. For women, self-report may include minimal vulval swelling or vaginal lubrication from any type of sexual stimulation and reduced sexual sensation from caressing genitalia. Subjective sexual excitement still occurs from non-genital sexual stimuli. This is a self-reported condition. *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).

**Persistent sexual arousal dysfunction** is spontaneous, intrusive and unwanted genital arousal (e.g. 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 unrelated by one or more orgasms and the feeling of arousal persists for hours or days. *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. *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 woman’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. *Sexual aversion disorder* is extreme anxiety and/or disgust at the anticipation of/or attempt to have any sexual activity.

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 described in Chapter 16.

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

**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-month 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 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.

It is the consensus of this international consultation that premature ejaculation, a term considered relatively inaccurate and pejorative, should be replaced by the term early ejaculation. *Early ejaculation* is ejaculation that occurs sooner than desired, either before or shortly after penetration over which the sufferer has minimal or no control. As all or most other dysfunctions this is primarily a self-reported diagnosis. A sexual history in which the patient uses language that explicitly communicates the circumstance of the condition is the fundamental basis of assessment with time to ejaculation as the most important feature. The opinion of the partner can provide a significant contribution of clinical understanding. A complete description is essential in distinguishing early ejaculation from erectile dysfunction because these conditions frequently coexist. Moreover, many men are unaware that loss of erection after ejaculation is normal; thus they may erroneously complain of ED when the actual problem is early ejaculation.

Definitions of other sexual dysfunctions for men include the following: 1.) *delayed ejaculation* is undue delay in reaching a climax during sexual activity, 2.) *orgasmic dysfunction* is inability to achieve an orgasm, markedly diminished intensity of orgasmic sensations or marked delay of orgasm during conscious sexual activity, and 3.) *anejaculation* is the absence of ejaculation during orgasm.

### Classification of Severity

During recent decades different clinically well validated indexes, some examples being for men the IIEF [17] and for women the FSFI, [18] have been introduced. However, aggregated scores have been questioned [19, 20] as a summed score may obscure a (sexual) aspirations-achievement gap within perti-
The first published, population-based study on incidence came from the MMAS (Massachusetts Male Aging Study)[27]; 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 3). 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. [28] 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 3). 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 is conducted in the town of Krimpen aan de IJssel (The Netherlands); this is a commuter town near Rotterdam with a predominantly Caucasian population. [29] Analyses were performed on 1458 “clinically-relevant-ED”-free men and 1432 ED-free men (see table 3 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 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 3).
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 3). 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.

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 surveys. 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 at home 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 like the one that participating men should have a sexual partner (MMAS) also theoretically results in a potentially healthier baseline population. There are probably large differences in SES (socio-economic status) between the studies. 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.

From the comparison of the different follow-up periods as was done in the Krimpen study, it becomes clear 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 come up with “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 of the potentially interested in the older population.

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 1999-2000 in men aged 40-79 years, which is somewhat younger than the Krimpen population. [31].

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 desire during the past 5 years [32]. 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 1990s in Sweden. [33]. 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 [34]. and, as discussed in Chapter 16, sexual desire, to a greater degree than sexual interest, may be seen as a partner-related aspect of sexuality, not really separable from arousal.

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 [2]. 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 previous chapter on ED from the first consultation [35], and surveys from Spector and Carey (1991) [36], Simons and Carey (2001) [37], Lewis [38], and Kubin et al [39]. 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 [1].

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, but 20-30% of
### Table 3. Incidence rates of erectile dysfunction in population based cohort studies.

<table>
<thead>
<tr>
<th>Authors [Ref]</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>Follow-up</th>
<th>Differences Non-responders</th>
<th>Study design</th>
<th>Instrument</th>
<th>Definition of ED</th>
<th>Alternative definition of ED</th>
<th>Time period</th>
<th>Mean follow-up (range) yrs.</th>
<th>Person years of follow-up</th>
<th>Crude Incidence: Cases / 1000 person years (95% CI)</th>
<th>Age specific incidence rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johanes et al [27]</td>
<td>Massachusetts (USA)</td>
<td>Random population sample</td>
<td>60-69</td>
<td>Men with sexual partner</td>
<td>At home interview</td>
<td>52%</td>
<td>2 years</td>
<td>Participants more LUTS and better health status compared to 261 non-responders questioned</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 intercourse</td>
<td>NA</td>
<td>18.8 (17.3-20.3)</td>
<td>76.75</td>
<td>25.9 (22.2-29.5)</td>
<td>40-49 12.4</td>
<td>50-59 29.8</td>
</tr>
<tr>
<td>Munshi et al. [28]</td>
<td>Salvador (Honduras)</td>
<td>Random population sample</td>
<td>60-70</td>
<td></td>
<td>At home interview</td>
<td>92%</td>
<td>93%</td>
<td></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 intercourse</td>
<td>NA</td>
<td>21.3 (20.0-22.7)</td>
<td>85.5 (49.6-85.2)</td>
<td>40-49 33.3</td>
<td>50-59 53.3</td>
<td>60-69 78.9</td>
</tr>
<tr>
<td>Schoot et al [39]</td>
<td>Knoepmen um des Vosel (The Netherlands)</td>
<td>All men registered in all general practices in Knoepmen</td>
<td>50-78</td>
<td></td>
<td>Self-administered questionnaire handed in at visit to health center / Clinic</td>
<td>50%</td>
<td></td>
<td>Participants more LUTS and better health status compared to 261 non-responders questioned</td>
<td>Cohort study</td>
<td>Validated single assessment question (scale: 4 grades)</td>
<td>Erections with severely reduced rigidity or erection not possible</td>
<td>NA</td>
<td>21.0 (18.6-23.3)</td>
<td>4.7 (3.6-5.8)</td>
<td>31.3 (28.0-34.4)</td>
<td>50-49 31.2</td>
<td>59-59 35.3</td>
</tr>
</tbody>
</table>
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 from which these investigations emanate, have a manifest sexual dysfunction per se.

4. Prevalence of Women's Sexual Dysfunctions

An overview of the valid studies on prevalence of women's sexual dysfunctions, when feasible, dichotomized into mild (MiD) and manifest (MaD) is given in Table 4. Among these 11 descriptive epidemiological studies seven were from Europe, two from the USA and one each from Morocco and Australia. There were pronounced methodological differences between these studies. Thus, seven of them used face-to-face interviews. Telephone interviews of very varying length were the bases of three; One of the studies used a mailed questionnaire. While interviews, whether face-to-face or by telephone for pragmatic reasons, can be regarded reliable [22], there is in the literature some doubt about the reliability of mailed questionnaires. A main reason being that a mailed questionnaire may be answered in consensus between partners. Such a questionnaire may also yield a relatively low response rate.

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). One of the British studies focused only on elderly women while others cover an age span from the teens and up to the early seventies. Only two studies, the Finnish and the Swedish, may, from the sample selection and definatory points of view, be regarded as twins. However, these two countries are neighbors with rather small total populations.

Even the period of sexual functions/dysfunctions differs considerably. Thus, while the Icelandic and French studies describe life long prevalence, others address the past year – or even a briefer period. A special case is the recent Australian study in which questions were initiated by the phrase: "During the last year has there been a period of one month or more when you” then followed by the dysfunctions per se.

Also definitions and classification of severity vary considerably ranging from DSM-III (or 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.

a) Interest/Desire:

As pointed out in chapter 16, the definatory category desire/interest is ambiguous because in women “desire” is probably not separable from the psychological aspects of arousal – yet another argument for universal consensus. Moreover, some authors may prefer to use the label “libido” (for women and men alike), a label that should be reserved for psychoanalytical descriptions/interventions.

In any case, using different methods and scalings, descriptive epidemiological investigations have found that the prevalence of manifest low level of sexual interest varies between 17% (GB) in 35-39 year old women [40] through 33% (USA 18-59 years and Sweden 18-74 years) and up to 55% in Australia [41]. Neither in the US [15]. nor in Sweden [24]. 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. As shown in Table 4, a major difference between the USA and Sweden in this respect was that the oldest Swedish women had considerably higher prevalence than had 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 dysfunction of sexual interest during the preceding year. This is very close to the French 55% prevalence [42] of mild desire dysfunction. These numbers are so high as are the numbers of mild orgasmic dysfunction and of dyspareunia that it might be contemplated if mild sexual dysfunction in women may best be professionally ignored. However, 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 [24].

Manifest low level of sexual desire was in Finland [32] reported in as much as 35% of 18-74 year old women, being about 15-25% in women younger than 55, but increasing to about 50% in women aged 55-74. Lower levels of manifest desire dysfunction were reported from Sweden [43], where among women at the same age about 10% up to the age of 49 had low level of desire. The prevalence then doubled to 22% in those aged 50-65 and again doubled (47%) in the 66-74 year olds. These numbers appear to agree rather well with those reported in Iceland [44] and in Morocco [21], while in France [42]
Table 4. Valid epidemiological investigations (arranged according to publication year) of prevalence of women’s sexual dysfunctions.

<table>
<thead>
<tr>
<th>Author(s), Performed/published</th>
<th>Country/Regional National</th>
<th>Method Scale steps</th>
<th>Age</th>
<th>n (% response Approx.)</th>
<th>Validity score (Prins)</th>
<th>Desire (D) 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>Osborn et al., [40] NG/1998</td>
<td>GB/R</td>
<td>Interview 5</td>
<td>35-59</td>
<td>436 (72%)</td>
<td>12</td>
<td>1-17%</td>
<td>L-17%</td>
<td>-16%</td>
<td>-18%</td>
<td>-</td>
</tr>
<tr>
<td>Lincal, Stefansson, [44] 1987-88/1993</td>
<td>ICL/N</td>
<td>Interview 2</td>
<td>55-57</td>
<td>417 (75%)</td>
<td>14</td>
<td>D 16%</td>
<td>6%*</td>
<td>4%**</td>
<td>3%</td>
<td>-</td>
</tr>
<tr>
<td>Kontula, Haavio-Manilla, [32] 1992/1995</td>
<td>FI/N</td>
<td>Interview 6</td>
<td>18-74</td>
<td>1146 (78%)</td>
<td>13-14</td>
<td>D -35%</td>
<td>L -15%</td>
<td>63%/30%</td>
<td>30%/7%</td>
<td>-</td>
</tr>
<tr>
<td>Berlow et al., [47] 1993/1997</td>
<td>GB/R</td>
<td>Interview 2</td>
<td>55</td>
<td>2011 (61%)</td>
<td>10</td>
<td>-</td>
<td>L-8%</td>
<td>2%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Johannes, Avis, [46] 1988-89/1997</td>
<td>USA/R</td>
<td>Telephone 3</td>
<td>51-62</td>
<td>349 (82%)</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-41%</td>
<td>-13%</td>
<td>-</td>
</tr>
<tr>
<td>Groupe ACSF Bajos et al., [42] 1991-92/1998</td>
<td>FR/N</td>
<td>Telephone 4</td>
<td>18-69</td>
<td>1137 (&gt;70%)</td>
<td>11</td>
<td>D 55%/8%</td>
<td>-</td>
<td>44%/11%</td>
<td>43%/5%</td>
<td>-</td>
</tr>
<tr>
<td>Dunn et al., [45] 1996/1998</td>
<td>GB/NG</td>
<td>Mailquest. 2</td>
<td>18-75</td>
<td>657 (33%)</td>
<td>10</td>
<td>-</td>
<td>A-17%</td>
<td>-27%</td>
<td>-18%</td>
<td>-</td>
</tr>
<tr>
<td>Laumann et al., [15] 1992/1994, 1999</td>
<td>USA/N</td>
<td>Interview 2</td>
<td>18-59</td>
<td>1486 (79%)</td>
<td>13</td>
<td>1-32%</td>
<td>L-21%</td>
<td>-26%</td>
<td>-16%</td>
<td>-</td>
</tr>
<tr>
<td>Fugl-Meyer group [14, 24, 43] 1996/1999-2003</td>
<td>SF/N</td>
<td>Interview 6</td>
<td>18-74</td>
<td>1475 (59%)</td>
<td>14</td>
<td>1 54%/33%</td>
<td>L-49%/13%</td>
<td>60%/22%</td>
<td>33%/6%</td>
<td>5%/1%</td>
</tr>
<tr>
<td>Kadri et al., [21] NG/2002</td>
<td>MO/R</td>
<td>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>
</tr>
<tr>
<td>Richters et al., [41] 2000-01/2003</td>
<td>AU/N</td>
<td>Telephone 2</td>
<td>16-59</td>
<td>8280 (65%)</td>
<td>13</td>
<td>1-55%</td>
<td>L-24%</td>
<td>-29%</td>
<td>-20%</td>
<td>-</td>
</tr>
</tbody>
</table>

MiD = mild, sporadically occurring dysfunction. MaD = manifest dysfunction occurring at least quite often. NG = Not given. *excitement ** anorgasmia
clearly fewer have manifest, but 55% have mild desire dysfunction.

b) Arousal and Lubrication

As previously mentioned, the conventional definition of arousal nearly exclusively covers genital events, foremost lubrication (and in men, erection). However, both in women and men, 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 will be discussed in chapter 16.

Using the DSM-IV definition, 16% of 55-57 year old Icelandic women were found to have low levels of excitement [44]. 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 different epidemiological studies (table 4). Generally, manifest lubrication disability is prevalent in 8-15%, while Laumann et al [15], Richters et al [41], and Dunn et al [45] reported this to be the case in 21-28% of sexually active women. These three investigations all used a dichotomous yes/no scale. Additionally, Öberg et al [24] 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 [43, 45], while others have not found age dependency in this respect [15].

c) Orgasm

This topic will be discussed in more detail in chapter 9. The prevalence of manifest orgasmic dysfunction varies considerably 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 [41], England [45], Sweden [43] and the USA [15] the prevalence of manifest orgasmic dysfunction is about 25% in 18-74 year old women. 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. A somewhat higher (30%) prevalence has been reported from Finland [32]. A significantly higher prevalence (41%) of manifest orgasmic dysfunction among 51-62 year old women has been reported from Massachusetts [46]. In other studies [21, 40, 42], 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.

d) Dyspareunia and Vaginismus

These conditions are discussed in chapter 16. The syndromes are clearly less prevalent in the general population. Thus, 6% of Moroccan [21] and Swedish [43] 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 2% in elderly British women [47] while another British study [45] and the Australian one [41] found that dyspareunia prevailed in as many as 18-20%. Mild (sporadically occurring) dyspareunia is 4-8 fold more common than is manifest. Several investigations have described increasing dyspareunia with increasing age [15, 43, 45] 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 [41].

5. Prevalence of Men’s Sexual Dysfunctions

a) Interest/Desire

Altogether we have identified 7 epidemiologically valid reports (table 5) that include men’s interest and/or desire. Whereas in the USA [15] and Sweden [43] 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 [41] a clearly higher prevalence, without any pronounced age effect, of about 25% was reported by 16-59 year old men. Generally dysfunction of sexual desire/drive is much less prevalent than dysfunction of interest, whether life-long (France [42] and Iceland [44]) or during the past year [43] or so. However, at higher ages (>65-70) both Panser et al [48] and the Swedes [43] have also demonstrated sharp increase in this prevalence. To sum this up: 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
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>Author(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>
</tr>
</thead>
<tbody>
<tr>
<td>Lindahl, Stefansson [44] 1987-88-93</td>
<td>ICL/N</td>
<td>405</td>
<td>Interview</td>
<td>55-57</td>
<td>(D) 4% (yes drive)</td>
<td>-</td>
<td>-</td>
<td>1%</td>
<td>-</td>
</tr>
<tr>
<td>Panser et al [48] 1989-90</td>
<td>USA/R</td>
<td>2115</td>
<td>Interview</td>
<td>40-79</td>
<td>6%</td>
<td>-</td>
<td>-</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40-49</td>
<td>0.6%</td>
<td>-</td>
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<td>-</td>
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</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>≥ 70</td>
<td>26%</td>
<td>-</td>
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</tr>
<tr>
<td>Kontulainen, Haavio-Mannila [32] 1992-1995</td>
<td>FIN</td>
<td>1104</td>
<td>Interview</td>
<td>18-74</td>
<td>(D)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18-24</td>
<td>5%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25-34</td>
<td>2%</td>
<td>-</td>
<td>-</td>
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<td>15%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>35-44</td>
<td>5%</td>
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<td>-</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45-54</td>
<td>13%</td>
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<td>-</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55-64</td>
<td>14%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>15%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>65-74</td>
<td>23%</td>
<td>-</td>
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<td>-</td>
<td>5%</td>
</tr>
<tr>
<td>Doon et al [45] 1998-1998</td>
<td>GBR/NG</td>
<td>789</td>
<td>Mailed questionnaire</td>
<td>18-75</td>
<td>-</td>
<td>14% (3 mths) 31% (ever)</td>
<td>-</td>
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</tr>
<tr>
<td>Groupe ACTS Bajos et al [42] 1991-92-1998</td>
<td>F/N</td>
<td>1355</td>
<td>Telephone</td>
<td>18-69</td>
<td>3%</td>
<td>16%</td>
<td>4%</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Laszlo et al [15] 1992-1993</td>
<td>USA/N</td>
<td>1249</td>
<td>Interview</td>
<td>18-59</td>
<td>(I) 16%</td>
<td>21%</td>
<td>-</td>
<td>8%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18-29</td>
<td>14%</td>
<td>30%</td>
<td>-</td>
<td>10%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30-39</td>
<td>13%</td>
<td>32%</td>
<td>-</td>
<td>8%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40-49</td>
<td>15%</td>
<td>28%</td>
<td>-</td>
<td>9%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>17%</td>
<td>55%</td>
<td>-</td>
<td>6%</td>
<td>-</td>
</tr>
<tr>
<td></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>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25-34</td>
<td>2% : 16%</td>
<td>7%</td>
<td>0</td>
<td>-</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35-49</td>
<td>1% : 13%</td>
<td>8%</td>
<td>2%</td>
<td>-</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-65</td>
<td>22% : 18%</td>
<td>9%</td>
<td>3%</td>
<td>-</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60-74</td>
<td>4% : 41%</td>
<td>14%</td>
<td>10%</td>
<td>-</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Blankers [70] 1995-98-2001</td>
<td>NL/R</td>
<td>3503</td>
<td>Questionnaire</td>
<td>50-78</td>
<td>-</td>
<td>15%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Richters et al [41] 2000-01-2003</td>
<td>A/U</td>
<td>8517</td>
<td>Telephone</td>
<td>16-59</td>
<td>(I) 25%</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>
<td>-</td>
<td>-</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20-29</td>
<td>25%</td>
<td>-</td>
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<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30-39</td>
<td>22%</td>
<td>-</td>
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<td>-</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40-49</td>
<td>29%</td>
<td>-</td>
<td>-</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>32%</td>
<td>-</td>
<td>-</td>
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<td></td>
</tr>
</tbody>
</table>

NG= not given
to decline already around the starts of their 6th decade of life.

**b) Erectile Dysfunction**

Table 6 is a compilation of the data from 24 studies around the world regarding prevalence of ED (male sexual arousal dysfunction) from 1993 to 2003. 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, of the 24 presented in this table, only six were included in the first consultation chapter. Many studies were performed after the book concerning the first consultation was published. There is a better global representation now.

Design of the studies included survey questionnaire only (survey) or cross-sectional study with additional measurements (CS) and the table shows 18 of the former and 6 of the latter. Self-administered questionnaires were the instrument used in 12 of the survey designed studies and interviews in the remaining 6 of these. In the cross-sectional studies all studies used the instrument of self-administered questionnaires except one study from Wales, 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 [49].

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. 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 a few months to one year, and 8 of the studies did not specify a time period questioned about ED. By region of the world, there were 15 studies from Europe (three from the United Kingdom, two each from the Netherlands, Sweden, Finland, and France and one each from Denmark, Germany, Italy, and Spain), 5 from the United States, one each from Thailand and Japan, and 2 from Australia.

Most were random population studies, some stratified by age or region. The Japanese study by Masumori et al included all men 40-79 years of age in a fishing village with 42.3% participating the study. In the study from Denmark reported by Solstad and Hertof, 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, one from the Netherlands, 50-75 years of age, with a 47% response, and one from Wales, UK, 55-75 years of age, with a 50% response rate. 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 and one from Italy, age 18 years and older, with a 82% response rate. 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 39 to 82%. The number of respondents was not below 200 in any of the studies and only five of the twenty-one were under 500 in number. Four of the studies reported no differences between responders and non-responders and the other 9 did report differences as summarized in the table. Eleven did not address this issue.

All the studies which were stratified by age showed rising prevalence of ED as the population aged. 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 prevalence of ED before the age of 61 years in the northern European studies were generally quite low. The same tools and methods were used in a United States study and a Japanese survey [48, 59]. 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.

In the studies from the United States, 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 [23, 25, 51-52, 64]. The Laumann data included men who were younger and reported only half the prevalence rate
Table 6: Worldwide Prevalence of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Authors/Year (Published)</th>
<th>Country of Study</th>
<th>Age of Erectile Dysfunction</th>
<th>Eligibility Criteria</th>
<th>Number of Participants</th>
<th>Differences Between Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bamboo, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>All men registered in RPS</td>
<td>18.992 (95% CI 16.10-21.88)</td>
<td>NS</td>
</tr>
<tr>
<td>Benski, et al. (2004)</td>
<td>UK</td>
<td>18-75</td>
<td>Stratified by age and gender</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Bhide, et al. (2008)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Bhatia, et al. (2009)</td>
<td>India</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Black, et al. (2008)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Bland, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Brown, et al. (2008)</td>
<td>UK</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Breslin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Bresin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Brown, et al. (2008)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Breslin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Bresin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Brown, et al. (2008)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Breslin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Bresin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
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<tr>
<td>Brown, et al. (2008)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
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<tr>
<td>Breslin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Bresin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Brown, et al. (2008)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Breslin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Bresin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Brown, et al. (2008)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
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<tr>
<td>Breslin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Bresin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Brown, et al. (2008)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
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<tr>
<td>Breslin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
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<tr>
<td>Bresin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Brown, et al. (2008)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
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<tr>
<td>Breslin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Bresin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Brown, et al. (2008)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Breslin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Bresin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Brown, et al. (2008)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
<tr>
<td>Breslin, et al. (2009)</td>
<td>USA</td>
<td>40-70</td>
<td>Stratified by age</td>
<td>30.46 (95% CI 27.35-33.57)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table 6. Worldwide Prevalence of Erectile Dysfunction (Continued)

<table>
<thead>
<tr>
<th>Authors/ 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 (% responders)</th>
<th>Differences/ Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fugl-Meyer 1999 [44, 33, 43] (14)</td>
<td>Sweden</td>
<td>RPS</td>
<td>18-74</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>Masumori, et al. 1999 [59] (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, antiandrogen, CVA or neurogenic bladder</td>
<td>289 (46.8%) 42.3% analyzed</td>
<td>NS</td>
</tr>
<tr>
<td>Pinnock 1999 [60, 61] (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>Panazzoli 2000 [62] (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>Kongkanand 2000 [63] (11)</td>
<td>Thailand</td>
<td>Region stratified RPS</td>
<td>40-70</td>
<td>NS</td>
<td>1259</td>
<td>NS</td>
</tr>
<tr>
<td>Ansong, et al. 2000 [64] (10)</td>
<td>USA</td>
<td>Age stratified RPS</td>
<td>50-76</td>
<td>NS</td>
<td>1408 (27)</td>
<td>Questionnaire to nonresponders – 21/110 prevalence of ED similar</td>
</tr>
<tr>
<td>Braun, et al. 2000 [65] (11)</td>
<td>Germany</td>
<td>Age and marital status stratified RPS</td>
<td>50-80</td>
<td>NS</td>
<td>4489 (56)</td>
<td>Comparison with German socioeconomic data – similar</td>
</tr>
<tr>
<td>Meuleman 2001 [66]</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 [68-70] (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>
</tbody>
</table>
Table 6. Worldwide Prevalence of Erectile Dysfunction (Continued)

<table>
<thead>
<tr>
<th>Authors/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 (% responders)</th>
<th>Differences/Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin-Morales, et al. 2001 [71] (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>
<tr>
<td>Green, et al. 2001 [72] (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>Bacon, et al. 2003 [73] (10)</td>
<td>USA</td>
<td>Health professionals</td>
<td>53-90</td>
<td></td>
<td>31742 (25)</td>
<td>NS</td>
</tr>
<tr>
<td>Richters et al. 2003 [41] (13)</td>
<td>Australia</td>
<td>Weighted RPS nationally representative</td>
<td>16-59</td>
<td>NS</td>
<td>8367 (57)</td>
<td>No difference from general population</td>
</tr>
</tbody>
</table>
Table 6. Worldwide Prevalence of Erectile Dysfunction  (Continued)

<table>
<thead>
<tr>
<th>Authors/ Year 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>Solstad, Hertoft 1993 [49, 50] (12)</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 109 of original group –7%]</td>
</tr>
<tr>
<td>Feldman, et al. 1994+ [23,25, 51-52] (13)</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 50 60 70</td>
<td>23 (%) 32 40 49</td>
</tr>
<tr>
<td>Kontula, Haavio-Manilla 1995 [32] (13-14)</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 18-24 25-34 35-44 45-54 55-64 65-74</td>
<td>6% 1% 0% 1% 7% 16% 32%</td>
</tr>
<tr>
<td>Panser, et al. 1995 [48] (12)</td>
<td>Survey/SAQ</td>
<td>Consant inability to have erection when sexually stimulated</td>
<td>Month</td>
<td>40-49 50-59 60-69 70-79</td>
<td>1 (0-1) 6 (4-8) 22 (18-26) 44 (38-51)</td>
</tr>
<tr>
<td>Groupe ACSF Bajos et al 1998 [42] (11)</td>
<td>Survey/Interview</td>
<td>Often not, erection</td>
<td>Lifetime</td>
<td>18-69</td>
<td>7%</td>
</tr>
<tr>
<td>Authors/Year 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>
<tr>
<td>Frankel, et al. 1998 [56] (10)</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>Kosinski, et al. 1998 [57] (10)</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>Laurmann, et al. 1999 [15] (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>Fugl-Meyer 1999 [14,33,43] (14)</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>Marumo, et al. 1999 [59] (10)</td>
<td>CS/SAQ</td>
<td>Ability to have an erection when stimulated none or little of the time</td>
<td>One month</td>
<td>40-49</td>
<td>15 (6-23)</td>
</tr>
<tr>
<td>Frake, 1999 [60, 61] (13)</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>Perazzini 2000 [62] (10)</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>5 (3-8)</td>
</tr>
<tr>
<td>Kongkanand 2000 [62] (11)</td>
<td>Survey/Interview</td>
<td>Sometimes or never able to achieve or keep erections good enough for intercourse</td>
<td>Six months</td>
<td>40-49</td>
<td>5 (3-8)</td>
</tr>
</tbody>
</table>
Table 6. Worldwide Prevalence of Erectile Dysfunction (Continued)

<table>
<thead>
<tr>
<th>Authors/Year 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>Ansorg, et al. 2000[64] (10)</td>
<td>Survey/SAQ</td>
<td>Recurrent inability to attain and 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>
<td></td>
<td></td>
<td>55-59</td>
<td>35 (29-41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60-64</td>
<td>47 (40-53)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65-69</td>
<td>58 (54-66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70-76</td>
<td>69 (62-75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40-49</td>
<td>10 (8-12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>16 (13-18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60-69</td>
<td>34 (32-37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70-76</td>
<td>53 (48-58)</td>
</tr>
<tr>
<td>Mueller et al. 2001 [66]</td>
<td>Survey/SAQ</td>
<td>Problems attaining or maintaining an erection hard enough for sexual intercourse</td>
<td>NS</td>
<td>40-49</td>
<td>6 (3-10)</td>
</tr>
<tr>
<td>Boyle, et al. 1999[67] (15)</td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>9 (6-12)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>60-69</td>
<td>22 (18-26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70-78</td>
<td>38 (32-44)</td>
</tr>
<tr>
<td>Blanker, et al. 2001[68-70] (13)</td>
<td>CS-SAQ</td>
<td>No erections or erections of severely reduced rigidity</td>
<td>NS</td>
<td>50-54</td>
<td>3 (1-5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55-59</td>
<td>5 (3-8)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>60-64</td>
<td>11 (8-14)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>65-69</td>
<td>19 (14-23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70-78</td>
<td>26 (19-33)</td>
</tr>
<tr>
<td>Martin-Morales, et al. 2001[71] (15)</td>
<td>Survey/SAQ</td>
<td>Moderate to severe incapacity for erection on single questions</td>
<td>NS</td>
<td>25-29</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40-49</td>
<td>3 (2-5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-59</td>
<td>8 (5-10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60-70</td>
<td>21 (18-25)</td>
</tr>
<tr>
<td>Green, et al. 2001 [72] (10)</td>
<td>CS/Interview</td>
<td>Complete erectile dysfunction – never able to attain an erection sufficient for satisfactory sexual activity</td>
<td>NS</td>
<td>55-60</td>
<td>7 (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>61-65</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>66-70</td>
<td>22</td>
</tr>
<tr>
<td>Bacon, et al. [73] 2003 (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>
<td></td>
<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>Richters et al 2000-04/2003 [41] (13)</td>
<td>Survey/Telephone Single question</td>
<td>Trouble keeping erection At least one month during year</td>
<td>At least one month during year</td>
<td>16-59</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16-19</td>
<td>4%</td>
</tr>
<tr>
<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>
</tbody>
</table>
for the men 50 to 59 years of age compared to the other two studies from the United States. The Olmsted County study from the United States also showed a lower prevalence rate by a large amount for the ages 40-59 and half the prevalence rate for the decades 60-69 years but similar rates for the decades 70-79 as the MMAS data [48]. The survey from France showed about 10% less prevalence for each decade stratified, 50-59 years, 60-69 years, and 70-79 years, than the MMAS study [55]. The single study from Germany showed similar results as the French study except for the age of 70 years and greater where the prevalence data matched the MMAS study. In the study from Italy similar prevalence rates to the ones stated above were found for these three decades of life and prevalence rates of 2-5% were seen for those aged 18-49 years of age. In the survey from Spain, very low rates were seen from ages 25 to 49 years, 2-3%, the rate doubled for the decades of 50-59 years to 8% and then rose sharply to 21% for those 60-70 years of age. In the two studies from the Netherlands, different age stratifications made comparisons of rates difficult but the prevalence was lower for ages 40-59 years, 3 to 9%, but seemed to rise after age 60 to rates about half those reported by the MMAS. The studies from the United Kingdom showed varied results but the definition of ED varied and the age cohorts reported varied greatly. However one of the studies agreed fairly well with the age reported prevalence data from the MMAS study [56]. Above the age of 60 years prevalence rates increased to almost double the rates before this age.

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 [15] 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), [17] which is, of course, also a scale based on self-reports [71]. 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 recently been reported [25]. 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 tool for population studies, in which detailed clinical measures of ED are impractical.

The Global Survey of Sexual Attitudes and Behavior (GSSAB) [74-75], has 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 6.) and the resulting difficulties posed in establishing the comparability of the estimates across studies [2, 37]. 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 1-9%. In the decades from 40-59 the prevalence ranges from 2-9% to as high as 20-30% with some populations showing marked differences between the 40-49 age groups compared to the 50-59 year age group. In fact, 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. Almost all of the reports show high prevalence rates for those men in their 70’s and 80’s, ranging from 50 to 75% prevalence of ED in these decades.

**c) 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 it was accepted that ejaculatory disorders may have a neurobiological origin rather than being a pure psychological issue [76].

We have been able to locate only five descriptive epidemiological investigations of ejaculatory disturbances fulfilling our validity criteria. These are given in [Table 5](#). The prevalence varies from 9% and up to 31%. The 15% life-time prevalence found in France [42] covers 5% who often had experienced ejaculation prior to penetration and 10% who often had ejaculated too rapidly after vaginal intromission. This prevalence appears to agree rather reasonably well with the 9% in Sweden [43] and the 13% and 14% (last 3 months) in the Netherlands [70] and the United Kingdom [45]. 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) used by Laumann et al [15], while the European investigations used pluri-step scales. Still fewer investigators have reported on the prevalence of delayed ejaculation. 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 [76].

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. Table 5 relates prevalence data for early (premature) ejaculation.

One of the problems of surveys regarding early ejaculation is the inconsistency of how the condition is defined. It can be defined by time to ejaculation, in the context of the sufferer’s or partner’s satisfaction, the number of penile thrusts after intromission, or even in the context of the amount of sexual stimulation. Some examples for surveys include the man reaches orgasm or ejaculation within one minute after the initiation of vaginal penetration or the man experiences ejaculation that occurs too early for the women’s partner satisfaction in at least 50% of the attempts [77]. Another definition for fast or premature ejaculation is ejaculation before or very soon after intromission that causes personal distress [78]. Timed definition of early ejaculation include ejaculation occurring within 1, 2, 3, or even 7 minutes after penetration. When penile thrusting is used the variance has been ejaculation occurring with 8 to 15 thrusts after vaginal penetration. One more recent study suggested the following definition, the persistent or recurrent inability to voluntarily delay ejaculation upon or shortly after penetration or with minimal sexual stimulation [79].

d) 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 [15]. A much lower prevalence (<1%) was reported in 55-57 year old Icelandic men [44]; while in France [42], the (life-time) prevalence of men’s orgasmic dysfunction was (7%).

e) Dyspareunia

The prevalence of genital pain in men during sexual intercourse has only been fragmentarily studied (Table 5). In France [42] 5% of the adult male population (of 18 to about 70 years) report that they at least quite often suffer such pain. Clearly lower prevalence of 1% or less has been found in Finland.
[32], Iceland [44], Sweden [43] and in the Netherlands [70]. With this low prevalence it is hardly surprising that no age-dependency of men’s dyspareunia has been found.

The increasing awareness of sexual health as a component of global health, not only in the general population but among physicians as well, together with a better understanding of the basis of human sexual response, will trigger research, including epidemiology, of facets of human sexuality distinct from ED. It’s our hope that this chapter and book will assist to a similar dramatic evidence-based change in the knowledge of FSD and MSD (female and male sexual dysfunction) as the knowledge expansion of ED that we have witnessed.

6. CONCURRENCE OF SEXUAL DYSFUNCTIONS

Both in the descriptive and analytical epidemiological literature there is very little on simultaneous occurrence of 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 [80]. In an older sample (50-78 year olds) from the Netherlands about 50% men with early ejaculation also reported ED [70]. 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” [81]. Recently it was found in Sweden that within both genders (aged 18-74) nearly all own sexual dysfunctions are closely associated (generally at a p level of < 0.001) [14]. The only exception is that for the men early and 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 dysfunctions had precisely the same close associations with men’s perception 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. Laumann et al also examine the co-occurrence of dysfunctions for the set of dysfunctions discussed in the latent class analysis, but the actual percentages of overlap are not given in the article [15].

7. SEXUAL DYSFUNCTIONS AND PERSONAL DISTRESS

It is of paramount importance to know to which extent sexual dysfunctions are accompanied by distress. Among women and men with manifest dysfunction per se generally less than half experience that it is accompanied by manifest personal distress. (Table 7). In fact 26% and 17% of women and men reported at least one distressing self or partner’s sexual disability. However, among the manifestly personally distressed, the vast majorities were not satisfied with their sexual life. This can be compared with the sexual satisfaction rate of 55% in the total population of 18-74 year olds [14].

<table>
<thead>
<tr>
<th>Manifest dysfunction – per se %</th>
<th>Manifest dysfunction with personal distress %</th>
<th>Sexually satisfied among those personally distressed %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Sexual interest (W)</td>
<td>33</td>
<td>14</td>
</tr>
<tr>
<td>Low Sexual interest (M)</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Lubricative insuff. (W)</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Erectile dysfunction (M)</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Orgasmic dysfunction (W)</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>Early ejaculation (M)</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Delayed ejaculation (M)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dyspareunia (W)</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Dyspareunia (M)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vaginismus (W)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
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.

When dealing with risk factors, comorbidities 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.

Some years ago Goldstein et al stated that only limited published information is available concerning risk factors for women’s sexual dysfunction [82]. This claim is endorsed by the relatively few reliable (according to the Oxford criteria) studies on risk factors, which we were able to locate through a series of database searches. Goldstein et al., moreover, pointed to the need for more research concerning the relation of medications and comorbidities with women’s sexual behavior.

**a) Health-Related Risk Factors**

Simultaneously, Laumann et al [15] and Fugl-Meyer & Fugl-Meyer [43] reported that less than good health leads to greater risks of sexual disabilities concerning desire/sexual interest and genital pain. Richters et al [41] in their very large scale investigation recently found that compared with women at 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.

**b) Diabetes**

Kadri et al [21] in their descriptive epidemiological study of Moroccan women reported (univariate) significant associations for diabetes with orgasmic disability, dyspareunia and sexual aversion. 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 [83]. However, women with “more” complications reported significantly more sexual disabilities.

c) **Cardio-vascular Diseases**

In a large-scale, well-controlled analytical study Duncan et al [84] reported that hypertension (univariately) was associated with decreased lubricative function and with orgasmic dysfunction. Among all the different aspects of women’s sexual function studied by them, Dunn et al [58] found that medication with antihypertensive drugs was a significant negative predictor (Odds ratios 0.3) of orgasmic function. Moreover, Hanon et al [85] described that 41% of treated hypertensive women (aged 58±12) experienced decreased sexual interest during treatment.

d) **Urinary Tract Diseases**

Stress urinary incontinence has been found by Osborn et al [40] 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, but analytical, investigation [86] urinary stress incontinence was (univariately) significantly associated with sexual interest, lubricative insufficiency, orgasmic disability and dyspareunia. Along these lines Laumann et al found that having urinary tract symptoms were predictors of lubricational insufficiency, orgasmic dysfunction, and dyspareunia while ever having had STD (sexually transmitted diseases) was a negative predictor for sexual interest and for lubricative function [15].

e) **Psychiatric/psychological Factors**

In women, a psychiatric disorder, according to Osborn et al, [40] is closely associated with orgasmic dysfunction and dyspareunia. The same authors found that degree of neuroticism (measured by the Eysenck index [87] was significantly correlated with dyspareunia and vaginismus. In their descriptive epidemiological investigation, Dunn et al [58] demonstrated significant likelihoods (odds ratios ranging between 1.8 – 4.5) of depression and anxiety to predict all their investigated parameters: arousal problems, insufficient lubrication, orgasmic dysfunction and dyspareunia. Moreover, by latent class analysis, Laumann et al [15] 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). Clayton et al in a large scale well-defined investigation of the effect of different “newer” antidepressants found that among women and men on monotherapy, negative “changes in sexual function” were significantly more likely to occur (odds ratios 2.2-2.9) with SSRIs (selective serotonin reuptake inhibitors) or venlafaxine than
with bupropion or netazodone [88]. 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 drugs during the period 1968-1997, 5000 were sexual in nature [89]. 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.

Besides these investigations we have been able to locate no reliable, evidence-based investigations of physical or mental health as risk factors for women’s sexual functions.

f) Socio-demographic Risk Factors

Several newer epidemiological investigations have addressed the impact of sexual abuse on women’s sexual behavior and it has been clearly shown that women’s current sexual life can be detrimentally influenced by abuse [15, 58, 90]. Thus, having ever been sexually forced by a man predicts (latent class) low levels of desire and arousal disorder in American women, for whom having ever been sexually harassed predicted arousal disorder and sexual pain [15]. In Sweden, 12% of 18–74 year old women had at some time of their life been sexually abused [90]. The abused women had a significantly higher number of sexual dysfunctions than had the non-abused and nearly all different types of 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. Having been sexually abused negatively influenced sexual interest in Moroccan women [21].

Being single is (univariately) associated with dysfunctions of sexual interest, vaginal lubrication, orgasm and with dyspareunia [43]. Low levels of sexual interest, arousal, orgasm and also dyspareunia are significantly most common in women with marital difficulties [40, 58]. In a large-scale-analytical epidemiological investigation of a gynecological 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 3 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 [91].

In Morocco, relatively low education is common in women with low level of sexual interest [21]. This is also the case in the USA [15] and in eastern Europe [91] for orgasmic dysfunction and, additionally, in the USA for dyspareunia [15]. In the USA women with more than 20% financial household decrease during the last year prior to the investigation have low level of interest and lubrication and also relatively high prevalence of dyspareunia [15].

2. RISK FACTORS FOR MEN

a) Health Related Risk Factors

Less than good overall health is likely to concur with men’s low level of sexual interest/desire and with ED [15,43]. Furthermore, Laumann et al [15] 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 [41] reported that Australian men who are not at excellent or good health are most likely to have a sexual dysfunction (not further specified).

b) Smoking or Other Tobacco Use

Cigarette smoking is a known risk factor for many health problems including cardiovascular disease, diabetes and stroke [92-95]. Further, cigarette smoking appears to deleteriously affect arterial endothelium on a micro vascular level [96-97]. 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. However, at the last consensus meeting it was felt that the evidence-based research which was available was not sufficient to allow a link to be made between cigarette smoking and ED. The present review encompasses the literature available on Med Line from 2001 to the present. Eight published works were identified which met the criteria for inclusion that were decided upon by the committee. Three are literature reviews and these cumulatively cover the last two decades of research.

In the first 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 [98]. 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 by searching MEDLINE to identify the prevalence of smoking among impotent men [99]. 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 a less comprehensive literature review, Nehra and Kulaksizoglu focused on the global epidemiology of ED [100]. These authors also found cigarette smoking to be correlated with ED.

The remaining 5 articles are population-based studies. Three of these also found cigarette smoking to be a risk factor for ED. The remaining two did not find this relationship to hold true.

Bortolotti et al reported on 9670 diabetic men who were categorized as: never smokers (30%), current smokers (30%), or ex-smokers (40%) [101]. 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 smokers 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.

Mirone et al performed a cross-sectional study on the prevalence and risk factors for ED in the general population in Italy [102]. 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 [103]. 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.

On the other hand, Mak et al performed a population-based study in Belgium [104]. 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 [105]. 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.

To summarize, these reports have investigated the association between cigarette smoking and ED by several different methods. The three studies that reviewed the literature presented a preponderance of evidence to link these two entities. The first three randomized population based studies collectively interviewed over 14,000 men and identified cigarette smoking as a significant risk factor for ED. Conversely, 2750 men were interviewed in the last two studies that did not find this correlation.

At the present time, after careful scrutiny against specific selection criteria, it appears that the preponderance of evidence available at this time would identify cigarette smoking as an independent risk factor for ED. It is possible that this view may change in the future as more evidence become available. However, for the present, cigarette smoking should be considered a 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. We, as 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) 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 [106-108]. Carani et al 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 [109]. In a study by Becker et al, [110] 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 [111-112]. Prolactin pituitary secreting tumors are associated with low level of sexual interest/desire and erectile dysfunction. Low levels of free and total testosterone are usually seen with this condition [113]. 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. [114-116]. 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 [117]. Four men, all who had surgical castration, of sixteen who were surgically or medically castrate, 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 have 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 [118]. 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 [119].

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) [23, 112]. 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.

d) Diabetes Mellitus

From the Netherlands, Enzlin et al [120] recently reported that men with complications of type I diabetes had significantly greater prevalence of decreased desire than had those without complications. This was also the case for prevalence of orgasmic dysfunction. However, diabetic men with sexual dysfunction(s) were older and had a longer duration of diabetes. Erectile dysfunction has been reported to occur in at least 50% of men with diabetes mellitus with the onset of ED occurring in an earlier age than those without diabetes mellitus. [121-123]. 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 [124]. Also, the incidence rate of erectile dysfunction is higher for each decade of diabetic men compared to non-diabetics [27]. Whitehead and Klyde reviewed a large amount of the associations between ED and diabetes mellitus in their literature review of 1990. [122]. Some of
their observations are reported in Table 8. 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 [23]. Diabetes mellitus has also been associated with retrograde and anejaculation [77].

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 age of patient
- DM microvascular complications related to duration of DM and glycemic control


Since the last WHO consultation on erectile dysfunction [35], there have been a few surveys for erectile dysfunction in patients seen in diabetic clinics and in general populations. 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 [125]. 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 [126]. 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 without ED at baseline were followed prospectively for 2.8 years to determine the incidence of ED associated with diabetes [127]. The crude incidence rate was 68 cases per 1,000 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 also with obliterator arterial disease of the lower legs, ischemic heart disease, renal disease, autonomic neuropathy, sensation and motor neuropathy, and diabetic foot and retinal disease.

e) 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 Burschell reported that 64% of 131 men, aged 31 to 86 years, hospitalized for acute myocardial infarction were impotent [128]. Sjögren and Fugl-Meyer reported a 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 [129]. 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. 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 [23]. 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. Wei et al found that a high level of total cholesterol and a low level.
of HDL are important risk factors for ED[30]. 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[130].

**f) Urinary tract diseases**

Chronic renal failure is a risk factor for ED[131]. In the USA general urinary tract symptoms predicted ED (odds ratio: 3.1), but not other investigated parameters (desire, ejaculation) of male sexual function. [15]. These findings principally agree with those of Blanker et al from the Netherlands [70]. 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.

**g) Other Chronic Diseases**

Polyneuropathy, which commonly involves autonomous dysfunction is another source of sexual dysfunction, particularly ED and ejaculatory dysfunction [132]. Thus, Vardi et al reported a 38% coincidence of polyneuropathy and ED in diabetics and a 10% coincidence of the two in non-diabetics [133]. 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. [134-136]. However, treatment with dopaminergic substances 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. The same goes for the older types of antiepileptic drugs [132]. 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 [137]. In multiple sclerosis, ejaculatory dysfunction may, according to clinical reports, prevail in about 50% as the disorder progresses [132]. Completed stroke is a very highly prevalent condition in many parts of the world. Somewhat perplexing there is not either for this condition truly evidence-based analytical literature at the lb level. In the USA Monga et al [138] 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 [139-140]. 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 a very wide latitude [138-139]. 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 [141]. Other diseases and chronic disorders reported to have a risk for ED include chronic obstructive lung disease[142], scleroderma [143], and Peyronie’s disease[144].

**h) 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 [132]). 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. Perineal pressure associated with bicycling as an association for ED lacks evidence- based support. 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[145].

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 [146] 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 [147-148]. Radiation therapy to the pelvis also is a source of damage to nerves involved in erectile and ejaculatory functions [149], while sexual functions remain stable after treatment for benign prostatic hyperplasia [150].

i) 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 [15] emotional problems or stress were significant predictors of low level of desire (odds ratio 3.2), ED (odds ratio 3.6) and early ejaculation (odds ratio 2.3). The association of ED with depression is well established [23]. Using the Hospital Anxiety and Depression Scale (HAD)[151]. Dunn et al [58] found that anxiety, but not depression, significantly predicted early ejaculation. Suppression and expression of anger indicate higher probabilities of moderate and complete ED[23]. Independently of medication, Araujo et al [51]. demonstrated that depression is closely associated (odds ratio 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.

j) Socio-demographic risk factors

Having been sexually touched before puberty predicts lower level of interest/desire (odds ratio 2.2), ED (odds ratio 3.1) and early ejaculation (odds ratio 1.8) [15]. Moreover, men who ever have forced a woman sexually are more likely (odds ratio 3.5) to have ED than are those who never have done so. Neither of these two descriptive investigations have found ejaculatory disturbance correlates of sexual abuse.

Both in the USA [15] and in Sweden [43] 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. [15]

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 [23] 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 nonthia-zide diuretics and benzodiazepines remaining statistically significant for association with prevalent ED [152]. Meinhardt and his co-authors have reviewed the influence of medication on erectile dysfunction in some detail [153]. Major classes of prescription drugs commonly reported to be associated with ED are histamine-2 receptor antagonists, hormones, anti-cholinergics, 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 [154-155]. 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 [156]. 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) [157]. Trazadone is one antidepressant that is unlikely to be associated with ED and, in fact, has a risk of associated priapism [153]. In general, it is suggested that antipsychotics with strong alpha-I 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 [121].

l) 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 [158]. 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 inci-
idence 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 once established at this age. 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.

VI. CONCLUSIONS

1. There is clearly a need to establish consistent definitions for sexual dysfunctions that effect men and women so that comparisons can be made from one epidemiological study to another on a world wide basis. This committee attempts to describe per-se English definitions for each of the sexual disorders.

2. For clinical applicability of the definitions, a degree of distress or bother for the sufferer, would aid greatly the interpretation of the data collected and possible later communication of that data.

3. Dysfunctions should be further characterized as to whether they are life-long or acquired and whether they are global or situational.

4. Definitions gain applicability for comparative studies by including the degree of dysfunction. Such a classification should be internationally accepted.

5. Evidence-based medicine was the standard that this committee evaluated incidence, prevalence, and risk factor articles. The details of this evaluatory standard are presented in the text.

6. There is a paucity of longitudinal reports in the literature regarding all sexual dysfunctions, including even ED, so incidence data are poorly reported. The incidence rate for ED, which is best backed by evidence-based reports, in two studies, one from the United States and one from Europe are about 25-30 cases per 1000 person years. This rate was higher in a study from Brazil and the rates increase markedly with each decade of age.

7. Prevalence rates for sexual dysfunctions are more strongly supported by evidence-based reports and are tabulated for the reader of this chapter in Tables 4-6. There is a variance in the prevalence rates reported because of different age groups reported on, difference in definitions used to describe the dysfunction, how the data was collected, how long the dysfunction was present, and the degree of the dysfunction. Prevalence of sexual dysfunctions, for the most part, increase as men and women age.

8. There are few studies that truly examine bother for the person with the sexual dysfunction and concurrence of sexual disorders for the couple.

9. There are common risk factor categories associated with sexual dysfunctions for men and women and include the following: general health status of the individual, the presence of diabetes melitus, the presence of cardiovascular disease, concurrence of other genitourinary disease, psychiatric/psychological disorders, other chronic diseases, and socio-demographic conditions. For ED smoking and hormonal factors also serve as well defined risk factor associated conditions. There are also evidence-based literature for medication related associations for ED.

10. Modification of risk factors have been reported essentially in only one longitudinal study and other than increasing physical activity, other modifications in lifestyle do not seem to change incidence data, at least in the male who starts to be followed well into middle age, middle 50’s.

VII. RECOMMENDATIONS

1. Uniform, universally acceptable definitions that include degree of dysfunctions are necessary to compare epidemiological studies across the world. This committee suggests using the definitions described in this chapter, particularly the per se definitions for the sexual dysfunctions for men and women described herein.

2. Definitions should not follow a sequential concept in term of phases.
3. A second set of definitions for each of the dysfunctions should include the elements of personal distress for better reporting of the effects of these dysfunctions on the individual and the relationship of that individual with others.

4. For clearer interpretation of data and application to clinical situations, it is recommended that definition include whether they are lifelong or acquired, whether they are global or situational, and include some degree of the dysfunction.

5. There is clearly a need for more longitudinal studies for all of the dysfunctions in order to obtain more accurate incidence data.

6. For prevalence data articles it is recommended that guidelines be followed, such as those listed in Table 1, so that literature can become more evidenced-based.

7. Evidence-based criteria should be established for evaluating risk factors for women and men’s sexual dysfunctions. A good source of this type of critical analysis is that provided in reference 124 in this report, which describes weaknesses in reports of the association between diabetes mellitus and erectile dysfunction.

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Committee 12B

Endocrine Aspects of Female Sexual Dysfunction

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Sexual activity in women involves interest and motivation, ability to become aroused and achieve orgasm, the pleasure of the experience and subsequent personal satisfaction. All components of the female sexual experience are interdependent and thus impairment of any specific aspect may affect others. Sexual problems experienced by women are generally divided into categories to assist with identification of the etiology and management as follows:

- Low interest or motivation to engage in sexual activity (libido),
- Diminished capacity for vaginal lubrication and arousal,
- Difficulty achieving/or absent orgasm, and/or
- Painful intercourse (dyspareunia).

Usually in the context of a sexual relationship these problems are associated with a decrease in the frequency and pleasure of sexual activity and can become a source of tension and distress for the individual and her partner.

The endogenous hormones that potentially influence female sexuality include estrogens, androgens, progesterone, prolactin, oxytocin, and glucocorticosteroids. These each interact with numerous neurochemicals within the central and peripheral nervous system. The latter include serotonin, catecholamines, dopamine, other neurotransmitters and other hormones. The factors that determine the outcome of these complex interactions include the absolute levels of each hormone, their absolute receptor content, the presence and levels of specific co-activator and co-repressor proteins that modify the transcriptional response and the up or down regulation of receptor levels by other hormones. Hormones also influence vascular function by both endothelium-dependent and independent mechanisms [1], and thus have a vital role in maintenance of the health of the female genital tract as well as in arousal and orgasm. Research into the specific effects of hormones in female sexual function has relied greatly on in vitro and in vivo animal models, with few published randomized placebo controlled trials (RPCT), or level 2 evidence, and insufficient data for a meta-analysis of RPCT to provide level 1 evidence at this time.

1. ESTROGEN PHYSIOLOGY (LEVEL 3-4 EVIDENCE)

Throughout the reproductive years the ovaries are a primary source of estradiol for action on peripheral target tissues under the control of FSH and inhibin. Androgens are obligatory precursors in the biosynthesis of estrogens. Thus, estrone is formed by the aromatization of androstenedione and estradiol by the aromatization of testosterone.

However synthesis of estrogens from adrenal and ovarian androgen precursors within extragonadal compartments occurs throughout reproductive life and takes on even greater significance following menopause [2]. In postmenopausal women the most abundant estrogen in the circulation is estrone sulfate, levels of which have been measured at ten to twenty-five times greater than levels of estrone and estradiol [3]. Estrone sulfate has a long plasma half-life and slow clearance rate and thus acts as a reservoir for the formation of estradiol and estrone in target tissues, such as the breast where it is readily
converted to estradiol by the sulfatase enzyme [4]. In their unsulfated forms estradiol and estrone are partly bound to SHBG and variations in the plasma level of SHBG impact significantly on the amount of free, or bioavailable estradiol to a greater extent than estrone as well as on bioavailable T [5]. Orally administered estrogen therapy also increases SHBG to a greater extent than parenterally administered estrogens [6, 7] and this may result in a clinically significant reduction in the percentage of non SHBG bound testosterone.

2. PROGESTERONE PRODUCTION

The cyclical production of progesterone by the ovary is lost after menopause, however progesterone, and its metabolites can still be detected in the serum and found within regions of the brain in postmenopausal women [8]. For both pre and postmenopausal women serum progesterone concentrations were significantly correlated with brain tissue concentrations suggesting that serum levels are a primary source for brain uptake [8, 9] although progesterone can also be synthesized within the brain [10].

3. TESTOSTERONE AND OTHER ANDROGENS

a) Androgen Production (Level 3-4)

The term 'androgens' refers to a group of 19-carbon steroid hormones which are associated with maleness and the induction of male secondary sexual characteristics. In women, androgens circulate in the concentration range nanomolar to micromolar, in contrast with the estrogens whose circulating concentrations are in the picomolar range. In descending order of their serum concentrations, the major androgens found in women include dehydroepiandrosterone sulphate (DHEAS), DHEA, androstenedione (A’dione), testosterone (T) and dihydrotestosterone (DHT). Giving T a reference potency of 100, the relative androgenic activities of the other members of the class are DHT, 300, A, 10 and DHEA and DHEAS, 5. Biosynthesis of the androgens takes place both in the adrenal and in the ovary and is modulated by two cytochrome P450 enzymes, P450 Scc which catalyses cholesterol side-chain cleavage and P450 C17 which catalyses 17-hydroxylation and 17-20 bond cleavage (17/20 lyase), which is required for the production of DHEA and A’dione from pregnenolone and progesterone respectively. The further metabolism of androgens involves other important enzymes including 3β-hydroxy steroid dehydrogenase (3β HSD), catalysing the conversion of pregnenolone to progesterone and DHEA to A’dione, and 17β-hydroxy steroid hydrogenase (17β-HSD), which catalyses the conversion of A to testosterone. DHEA secretion is acutely stimulated by adrenocorticotropic hormone (ACTH) [11, 12] however DHEA-S, which has a long plasma half-life, may not acutely increase following ACTH administration [13]. Adrenal androgen and cortisol production are not always linked. Circulating adrenal androgen levels have been observed to be normal or suppressed in acute stress [14], severe systemic illness [15], anorexia nervosa [16] and Cushing’s syndrome [17] which are otherwise characterized by elevated cortisol levels. Increased adrenal androgen production may also be seen in association with hyperprolactinemia [12] although the majority of patients with this disorder have normal androgen levels.

b) Metabolism and action of androgens

Traditionally hormonal action has been understood as endocrine and paracrine and measurement of circulating hormone levels has been used as a determinant of tissue exposure. However more recently the complexity of steroid action has been appreciated [18]. Labrie et al., have addressed the issue of hormone intracrinology and produced the definition : “Intracrine activity describes the formation of active hormones that exert their action in the same cells in which synthesis took place without release into the pericellular compartment” [19]. Specifically in terms of tissue exposure to androgens, the precursor hormones of adrenal and ovarian origin, A’dione and DHEA, and DHEAS from the adrenals, can be converted in extra-gonadal target tissues such as the brain, bone, adipose either by aromatization to estrogen, or by 5α-reduction to testosterone, with the latter being converted to either estradiol or DHT in the same cells [19, 20]. Thus tissue sensitivity to androgens will vary according to the amount and activity of the enzymes 5α-reductase and aromatase which may vary considerably between individuals. The AR also differs between individuals, with the most researched aspect being differing numbers of CAG repeats resulting in considerable inter-individual differences in AR length. This and other differences in the AR may result in variability in end organ response to absolute circulating levels of androgens. This is an area of androgen physiology that requires further investigation. Thus even with highly sensitive assays for total and free T, measurement of testosterone will provide only an indication of androgen deficiency or excess, but not an absolute measure of tissue exposure or tissue sensitivity and responsiveness, and the
clinical features will be the mainstay of diagnosis. This unfortunately is a limitation to much of the data pertaining to sex steroids and female sexual function.

c) Importance of sex hormone binding globulin (SHBG)

SHBG is a pivotal determinant of the bioavailability of sex steroids and variations in the plasma levels of SHBG impact significantly on the amount of free, or bioavailable testosterone and other bound sex steroids [5]. In normal reproductive aged women 82% of the binding sites of SHBG are unoccupied. For the occupied binding sites, androstendiol (5.1%) is the major SHBG ligand followed by DHEA (3.6%), testosterone (2.3%), cortisol (2%) cortisone (1.9%), DHT (1.4%) and androstenedione (1.0%). Conversely, the binding affinity for steroids bound by SHBG is DHT > testosterone > androstenediol > estradiol > estrone. SHBG also weakly binds DHEA, but not DHEA-S [5]. Under normal physiological conditions in women only 1 to 2% of total circulating testosterone is free or biologically available. The rest is bound by SHBG (66%) and albumin (30%) [5]. Elevations in estradiol (as occurs during pregnancy), hyperthyroidism and liver disease cause a marked increase in SHBG levels, whereas hypothyroidism, obesity, and hyper-insulinemia are associated with decreased SHBG levels. In addition oral administration of steroid hormones and their analogues can markedly alter SHBG levels whereas parenteral administration of these compounds typically has a much weaker influence. Standard doses of oral estrogen as used in hormone therapy (HT) will increase SHBG with little or no effect seen with standard estradiol patch therapy. However when very high levels of estradiol are achieved for several weeks to months with parenteral therapy (as seen with estradiol implants) SHBG will increase (S Davis, Australia. Clinical observation in women treated with estradiol implants). SHBG also increases markedly from baseline with the new contraceptive patch delivering norelgestromin and ethinyl estradiol (Ortho-McNeil Pharmaceutical, Inc.; data on file).

The plasma free testosterone concentration in women is determined by the testosterone production rate, the metabolic clearance rate (MCR), and the SHBG level (which influences the free fraction of testosterone). Elevated androgen production rates in obese eumenorrheic women have been associated with 2 to 3-fold increases in MCRs, presumably due to decreased levels of SHBG [21]. However, in hirsute women increased production rates are associated with elevated plasma androgens as well as increased MCRs [21]. BIRD et al reported that estrogen treatment reduces the MCR of testosterone [22]. Taken together, lower SHBG levels enable increased clearance of testosterone, whereas higher SHBG levels are associated with a decrease in clearance. When exogenous testosterone is administered the rise in concentration of total testosterone will greatly depend upon SHBG concentration. Thus women with high SHBG will have a marked increase in total testosterone whereas women with low SHBG will have little change in their total testosterone level with exogenous therapy. As total testosterone is a poor indicator of androgen exposure, following testosterone therapy, the concentration of free testosterone or non-SHBG-bound testosterone, so called bioavailable testosterone, should be measured. Such assays may not always be reliable or available (see below, section 6.2).

As SHBG levels may fall somewhat with increased circulating testosterone, baseline SHBG may be a useful predictor of risk of excess androgenization with testosterone treatment, and should be measured in all women prior to such therapy. RANNEVIK and BURGER both showed a clear-cut fall in SHBG concentration related to the menopause, while Bancroft showed no significant change in SHBG levels in comparing pre-, peri-, and postmenopausal women [23-25]. Guay et al and Davis et al. found no difference in SHBG levels in premenopausal women, 20-49 years old by decade [26, 27].

d) Androgen physiology (Level 2-4 data from observational studies)

In humans, androgens produced by the adrenal glands and ovaries are obligatory precursors for the biosynthesis of estrogens by the aromatase cytochrome P450 enzyme (P450arom, the product of the CYP19 gene). Phylogenetic analysis of steroid receptors in lower vertebrates indicates that the first steroid receptor was an estrogen receptor (ER), followed by a progesterone receptor (PR) [28]. Specific regulation of physiological processes by androgens and corticoids are relatively recent innovations that emerged after these duplications [28]. Thus the role of androgens was initially solely as precursors for the estrogenic steroids and the specific physiological roles for these hormones only emerged later.

Androgen production in women during the young reproductive years has been reviewed in detail elsewhere [29]. In premenopausal women with regular menstrual cycles, there is a rise in testosterone and A'dione in the late follicular phase of the mens-
trual cycle and in the luteal phase [30, 31]. There is also a diurnal variation in testosterone in women with the peak in the morning [32]. In contrast to the negative feedback loop that controls ovarian estrogen production involving inhibin and follicle stimulating hormone (FSH), no feedback loop has been identified for the control of androgen production in women.

The levels of the pre-androgens, DHEAS and DHEA fall with increasing age although the numbers of subjects in this study per decade were very small [20]. This may contribute significantly to the decline in total and free testosterone level with age as DHEAS serves as a pre-hormone for about half of ovarian testosterone production [33]. There may be a transient rise in DHEA-S levels around the time of the menopausal transition, however, the clinical significance of this is not known [34].

Zumoff et al showed lower mean 24 hour values for total and calculated free testosterone amongst older versus younger reproductive aged women (n=33 women). Most recently a study of 149 healthy premenopausal women with regular cycles, no exogenous hormone therapy and no complaint of low libido showed a statistically significant decline with age for each of free testosterone, DHEAS, androstenedione and DHT measured after organic solvent extraction by validated methodology [27]. In the late reproductive years there is failure of the midcycle rise in free testosterone which characterizes the menstrual cycle in young ovulating women [35]. This occurs despite preservation of normal free testosterone levels at other phases of the cycle. The mean plasma concentrations of testosterone in women transitioning through the menopause are also significantly lower than younger ovulating women sampled in the early follicular phase [36]. Acutely, across the perimenopausal period, neither A’dione, DHT or the ratio of total testosterone to SHBG (the free androgen index) appear to change [24, 36].

There is considerable controversy as to whether the postmenopausal ovary is a significant source of androgen production. Concentrations of testosterone in the ovarian vein of post-menopausal women have been shown to be higher than those in systemic venous blood, suggesting that the postmenopausal ovary continues to be an androgen secreting organ [31]. In addition, testosterone levels decrease in postmenopausal women following oophorectomy [37]. Couzinet, et al have proposed that the postmenopausal ovary is not a major source of androgens [38]. This group found low levels of total and bioavailable testosterone in postmenopausal women with intact ovaries (n=15) that were not different from oophorectomized postmenopausal women (n=15). Similarly Davis et al have reported no difference in levels of total and free testosterone, DHEAS, DHT, A’dione and SHBG for 309 surgically menopausal women with low libido on HT versus naturally menopausal controls with normal libido also on HT [27]. Immunocytochemistry of the ovarian tissue of women with adrenal insufficiency did not detect significant quantities of steroidogenic enzymes [38]. Human chorionic gonadotrophin stimulation produced no changes in androgen levels in women with adrenal insufficiency [38], a fact that was also shown earlier by Vermeulen, who studied the effects of HCG stimulation of postmenopausal women (4 to 10 years into menopause) [39]. Consistent with this DHEAS has been shown to serve as a pre-hormone for about half of ovarian testosterone production [33]. Some postmenopausal women have elevated ovarian androgen production - hyperthecosis, a well-established but poorly studied entity. The androgen production of the postmenopausal ovary is variable. This variability needs better study along with associated factors.

II. HORMONES AND HYPOACTIVE SEXUAL DESIRE DISORDER (HSDD)

As sexuality is multifactorial and mechanistic studies in humans cannot clearly elucidate the role of hormones in sexual function, other models have been employed. Rodent models of sexually receptive behaviors have been used to gain insight into some of the actions of sex steroids. There is however no animal model for female arousal or orgasm, and the influence of cognitive factors, including fantasy cannot be studied in animals. Vaginal plethysmography has been used in human studies, however the correlation between blood flow measures and verbal reports of arousal is poor [40-42]. A few RPCTs have now been completed that demonstrate the effects of hormone therapy, however from among these, investigations on the effects of endogenous hormones, or the clinical consequences of low hormone levels is only implied.

1. THE CENTRAL ROLE OF ESTROGENS IN SEXUAL FUNCTION

Low estrogen levels as a consequence of spontaneous or surgical menopause may result in generalized physical symptoms, and symptoms that are a
Consequence of central nervous system effects. The latter includes effects on cognition, mood, and motivation, and specific effects on sexual behavior and sexual responsivity.

Estradiol and testosterone are both present in the human female brain, with highest concentrations of estradiol measured in the hypothalamus and the preoptic area, and of testosterone, in the substantia nigra, hypothalamus and the preoptic area [43]. The concentration of testosterone is several-fold higher than estradiol in each of these regions, with the highest ratio of testosterone to estradiol demonstrated in the hypothalamus and preoptic area. This distribution corresponds with high aromatase activity found in these regions in animals [44]. It is biologically plausible that within these regions testosterone is aromatized to estradiol resulting in high estradiol concentrations that then modify sexual behavior. This would be consistent with extremely high circulating estradiol levels resulting in increased central estradiol levels and thus enhancing sexual behavior, whereas no effect is seen with standard dose estrogen therapy. Rodent models further support this hypothesis as described below.

a) Animal studies of hormones and female sexual function (Level 5)

Both estrogen receptors (ERα and β) are expressed in the primate brain [45]. Estrogen exhibits widespread actions throughout the brain, both via its receptors, and nongenomically, with interactions with many neurotransmitter systems including catecholaminergic, serotonergic, cholinergic and g-aminobutyric acidergic systems [46, 47]. Oophorectomized rats and mice exhibit no lordotic behavior, but they have no estrogens or androgens because their adrenals do not make C19 steroids. Estrogen therapy alone has little or no effect on restoration of lordosis in oophorectomized mice however following estrogen priming, progesterone restores lordosis [48]. Progesterone alone does not restore sexually receptive behavior [48]. Microinjection of sodium nitroprusside, which spontaneously releases nitric oxide, directly into the third ventricle of estrogen primed oophorectomized rats facilitates lordosis in the absence of progesterone [49].

To further investigate the possible role of each of the ERs and estrogen action in sexual behaviors, mice in which each or both ERs have been knocked out, or in which the aromatase enzyme has been mutated (aromatase knock out (ArKO)) have been studied. In each of these models serum testosterone is normal or elevated. Behavioral changes that have been evaluated have included female sexual receptivity (lordosis posturing), aggression and pup caring behavior. Mice in which the ERα has been knocked out (ERKO mice) exhibit no lordosis behavior, reduced pup caring and increased aggression [50]. In contrast the mice in which the ERβ receptor has been knocked out (BERKO mice) exhibit normal sexual function [50]. In female ArKO mice, which are completely estrogen deficient, there is marked loss of lordosis [51]. Residual lordotic behavior in the ArKO mice indicates that neuronal pathways may be activated in a ligand-independent manner by the intact ER. When both ERα and β are knocked out there is complete loss of sexual function in the animals despite the presence of normal testosterone levels [50]. Taken together, this data indicates that in the mouse model, ERα is crucial for lordotic behavior. Thus it appears that despite lack of a relationship between circulating estradiol levels and sexual parameters, estradiol and the ERβ have an essential role in the neurobiology of sexual behavior in animal models.

In addition to exerting actions via its own receptor, estradiol influences other neuronal pathways related to sexual function. For example, estradiol increases the expression of the α1 norepinephrine (NE) receptor and this enhances sexually receptive behavior (lordosis) in female rodents. In contrast the α2 and β NE receptors inhibit the lordosis response. Estradiol promotes stable phosphorylation of the α2 and β NE receptors and this results inability of these receptors to inhibit reproductive behavior [52].

b) Clinical studies of estrogen and sexual function in women (Level 2b-4)

In a cross sectional study of 141 women aged 40 to 60 years, no hormonal measures significantly predicted aspects of sexuality. The most important predictors were other aspects of the sexual relationship, sexual attitudes and measures of well-being [53]. In a well-designed, population-based, longitudinal study of women’s sexual functioning in midlife, 438 Australian women were studied for 8 years across the menopausal transition. Menstrual histories and laboratory data allowed the investigators to differentiate between changes due to aging versus menopause [54]. Sexual responsivity 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 passing from the early to the late menopausal transition, the percentage of women with sexual dysfunction, assessed using the Short
Personal Experiences Questionnaire (SPEQ) rose from 42 to 88% whereas there were no significant changes in mood scores. Those who showed low SPEQ total scores in the early transition had lower estradiol levels, but similar androgen levels to those with higher scores, and decreasing scores correlated to decreasing estradiol, but not to total testosterone. Hormone levels did not correlate with mood scores. It was concluded from that study that “the dramatic decline in female sexual functioning with the natural menopausal transition relates to decreasing estradiol rather than androgens”. A limitation to this data is that a sensitive testosterone assay was not employed.

Systemic estrogen therapy improves vasomotor and other general symptoms ([Level 1 Evidence [55-57]]) and vaginal dryness and urogenital atrophy are effectively treated with either systemic or vaginal estrogen therapy ([58] Level 1 evidence). Exogenous estradiol improves not only vasomotor symptoms, but also well-being. However, this effect appears to be partly a result of the relief from vasomotor symptoms and vaginal dryness ([59]). Oral estrogen therapy improves sexual satisfaction in women with atrophic vaginitis causing their dyspareunia, but women lacking this symptom may benefit little or not at all [57, 60-63] (Level 2 and 3 evidence). Most of these studies have involved restoring circulating estradiol to levels seen in the early follicular phase of the menstrual cycle. However when supraphysiological estradiol levels have been achieved with repeated estradiol implant therapy, improvements in fantasy, libido, sexual pleasure and sexual satisfaction have been documented (Level 2 Evidence [64]).

In a retrospective study that controlled for post-operative estrogen therapy use, approximately 100 women between the ages of 47-55 years, who had undergone hysterectomy 2-6 years previously, completed the McCoy Sexual Rating Scale, Psychological Well-Being Index, and a semi-structured interview [63]. Three age-matched groups were identified: oophorectomized women not using estrogen therapy (ET), oophorectomized women using ET, and non-oophorectomized post menopausal women. Overall, there were no differences in the frequency of intercourse or orgasm, dyspareunia, arousal, or partner satisfaction between groups. 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.

Cross sectional research indicates an association between the decline in sexual function at menopause and estradiol. A correlation with testosterone cannot be excluded as no study has been undertaken that has used a sensitive measure of free testosterone. An effect of exogenous estrogen therapy on sexual function has not been demonstrated independent of alleviation of vasomotor symptoms and vaginal atrophy.

2. CENTRAL EFFECTS OF PROGESTERONE (LEVEL 5)

The PR exists in two different molecular forms, PR-A and PR-B. PRs are also present in the brain [65]. The function and role of the two different isoforms in the brain have not been defined, and pharmacological approaches using ligand antagonists and knock out models do not distinguish between the two isoforms. Progesterone, like estrogen, modulates gene expression in the rodent hypothalamus and thus regulates neuronal networks that control female sexual behavior. Estradiol increases the expression of PR which in turn functions as a critical co-ordinator of key regulator events associated with the sexual response [65]. The results of various studies using the progesterone antagonist RU 486, intra-cerebral administration of anti-sense nucleotides and PR knock out mice confirm that facilitation of sexual behavior of rodents by progesterone is mediated both by estradiol-induced genomic activation of neural PR and by a process involving ligand independent action of the PR via the cell membrane dopamine1 receptor (D1) [65]. It is believed that activation of cell membrane receptors results in a signal transduction cascade that leads to phosphorylation of the PR or a specific co-activator, and hence neuronal effects. In animal models progesterone facilitation of lordosis is also influenced by the cannabinoids [66].

3. ADRENAL PRE-ANDROGENS (LEVEL 2B-4)

A’dione and DHEA are produced by the ovaries and adrenals, whereas DHEAS and DHEAS is a unique secretory product of the adrenal zona reticularis. Each is an important precursor for peripheral biosynthesis of both testosterone and estrogen. DHEAS and DHEA levels decline with age [27, 67, 68], and there has been considerable conjecture that this results in loss of libido and well being [69]. The effects of oral DHEA on the sexual function of women have been evaluated in a number of placebo-controlled RCTs with inconsistent findings. In a crossover study of 24 women with adrenal insufficiency, sexual thoughts, interest and satisfaction (mental and physical) increased significantly after 4 months of active treatment (50 mg/day) [70]. In this study, serum testoste-
Androstenedione was increased from below normal to the lower part of the normal range by the therapy. Two other studies of women with Addison's disease found no effect of the same dose of DHEA on cognitive or sexual function, body composition, or bone mineral density. In a parallel group study in 39 women with adrenal failure, treatment with 25 mg DHEA did not produce significant changes in desire, satisfaction or sexual problems [71]. A smaller RCT crossover study in Addisonian patients using 50 mg DHEA also failed to show improvements in sexual parameters (although the increments in testosterone levels were lower than expected) [72]. Significant improvements in self-esteem, mood, and fatigue were observed [71, 72]. In perimenopausal women without adrenal deficiency a parallel group placebo-controlled RCT did not show improvements in libido in 66 perimenopausal treated with 50 mg/day DHEA for 4 months [73]. Whereas an open-label study of DHEA treatment (50 mg/day) in 113 healthy women with diminished desire, arousal and orgasmic capacity showed improvement in desire, arousal, lubrication, orgasm and satisfaction (P<0.05) [74] (level 3).

In postmenopausal women, high dose DHEA (300 mg) resulted in greater subjective mental (p < 0.016) and physical (p < 0.036) sexual response to an erotic video versus placebo in a small RCT [75]. Both therapy and placebo increased vaginal pulse amplitude and vaginal blood volume with no difference between treatments [75]. BAULIEU et al reported improved libido in women over 60 years treated with DHEA 50mg daily in a RCT, however sexual function assessment did not involve a validated questionnaire and the visual analogue scale used was only understood by 25% of the women [69]. Libido was reported as unchanged in women less than 70 years of age and increased in women over 70 years of age with DHEA versus placebo.

As stated above DHEA is converted to both testosterone and estradiol. Therefore any study that demonstrates positive effects of oral DHEA on sexual function cannot distinguish between the role of DHEA alone or as a precursor of testosterone and/or estradiol. In summary there are no strong data to support beneficial effects of exogenous DHEA on sexual function in health or in adrenal insufficiency. To date there have been no RCTs evaluating sexual function with androstenedione in women.

4. ROLE OF TESTOSTERONE IN HSDD

a) Evidence from basic research and physiology (Level 5)

Androgen receptor (AR) mRNA-containing neurons are widely distributed in the female rat brain, with the greatest densities in neurons in the hypothalamus, and in regions of the telencephalon that provide strong inputs in the medial preoptic and ventromedial nuclei, each of which is thought to play a key role in mediating the hormonal control of sexual behavior, as well as in the lateral septal nucleus, the medial and cortical nuclei of the amygdala, the amygdaloid-hippocampal area, and the bed nucleus of the stria terminalis [76]. In the adult male cynomolgus monkey high densities of P450 aromatase and AR mRNA-containing neurons were observed in discrete hypothalamic areas involved in the regulation of gonadotropin secretion and reproductive behavior [77]. All areas that contained P450aromatase mRNA-expressing cells also contained AR mRNA-expressing cells. However there were areas in which AR mRNA was expressed but not P450aromatase mRNA suggesting testosterone acts via different signalling mechanisms in specific brain regions [77]. No equivalent data is available for humans or female primates. In rodent models, as reviewed above, testosterone does not maintain normal sexual behaviour in the absence of estrogen action.

Evidence from observational and population-based, epidemiologic studies (Level 3-4).

Studies examining the relationships between circulating endogenous testosterone levels and sexual activity have produced varying results. This is likely due to testosterone levels in the circulation being of limited value as an indicator of tissue androgen exposure as described above. Nonetheless, peripheral androgen levels (nonSHBG bound testosterone and its precursors) may be indicative of the hormonal milieu of the brain, and may influence sexual behaviour either directly or via aromatization to estrogen within the brain. ALEXANDER et al reported that premenopausal non oral contraceptive pill users (n=13) reported decrease in sexual desire during perimenstrual phase associated with decline in free testosterone [78].

However other sexual function parameters in this study were not found to correlate with free testosterone. RILEY and RILEY found an association between low sexual drive and androgen levels in 15 women with low sexual desire versus 15 controls aged 18 to 45 years matched for age, parity and weight who completed daily diaries for at least 1 cycle and had mid cycle blood samples performed [79]. This study measured testosterone only once in women with lifelong low libido so the methodology of this study is problematic.
In a national probability sample study of sexual behavior in a cohort of almost 2,000 women between the ages of 18 to 59 years, the older age group, women between the ages of 50 to 59 years, were less likely to report lack of interest in sex, inability to achieve orgasm, or sex not pleasurable than were younger women [80]. These are not the findings that would be expected if androgens were a major factor governing women's sexuality, given that the woman in the older age group would be predicted to have approximately half the testosterone concentrations as the younger women in the study.

McCoy reported that low total testosterone levels were closely correlated with reduced coital frequency and loss of sexual desire [81] and Bachmann and Leiblum reported a positive relationship between free testosterone and ratings of sexual desire by interview questioning in 59 women aged 60-70yrs [82]. In contrast, Cawood and Bancroft reported no relationship between androgens and sexual parameters in 141 volunteer non hormone therapy users aged 40-60yrs [53]. Each of these and other studies that have addressed this issue have significant methodological limitations, with a consistent limitation being lack of sensitivity of the testosterone assays used and reliance on total, not free testosterone levels.

In a cross-sectional analysis of data from 201 women aged 48-58 years in the Melbourne Midlife Heath Study, sexual responsivity declined with age, but testosterone levels were reported not to be associated with any aspects of female sexual functioning. However the assay used could not differentiate normal from low testosterone levels [83].

b) Evidence from observational studies in oophorectomized women (Level 3)

Young women who undergo bilateral oophorectomy (BSO) experience an approximately 50% reduction in circulating testosterone concentrations [37]. Studying women following oophorectomy, therefore, is a way to evaluate the effects of low testosterone levels on libido, psychological state, body composition, bone mineral density, and other factors that may result from decreased androgen concentrations. Identifying consistent signs and symptoms in oophorectomized women that are not present in women who retain their ovaries, would provide support for the existence of a female androgen insufficiency syndrome. As the majority of women have oophorectomy at the time of hysterectomy, to evaluate the isolated effects of androgen loss, oophorectomized women should be receiving estrogen therapy and be compared to hysterectomized women who retain their ovaries. These studies are imperfect, though, as the indications for surgery, the surgical procedures, and the accompanying estrogen deficiency or estrogen therapy following oophorectomy all may impact function post-operatively.

In the Maryland Women's Health Study, over 1,000 women were interviewed before and after hysterectomy [84]. ET users vs. non-users were not analyzed separately, but the authors stated that 88% of the premenopausal women undergoing concurrent BSO were taking hormone therapy 12 months after hysterectomy. Despite the fact that approximately 44% of the women had concurrent BSO, the investigators observed significant improvements in sexual functioning post-operatively. Removal of the ovaries did not influence the improvements seen following hysterectomy for measures of frequency of sexual relations, dyspareunia, vaginal dryness, and libido. In this study, BSO was associated with a statistically significant 2.7-fold increase in the likelihood of not experiencing orgasms 12 months post-operatively [84]. Similar results were found in a retrospective European study. Approximately 700 women under 55 years of age who underwent hysterectomy for benign disease over a 5-year time period at a Swedish hospital completed questionnaires post-operatively. Although the majority of women reported improved sexual life following hysterectomy, oophorectomized women were significantly less likely to report improvement than non-oophorectomized women (55% vs. 74%, respectively) [85]. Twenty-four percent of oophorectomized women reported an overall worsening of their sexual life post-operatively, which was more than twice the rate for women following simple hysterectomy (11%). Ratings of experience of intercourse and coital frequency post-operatively also were significantly lower in oophorectomized women compared to those who retained their ovaries. To specifically examine the isolated effects of decreased testosterone levels, estrogen-treated oophorectomized women were compared to those with intact ovaries; the women without ovaries described decreased pleasure from intercourse and increased anxiety, but there were no significant differences between these two groups for sexual fantasies, depression, or overall psychological well-being. No correlations were found between the psychological or sexual variables and androgen measurements, including total testosterone, free testosterone, androstenedione, and DHEAS.
Observational studies of oophorectomized women are consistent with the hypothesis that decreased testosterone levels may affect sexual function in some women. The strength of the evidence is limited, though, by the fact that many women report an improved sexual life post-operatively.

c) Evidence from clinical trials of androgen therapy (Level 2)

Several studies of supraphysiological testosterone treatment in oophorectomized and naturally menopausal women demonstrate clear improvements in sexual function. In a prospective, cross-over study of 53 surgically menopausal women, those treated with supraphysiological doses of intramuscular testosterone or testosterone-estradiol combined had significant improvements in sexual desire, fantasies, and arousal compared to women treated with estradiol alone or placebo [61]. The dose of testosterone enanthate administered in this study was 150 mg per month, which is a dose producing full virilization when given to hypogonadal males. BURGER et al treated 17 patients with combined subcutaneous implants of estradiol (40 mg) and testosterone (100 mg) because oral estrogen (CEE 1.25 mg daily or estradiol valerate 4 mg daily) had not adequately relieved decreased libido in particular [62]. Significant improvements were noted in libido, enjoyment of sex and tiredness (p<0.01) without significant changes in flushes, sweats and depression. Libido increased from a mean basal level of 13.5 to a maximum of 86.1 (on an analogue scale, maximum 100) at 3 months and increased in all evaluable subjects. Symptomatic improvement was maintained for 4-6 months. No significant changes were seen in total serum cholesterol, triglyceride or cholesterol subfractions. Total testosterone plasma concentration rose from 2.3 (measured at the point of discontinuing oral estrogen) to 6.7 nmol/l at 1 month, and had returned to baseline at 5 months. Again, this dose of the testosterone can be considered pharmacological. A single blind controlled study was undertaken with lower dose testosterone implants in 20 post-menopausal women complaining of loss of libido, unresponsive to adequate estrogen replacement [86]. Treatment was with implants of either estradiol alone (40 mg) or estradiol in combination with testosterone (50 mg) at concentrations raising the total testosterone level to just above the upper limit of normal (3.5-3.7 nmol/l). Those receiving combined implants showed a marked improvement in the various sexual measures recorded, similar to that observed in the earlier study. The dose of testosterone used here could be considered to be in the high physiological or low pharmacological range. Again, no significant changes were seen in serum lipids. DAVIES et al conducted a single blind randomised trial of 34 post-menopausal women not identified as having sexual dysfunction over a 2 year period. Women received either estradiol implants 50 mg alone or estradiol 50 mg with testosterone 50 mg. The combined treatment increased serum testosterone concentrations to high in the normal range and improved all parameters of sexual function measured using the Sabbatberg Sexual Self-rating Scale as compared with estradiol alone [64].

SARREL et al compared esterified estrogen alone with esterified estrogen plus methyltestosterone (MT) in postmenopausal women who were “dissatisfied” with their HT. Those taking combined therapy reported improved sexual desire, satisfaction and coital frequency, with their being no such improvement in the estrogen alone group [87]. As the combined MT-esterified estrogen treatment lowers SHBG levels markedly, it is unclear if the beneficial effects on sexual function are caused by an elevation in endogenous free testosterone and DHT levels, an elevation in free estrogen levels or by the androgenic action of MT itself.

In contrast MYERS et al conducted a 10 week double blind study of 40 naturally menopausal women with four treatments: CEE 0.625 mg, CEE 0.625 mg plus MPA 5 mg, CEE 0.625 mg plus MT 5 mg or placebo. The CEE 0.625 mg plus MT 5 mg group had increased reports of pleasure from masturbation versus the other 3 groups, but there were no differences in mood ratings, sexual behavior or sexual arousal [88]. This outcome may reflect inadequate treatment time, too small study numbers, inability of MT to be aromatized or no true difference of therapy.

In a double-blind RCT, the effects of oral testosterone undecanoate vs. placebo (in combination with oral estrogen) on sexuality and mood were evaluated in a crossover design in 50 surgically menopausal women [89]. The addition of testosterone undecanoate (40 mg/day), which raises testosterone levels into the supraphysiological range in a significant proportion of women, was associated with significant improvements in “enjoyment of sex”, “satisfaction with sexual frequency”, and “interest in sex” using the McCoy scale.

Shifren et al conducted a short-term study of physiological testosterone therapy in estrogen-replaced, surgically menopausal women with decreased libido.
that also demonstrated significant improvements in sexual function [90]. Seventy-five women who experienced impaired sexual function following hysterectomy and oophorectomy despite estrogen therapy were treated with physiological testosterone matrix patches (150 or 300 mcg/day) or placebo, each for 12 weeks, in a RCT cross-over trial. Although there was a considerable placebo response, women receiving the higher testosterone dose experienced significant increases in the frequency of sexual activity and pleasure-orgasm [90]. At this dose the percentages of women who had sexual fantasies, masturbated or engaged in sexual intercourse at least once a week increased 2 to 3 fold over baseline. A post-hoc analysis showed that in contrast to the younger subjects in the study (under the median age of 48 yr), the “older half” of the population had a much smaller placebo response and exhibited significant improvements in sexual function parameters at both doses of testosterone (150 or 300 mcg/day).

Positive well-being and depressed mood (measured by the Psychological General Well Being Index) also improved at the higher testosterone dose. Subsequently, two more studies of transdermal testosterone patches in over 500 surgically menopausal women treated with either oral or transdermal estrogen have been completed and the findings, to be presented this fall, will add significantly to the body of evidence. Two additional larger studies with the testosterone patch are ongoing.

Another RPCT with a cross over design of 45 premenopausal women presenting with low libido demonstrated that transdermal testosterone significantly improved sexual motivation, fantasy, frequency of sexual activity, pleasure, orgasm and satisfaction [91]. In addition to the positive effects on sexual function, testosterone significantly improved the total score and all subscale scores of the Personal General Wellbeing Index in the premenopausal women [91]. The mean free androgen index was just above the proposed upper limit for young women, although no true range has been formally established for this estimate of free testosterone.

No clinical human studies to date have differentiated whether any of these effects are AR or ER mediated, or both. The effect of aromatase inhibition on sexual function in women treated with transdermal testosterone is currently underway and may help resolve this issue.

Female androgen insufficiency syndrome (FAIS) has been described as a pattern of clinical symptoms and signs in the presence of decreased bioavailable testosterone and normal estrogen status [92]. Clinical symptoms of the proposed deficiency state may include decreased libido, sexual receptivity, and pleasure; a diminished sense of well-being or dysphoric mood; and persistent unexplained fatigue. Clinical signs might include bone loss, decreased muscle mass and strength, adipose tissue redistribution, decreased sexual hair, and changes in cognition or memory. The study of possible female androgen deficiency states is limited by the sensitivity and specificity of testosterone assays for women, and the lack of a large normative data base of androgen levels for women. In addition, the proposed signs and symptoms of FAIS are very non-specific, and may be secondary to other common problems in women, including depression and thyroid disease. The fact that the states in which women have significantly reduced androgen levels, such as oophorectomy and adrenal disease are often associated with other medical conditions, medications, and aging also contributes to the difficulty in providing evidence to support the existence of FAIS. In addition, the more broadly a syndrome is defined, the harder it is to support with data from well designed studies. A review of the available studies provides greater evidence to support a specific association between low androgen concentrations and decreased libido and other changes in sexual function, than for the entire syndrome.

**d) Conclusions**

Clinical studies of supraphysiological testosterone therapy have shown improvements in sexual parameters in postmenopausal women. More recent studies employing physiological doses have shown benefits in sexual function and mood, including 2 studies the results of which will soon be available.

Although a group of clinical investigators from a wide variety of fields related to women's health (including epidemiology, endocrinology, urology, obstetrics and gynecology, psychology, and psychiatry) have proposed a set of symptoms and signs describing a FAIS this still must be considered a working definition, on which to base future research. The present evidence for the existence of a FAIS is based primarily on clinical experience, limited observational studies and few RPCTs. It has not been shown that the symptoms attributed to FAIS are more common in women with lower testosterone levels. A study of the relationships between sexual parameters and free and total testosterone and other
sex steroids in a randomly recruited sample of women from the community aged 18 to 75 years will soon be reported on.

5. TIBOLONE AND HSDD (LEVEL 2-3)

Tibolone is a synthetic steroid possessing a 3 keto-group with a 7α methyl group. It has been described as a pro-drug as following ingestion it is quickly metabolized in the gastro-intestinal tract to two estrogenic metabolites 3α andβ which then circulate predominantly in their sulfated inactive forms [93]. These metabolites only become estrogenically active when desulfated by the sulfatase enzyme in target tissues. The global effect of tibolone would thus be expected to be estrogenic. However tibolone itself and its 3β metabolite may be converted to a Δ4-isomer by the enzyme 3β-hydroxysteroid dehydrogenase (HSD)-isomerase [94].

Studies of tibolone on sexual desire indicate a benefit. In a randomized placebo controlled study of 12 months duration postmenopausal women completed a sexual function questionnaire that comprised 10 self-evaluations of sexual attraction, desire and fantasy, intensity and frequency of orgasmic response and coital activity [95]. Scores for all 10 items on the questionnaire improved in the tibolone group, but not the placebo group at 12 months of study (p<0.01). In another randomised placebo controlled cross-over trial tibolone resulted in significant increases in sexual desire, the frequency of arousability and of sexual fantasies compared with placebo [96]. Nathorst-Boos and Hammar studied the effect of tibolone or 17β-estradiol (2 mg) plus NETA on sexual function [97]. A modified McCoy sexual questionnaire was administered to 437 postmenopausal women and both preparations significantly improved libido (p<0.001). A greater effect was seen with tibolone after 24 and 48 weeks of treatment in terms of overall scores for “frequency of sexual activity”, “satisfaction” and “enjoyment” [97]. The baseline was lower for several of the parameters in the tibolone group and improvement was greater for individuals with a lower baseline.

CASTELLO-BRANCO et al., in an open label study randomized 120 surgically menopausal women to either oral estradiol valerate (4 mg/day) with dihydroandrosterone enanthate (monthly, intramuscularly), transdermal 17β-estradiol (50 mcg/day), tibolone (2.5 mg/day) or placebo for 12 months [98]. There were significant improvements in all parameters of sexual function in all active treatment groups. However sexual responsiveness and frequency of orgasm improved with oral estradiol/dihydroandrosterone and tibolone to a greater extent than estradiol alone (p<0.05 for difference between treatments). The doses of oral and transdermal estradiol were not equivalent, possibly biasing this comparison; however this would not have influenced the more favorable effect of tibolone over transdermal estradiol.

Hormonal factors contributing to decreased sexual function in women may include estradiol deficiency, testosterone insufficiency and reduced bioavailability of estradiol and testosterone due to elevated SHBG [99, 100]. Tibolone may improve libido and other aspects of female sexuality because of its combined estrogenic, androgenic and SHBG-lowering effects.

6. RALOXIFENE (LEVEL 2-3)

Raloxifene is a selective estrogen receptor modulator (SERM) indicated for the treatment of osteoporosis in postmenopausal women. It has antiresorptive estrogen-like activity on bone, but is an estrogen antagonist in the uterus and breast, and does not alleviate (and may exacerbate) hot flashes and urogenital atrophy [101]. Because of the latter findings a large placebo-controlled RCT has recently evaluated the effects of raloxifene (60 and 120 mg/day) on the sexual function of postmenopausal women with osteoporosis [102]. After 36 months of treatment, no statistically significant differences between active and placebo treatments were found for any of the sexual function parameters, which included desire, activity, enjoyment, pain during intercourse, orgasm, arousal and global score for sexual problems. In comparison to oral CEE raloxifene produces only a small increase in SHBG levels [103]. Consistent with this, in healthy postmenopausal women with normal androgen levels, raloxifene 60 mg/day does not lower levels of total or free testosterone, or DHEAS. As previously reported, raloxifene selectively lowers FSH levels while leaving LH levels unaffected. This may contribute to the neutral effect on circulating androgens [104]. Further studies are necessary to establish the full clinical implications of these findings relative to other osteoporosis therapies. While raloxifene would not be used to treat sexual problems, from this study it seems unlikely to cause them.

7. OXYTOCIN AND SEXUAL BEHAVIOR

Circulating levels of the neuropeptide oxytocin have been reported as increased during sexual arousal and
orgasm in humans and its receptor may have a role in sexual behavior. When oxytocin has been infused into the brains of estrogen treated female rats (which are not very sexually receptive) their sexual activity was considerably stimulated [105]. Estradiol increases the expression of oxytocin and its receptor in the ventromedial hypothalamus (VMH) of the rat [52]. The authors are unaware of any correlates to this finding in humans.

8. PROLACTIN (LEVEL 4-5)

Hyperprolactinemia results in hypogonadotrophic hypogonadism and loss of libido, and distress [106]. These adverse effects have been attributed to loss of ovarian function. LUNDBERG and HULTER reported that 53 (84.1%) out of the 63 women with hypopituitary disorders who had hyperprolactinemia had diminished sexual desire, but only 15 (32.6%) out of the 46 women with normal serum prolactin had this symptom (p < 0.001) [107]. EXTON et al reported elevated prolactin in women following orgasm that remained elevated when re-measured at 60 minutes [108].

9. GLUCOCORTICOSTEROIDS (LEVEL 5)

Adrenal insufficiency is associated with reductions in DHEAS and free and total testosterone [109]. Similarly glucocorticosteroid excess, either endogenous or exogenous, leads to adrenal suppression and androgen insufficiency and thus may indirectly inhibit sexual function [110]. However there are no clinical data to support that this is an effect independent of the disease process for which glucocorticosteroids therapy is being used.

III. HORMONES AND SEXUAL AROUSAL (LEVEL 2-3)

It is becoming clear that inadequate sexual arousal may in part be due to decreased blood flow to the sexually responsive organs. While atherosclerosis may be implicated in older women with vascular risk factors, it seems that hormonal changes may play a part in younger women.

Estrogen influences vascular function via genomic and nongenomic mechanisms [1]. Estrogen has direct effects on genital anatomy, enhancing peripheral blood flow and peripheral nerve function and improving vaginal lubrication [111].

The endothelium plays a critical role in determining the contractile state of the vessel [112] and modulates several other vital vascular functions including platelet aggregation, monocyte adhesion, smooth muscle proliferation and lipid oxidation [113]. Age, hypercholesterolaemia, diabetes and smoking severely impair endothelial function [114, 115]. Although exogenous estrogen will restore impaired endothelial dysfunction consequent to estrogen deficiency [116], there is no evidence that exogenous estrogen will reverse the endothelial dysfunction due to other causes [117]. Thus although estrogen therapy may restore peripheral blood flow in estrogen deficient women with normal vascular integrity, this may not be the case for women who have established vascular dysfunction.

Testosterone appears to be important for its vasomotor effects [118], enhancing vaginal blood flow and lubrication [119, 120]. These effects may be due to direct androgen actions or in part be due to estradiol biosynthesis from testosterone in the vascular bed [121]. Cellular research indicates that vaginal tissue may express a specific nuclear receptor for the very powerful androgen, D5-βandrostenediol [122].

In a RCT with a cross over design, acute testosterone administration at pharmacological levels was found to increase vaginal pulse amplitude (VPA) in eugonadal women with a strong statistical correlation between VPA and self reporting of genital sensations [119]. In an earlier open label study of MT combined with micronized estradiol versus estradiol alone, both therapies increased vaginal blood flow with no difference between the two groups [123]. LAAN et al conducted a RCT (cross-over design) of tibolone versus placebo in 38 postmenopausal women. VPA increased with tibolone compared with placebo and there was a significantly greater increase in VPA with erotic fantasy but not erotic visual stimulation with tibolone versus placebo [96]. In a single blind study acute DHEA had no significant effect on either VPA responses or subjective responses to the erotic films 30 minutes post dose in 12 healthy premenopausal women [124]. As sublingual testosterone did not result in an effect until 1.5 hours [119] it is possible that evaluation of VPA may have been performed at too early a time point for a true effect to be measured resulting in a type 1 error.

IV. HORMONES AND DYSPAREUNIA (LEVEL 1-2)

Urogenital symptoms adversely influence sexual desire. Symptoms such as vaginal atrophy and dry-
ness, urinary frequency and incontinence occur in approximately one-third of women over 50 years of age and are not easily resolved. A recent study by UTIAN and SCHIFF found that 55% of those questioned experienced vaginal dryness, while 32% complained of dyspareunia [125]. Dyspareunia has a number of causes, but lack of estrogenization is a common cause in women experiencing estrogen deficiency due to any etiology at any age. After the menopause, the vaginal pH increases as lactobacilli disappear from the vaginal flora. Estrogen replacement, whether locally applied or by oral administration, improves vaginal wall glycogenization and vaginal blood flow. This results in the restoration of the normal vaginal bacterial flora and a concomitant lowering of the vaginal pH [126]. Estrogen treatment relieves vaginal dryness leading to a subsequent improvement in sexual function [127].

Since the urogenital tissues are highly sensitive to estrogens, vaginal administration of low-dose estrogen treatment provides an alternative approach to systemic estrogen therapy for the management of urogenital atrophy that is safe and acceptable [58]. This is an important requirement in a treatment that will have to be used long term, as urogenital atrophy is a lifelong disorder. Vaginal treatment is also an effective adjunct in women already taking oral HT but who continue to have symptoms of urogenital aging. For women with severe urogenital estrogen deficiency, maintenance therapy with low-dose vaginal estrogen results in sufficient absorption to induce maturation of the vaginal and urethral epithelium, without gradual accumulation of circulating unconjugated estrone and estradiol.

Tibolone relieves such urogenital symptoms, and this may contribute to the improvement in libido seen with tibolone [96]. Tibolone normalizes the vaginal karyopyknotic and maturation indices and alleviates symptomatic atrophic vaginitis [128] with effects sustained over the long term [129].

LEIBLUM et al in a prospective study reported a significant negative associations between androstenedione and testosterone levels and vaginal atrophy [120]. Androgen receptors have been reported in the vagina and these may play a role in vaginal health.

Local and systemic estrogen therapy can be effectively used to treat vaginal atrophy. Tibolone is also effective for management of urogenital symptoms. A therapeutic role for androgens for urogenital atrophy needs to be established.

**V. HORMONAL EVALUATION OF A WOMAN PRESENTING WITH LOW LIBIDO**

Evaluation of loss of libido requires a multi-system approach such that both physical and psychosocial factors must be evaluated for all patients.

**1. HISTORY AND EXAMINATION**

In defining the problem it is important to determine whether the problem of low libido is causing the women personal distress. The duration of decreased libido and when the women last felt she had normal libido should be established. Assessment should be non judgmental as what is normal for one woman may not be acceptable to another. Evaluation of psychosocial factors as discussed elsewhere is vital, however the presence of psychosocial components do not exclude a contributing organic component and should not exclude a woman from full biological assessment. All women should be carefully screened for depression as a cause of their sexual difficulties. Similarly the presence of chronic illness does not exclude a hormonal cause. Indeed a hormonal cause may be more likely in women with illness or therapy that causes adrenal suppression.

A complete gynecological history should be taken. History should also identify possible iron deficiency, thyroid disease and galactorrhea. In premenopausal women adequacy of estrogenization should be evaluated by taking a menstrual history. In the presence of regular cycles (periods every 21 to 35 days) dysfunction of the hypothalamic-pituitary-ovarian axis is extremely unlikely, such that estrogen is usually adequate and prolactin is normal. Amenorrhea prior to the age of 40 years requires full assessment.

A general physical examination should include assessment of thyroid status, presence of anemia or galactorrhea. Gynecological examination should include a pelvic examination with attention to signs of vaginal atrophy, size of introitus, presence of discharge or evidence of infection, vulvodynia and deep tenderness. Evaluation of the vulvar and vaginal tissues on exam relates more closely to sexual function than estradiol levels.

**2. LABORATORY ASSESSMENT**

*a) General*

Women presenting with low libido and fatigue
should have routinely measured: iron stores (which might be low despite normal hemoglobin); thyroid stimulating hormone (TSH) to exclude subclinical thyroid disease, and on clinical suspicion a screen for autoimmune disease causing chronic fatigue. The incidence of undiagnosed subclinical hypothyroidism is high - about 10% of women over 40. The relation of mild hypothyroidism to symptoms of fatigue and sexual complaints is unclear. Women treated with thyroxine who are started on oral (but not parenteral) estrogen therapy need to have their TSH measured 6 weeks after commencement as estrogen, as oral estrogens may increase the thyroxine requirement by increasing thyroid binding globulin.

Measurement of estradiol and FSH is indicated to diagnose premature ovarian failure in amenorrheic young women or to evaluate menopausal status in hysterectomized women. However in the latter a full symptom history is often more useful. Amenorrhea with low FSH and low estradiol is suggestive of hypothalamic amenorrhea, hyperprolactinemia or other rare pituitary disease. Not all immunoassays reliably distinguish normal estradiol from low levels.

**b) Prolactin** should be measured in premenopausal women with oligomenorrhea, amenorrhea and/or galactorrhea.

**c) Testosterone**

Free or bioavailable (non-SHBG-bound) testosterone measures are the most reliable indicators of tissue testosterone exposure. High levels do not predict higher libido, however, a level above average probably rules out androgen insufficiency.

Timing of measurement to prevent misdiagnosis of low testosterone: Ideally blood should be drawn between 8:00 and 10:00 am due to the diurnal variation of testosterone, resulting in higher levels at this time [32]. In premenopausal women, testosterone is at its nadir during the early follicular phase, with small but less significant variation across the rest of the cycle [30, 130]. Thus, blood should be drawn after day 8 of the cycle, and preferably before day 20. A serum sample is preferred over plasma.

**Free testosterone**: The gold standard methodology for measurement of free testosterone is considered by many investigators to be equilibrium dialysis. However, this method is influenced by dilution of the analyte. Furthermore, it is labor intensive and expensive, and not feasible for clinical practice. Bioavailable testosterone, which correlates highly with free testosterone quantified by equilibrium dialysis, can be measured by the ammonium sulfate precipitation technique [131]. However, frequently encountered sources of error in this assay include incomplete precipitation of globulins, use of impure tritiated testosterone, and insufficient counting time of the relatively small amount of radiolabeled bioavailable testosterone in the assay. The equilibrium dialysis and ammonium sulfate precipitation methods generate a percentage of free testosterone and bioavailable testosterone, respectively. This percentage is then multiplied by the concentration of total testosterone to determine the free and bioavailable testosterone concentrations. The Sodergard equation can be reliably used to calculate free testosterone if total testosterone, albumin and SHBG are known [131, 132]. This method requires a reliable determination of total testosterone and SHBG; albumin is quantified by routine methodology. Measurement of free testosterone by analogue assays are notoriously unreliable, particularly at the lower end of the normal female range and are not recommended for use [133].

**Salivary testosterone** has been used reliably in studies of women with hyperandrogenism, but has never gained wide support because the normal range seems excessively large and also has questionable accuracy in the lower ranges [134]. It is important to realize that salivary testosterone levels should not be equated to levels of free testosterone in serum. The free androgen index (FAI) [nmol/L total testosterone x 100/nmol/L SHBG] has been used as a surrogate for free testosterone, but it is unreliable when SHBG levels are low [135].

**Total testosterone**: No rapid, simple assay of total testosterone has been shown to produce reliable results in women with low testosterone levels. Direct testosterone immunoassays are limited by “noise” from assay interference and by cross-reactivity with other steroids, which become worse at low testosterone concentrations [133]. Furthermore, testosterone is sometimes not completely dissociated from SHBG in a direct assay. Inclusion of organic solvent extraction will increase specificity, and if combined with chromatographic separation of testosterone from interfering steroids, a reliable result can be obtained. However, this technique is frequently not available or cost-effective in clinical settings.

Gas chromatography combined with mass spectrometry (GC-MS) for total testosterone measurement requires multiple steps including liquid-liquid extraction, and may not be reliable when testosterone...
levels are very low [133]. However, liquid chromatography (LC)-MS/MS appears to provide reliable measurement of low testosterone concentrations.

Regardless of which assay method for measuring an analyte is used, a thorough validation of each method is required. The validation should include assay sensitivity, precision, accuracy and specificity.

d) Other parameters: SHBG binds with high affinity to testosterone and is an important regulator of circulating total testosterone concentration. The measurement of SHBG is not controversial and is relatively simple to perform with good reproducibility.

The chief androgen precursor in the adrenal gland is DHEA. It is usually measured in the sulfated form, DHEAS, because the half-life is much longer, resulting in more stable levels. The immunoassay for DHEAS is relatively stable, gives consistent results, and is simple to perform. Several companies provide kits for this clinical assay, and their performance is generally considered to be acceptable. There is a consensus that DHEAS does not vary in concentration within the various phases of the menstrual cycle, and that it is not bound to SHBG. It also does not seem to be affected by estrogen therapy at standard doses.

A number of authors have shown normal, age-related decline curves for DHEAS, which are all quite compatible. If low levels are found, a morning cortisol level should be drawn to rule out adrenal insufficiency.

e) Summary of androgen measures:

1. Free testosterone and/or bioavailable testosterone are felt to be most reflective of the hormone available to tissues. Free testosterone should be measured by equilibrium dialysis or calculated using the Sodergard equation from total testosterone, SHBG, and albumin. Since total testosterone levels play an important role in determining free testosterone concentrations in those methods, a reliable total testosterone assay is essential. None of the direct commercial immunoassays can be recommended for reliably determining low total testosterone in women.

2. SHBG provides additional information regarding overall androgen exposure, as it is sensitive to total body androgen status. Low SHBG levels indicate a considerable increase in risk of androgen excess with testosterone therapy, whereas high levels indicate a reduced MCR of testosterone.

3. Serum for testosterone measurement should be drawn between 8:00 and 10:00, and not during the early follicular phase in premenopausal women for either research or diagnostic purposes.

4. There is no established level of free testosterone below which a woman can be said to be deficient, nor any level to which a woman should be restored that determines that she is replete. Such absolute levels are not likely to be established because of the large inter-individual variability and the intracrinology of androgens in women.

5. To date a relationship between a specific level of free testosterone and sexual symptoms has not been established. The diagnosis of diminished sexual function due to low testosterone is a diagnosis of exclusion. In the absence of a reliable free/total testosterone assay the error of the available assay should be understood, and the measurement of testosterone used to exclude women in whom testosterone therapy might be dangerous. Other factors must be used as guidance such as a low SHBG indicating increase treatment risk and clinical presentation.

6. DHEAS measurement may help elucidate the cause of testosterone insufficiency, and should be measured if treatment with DHEA is considered. Testosterone levels decline with age prior to menopause [27, 136] but normal ranges for women by decade have not been established.

VI. HORMONAL THERAPIES FOR THE TREATMENT OF SEXUAL PROBLEMS IN WOMEN: INDICATIONS FOR THEIR USE, EVIDENCE OF EFFECTIVENESS, AND SAFETY ISSUES

This section summarizes the indications for use and the safety issues associated with six classes of hormonal therapies suggested for treating sexual problems in women:

- estrogens,
- estrogen-progesterin combinations,
- progestins,
- androgens,
- androgen precursors, and
- miscellaneous hormones (including raloxifene, tibolone and pheromones).

Distinctions between oral, transdermal and other routes of hormone administration have been made.
where possible. In addition to their direct effects, the influence of estrogens, progestins and SERM administration on the endogenous production and binding of androgens is also considered. A synopsis of the principle findings of this review is given in Table 4.

1. ESTROGEN THERAPIES

Estrogen therapies include oral, transdermal, subcutaneous, intranasal and vaginal preparations of 17-β estradiol (E2) as well as micronised or esterified estrogens (EE) and conjugated equine estrogens (CEE). For sexual problems the most relevant approved indication for these preparations is the treatment of vulval and vaginal atrophy and related vaginal symptoms associated with menopause. All types of estrogen preparations appear to be effective (level 1-2) at treating urogenital atrophy, increasing vaginal glandular secretions, and ameliorating dyspareunia [137-140] although some disagreement exists as to the linkage between these three symptoms [141]. Aside from these effects, estrogen therapy does not appear to be effective for treating decreased libido, reduced activity and/or orgasmic difficulties [142, 137].

Safety issues with oral and parenteral estrogen monotherapy include an increased risk of endometrial cancer in non-hysterectomized women and vaginal bleeding [143]. The relationship between estrogen alone and breast cancer risk remains unclear in that epidemiological studies do not indicate a link [144, 145], and the results of the WHI estrogen only arm are not yet available. Oral but not transdermal estrogen therapy has been shown to produce dose-dependent increases in the circulating levels of a number of hepatic proteins including SHBG, thyroxine-binding globulin (TBG), corticosteroid-binding globulin (CBG), and renin substrate (146). Oral estrogen increases markers of coagulation activation (prothrombin fragment 1+2) and lowers anti-thrombin activity in postmenopausal women but transdermal estrogens do not seem to have any effect on coagulation and fibrinolysis [147]. Most recently SCARABIN and co-workers have shown in the ESTHER study that oral estrogen users have a 4-fold increased risk of VTE compared to non users and a 4-fold increased risk compared to transdermal users.

The levels of both C-reactive protein and interleukin -6, circulating markers of systemic inflammation produced by the liver, which correlate with cardiovascular risk, also have been shown to increase during oral but not transdermal estrogen therapy [148]. Oral estrogen therapy has also been associated with an increased risk for cholestasis and gallstones, and despite beneficial effects on HDL and LDL cholesterol levels is associated with an increase in triglycerides, which may be unfavorable [149]. In contrast to oral estrogens, transdermal preparations have minimal effects on lipid parameters but transdermal patches may produce skin irritation in susceptible individuals [150]. Vaginal administration of low-dose estrogens may also produce local irritation but would be expected to cause fewer systemic side effects than oral or transdermal preparations.

Oral estrogens (CEE and estradiol) have been shown to reduce free testosterone concentrations by approximately 60% in postmenopausal women with intact ovaries, whereas transdermal estradiol has a much smaller impact on free testosterone [151, 152]. The difference is primarily due to the marked elevation in SHBG levels that occurs with oral but not standard dose transdermal estrogen therapy. A secondary factor is that estrogen therapy reduces secretion of LH (negative feedback), which in turn reduces the production rate of androgens by the postmenopausal ovary [152]. Thus it would seem that the prescription of oral estrogen therapy should be at the lowest available dose to minimise effects on circulating estrone sulphate and SHBG. Intranasal estradiol is now available in Europe and Australia. This form of administration takes advantage of the highly vascular nasal mucosa, with a single spray in each nostril resulting in a peak level of estradiol after about 10-30 minutes, returning to 10% of the peak value by 2 hours [153]. Like other parenteral estrogen therapies, intranasal estradiol does not increase SHBG and does not result in a high estradiol to estrone ratio [55]. It has been shown to have clinical therapeutic equivalence to oral and transdermal estradiol, and to be associated with significantly lower reporting of mastalgia [55].

2. ESTROGEN-PROGESTIN COMBINATIONS

When estrogen therapy is given to a woman with an intact uterus a progestational agent should be co-administered to minimize the risk of developing endometrial hyperplasia and cancer. This may be done daily on a continuous-combined (ie daily) basis, on a sequential (or cyclic) basis for 12 to 14 days of each month, or at less frequent intervals, e.g., every 3-4 months (although such “long cycle” regimens have not been FDA approved and remain controversial). Continuous-combined regimens are intended to produce a non-bleeding atrophic endometrium, whereas the sequential regimens are designed to induce predictable bleeding patterns. Oral
Table 4. Hormonal therapies for treatment of sexual problems in women

<table>
<thead>
<tr>
<th>Hormone Therapy</th>
<th>Relevant Indication/Regulatory Status</th>
<th>Evidence for Effectiveness (level 1 – 5)</th>
<th>Safety Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogens</td>
<td>Treatment of vulval and vaginal atrophy/ FDA approved</td>
<td>Libido: ↑ (1-2) Arousal: ↑ (1-2) Orgasm: None (2) Dyspareunia: None (2) Frequency: None (2)</td>
<td>Endometrial &amp; Breast Ca, Vaginal bleeding, VTE, ↑ hepatic proteins, ↑ TG, cholestasis</td>
</tr>
<tr>
<td>- oral preparations (CEE, EE, E2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- transdermal prep.(E2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- vaginal prep.(E2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen + Progesterin Combinations</td>
<td>Treatment of vulval and vaginal atrophy in women with intact uterus/ FDA approved</td>
<td>Libido: ↑ (1-2) Arousal: ↑ (1-2) Orgasm: None (2) Dyspareunia: None (2) Frequency: None (2)</td>
<td>Breast Ca, VTE, Vaginal bleeding, ↑ hepatic proteins, ↑ TG, cholestasis, CVD</td>
</tr>
<tr>
<td>(MPA, NETA, LNG or MP)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- oral prep.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- transdermal prep</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- vaginal prep.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progesterin only</td>
<td>Claimed to enhance Libido: Not FDA approved</td>
<td>Libido: ↑ (1-2) Arousal: ↑ (1-2) Orgasm: None (2) Dyspareunia: None (2) Frequency: None (2)</td>
<td>Drowsiness, fluid retention, breast tenderness</td>
</tr>
<tr>
<td>Androgens</td>
<td>None approved for treatment of sexual problems in women; (investigational and other indications given) Off-label use of low dose regimens contraindicated for use in women</td>
<td>↑ (2-3)</td>
<td>↑ (2-3)</td>
</tr>
<tr>
<td>T products for men, e.g., IM T-esters, T implants, oral TU, T reservoir patches, T gels</td>
<td>↑ (2)</td>
<td>↑ (2)</td>
<td>↑ (2)</td>
</tr>
<tr>
<td>Estradiol patch for women (investigational)</td>
<td>Treatment of hypoactive sexual desire in postmenopausal women (phase III)</td>
<td>↑ (2)</td>
<td>↑ (2)</td>
</tr>
<tr>
<td>Topical T preparations (compounded, investigational)</td>
<td>Treatment of hypoactive sexual desire in postmenopausal women (phase III)</td>
<td>↑ (2)</td>
<td>↑ (2)</td>
</tr>
</tbody>
</table>
| Estradiol + estradiol preparations (compounded, investigational) | Treatment of surgical menopause | ↑ (2) | ↑ (2) | ↑ (2) | Possible hepatotoxicity, abnormal liver function, virilization, acne, hirsutism, ↓ HDL-cholesterol and hepatic proteins. 
Same as MT |
| Oral MT | Metastatic Breast Ca: FDA approved | ↑ (2) | ↑ (2) | ↑ (2) | Local irritation, acne, hirsutism, possibly less effect on liver. Application to genitals may cause clitoral enlargement. |
| Oral MT - EE combination | Vasomotor symptoms not improved by E alone: FDA review | ↑ (2) | ↑ (2) | ↑ (2) | Local irritation, acne, hirsutism, possibly less effect on liver. Application to genitals may cause clitoral enlargement. |
| Topical MT (compounded) | Available by Rx/Not FDA approved | ↑ (2) | ↑ (2) | ↑ (2) | Local irritation, acne, hirsutism, possibly less effect on liver. Application to genitals may cause clitoral enlargement. |
| Topical DHT gel (for men) | Off-label use in Europe | ↑ (2) | ↑ (2) | ↑ (2) | Local irritation, acne, hirsutism, possibly less effect on liver. Application to genitals may cause clitoral enlargement. |
Table 4. Hormonal therapies for treatment of sexual problems in women (Ltd)

<table>
<thead>
<tr>
<th>Androgen Precursors</th>
<th>Available in U.S. as dietary supplements or as compounded formulations/ not FDA approved</th>
<th>↑ (2-3)</th>
<th>↑ (2-3)</th>
<th>↑ (3)</th>
<th>↑ (2-3)</th>
<th>Acne, hirsutism, possible hepatotoxicity, ↓ HDL-cholesterol and hepatic proteins</th>
<th>Less hepatic effects</th>
<th>Less hepatic effects</th>
<th>Virilization, acne, hirsutism, ↓ HDL-cholesterol and hepatic proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral DHEA preparations</td>
<td></td>
<td>↑ (2-3)</td>
<td>↑ (2-3)</td>
<td>↑ (3)</td>
<td>↑ (2-3)</td>
<td>Acne, hirsutism, possible hepatotoxicity, ↓ HDL-cholesterol and hepatic proteins</td>
<td>Less hepatic effects</td>
<td>Less hepatic effects</td>
<td>Virilization, acne, hirsutism, ↓ HDL-cholesterol and hepatic proteins</td>
</tr>
<tr>
<td>Topical DHEA (compounded)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acne, hirsutism, possible hepatotoxicity, ↓ HDL-cholesterol and hepatic proteins</td>
<td>Less hepatic effects</td>
<td>Less hepatic effects</td>
<td>Virilization, acne, hirsutism, ↓ HDL-cholesterol and hepatic proteins</td>
</tr>
<tr>
<td>Vaginal DHEA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acne, hirsutism, possible hepatotoxicity, ↓ HDL-cholesterol and hepatic proteins</td>
<td>Less hepatic effects</td>
<td>Less hepatic effects</td>
<td>Virilization, acne, hirsutism, ↓ HDL-cholesterol and hepatic proteins</td>
</tr>
<tr>
<td>Oral A-dione</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acne, hirsutism, possible hepatotoxicity, ↓ HDL-cholesterol and hepatic proteins</td>
<td>Less hepatic effects</td>
<td>Less hepatic effects</td>
<td>Virilization, acne, hirsutism, ↓ HDL-cholesterol and hepatic proteins</td>
</tr>
<tr>
<td>Miscellaneous hormones</td>
<td>Treatment and prevention of osteoporosis in postmenopausal women</td>
<td>None (2)</td>
<td>None (2)</td>
<td>None (2)</td>
<td>None (2)</td>
<td>Acne, hirsutism, possible hepatotoxicity, ↓ HDL-cholesterol and hepatic proteins</td>
<td>Less hepatic effects</td>
<td>Less hepatic effects</td>
<td>Virilization, acne, hirsutism, ↓ HDL-cholesterol and hepatic proteins</td>
</tr>
<tr>
<td>Rafloxifene (SERM)</td>
<td></td>
<td>↑ (2-3)</td>
<td>↑ (2-3)</td>
<td>↑ (3)</td>
<td>↑ (2)</td>
<td>Acne, hirsutism, possible hepatotoxicity, ↓ HDL-cholesterol and hepatic proteins</td>
<td>Less hepatic effects</td>
<td>Less hepatic effects</td>
<td>Virilization, acne, hirsutism, ↓ HDL-cholesterol and hepatic proteins</td>
</tr>
<tr>
<td>Tibolone</td>
<td></td>
<td>↑ (2-3)</td>
<td>↑ (2-3)</td>
<td>↑ (3)</td>
<td>↑ (2)</td>
<td>Acne, hirsutism, possible hepatotoxicity, ↓ HDL-cholesterol and hepatic proteins</td>
<td>Less hepatic effects</td>
<td>Less hepatic effects</td>
<td>Virilization, acne, hirsutism, ↓ HDL-cholesterol and hepatic proteins</td>
</tr>
<tr>
<td>Pheromones</td>
<td></td>
<td>↑ (2)</td>
<td></td>
<td></td>
<td>↑ (2)</td>
<td>Acne, hirsutism, possible hepatotoxicity, ↓ HDL-cholesterol and hepatic proteins</td>
<td>Less hepatic effects</td>
<td>Less hepatic effects</td>
<td>Virilization, acne, hirsutism, ↓ HDL-cholesterol and hepatic proteins</td>
</tr>
</tbody>
</table>

Abbreviations: A-dione = androstenedione, CEE = conjugated equine estrogens, CVD = cardiovascular disease, DHEA = dehydroepiandrosterone, DHT = dihydrotestosterone, E2 = estradiol, EE = esterified estrogens, FDA = U.S. Food and Drug Administration, HDL = high density lipoprotein, LNG = levonorgestrel, MP = micronized progesterone, MPA = medroxyprogesterone acetate, MT = methyltestosterone, NETA = norethindrone acetate, SERM = selective estrogen receptor modulator, T = testosterone, TG = triglycerides, VTE = venous thromboembolism
combinations, transdermal combinations and vaginal combinations involving the synthetic progestins, e.g., medroxyprogesterone acetate (MPA), norethindrone acetate (NETA), and levonorgestrel (LNG), as well as an oral capsule of micronised progesterone (MP), are available.

For sexual problems, the treatment of urogenital atrophy remains the most pertinent indication for estrogen therapy. When systemic symptoms are absent this can ideally be administered by a vaginal preparation alone. Systemic therapy with combined estrogen-progesterin is indicated for women who require treatment for vasomotor and/or other systemic symptoms. The improvement in well being achieved by relief of vasomotor and other symptoms may improve libido in some women and abrogate the need for further intervention. There is little evidence that any of the added progestins improves or worsens sexual problems when given with estrogen [137, 154].

The risk-benefit profile of combined oral CEE-MPA treatment was recently judged by some, but not all, to be unfavorable for long term use (beyond 5 years) on the basis of the Womens Health Initiative study (WHI), the largest RCT ever conducted on HT [155]. Nominal hazard ratios for oral CEE-MPA treatment, for which the study was prematurely terminated were significantly greater than one for breast cancer (1.26), coronary heart disease (1.29), stroke (1.41) and pulmonary embolism (2.13) [155]. However adjusted hazard ratios were only statistically significant for an increase in VTE and decrease in fracture with treatment. At the present time the risk-benefit ratio for oral CEE monotherapy is still being evaluated in a WHI study of hysterectomized women. Other oral regimens or parenteral administration of estradiol alone and/or in combination with progestins may be associated with fewer adverse cardiovascular outcomes than with oral CEE-MPA treatment, but this requires confirmation [156, 157].

The WHI findings of the effects of CEE plus MPA on health related quality of life (QOL) have recently been reported [158]. There was a statistically significant but not clinically relevant improvement in sleep disturbance, physical functioning and bodily pain at one year follow up. The findings were no longer significant at the three year follow up. There was no significant improvement in general health, limitations (either physical or emotional) on usual role-related activity, vitality, social functioning, mental health, depressive symptoms, or sexual satisfaction. It is essential to note that the questionnaires used to evaluate general health parameters and mental health were completely inappropriate for this population and sexual satisfaction was evaluated with the response to a single question.

In addition WHI was not designed to test the effect of HT on menopausal symptoms, which plays a large role in QOL for many peri/post-menopausal women. The majority of women in WHI were 15 years post-menopause, only 12 percent had moderate or severe vasomotor symptoms and the effect on urogenital symptoms was not assessed. Furthermore, vasomotor symptoms were unlikely to be disabling, as women were willing to be randomly assigned to placebo. Among the women with vasomotor symptoms at one year follow up, 76.7 percent of HT users had improvement compared with 51.7 percent in the placebo group (p<0.001). At three year follow up, 71 percent of HT users had improvement compared with 52.8 percent in the placebo group (p<0.001), thereby improving QOL. However, this was not included as a QOL measure in WHI.

The ability of progestins to alter endogenous free testosterone levels is primarily related to their effects on SHBG and secondarily to their suppressive effect on LH [159-161]. The androgenic progestins (LNG, NETA) partially attenuate the increase in SHBG associated with oral estrogen [162, 163], whereas oral MPA has a smaller attenuating effect and oral MP has virtually no influence on SHBG [164]. Similarly the transdermal administration of progestins would be expected to have a minimal impact on SHBG [154]. As a consequence of their effects on SHBG and LH, free testosterone levels should be lowest for oral estrogen - MP combinations, higher for combinations of oral estrogen with MPA, NETA and LNG (in that order), and highest for transdermal/intra-nasal estrogen-progestin combinations.

3. PROGESTIN-ONLY

Natural micronised progesterone taken orally may induce sedation and undesirable hypnotic effects [165]. A recently conducted RCT evaluating a non-prescription progesterone cream (32 mg applied daily) in 80 postmenopausal women found a minimal increase in serum progesterone levels and no evidence of improvement in sexual function after 12 weeks [166]. There are no reports on the use of oral progesterone or other progestins alone for treating sexual problems in women. A progesterone gel administered intravaginally for systemic delivery has been...
used for luteal phase support in women undergoing in vitro fertilization [167]. As noted above, oral and non-oral administration of micronised progesterone (MP) has not been shown to influence SHBG levels significantly and should therefore have a minimal effect on free testosterone levels. Although progesterone is an early precursor in the ovarian biosynthesis of androgens and estrogens [168], it does not appear to undergo extensive conversion to either hormone when administered orally or transdermally. In contrast the oral administration of the synthetic progestin NETA has been shown to produce small amounts of ethinyl estradiol (approximately 6 mcg per mg of NETA), which is probably of little clinical significance [169].

4. TESTOSTERONE

As summarized in Table 4, a variety of testosterone containing preparations are currently being used in clinical practice or in investigational research protocols for the treatment of sexual problems in women. These include:
- Testosterone products for men that are used off-label at lower doses (IM T-esters, T implants, oral testosterone-undecanoate (TU), transdermal testosterone reservoir patches, and transdermal testosterone gels),
- An investigational transdermal testosterone matrix patch designed for women,
- An investigational testosterone gel for women,
- Subcutaneous testosterone implants,
- Testosterone IM depot formulations,
- Oral methyltestosterone (MT) alone and in combination with esterified estrogens (EE),
- Compounded MT for topical application,
- A transdermal testosterone cream available in Australia,
- A transdermally absorbed metered testosterone spray.

In postmenopausal women these preparations are typically given concomitantly with an estrogen +/- progestin (as appropriate).

Evidence for the effectiveness and safety of all of these preparations in women is limited. Distinctions must also be made between pharmacologic regimens that produce supraphysiologic testosterone levels (as determined by the levels of free or non-SHBG-bound testosterone, not total testosterone) and physiologic regimens that produce free testosterone levels within the normal range for healthy young women. It remains to be established whether improvement in libido with short term therapy will result in a sustained improvement or whether long term therapy is required. If the latter is the case long term safety data are required before long term therapy can be recommended.

In additional to transdermal T preparations, topical preparations containing MT and DHT have also been suggested for use in women, as neither is aromatizable to estrogen.

Oral androgen-estrogen combinations of MT and EE are currently approved for the treatment of vasomotor symptoms in menopausal women who do not have relief from estrogen alone. Although the FDA has recently questioned the evidence for the effectiveness of the androgen component [170], the MT-EE combination is presently the only prescription androgen product for women available in the U.S.A. Subcutaneous testosterone implants are approved for use in women in the United Kingdom.

The safety issues associated with testosterone treatment depend on the dose and hormone levels attained, the duration of treatment, the type of androgenic agent and its route of administration. Long term use of injectable T-esters (in combination with injectable estrogens) at doses of 150 mg every 2-4 weeks has been shown to produce virilization in women (including temporal balding, voice deepening, and clitoral enlargement) [171]. Other symptoms associated with exogenous androgen excess include hirsutism, acne, menstrual disturbances (in premenopausal women) and polycythemia. In the polycystic ovarian syndrome (PCOS), androgen excess is also associated with abnormal carbohydrate metabolism. However insulin resistance may underlie the etiology of this disorder, such that it is inappropriate to extrapolate the metabolic consequences of PCOS to that of simple androgen excess. However, there is evidence that some women with adrenal androgen excess, for example congenital adrenal hyperplasia, have insulin resistance. There is no evidence that parenteral testosterone therapy has adverse cardiovascular effects [118, 172, 173, 174]. High doses of orally administered androgens such as MT and to a lesser extent testosterone undecanoate may be associated with hepatoxicity (pelirosis hepatitis, hepatic neoplasms and cholestatic jaundice) but this has not been a problem for lower dose therapy [175]. At lower doses oral MT reduces the levels of HDL-cholesterol and other hepatic proteins, including SHBG, TBG and CBG.
In contrast, transdermal administration of testosterone at doses comparable to premenopausal hormone production has not been associated with virilization, polycythemia, abnormal carbohydrate metabolism, adverse effects on the liver, or reductions in HDL-cholesterol and other hepatic proteins in the published short term studies [90, 91] and longer term data (up to 12 months) on file from subsequent unpublished studies (Procter and Gamble Study File data 2003) [176]. Although studies of the testosterone patch have not shown a change in insulin levels, this needs to be verified in long term studies, as there may be a duration effect. Two additional larger studies with the testosterone patch are ongoing.

To date the investigational matrix patches have been well tolerated locally and local androgenic effects on the skin have not been reported. In treating premenopausal women the risk of exogenous androgen to a fetus is a separate and genuine concern. However virilization of a female fetus does not appear to be tightly correlated with maternal testosterone levels, with the occurrence limited to women exhibiting masculinization [177, 178].

Nonetheless treatment of any women who have the potential to become pregnant should involve reliable contraception and extremely cautious monitoring. Although not well documented, genital application of topical androgens may cause clitoral enlargement. While a theoretical risk of testosterone therapy is its potential conversion to estradiol, this has not been demonstrated.

5. ANDROGEN PRECURSORS

In the U.S. oral formulations of the androgen precursors DHEA and A’dione are both available without prescription as “dietary supplements”. In pharmacokinetic studies a 50 mg dose of DHEA administered orally to elderly women elevated serum testosterone levels by approximately 1 nmol/L (28 ng/dL) [179], comparable to the increment seen with 150 mcg/day testosterone patches [152].

The corresponding increments in E2 and E1 levels were approximately 25 pmol/L (6.8 pg/mL) and 100 pmol/L (27 pg/mL), respectively. Vaginal and topical administration of DHEA to women has also been shown to increase testosterone levels appreciably [180, 181]. In comparison, 100 mg of A’dione administered orally to women raised testosterone levels by approximately 3.5 nmol/L (100 ng/dL) in one study [182] and by more than 25 nmol/L (720 ng/dL) in another [183]; the latter corresponding to the upper normal range for men. The disparity in results could reflect differences in the purity and formulation of the A’dione products used in the studies.

Safety issues for oral DHEA are similar to MT and include acne, hirsutism, possible hepatotoxicity, and a reduction in HDL-cholesterol and other hepatic proteins (including SHBG) [70, 73].

Transdermal and vaginal administration would be expected to have fewer hepatic effects. In view of the markedly supraphysiologic testosterone levels attained with A’dione the risk for virilization during chronic use in women is considerable [183].

Androgen precursors are also estrogen precursors and thus may raise both testosterone and estradiol/estrone levels. There are insufficient data to support their use for the purpose of managing female sexual dysfunction.

6. MISCELLANEOUS HORMONES

Raloxifene is primarily used for the prevention of bone loss in postmenopausal women. It appears to have neutral effects on sexual function. The safety issues of raloxifene are reviewed elsewhere [184].

Tibolone is in widespread use outside the USA for the symptomatic management of postmenopausal women. It is not known whether the positive effects of tibolone on sexual function level (2-3 evidence) are a consequence of its effects on lowering SHBG and increasing endogenous free testosterone levels [100]. The primary concern with tibolone is a reduction in HDL-cholesterol (and other hepatic proteins). Increased risks for cardiovascular disease and breast cancer with tibolone have not been demonstrated, but these are the subject of ongoing research [185].

A putative female pheromone, applied as a perfume, has been evaluated for its effects on sexual behavior in a placebo-controlled RCT of 36 healthy young sexually active women [186]. After 6 weeks of maximal use, the pheromone group reported significant increases in the frequency of intercourse, sleeping next to a partner, and erotic kissing. It was concluded that the pheromone increased the sexual attractiveness of women to men. No safety issues were reported.
VII. CONCLUSIONS AND RECOMMENDATIONS

Based on a systematic review of the clinical trials evidence of hormonal therapies for treating sexual problems in women, we conclude the following:

1. The decision to institute any hormonal therapy must be individualized and the patient adequately informed about risks and benefits. Grade A

2. Specific therapies:

   a) Vaginal estrogen preparations are effective and generally safe for ameliorating urogenital atrophy and can improve vaginal lubrication and reduce dyspareunia. Grade A

   The risk of endometrial stimulation with vaginal estrogen preparations while uncommon appears to be related to the dose and estrogen type used.

   b) Systemic estrogen/estrogen progestin therapy alleviates vasomotor and other menopausal symptoms, but are only indicated in symptomatic women Grade A

   Oral estrogen increases the risk of VTE in the initial years of use Grade A. Parenteral therapy appears to have less risk for VTE although this requires confirmation Grade B.

   A set regimen of oral CEE+MPA is associated with an increase in breast cancer risk beyond 5 years use Grade A however it remains unclear whether oral estrogen alone, other oral estrogen -progestin regimens (including lower doses, non oral estrogen +/-progestin therapy or tibolone convey this risk Grade B-C.

   Oral CEE+MPA is associated with an increase in cardiovascular events in the first years of use and this risk wanes over 4 years Grade A. Other estrogen regimens and modes of administration and other steroids (tibolone) do not necessarily convey the same risk Grade B.

   c) Progestins appear to have little impact in either direction on the urogenital effects of estrogen, and have no proven benefit on other aspects of sexuality when given alone Grade B

   d) There is increasing use of estrogen +/- progestin therapy after breast cancer. Although there is no evidence that hormone therapy increases either recurrence or mortality from breast cancer Grade B, this therapy should be limited to moderate to severely symptomatic women, as for any therapy requires informed patient consent, and management of the patient should be in partnership with the physicians monitoring the woman's cancer.

   Based on the available information it is not possible to recommend use of, or avoidance of specific estrogen +/- progestin therapies, as availability varies considerably between countries, as does the preference of women and the cost. It could generally be recommended that the minimal dose that alleviates symptoms and avoids side effects should be prescribed, and that careful attention to cardiovascular, thrombotic and breast cancer risk and thorough examination should be undertaken before any treatment is prescribed.

   e) Testosterone, and its derivatives, appear to be useful in the short term for increasing libido, arousal and orgasm in oophorectomized women already treated with systemic estrogen Grade A. There is some, but less data from RCTs for use in naturally menopausal women, but as the latter have similar testosterone profiles to oophorectomized women when treated with estrogen, they can be considered a continuum of the same physiological state. Given the intracrino-logy of androgen action clinical outcome is difficult to predict from blood levels alone even if superior assays are available.

   f) Long term safety data for testosterone therapy is lacking and long-term safety of exogenous testosterone in women requires study before long term use can be recommended.

   g) Safety data for the use of testosterone in non estrogen replaced postmenopausal women is lacking

   h) Further data on the use of testosterone in premenopausal women is required.

   i) Achieving physiological free testosterone levels by transdermal delivery appears to be the best approach for minimizing the adverse effects of androgens Grade D. Contraindications to testosterone therapy include androgenic alopecia, seborrhea or acne, hirsutism, pregnancy, lactation as well as a history of polycystic ovary syndrome Grade C-D. Androgen therapy is relatively contraindicated in women with hyperlipidemia or liver dysfunction Grade C-D. The safety of androgen therapy in wome with or at high risk for CVD, VTE or breast cancer is uncertain.
Based on available data no specific testosterone therapy or dose can yet be recommended.

j) The current evidence for the effectiveness of androgen precursors (DHEA and A-dione) is inconclusive Grade B. DHEA appears to be less likely to cause virilizing side effects than A-dione Grade D.

k) Raloxifene appears to have no adverse or beneficial effects on sexual function in postmenopausal women Grade B.

l) Tibolone may be an alternative to estrogen-androgen therapies for treating sexual problems in postmenopausal women Grade C. Further RPCT of the effects of tibolone on sexual function are required.

3. CLINICAL CARE: EXPERT OPINION BASED ON FINDINGS FROM VARIOUS STUDIES AND UNDERSTANDING OF HORMONE PHYSIOLOGY AND PATHOPHYSIOLOGY:

- Any woman treated with hormonal therapy requires ongoing monitoring which should include regular breast and pelvic examination, mammography and, in the presence of abnormal bleeding, endometrial biopsy.
  - When testosterone is administered, continuation for longer than 6 months should be contingent on a clear improvement in sexual function and satisfaction. The clinician should be mindful of the substantial placebo effects found in all studies to date.
  - Physical examination at follow-up visits should include inspection of skin and hair for seborrhea, acne, hirsutism and androgenic alopecia. These may appear very gradually, even after a year or more of treatment.
  - Laboratory monitoring should include free/bioavailable testosterone levels and SHBG with the goal of keeping these values at least within the normal range for premenopausal women to reduce the likelihood of side effects. Whether in fact a target level for older women should be even lower remains a matter requiring clarification.
  - Although no adverse effects on lipids have been found with short term parenteral therapies, a lipid profile, and, in the presence of a family history of diabetes or significant obesity, fasting insulin and glucose levels should be considered.
  - Additional biochemical investigations such as liver function tests, should be based on clinical judgement.

VIII. RESEARCH AGENDA

- Hormonal influences on female sexual function requires further investigation including validation of efficacy of testosterone therapy in RPCTs and research into mechanisms of effects
- The characteristics of female androgen insufficiency syndrome require further validation
- Improved methods for total and free testosterone measurement in the female range are urgently needed with an emphasis on methodology that can be put to routine use.
- Normal ranges for the various androgens in women by decade and ethnic background need to be established: this is currently being addressed in a large cross-sectional study being conducted in Australia.
- Preparations of testosterone specifically designed for use in women are required
- Long-term safety of exogenous testosterone in women requires study before long term use can be recommended, specifically, the incidence and severity of effects on hair and skin need to be assessed by more sensitive measures, and their relation to testosterone preparation and dose needs to be determined.

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Table 1. Female Androgen Insufficiency Syndrome: proposed pattern of clinical symptoms and signs of in presence of decreased bioavailable testosterone and normal estrogen status (92)

**Clinical symptoms**
- decreased libido, sexual receptivity, and pleasure
- low energy - persistent, unexplained fatigue
- dysphoric mood
- diminished psychological well-being
- blunted motivation

**Clinical signs**
- decreased bone density
- decreased muscle mass and strength
- adipose tissue redistribution
- decreased sexual hair
- changes in cognition or memory

Table 2. Causes of low bioavailable testosterone in women

**Normal aging**
- Symptomatic pre/postmenopausal women with low bioavailable testosterone

**Ovarian insufficiency**
- Uni/bilateral oophorectomy
- Hysterectomy
- Premature ovarian failure
- Post chemo/radiotherapy

**Adrenal insufficiency**
- Adrenal failure/surgery

**Combined**
- Hypopituitism

**Iatrogenic -**
- Treatment with exogenous oral estrogen
- Chronic glucocorticosteroid therapy

Table 3. Basic biochemical investigations for women presenting with low libido

**General:**
- TSH, iron stores

**Specific:**
- "Premenopausal" and amenorrhea:
  - Estradiol + FSH (for diagnosis of hypothalamic amenorrhoea / premature ovarian failure)
  - Prolactin

**Androgen profile:**
- SHBG
- Free testosterone by equilibrium dialysis (gold standard)
  OR
  Total testosterone after organic solvent extraction and calculation of free testosterone*
  OR
  Total testosterone by RIA (with awareness of limitations) and calculation of free testosterone*
- DHEA-S
- Early morning cortisol: if adrenal insufficiency suspected

* calculated by Sodegard equation
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CHAPTER 21

Committee 9 B

Women’s Orgasm

Chairman

*C.M. MESTON (USA)*

Members

E. HULL (USA),
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### I. PSYCHOSOCIAL FACTORS RELATED TO WOMEN’S ORGASM

- **A. INTRODUCTION TO THE WOMEN’S ORGASM**
  - I. DEFINITION OF WOMEN’S ORGASM
  - II. TYPOLOGIES OF WOMEN’S ORGASM
  - III. GENDER DIFFERENCES IN ORGASM
  - IV. WHY DO WOMEN HAVE ORGASM?

- **B. OBJECTIVE SIGNS OF ORGASM**
  - I. PROSPECTIVE CHANGES - LABIA MINORA COLOR CHANGES
  - II. CURRENT INDICATORS OF ORGASM
  - III. RETROSPECTIVE CHANGES

- **C. PHYSIOLOGICAL ASPECTS OF WOMEN’S ORGASM**
  - I. CENTRAL NERVOUS SYSTEM CONTROL OF WOMEN’S ORGASM
  - II. SPINAL CORD PATHWAYS INVOLVED IN WOMEN’S ORGASM

- **D. PSYCHOLOGICAL/CULTURAL ASPECTS OF WOMEN’S ORGASM**
  - I. PSYCHOSOCIAL FACTORS RELATED TO WOMEN’S ORGASM
  - II. ORGASM AS A GOAL OF WOMEN’S SEXUAL ENCOUNTERS
  - III. CULTURAL ASPECTS OF WOMEN’S ORGASM

- **E. FEMALE ORGASMIC DISORDER**
  - I. INTRODUCTION
  - II. ORGASM IN MENOPAUSE
  - III. TREATMENT

- **F. CONCLUSIONS AND RECOMMENDATIONS**

### REFERENCES
More than one author has commented on the extensive literature that exists about the human female orgasm. It has been discussed from clinical, ethological, philosophical, physiological, psychological, sociological and typological perspectives [1]. Symons [2, p. 86] observed that although “the human female orgasm definitely exists [it] inspires interest, debate, polemics, ideology, technical manuals and scientific and popular literature solely because it is so often absent!” It is clear that natural selection has not favored females who could orgasm easily, hence it is not likely an essential feature of the reproductive process. Even its definition is hard to pin down because enigmatically it has both nomothetic (the study or discovery of general laws) and idiographic (individual’s performance) aspects. Because the exact neural activity of the cerebral neuronal discharge is so poorly understood, most definitions use reported or observed physical changes (usually muscular and cardiovascular) with an emphasis that this is the culmination or most intense moment of sexual arousal. Levin [3] tabulated some 13 definitions by authors from a variety of backgrounds, and 20 years later Mah & Binik [4] repeated the exercise with a doubling of the author definitions. They divided them into three groups: those primarily with a biological perspective, those with a psychological one and those with an integrated biopsychological perspective. The authors still had to conclude that a satisfactory universal definition of orgasm could not be accomplished. Considering that the human orgasm is regarded as the ultimate state of ecstatic feeling without recourse to drugs, it is remarkable how few of the definitions incorporated the word “pleasurable”. The more recent reports that women with complete spinal cord injury (SCI) can experience orgasm further complicate an all-encompassing definition of orgasm [5]. A major problem in defining orgasm is the emphasis that is given to the subjective or self-report as opposed to objective physiological signs. Despite all these difficulties, it is useful to devise at least an operational definition for women’s orgasm, thus:

“An orgasm in the human female is 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, often 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”.

Typologies of orgasm intriguingly only exist for women; those for men have not been explored even though some therapists have suggested that they exist [6]. Most of the typologies [7] are from self-reported perceptions of women distinguishing orgasmic sensations induced by clitoral stimulation (warm, ticklish, electrical, sharp) from those obtained by vaginal stimulation (throbbing, deep, soothing, comfortable). A frequently quoted typology is that of Singer [8, pp. 72-73], a philosopher with no experience of laboratory studies, but who analyzed the descriptions of orgasms from a limited literature and characterized three:

1. “vulval”, rhythmic contractions of the vagina activated by either clitoral or coital stimulation,
2. “uterine”, no vaginal contractions but accompanied by apnoea and gasping activated during coitus alone and largely due to penile-cervix contact,

3. “blended”, containing elements of both vulval and uterine orgasms activated by coitus and accompanied by apnoea.

Great play was made about the importance of apnoea and especially cervical stimulation. The latter was not so much about stimulation of the cervix per se, but rather its displacement by the thrusting penis causing the uterus to rub against the peritoneum claimed by Singer & Singer [9] to be a “highly sensitive organ”. Unfortunately, the total evidence for this typology rests on limited scientific observations obtained in remarkably few individuals [10]. Furthermore, the role of the cervix in a woman's sexual response (viz uterine orgasm) is unclear. One reviewer declared that, depending on the studies cited, any position can be supported [11], while a more recent reviewer concluded that evidence for and against a role of the cervix in orgasm is weak and that observational studies cannot answer the question [12]. Another difficulty with this typology is that according to Ingelman-Sundberg [13], the anterior vaginal wall acts like a hammock around the urethra, and during coitus the penis stretches two of its ligaments that insert around the base of the clitoris thus effectively stimulating it during thrusting. If this mechanism operates in all penile-vaginal coital penetrations it would create both “uterine” and “vulval” stimuli or the so-called “blended” stimulus.

Although Masters & Johnson [14] claimed that all orgasms in females were physiologically identical regardless of the source of stimulation, they did not have the instrumentation to obtain detailed muscular recordings for possible differences between clitoral and so-called G-spot (anterior vaginal wall) induced orgasms. There is now some limited physiological laboratory evidence that different patterns of uterine (smooth muscle) and striated pelvic muscular activity may occur with vaginal anterior wall (G-spot?) stimulation as opposed to clitoral stimulation; one such set of recordings is shown in Levin [10]. The case for such a dual typology may well be made more credible by this type of evidence.

Bohlen, Held, Sanderson and Ahlgren [15] characterized the vaginal muscular contractions at orgasm in their 11 nulliparous subjects into three typologies which varied greatly in terms of orgasm duration. The typologies were: those that had regular rhythmic contractions (mean duration of orgasm 13 seconds), those that had regular contractions with later irregular ones (mean orgasm duration 50.6 seconds), and those that had no regular rhythmic contractions during their orgasms (mean duration of orgasm 24.4 seconds). To create a muscular typology of such a range with so few subjects is premature but unfortunately no further studies have been reported. There is a need for simultaneous recordings of the uterine and vaginal motility at orgasm in a large sample of women.

### III. GENDER DIFFERENCES IN ORGASM

Written descriptions/accounts of orgasms by men and women with any obvious gender clues removed could not be differentiated by sex when read by other men and women [16]. This suggests that men and women share common mental experiences during orgasm. Four differences in male and female orgasms, however, have been proposed:

1. unlike the male, the female can have repeated (multiple) orgasms separated by very short intervals [14, p. 131]
2. the female can have an extended orgasm lasting for a long time (so-called “status orgasmus”, [14, p. 131]),
3. there are differences in the recorded pattern of pelvic muscular contractions; specifically, men have a divided rhythmic pattern not seen in women [15], and
4. once the male orgasm is initiated, its further expression is automatic even if sexual stimulation is stopped; if stimulation is stopped in the middle of either clitoral-induced or vaginal-induced female orgasm, the female orgasm is halted [17, p. 121].

### IV. WHY DO WOMEN HAVE ORGASM?

It is generally accepted that female orgasms are not essential for reproduction. Any benefit for various aspects of female biology is, as of yet, unclear. There are a number of explanations from the literature regarding why the human female has orgasms:

1. the reward of intense pleasure for acceptance of the danger of coitus with its possibility of pregnancy (and of possible death in childbirth)
2. to end coitus
3. for resolving pelvic vasocongestion/arousal
4. for resolving vaginal tenting (allows the cervix to enter the seminal pool)
5. orgasmic uterine contractions may create a possible sperm upsuck
6. to create arousal in the male by felt vaginal contractions on the penis and cause ejaculation (capturing the semen)
7. for inducing lassitude to keep the female horizontal and thereby reducing seminal “flowback”
8. because of the difficulty in attaining orgasm (especially coitus), orgasm acts as a “Mr. Right” indicator and aids the creation of a strong “pair bond”
9. to create the loss of body boundaries and separateness allowing a merger or fusion with the chosen coital partner
10. to create psychological resuscitation-like an electric shock redistributing the potentials of the brain
11. to release oxytocin which affects motility of the uterus and fallopian tubes and possibly to induce bonding feelings and emotions
12. to release ADH for the possible contraction of uterine musculature and to inhibit urination and delay sperm losses from "flowback"
13. for manipulation of the uptake or rejection (flowback) of deposited sperm
14. by its activation of muscular contractions and the concomitant increased blood flow, orgasms maintain the functionality of the genital tract [18].

The history of the claimed importance of the female orgasm to reproduction is full of speculative functions with little or no scientific data for their support. Orgasmic coitus was said to activate ovulation and close off the womb to air, thus facilitating conception [19]. When it was later shown that the human female was a spontaneous ovulator at mid-cycle unconnected with coitus, the discourse re-focused on the role of uterine orgasmic contractions in the movement of ejaculated spermatozoa through the cervix into the uterus and then fallopian tubes. Singer [8], in the light of his protagonism for his dual typology of female orgasm (so-called uterine and vulval), published an extensive discussion about fertility and the female orgasm which explored issues of
1. uterine suction,
2. extraterine factors affecting the mechanics of uterine suction (viz vaginal tenting), and
3. the ejaculatory timing in coitus (i.e., ejaculation must occur before orgasm to assist sperm transport, but see discussion below, re Baker & Bellis’s [20] proposals).

It has often been suggested that uterine suction created by the contractions of the uterus at orgasm would facilitate the transport of spermatozoa into the uterus and then to the fallopian tubes. Evidence now shows the fastest transport of spermatozoa into the human uterus is actually in the sexually unstimulated condition [21-22]. One essential feature of sexual arousal of the female genitalia is to create the expansion of the vagina (vaginal tenting) and elevation of the uterocervix from the posterior vaginal wall to reduce the possibility of the rapid entry of ejaculated spermatozoa into the uterus. This gives time for the initiation of the decoagulation of the semen and the capacitation of the spermatozoa to begin, and it reduces the chance of incompetent sperm being too rapidly transported into the fallopian tubes. The female orgasm, by dissipating arousal and initiating the resolution of the tenting, will in fact allow the earlier entry of the spermatozoa into the cervical canal and their subsequent rapid transport to the fallopian tubes, although there is some evidence that the motility of the uterus is reduced after sexual arousal and orgasm [see 21]. Not experiencing orgasm during coitus may thus have a reproductive utility unrealized by previous authors.

Another suggested reproductive function of female orgasms, initiated either from coitus or masturbation, is their use by women to manipulate the ejaculate in the vagina [20, 23]. This highly contentious claim is based on the amount of “flowback” (semen/ fluid) lost from the vagina. According to these authors, the amount of flowback containing spermatozoa varies exquisitely with the precise timing of the female orgasm in relation to the time of deposition of the ejaculate into the vagina. Low sperm retention was said to be associated with female orgasms earlier than one minute before vaginal deposition while maximum retention was claimed with orgasms from greater than 0 to 1 minute after deposition. If orgasm occurred earlier than 1 minute before the ejaculation, deposition sperm retention was the same as when there was no orgasm. According to Baker and Bellis [20] the effect of orgasm on sperm retention lasts only for the period of one minute before semen deposition and up to 45 minutes later. During the period when the seminal fluid was coagulated (15 minutes),
orgasms have a significantly reduced effect on sperm retention. These complicated scenarios for the effects of female orgasm on sperm retention still depend on a contractile uterine “upsuck” sperm mechanism. During orgasm, the cervix “searches and dips” into the seminal pool, and the orgasm-induced movements either facilitate the dipping, and/or the mixing of the cervical mucus with the pool and/or increase the time that the cervix is in the pool.

The coital scenario previously described [18, 21] where “vaginal tenting” removes the cervix from the seminal pool, thus delaying the uptake of sperm in order to allow the initiation of its liquefaction and the capacitation of the sperm, contrasts dramatically with the above hypothesis of Baker and Bellis. The crucial factor is the presence or absence of vaginal tenting. Masters & Johnson [14, pp. 113-114] reported it is only absent in women with retroverted or retroflexed positioned uteri but Singer [8] speculated that it may not occur in either his “uterine” or “blended” orgasm. The only evidence for this speculation is a preliminary report by Perry & Whipple [24] who claimed that “tenting never occurred in response to Grafenberg (G-spot) stimulation”. It led to a “direct descent of the uterus and places the cervix immediately and directly into the seminal pool, where it may facilitate conception”. So-called “uterine” orgasms in Perry & Whipple's preliminary analysis would facilitate conception while “vulval” ones would not. The cervical disposition created by the former orgasm would allow rapid sperm entry before capa-
citation had been initiated and thus facilitate the uter-
ine/tubal entry of sperm incompetent to fertilize. Ultrasound imaging of face-to-face coitus did not show penile cervical contact [25] as would be expected if Singer's “uterine” orgasm were to be induced while the recent imaging by MRI of the relationships between the penis, cervix and the uterus during coi-
tus and masturbation has confirmed the concept of vaginal tenting in a relatively small number of couples [26-28]. It is thus likely that tenting occurs in face-to-face coitus and that its effect on fertilization is positive [18, 21]. It is clear that more MRI scans of human coital activity are needed to confirm this definitively.

A less controversial claim of one of the functions of orgasm to aid in the reproductive process is that if the female allows the expression of orgasm during coitus, its contractions of the vagina can excite the male ejaculate thus allowing the female to capture the sperm of her chosen inseminator. Orgasm increases the secretion of prolactin. If this increased secreted prolactin in plasma is able to enter into the vaginal, cervical or uterine fluids, it might be a factor in influencing the entry of calcium into the sperm as it acts as a physiological ionophore. This action could play a role in the activation of spermatozoa in the female tract [29]. Finally, one area of the putative involvement of orgasm in reproduction that is generally not discussed is its use to induce and encourage the first stage of or to relieve the pain of childbirth [30]. Some women have spontaneous orgasms during the passage of the fetal head through the vaginal canal, probably through the stretching activation of the cluster of erotic sites along the ante-
rior vaginal wall.

B. OBJECTIVE SIGNS OF ORGASM

Orgasm is a subjective experience accompanied by a number of physiological body changes. The degree to which these changes vary between individuals is not known. Males have little difficulty in identifying orgasm because although orgasm and ejaculation are created by distinct mechanisms (see [22] for references), it is rare for the former not to accompany the latter. In women, the achievement of orgasm appears to be less facile than for males and recognizing that it has occurred can be difficult for some. Thus, just asking previously anorgasmic subjects whether or not they experienced an orgasm after a treatment or therapeutic session is somewhat unreliable. An objective indicator(s) that an orgasm has occurred to confirm or inform any subjective report would be of real clinical and therapeutic value.

Objective indicators of orgasm have been sought after for many years often with little regard for their utility in the clinical context. Kinsey, Pomeroy, Martin & Gebhard [31] proposed “the abrupt cessation of the oftentimes strenuous movements and extreme ten-
sions of the previous sexual activity and the peace of the resulting state” as the most obvious evidence that orgasm had occurred and of identifying it in the human female. Masters & Johnson [14] described the onset of orgasm as a “sensation of suspension or stoppage”. Clearly, however, the indicator must involve a body change that is unique to orgasm, which rules out simple measures like peaks of blood pressure, heart and respiratory rates or even a naïve subject's own vocalizations indicating it is impen-
dring or is occurring because such peaks can arise
even if no orgasm occurs. Remarkably, most of the so-called objective indicators of female orgasm rely on the original, nearly 40-year old observations and descriptions of Masters & Johnson [14]. They are of three types: prospective- those indicating an impending orgasm, current- those occurring during the actual orgasm, and retrospective- those indicating that an orgasm has occurred: they are listed in Table 1 and described in detail below. Surprisingly, even such a simple classification system has its problems as it is possible to place some of the indicators in either the current or retrospective category depending on the chosen definition of the initiation of the orgasm. It is unclear whether orgasm should be defined as starting when the woman first mentally perceives it, or whether it starts when the first physical manifestation occurs. Kinsey, Pomeroy, Martin & Gebhard [31] tried to limit the definition of orgasm to the sudden and abrupt reduction of sexual tension. The “spasms” into which individuals are thrown was argued to be the “after effects” of the orgasm while the “vaginal spasms” were regarded simply as “extensions of the spasms that may involve the whole body after orgasms”. Hite [32] also regarded orgasm as a brief intense feeling followed by contractions.

Table 1. Characteristic changes that occur during orgasm (mainly from Masters & Johnson, 1966).

<table>
<thead>
<tr>
<th>Extragenital</th>
<th>Genital/Pelvic</th>
<th>Hormonal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td>- usually peaks to a maximum at initiation of orgasm (&gt;40/min)</td>
<td>- No specific change</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td>- usually peaks at initiation of orgasm and then decreases (systolic +30-80mmHg, diastolic + 20-40mmHg)</td>
<td>- increased secretion of prolactin</td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td>- usually peaks at initiation of orgasm then decreases (110-180 beats/min)</td>
<td>- No specific change</td>
</tr>
<tr>
<td><strong>Sex flush</strong></td>
<td>- superficial maculo-papular (vasocongestive) over epigastrium, anterior chest wall spreading to neck and face has greatest intensity at orgasm</td>
<td>- increased secretion of ADH (Vasopressin) and Oxytocin</td>
</tr>
<tr>
<td><strong>Perspiration</strong></td>
<td>- approximately 33% women in back, thighs and chest</td>
<td>- dilation of os immediately after orgasm lasting 20-30 minutes</td>
</tr>
<tr>
<td><strong>Breasts</strong></td>
<td>- No specific change</td>
<td>- increase in plasma VIP</td>
</tr>
<tr>
<td><strong>Nipples</strong></td>
<td>- No specific change</td>
<td>- No specific change</td>
</tr>
<tr>
<td><strong>Areolae</strong></td>
<td>- rapid detumescence of congestion leading to transient corrugation</td>
<td>- rhythmic contractions (throbbing) of outer third (orgasmic platform) due to pelvic striated muscle</td>
</tr>
<tr>
<td><strong>Myotonia</strong></td>
<td>- contractions in neck, face, arms &amp; legs may become spastic, carpopedal spasm (generalized)</td>
<td>- expulsive contractions of smooth muscle</td>
</tr>
<tr>
<td><strong>Clitoris</strong></td>
<td>- No specific change</td>
<td>- contractions mirroring vaginal contractions</td>
</tr>
<tr>
<td><strong>Labia (majora and minora)</strong></td>
<td>- No specific change</td>
<td>- dilation of os immediately after orgasm lasting 20-30 minutes</td>
</tr>
<tr>
<td><strong>Vagina contractions</strong></td>
<td>- rhythmic contractions (throbbing) of outer third (orgasmic platform) due to pelvic striated muscle</td>
<td>- increased secretion of ADH (Vasopressin) and Oxytocin</td>
</tr>
<tr>
<td><strong>Uterus</strong></td>
<td>- expulsive contractions of smooth muscle</td>
<td>- increased secretion of prolactin</td>
</tr>
<tr>
<td><strong>Rectal sphincter</strong></td>
<td>- contractions mirroring vaginal contractions</td>
<td>- No specific change</td>
</tr>
<tr>
<td><strong>Cervix</strong></td>
<td>- dilation of os immediately after orgasm lasting 20-30 minutes</td>
<td>- No specific change</td>
</tr>
</tbody>
</table>

The paired labia minora on either side of the vaginal introitus are continuous ventrally with the prepuce and frenulum of the clitoris and join the labia majora posteriorly. They are composed of adipose tissue, connective tissue rich in elastic fibers with smooth muscle fibers and numerous wide veins. The amount of cavernous tissue present is variable in individuals, in some it is extensive and in others it is hardly present. The tissue is a spongy mass like that of the clitoris except that it does not have a capsule around it and has fewer nerves in the trabeculae. Merkel tactile discs and genital corpuscle (Dogiel/Krause) are found in the prepuce and ventral part with a rich network of nerves. Free nerve endings (pain ?) lie just beneath the germinative stratum and Pacinian corpuscles (pressure ?), and are frequently noted along the courses of nerves [33-34]. Numerous eccrine sweat glands and a few apocrine glands are present. During sexual arousal, the labia become engorged with blood and increase in size adding on about 1 cm to the length of the vagina. According to Masters &
Johnson [14, pp. 41-42], once their initial engagement has been induced, vivid color changes occur with further sexual arousal. The color changes were said to be “clinically pathognomonic” of impending orgasm as the claim was made that “No premenopausal woman has been observed to reach plateau-phase levels of sexual tension, develop the ‘sex skin' color changes and then not experience an orgasm”. After the orgasm occurs, the color changes rapidly within 10-15 seconds, from deep red to light pink. If the color change takes place and then the sexual stimulus is removed, it rapidly fades well ahead of the slower loss of the engorgement. No other study has confirmed these findings despite this highly specific claim of impending orgasm on the minora labia color change. In fact, there has been little detailed study of the minora labia apart from the suggested mechanism by which they become lubricated [35] and that their increased temperature during sexual arousal has been used as an objective indicator of arousal [36] prior to and after orgasm [37]. The color changes of the labia are presumably due to the changing hemodynamics of the tissue in relation to increased blood flow, tissue congestion and tissue metabolism (oxygen consumption) indicating the balance between oxygenated (red/pink) and deoxygenated or reduced hemoglobin (blue). The blue color of cyanosed mucous membranes occurs when the absolute amount of reduced hemoglobin is greater than 5 gms/100 mls blood. The percentage saturation oxygenation of the blood (s02) is usually measured by light absorbancy but no quantitative studies have been made on the labia minora during sexual arousal. In the basal state the vaginal surface which has a very low p02, practically hypoxic [38], rapidly increases during sexual arousal up to a maximum at orgasm. Repetition of this study [39] confirmed the vaginal findings and showed that the labia minora followed a similar pattern.

II. CURRENT INDICATORS OF ORGASM

1. VAGINAL RHYTHMIC CONTRACTIONS

The resting vagina is a collapsed tube lined with a stratified squamous epithelium, approximating an elongated S-shape in longitudinal section and an H-shape in cross-section, invested with an outer longitudinal and inner circular layer of smooth muscle. It is anchored amid a bed of powerful, voluntary, striated muscles (pelvic diaphragm, consisting of the pubococcygeus and iliococcygeus muscle) of which the pubococcygeus has fibers that insert into the smooth muscle [22, 40]. Balloon recordings of the pressure inside the vagina show that just before orgasm is initiated there is a slow increase, probably due to an increase in tone of these circumvaginal muscles (Figure 1), although the tone of the vaginal smooth muscle per se may also be involved. According to Masters & Johnson [14, p. 118], the contractions recorded in the vagina begin some 2-4 seconds after the subjective appreciation of the start of the orgasm. They occur in many pre- and postmenopausal women and are due to the activation of the circumvaginal striated muscles (especially the pelvic diaphragm, bulbospongiosus, ischiocavernosus) which involuntarily contract in 0.8 second repetitions. This squeezes the outer third of the vagina (designated the “orgasmic platform” by [14]) with some force that gradually becomes weaker as the interval between contractions increases.

Contractions were not thought to be the primary initiator of the orgasmic experience because they began a few seconds after the woman perceived that orgasm had started (but see later section on “What triggers female orgasm ?”). Their number (and power) varies enormously between individuals and is obviously dependent on the duration of the orgasm and the strength of the pelvic musculature. Masters & Johnson reported that the stronger the orgasm the greater the number of contractions and, thus, indirectly the longer the duration of orgasm (as each contraction was approximately 0.8 seconds apart). However, if the number of contractions and their approximate duration are multiplied together this gives an approximate duration of each grade of orgasm; “mild orgasms” had an average of 3 - 5 contractions (2.4 to 4 seconds long), “normal” ones 5 - 8 (4 to 6.4 seconds long) while “intense” orgasms had 8 - 12 contractions (4 to 9.6 seconds long). This claim and quantification was given without any supporting data. Using physiological (pressure) recordings, there has been difficulty proving any link between the contractions and the perceived intensity of the orgasm [41, 42]. The durations of the orgasms recorded were mean 35.6 seconds (SD 24.5, n= 11) [15]; mean = 19.9 seconds (SD= 12, n = 26) [43]; mean = 21.9 seconds (SE 6.4, n=9) [42]). Bohlen, Held & Sanderson [41] reported, in their small group of subjects, a precise correspondence between the start of orgasm and the onset of regular “vaginal” contractions, the end of orgasms and the end of regular contractions was not observed. In some subjects,
the perceived start of orgasm preceded regular contractions by some 2-4 seconds (see report of [14] above), in others it coincided with the contractions, and a further group perceived orgasm followed the onset of contractions. Some of this variation could well depend on how accurate and quickly different subjects can report on their internal states. Contractions of the pelvic muscles at orgasm can also be monitored by recording their electromyogram that was undertaken in the study of Gillan & Brindley [44] using suction or fine wire electrodes in the circumvaginal muscles.

Masters & Johnson [14] confidently proposed that the vaginal contractions would “remove any doubt as to whether a women is pretending or experiencing orgasm”, but other authors have noted that not all women who claim to experience orgasms show these contractions [3, 15, 41, 45-48]. It is especially interesting to note in this context that Bohlen et al. [15] stated that although two of their 11 subjects did not show distinct muscular evidence of orgasm they were not prepared to conclude that “physiological characteristics are more valid than self-reported perceptions for identifying orgasm” … “At least until more data are collected … we will continue our analyses of physiological changes based on subject’s self-defined orgasms”. Unfortunately there has been no further detailed analysis of female orgasms so there is no large body of subjects who have had their vaginal muscular activity recorded during orgasm to assess the usefulness of the original contractile pattern classification. There has been little or no advance in the area since these studies in the 80’s. The vaginal contractions have been used to objectively track the attainment of orgasmic capacity by a single initially anorgasmic subject [49].

It should also be noted that in the above account of the muscular activity at orgasm, there is no mention of the pattern of activity of the involuntary, longitudinal and circular vaginal smooth muscle during sexual arousal and at orgasm. Indeed, it is not even known whether they are relaxed, contracted or have a high tonus. One author has interpreted intravaginal balloon recordings from one subject as evidence for an enhanced tonus of the vaginal smooth muscle at arousal [50]. The slow rise in pressure in the vaginal lumen shown in Figure 1 may be due to such an increase in smooth muscle tone rather than that of the circumvaginal striated muscles; nevertheless, no routine, simultaneous recordings have been published with any instrumentation that has definitively separated their contractile activity in a series of subjects.

2. UTERINE CONTRACTIONS

In their review on the “after-effects of orgasm”, Kinsey et al. [31] commented that studies had shown that the “upper end of the uterus goes into rhythmic contractions of considerable frequency whenever there is sexual arousal”. Masters & Johnson [14] however claimed, “Specific uterine patterns do not develop unless the individual study subject undergoes an orgasmic experience that is recognizable both by trained observers and by the individual
involved” (pp.116-119). Uterine motility was one of the physiological measurements that Masters & Johnson attempted, monitored by “intrauterine and abdominal electrode placement” (p. 116). Unfortunately, apart from this phrase, no details of the technique were ever published so we have no idea of the exact placement of the electrodes, their type or the equipment to which they were attached. The one published orgasmic record from the “intrauterine electrodes” (p. 117, Fig 8-2) is difficult to interpret, as it looks more like an increase in tone of the uterus rather than a series of contractions. Masters & Johnson claimed that the degree of contraction of the uterus paralleled “the study subject's subjective and the observer's objective evaluations of the physical and emotional intensity of the orgasmic experience”. Few other investigators have examined uterine contractile function at orgasm. Fox, Wolff & Baker [51] used an intrauterine pressure transducer in a single subject who had sequentially a non-terminative and then terminative orgasm in the same sexual scenario, and uterine (and vaginal) contractions were recorded during the final orgasm. Caution is warranted in interpreting these conclusions because of the idiosyncratic orgasmic behavior of the female subject and the possible artifacts created by the large size and malfunctioning of the intrauterine transducer [1]. It has been proposed that orgasmic uterine contractions are the terminative signal for sexual arousal in multiorgasmic women [52] but again caution has been expressed [10]. Too few investigations have assessed orgasmic uterine contractions to make such a definitive statement.

3. CONTRACTIONS OF THE ANAL SPHINCTER

While voluntary contractions of the anal sphincter can occur during sexual arousal and are sometimes used by women to facilitate or enhance arousal, involuntary contractions of the anus occur only during orgasm [14, p. 34]. However, few measurements of anal contractions have been published aside from Bohlen and colleagues, who created a special anal pressure-measuring device [53] that could record the tone and contractions of the anal sphincter in both sexes during orgasm [15]. They reported that the anal contractions were synchronized with the vaginal contractions, yet the waveforms differed (vaginal = square wave, anal = sinusoidal), and those of the anus showed greater variability. Despite the obvious utility of recording the same muscular activity in both men and women at orgasm, little or no use has been made of the device since its creation in the 80's [15]. The genital and extra-genital changes that occur at or immediately after orgasm are listed in Table 2.

Table 2. Extragenital and genitai/pelvic changes during female sexual arousal (mainly from Masters and Johnson, 1966);

<table>
<thead>
<tr>
<th>Extragenital</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperventilation</td>
<td>- from a basal of 14 breaths/minute to a max of 40</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>- from a basal of 80 beats/minute to a max of 180</td>
</tr>
<tr>
<td>Hypertension</td>
<td>- Diastolic blood pressure elevated by 20-80 mmHg, Systolic blood pressure elevated by 80 - 100 mmHg</td>
</tr>
<tr>
<td>Sex flush</td>
<td>- superficial maculo-papular (vasocongestive) rash initially over epigastrium and anterior chest wall then on neck, face and forehead</td>
</tr>
<tr>
<td></td>
<td>Breast engorgement (increase in size)</td>
</tr>
<tr>
<td></td>
<td>Areolae engorgement (increase in size)</td>
</tr>
<tr>
<td>Nipple erection</td>
<td>- elongation + 0.5 -1cm, base diameter + 0.25 - 0.5 cm</td>
</tr>
<tr>
<td>Myotonla</td>
<td>- elevated tension in muscles (legs, arms, neck, face (grimacing), abdomen)</td>
</tr>
<tr>
<td>Emission sounds</td>
<td>- sighs, moans, groans, grunts</td>
</tr>
<tr>
<td>Pupil dilation</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genital/Pelvic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Labia majora</td>
<td>- thins out and flattens against perineum</td>
</tr>
<tr>
<td>Labia minora</td>
<td>- expands in diameter, color changes, lubrication</td>
</tr>
<tr>
<td>Clitoris</td>
<td>- tumescence of glans (50% subjects) and shaft, retraction under clitoral hood</td>
</tr>
<tr>
<td>Vagina</td>
<td>- increases in blood flow, surface pO2, lubrication, Na+ and Cl-, length (+2.5 cm), tenting concomitant with utero-cervical elevation (width +3.75 to 4.25 cm)</td>
</tr>
<tr>
<td>Uterus</td>
<td>- elevation into false pelvis (increase in size?)</td>
</tr>
<tr>
<td>Cervix</td>
<td>- no specific response</td>
</tr>
</tbody>
</table>
1. Areolae Congestion and Decongestion

The primary areolae, the usually large pigmented skin area around the nipple of the breasts, contain the follicles of Montgomery (small sebaceous glandular structures), occasional hair follicles, an underlying network of smooth muscle of interlacing bundles some 2 mm thick, blood vessels, elastic tissue, melanoblasts, Pacinian corpuscles, nerve fibers and a nerve (sympathetic ?) plexus [54-56]. The neural basis for areolar sensation was reported by Jones & Turner [57] to be “typically protopathic or thalamic in its character. The appreciation of the stimulus of cotton wool or testing hairs ceases abruptly at the margin of the specialised pigmented areola area”. A later study [58] testing the cutaneous sensitivity of the breasts using Semmes-Weinstein monofilaments to obtain normal values found that the skin of the superior quadrant was the most sensitive, the areola less sensitive and the nipple the least sensitive. All areas were less sensitive the larger the breasts.

Swelling of areolae with arousal is likely due to both vasocongestion and smooth muscle contraction. The volume expansion can become so marked that the swollen/contracted areolae hide a large part of the base of the erect nipples making it look like they lose their erection. At orgasm, the loss of volume is so rapid that the areolae become corrugated before becoming flatter. This provides a “visual identification of the female orgasmic experience” [14]. In the absence of an orgasm, the areolar detumescence is much slower and the corrugation does not develop. There is minimal study of areolar changes as an indicator that orgasm has taken place. Detailed descriptions of pre- and post-orgasmic changes of the areolae have not been fully explored, likely because they are difficult to monitor either quantitatively or qualitatively.

2. Enhanced Post-orgasmic Vaginal Pulse Amplitude (VPA)

Recordings of changes in the blood supply to the human vagina during sexual arousal to orgasm were made using the photoplethysmographic technique of Palti & Bercovici [59] with a superior vaginal photoplethysmograph created by Sintchak & Geer [60]. Geer & Quartararo [61] were the first to publish actual records of the vaginal pulse amplitudes (VPA) of the AC trace of each individual heart beat from their luminal, free-dwelling, vaginal photoplethysmograph before, at, and after orgasm in seven young women. Sexual arousal by masturbation caused an increase in the VPA signal compared to the basal values in all subjects, but immediately after the end of orgasm VPA was actually significantly greater than before orgasm in 5 of the 7 women (71%) and was not significantly less in the other two. The post-orgasmic period of maximum amplitude lasts for approximately 10-30 seconds and then VPA slowly returns to its basal value (Figure 2). This behavior has been observed in VPA signals recorded in other photoplethysmographic studies of orgasm [37, 44, 62-63]. There have been over 50 papers published using photoplethysmographic recording in the vagina but, unfortunately, these studies never took the induced sexual arousal to orgasm and beyond. Because there are so few photoplethysmographic recordings of the actual pre and post-orgasmic VPA traces published (less than a dozen), its utility as an indicator of orgasm in women is unclear. One basic

Figure 2: Recordings of vaginal pulse amplitude (VPA) and vaginal blood volume (BV) obtained by a free dwelling luminal photoplethysmograph for i) basal, non-sexually stimulated trace, ii) BV (10 secs) during clitoral stimulation, iii) VPA during clitoral stimulation to orgasm and after, iv) BV (10 secs) post orgasm, iv) VPA post orgasm. The start and finish of the orgasm as reported by the subject is shown by the two arrows and is self-graded 2-5 on a scale 1= poor to 5 = excellent. The transient, enhanced, immediate post orgasmic VPA signal is clearly seen.

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disadvantage in photoplethysmographic recording during orgasm using luminal free-dwelling instruments is that in many subjects the vaginal motility and orgasmic contractions can create severe movement artifacts in the records and make interpretation of the VPA signals extremely difficult. However, the development and exploitation of a suction photoplethysmograph [3] that is attached to the vaginal wall and thus moves with the wall would overcome such difficulties and allow interpretable recordings to be taken throughout orgasm. Contemporary collection and computerized processing of the VPA data also uses relatively long time periods (1 - 3 minutes) during an experiment. Given the effect is transient and usually only lasts for up to 30 seconds, the response can get lost when calculating overall mean amplitudes. Visual inspection of the data is essential.

3. RAISED PROLACTIN PLASMA LEVELS AFTER ORGASM

Prolactin is a hormone secreted by the lactotrophic cells of the anterior pituitary gland. Its sequence of 199 amino acids was identified in 1969 [64] and was primarily thought to regulate lactation as early as the 1920's. Since its sequencing, prolactin has been shown to be involved in a huge variety of actions involving over 300 functions and is known to be produced or stored in a variety of cells. Its release from the pituitary lactotrophs is unusual in that it is under tonic inhibitory control by the hypothalamus primarily via the neurotransmitter dopamine, although other substances and hormones can inhibit (e.g., Somatostatin, Endothelin, Acetylcholine) or facilitate (e.g., VIP, Oxytocin, TRH) its release [65]. Prolactin acts on the hypothalamic dopamine neurons to create a negative feedback loop to control its own release, similar to the other anterior pituitary hormones. The receptors for prolactin action are distributed in a variety of tissues (e.g., skin, bone, liver, male and female reproductive organs), but those of essential relevance are in the central nervous system (hippocampus, cortex, amygdala, hypothalamus) in areas known to regulate sexual behavior. A central role for prolactin in modulating sexual behavior and function in animals and in humans is now accepted. Studies by Exton and colleagues have reported that prolactin secretion is not activated by sexual arousal per se but is specifically activated and doubled in plasma concentration by orgasm, whether generated by masturbation or coitus. This elevation occurs directly after orgasm and is maintained for approximately 60 minutes. Apart from its claimed indicator function for orgasm, the authors proposed that it also acts as a feedback control of sexual drive probably inducing its inhibition (refractory period), especially noted in the male after ejaculation and orgasm [65]. Females, of course, do not appear to have this refractory period after only one orgasm and can often undergo a whole series before satiation occurs [14]. If prolactin is the orgasmic-linked “off” switch for sexual arousal in men, why does it not act similarly in women? Less well known, prolactin can also be released by tactile stimulation of the nipples in both women and in men especially when they are sexually aroused [66-67]. Thus, increase in prolactin secretion may be a retrospective signal that orgasm has indeed taken place. Its great disadvantage is the intrusiveness of its measure—it needs the pre-insertion of a butterfly cannula into a vein so that repeated venous samples can be withdrawn. Further studies need to be undertaken to see whether prolactin concentrations in other more easily accessible body fluids such as saliva, vaginal or cervical fluid or urine could be used (Table 3).

4. THE FEMALE PROSTATE, FEMALE EJACULATION, AND THE G-SPOT

In all the areas related to female sexuality, perhaps none have been surrounded with more aura than the concept of the G-spot [47] (named after Grafenberg who reportedly first anecdotally described the phenomenon [68]). Unfortunately, the popularization of this concept appears to have clouded our ability to make an accurate determination of its existence. To follow is a critical discussion of the scientific evidence for the female prostate, female ejaculation, and the G-spot.

Anatomic evidence from multiple autopsy studies
has demonstrated the presence of paraurethral glands [69-72]. In addition to the presence of these glands, histochemical evidence of prostatic acid phosphatase has been documented [70-71]. These reports provide strong evidence for the existence of periurethral glands in the female and for the presence of prostatic acid phosphatase. They also lead to the question of female ejaculation, and whether women expel fluid from their urethra concomitant with orgasm from G-spot stimulation, and what the components of this fluid are.

After the popularization of the term G-spot, a number of questionnaire studies reported that a significant number of women have acknowledged that they expelled fluid through their urethra at the time of orgasm [73-75] but these reports were anecdotal and did not provide any evidence of the source of fluid. Additionally, the reports were often preceded by the women hearing or being educated about the topic before they gave report of their own situations. This may have provided a suggestion to women that the correct answer was to say that they did ejaculate. There is essentially no scientific evidence to support the belief that women ejaculate with a fluid distinguishable from urine at the time of orgasm [77]. Laboratory studies [68, 77-79] have not revealed consistent evidence for any anatomical structure or “spot” on the anterior vaginal wall apart from the known paraurethral glands and spongiosal tissue around the urethra which could create sexually pleasurable sensations when stimulated.

5. WHAT TRIGGERS WOMEN’S ORGASM?

Women’s orgasms can be induced by erotic stimulation of a variety of genital and non-genital sites. The clitoris and vagina (especially the anterior wall including Halban’s fascia and urethra) are the most usual sites of stimulation, but stimulation of the periurethral glans [10], breast/ nipple ormons ([14, p. 54; 66]), mental-imagery or fantasy [14, 80] or hypnosis [1] have also been reported to induce orgasm. Orgasms have been noted to occur during sleep in the able-bodied [31, 81-82], hence consciousness is not an absolute requirement. Rare cases of so-called “spontaneous orgasm” have been described in the psychiatric literature where no obvious sexual stimulus can be ascertained [83] and which are different from the not uncommon “hyperesthesia sexualis” (orgasm following an extremely variable group of tactile, visual, auditory stimuli).

Exactly what initiates the orgasm has been a topic of discourse and speculation for many years. Four pseudo-neurophysiological models have been proposed. Sherfey’s [84] model was based on the firing of stretch receptors in the pelvic striated muscles activated by the pelvic engorgement which initiated a spinal reflex. In Kaplan’s model [85] the clitoris was the source for the sensory impulses activating the reflex. Mould’s contribution [86-87] was to combine the Sherfey and Kaplan models and incorporate the gamma biasing of the muscle spindle of the striated musculature, which would then allow the generation of their clonic reflex contractions. Mould’s hypothesized trigger was the dynamic stretch of the intrafusal fibers of the pelvic striated muscles via the alpha-fusimotor systems.

Davidson’s model based on male ejaculation/orgasm [52] was grandly called the “Bipolar hypothesis” but it was in fact a “dual bipolar hypothesis”. In brief, he proposed that when sexual arousal reached a critical level, a hypothetical central “orgasm centre” with upward links to the cortex and downward links to activate the smooth and the striated genito-pelvic musculature was triggered. The neural elements involved in seminal emission and in female uterine contractions fired to contract the smooth muscles and to inhibit arousal, while those involved in the contractions of the striated muscles caused the sensation of orgasm and its altered state of consciousness.

A more detailed exposition of the Davidson male model was attempted by Tuckwell [88] who explained the well-known refractory period for men after ejaculation/orgasm by a central build-up of neuronal extracellular K+. Women do not experience this inhibited arousability after orgasm presumably because they do not have the male emission/ejaculation mechanisms. Alternatively, the strong contractions of the uterus at orgasm are thought to be the comparable terminal event in females [52].

A more recent explanation is that the “switch off” is due to prolactin release. None of the models of orgasm initiation appear satisfactory [89]. While no new definitive mechanism(s) with laboratory-backed data has yet emerged, comparing brain imaging during female sexual arousal without orgasm [90-91] to brain imaging at orgasm offers at least the possibility of seeing whether there are any areas of the brain specifically involved in generating the orgasm.
1. Overview

Studies of animals have provided some insights into the CNS control of sexual climax and are often the only avenue of information about the neural functions that coordinate the complex events leading up to and following orgasm. This section will first review the animal models of sexual climax and the brain areas that control genital reflexes. Because there has been very little research on genital function in female animals, studies in males are briefly described and comparisons with females are made. Then, studies of brain imaging during sexual arousal and orgasm are described and comparisons with the animal literature drawn. Next, information about brain disorders in humans is reviewed to provide insight into the function of relevant brain areas. Finally, brain areas that may mediate the inhibitory effects of antidepressant and antipsychotic medication are discussed, as well as the beneficial effects of drug and hormonal treatments.

2. Animal Models of Orgasm

There are a number of physiological markers that suggest the presence of orgasm in female animals, including increases in blood pressure and heart rate and uterine contractions during copulation in female rats, rabbits, cattle, and monkeys [92]. Much of the information about the physiological control of orgasm has come from studies of the urethrogenital (UG) reflex in male and female rats. This reflex, elicited by mechanical stimulation of the urethra or by electrical stimulation of certain brain areas, is characterized by a series of muscle contractions similar to those of orgasm in humans [93-94]. These contractions result from the coordinated firing of the pelvic, hypogastric, and pudendal motor nerves [93, 95]. In female rats this reflex includes rhythmic contractions of vaginal and uterine musculature as well as anal sphincter contractions [95].

Both the UG reflex in rats and orgasm in humans are thought to be controlled in part by a spinal pattern generator [92, 96-98]. Input to the pattern generator comes primarily from the sensory branch of the pudendal nerve; output is sent via pudendal motor neurons to the ischiocavernosus and bulbocavernosus muscles, the urethral and anal sphincters, and striated muscles of the pelvis [99-101] and via hypogastric and pelvic nerves to sympathetic and parasympathetic preganglionic neurons.

3. Brain Areas Controlling Orgasm

a) Tonic inhibition of the UG reflex

Animal studies have shown that genital reflexes are under tonic inhibitory control by the nucleus paragigantocellularis (nPGi) in the ventrolateral medulla. A majority (78%) of nPGi axons that project to the lumbosacral spinal cord contain serotonin (5-HT) [102], suggesting that the lumbosacral cord may be one site at which antidepressants of the selective serotonin reuptake inhibitor (SSRI) class act to inhibit orgasm in humans.

b) Excitatory influences on the UG reflex

The medial preoptic area (MPOA) is a major integrative site for the control of both male and female sexual behavior (reviewed in [103]). Electrical or chemical stimulation of the MPOA of anesthetized male or female rats elicited the UG reflex in the absence of genital stimulation and without spinal transection or lesions of the nPGi [92, 104]. Electrical stimulation also significantly decreased vaginal vascular resistance (increased engorgement) in anesthetized female rats and increased their blood pressure [105]. Thus, both sympathetic and parasympathetic influences were produced by MPOA stimulation, in accord with the integrated nature of the arousal and orgasmic response. In addition, one group of MPOA neurons fired during proceptive behavior of female rats and a different subset was active during lordosis [106]. Therefore, different neurons within the preoptic area appear to promote the female's sexual motivation and her receptive posture.

The MPOA does not send axons directly to the spinal cord but connects with the nPGi [107], which it presumably inhibits. In addition, the MPOA has reciprocal connections with the paraventricular nucleus (PVN) of the hypothalamus and the periaqueductal gray (PAG) of the midbrain [107-108]. The PVN is an integrative site for the sympathetic nervous system [109]. It also contains neurons that release oxytocin into the general circulation via the posterior pituitary and that project to the lumbosacral spinal cord.
cord of male and female rats [110] and to the hippocampus [111]. Systemic oxytocin stimulates smooth muscle contractions, including those of orgasm.

The PAG consists of columns that subserve autonomic functions, pain perception, and female rat sexual behavior [112]. It receives input from the MPOA and from the area of the spinal cord in which the pudendal and pelvic nerves terminate [113], and it sends output that ultimately reaches the clitoris and penis [114-115]. The PAG also sends presumably inhibitory input to the nPGi [116]. Thus, the MPOA can inhibit the nPGi both directly and via its outputs to the PAG.

4. AN ORGASM-RELATED CIRCUIT

The first study of brain activation in women during sexual arousal used blood-level-dependent functional magnetic resonance imaging (BOLD fMRI) during erotic or neutral visual stimuli [91]. All six women reported moderate sexual arousal in response to the erotic film, but not to the neutral film. Areas of greatest activation included the inferior temporal lobe, anterior cingulate gyrus, insular cortex, corpus callosum, thalamus, caudate nucleus, globus pallidus, and inferior frontal lobe. These areas are similar to those previously reported to be activated in men, although the men showed primarily unilateral activation [117].

A second study using BOLD fMRI compared activation in 20 female and 20 male undergraduates who were presented visual erotic or neutral stimuli [91]. Male students reported greater sexual arousal in response to the erotic film than did female students. Both male and female subjects showed increased bilateral activation in five cortical areas: the medial prefrontal cortex, the orbitofrontal cortex, the anterior cingulate cortex, the insular cortex, and the occipitotemporal cortex. In addition, both sexes showed bilateral activation of the amygdala and the ventral striatum. However, only males showed significant activation of the hypothalamus and the thalamus, although there was a nonsignificant trend toward activation of the hypothalamus in women. The only significant sex difference in activation was in the hypothalamus. However, when perceived sexual arousal was used as a covariate, the sex difference in hypothalamic activation was not significant. Thus, the lower level of perceived arousal in women was associated with lower hypothalamic activity. Several of the cortical and subcortical areas that were activated during sexual arousal have been associated with perception of emotional stimuli. These include the occipitotemporal (or inferior temporal) area, medial prefrontal cortex, and amygdala [118-120]. Activity in both the orbitofrontal cortex and ventral striatum have been associated with the presentation of rewards [121]. The anterior cingulate gyrus has been associated with autonomic and emotional processing [117] and goal-directed behavior [122].

The first studies of brain imaging (positron emission tomography, PET, coupled with MRI) during orgasm in women have recently been reported [123-124]. Two women with spinal cord injury (SCI) above the 10th thoracic segment (T10; i.e., at or above the level at which the hypogastric, pelvic, and pudendal nerves enter the spinal cord), as well as one non-injured woman, showed increased activation at orgasm, compared to pre-orgasm, of the paraventricular nucleus (PVN) of the hypothalamus, the central (or periaqueductal, PAG) gray of the midbrain, the amygdala, the hippocampus, anterior basal ganglia (striatum), cerebellum, and several regions of cortex, including the anterior cingulate, frontal, parietal, temporal, and insular cortices [124]. During self stimulation preceding orgasm, there was significant activation of the nucleus of the solitary tract (NTS, in the medulla), which receives sensory input from the vagus nerve, as well as of somatosensory and motor cortices, thalamus and sensory areas of the spinal cord and medulla. Several of the areas activated in women with SCI have previously been associated with orgasm, epileptogenic orgasmic auras, or sexual arousal in humans, including the prefrontal cortex (especially the right side: see [125]), anterior cingulate cortex [126], amygdala [126-129], and temporal and insular cortex [129].

A comparison of the areas activated by orgasm [124] with those activated during sexual arousal without orgasm [90-91, 124] reveals several differences. The most important appear to be the activation of the PVN, the PAG, the hippocampus, and the cerebellum with orgasm, but not with visual erotic stimuli. The PVN, as noted above, is an important integrative site for the sympathetic nervous system and supplies oxytocin to the peripheral circulation, via the posterior pituitary, and to the lumbarosacral spinal cord. The central gray (PAG) receives and integrates autonomic input from the MPOA and PVN and appears to inhibit the nPGi in rats, thereby disinhibiting sexual reflexes. The roles of the hippocampus and cerebellum in elicitation of orgasm are unknown (Figure 3).

5. CENTRAL EFFECTS OF DRUGS ON WOMEN’S ORGASM

a) Serotonin

Selective Serotonin Reuptake Inhibitors (SSRIs) are
noted for their inhibitory effects on orgasm/ejaculation and libido (reviewed in [130]). However, fewer inhibitory side effects have been reported with some antidepressants than with others. For example, bupropion produced fewer adverse sexual effects in both men and women than did SSRIs [131-134]. (See Table 4 for a summary of effects on orgasm of centrally acting drugs.) Bupropion is a weak inhibitor of serotonin and norepinephrine transport and a more potent inhibitor of dopamine transport, as well as an agonist at 5-HT1A receptors; both the increase in extracellular dopamine and the stimulation of 5-HT1A receptors may explain its lower incidence of sexual side effects [135]. Furthermore, this profile of effects suggests a similarity with the facilitation of ejaculation in male rats and monkeys by 5-HT1A receptors, rather than the inhibition of the lordosis posture in female rats by that receptor subtype. Nefazodone also has a lower incidence of sexual side effects, perhaps because it is a 5-HT2 antagonist, as well as an SSRI [136-138]. Stimulation of 5-HT2 receptors has been reported to inhibit the release of both norepinephrine and dopamine from several brain areas (reviewed in [139]). Because dopamine and norepinephrine facilitate sexual behavior (see below), the increase in serotonergic activity at 5-HT2 receptors could explain some of the inhibitory effects of SSRIs on orgasm [139-140]. Moclobemide (a monoamine oxidase A inhibitor, which would increase levels of both 5-HT and norepinephrine) and aminptine (a dopamine transport inhibitor) are also antidepressants with a lower incidence of anorgasmia than the SSRIs [137, 141-142]. Indeed, there is a single case report of hyperorgasmia in a woman taking moclobemide [143]. Therefore, the coordinated increases in either norepinephrine or dopamine appear to offset the inhibitory effects of serotonin on orgasmic ability.

Noradrenergic activity may also improve the profile of effects of the antidepressant mirtazapine. It inhibits a2 autoreceptors on norepinephrine terminals and also a2 heteroreceptors on 5-HT terminals [144]. As a result both norepinephrine and 5-HT levels are increased. It is also an antagonist at postsynaptic 5-HT2 and 5-HT3 receptors [144]. A prospective, 12-week, open-label trial with 18 women reported a 48% improvement of ease and satisfaction with

Figure 3: Brain areas that affect orgasm. The medial preoptic area (MPOA) has reciprocal excitatory connections with the amygdala (AMYG), which in turn has similar connections with the hippocampus (HIPP). The MPOA also activates the paraventricular nucleus of the hypothalamus (PVN) and the periaqueductal gray (PAG, or central gray), but inhibits the nucleus paragigantocellularis (nPGi) of the medulla, which, in turn, inhibits the orgasm control area in the lumbosacral spinal cord (L-S CORD). The PVN sends excitatory oxytocinergic axons to the hippocampus (HIPP), the L-S CORD, and the posterior pituitary (POST PIT); the oxytocin is released from the POST PIT into the general circulation and stimulates smooth muscle. The PAG activates components of the sympathetic and parasympathetic nervous systems (SNS, PNS) and also inhibits the nPGi. Thus, the MPOA, both directly and via the PAG, can inhibit the nPGi, and thereby disinhibit the L-S CORD. The L-S CORD, the SNS, and oxytocin from the POST PIT trigger striated and smooth muscle contractions and alter patterns of blood flow to the genitals. In addition, the anterior basal ganglia, cerebellum, and several regions of cerebral cortex (anterior cingulate, frontal, parietal, temporal, and insular cortices) are activated by orgasm, although the anatomical pathways interconnecting those areas are not well understood.
orgasm [145]. However, 50% of the participants dropped out of the study, suggesting that other side effects outweighed the improved orgasmic ability in some women.

Among the typical SSRIs there may also be differences in inhibition of orgasm. Paroxetine delayed orgasm more than fluoxetine, fluvoxetine, and sertraline [141] and more than nefazodone, fluoxetine and venlafaxine [138]. One explanation for this greater impairment may be that paroxetine is a more potent inhibitor of the serotonin transporter than are fluoxetine and fluvoxetine, and does not inhibit the dopamine transporter, as does sertraline and, to a lesser degree, fluoxetine and fluvoxetine (reviewed in [130]). As noted below, dopamine antagonists impair several aspects of sexual function, whereas the dopamine precursor, L-Dopa, is facilitative. Both women and men treated with fluoxetine, paroxetine, and sertraline for anxiety disorders reported delays in reaching orgasm and decreased quality of orgasm at one- and two-month follow-ups [146]. However the impairments in the fluoxetine group (but not the other two groups) had abated by the end of the third month. There have been some reports of little or no effect of SSRIs on orgasm. Indeed, one multi-center open-label study of fluoxetine, conducted by the manufacturer, reported an improvement in women's orgasmic ability, associated with improvement in depressive symptoms [147]. Similarly, a small pilot study found no effect of fluoxetine on orgasm [148], and two industry-sponsored trials found either no effects of fluoxetine or clomipramine on orgasm, or that there were too few complaints to analyze statistically (reviewed in [149]).

Several factors may account for the variability of response to a given drug. First, there are individual differences in the numbers and anatomical distributions of the relevant receptor subtypes. Thus, increases in extracellular serotonin, resulting from inhibition of uptake, may activate different ratios of 5-HT2 and 5-HT1A receptors in different people. There may also be individual differences in the inhibition of dopamine and norepinephrine release by 5-HT2 receptors. In addition, improvements in general and interpersonal functioning may tend to offset perceptions of sexual impairment in some women. A major factor in assessing the effects of drugs on orgasm is the method of questioning the subjects. Retrospective reports are less reliable than are daily logs.

b) Dopamine

The effects of dopaminergic drugs in humans parallel those reported in animals [150-155]. Although most reports on the effects of antipsychotic drugs have studied male patients, women patients also reported inhibited orgasm from the antipsychotic drugs trifluoperazine, fluphenazine, and thioridazine [156; reviewed in 157]. Antipsychotic-induced sexual dysfunction may result directly from blockade of dopamine receptors in areas critical for sexual function, such as the MPOA and PVN, or indirectly from increased prolactin levels, extrapyramidal side effects, or sedation. One open-label ongoing-treatment study found no effect of either haloperidol or clozapine on orgasmic ability; however, the authors noted that the women may have under-reported sexual side effects [158].

c) GABA

A retrospective clinical study of women taking antiepileptic drugs (primarily benzodiazepines) reported that women with epilepsy who were taking antiepileptic drugs found orgasm less satisfying than did the healthy, unmedicated controls [159]. Untreated women with epilepsy were not significantly different from either of the other two groups. In the treated women antiepileptic drugs increased both total testosterone and steroid hormone binding globulin, but did not affect levels of free testosterone, compared to the other two groups. Thus, alterations in free testosterone cannot explain the impairment in orgasmic enjoyment.

d) Nitric oxide

Sildenafil (Viagra) selectively inhibits phosphodiesterase V, and thereby prolongs the vasodilatory effect of nitric oxide. Although sildenafil has been used successfully for treatment of erectile dysfunction in men, there have been mixed reports of the effects of sildenafil on women's orgasmic function. Caruso et al. [160] found improved sexual arousal and orgasm with sildenafil. However, a minority of women responded positively in three other studies [161-163].

e) Norepinephrine/epinephrine

A retrospective study of 1080 women, who responded via a self-administered questionnaire, reported no significant increase in difficulty achieving orgasm while taking hydralazine, beta-adrenergic antagonists or methyl dopa [164]. Similar results were obtained in a prospective randomized double-blind study of 345 women over a period of 24 months [165] and in unmedicated healthy controls [166]. Therefore, drugs that inhibit beta-adrenergic receptors appear not to affect women's orgasmic ability.
However, SSRI-induced inhibition of norepinephrine release onto α1 receptors could explain some of the impairment of orgasm, as noted above.

f) Acetylcholine

As in female rats [167], atropine failed to affect blood flow in women during sexual arousal and also did not affect subjective sexual arousal or orgasm [168]. Therefore, acetylcholine appears to play a minor role in the control of vaginal blood flow, sexual arousal, and orgasm.

g) Estrogens

There is little evidence of estrogenic facilitation of orgasmic function in women. In an uncontrolled, open-label trial, 25% of 188 premenopausal women reported an improvement in orgasmic ability [169]. However, a retrospective study of 66 women who were oophorectomized and hysterectomized found no difference in orgasmic ability between the 33 who received conjugated estrogens and the 33 who did not [170]. Similarly, two prospective studies of postmenopausal women found little effect of estrogen plus progestin hormone replacement therapy (HRT) [171-172]. Each compared HRT to tibolone, which can be metabolized into estrogenic, androgenic, and progestogenic compounds. The former, single-blind study of 50 women found no effect of either treatment, based on a questionnaire at baseline and after one year. The latter, open-label study of 48 women found a significant improvement after three months of tibolone treatment, but not HRT.

h) Androgens

A prospective, three-month, open-label study of 44 oophorectomized and hysterectomized women found that a monthly injection of estrogen and testosterone (E+T) increased the rates of orgasm during the first three weeks after the injection [173], compared to these women’s own baseline and estimated to estrogen plus progestin hormone replacement therapy (HRT) [171-172]. Each compared HRT to tibolone, which can be metabolized into estrogenic, androgenic, and progestogenic compounds. The former, single-blind study of 50 women found no effect of either treatment, based on a questionnaire at baseline and after one year. The latter, open-label study of 48 women found a significant improvement after three months of tibolone treatment, but not HRT.

Our ability to assess the impact of spinal lesions on orgasm in humans is unique because spinal cord lesions are relatively easily located and described via detailed neurologic exam. Thus, the subject of female orgasm and the impact of spinal cord injuries (SCIs) on orgasm has received significant attention in recent years and the level and degree of evidence for this phenomenon has increased greatly. Once flippantly considered “phantom” [176], the orgasmic experiences of women with SCIs have recently been described through multiple controlled studies that have consisted of documented the existence of orgasm in women with SCIs. Moreover, these studies have been to describe the attributes of orgasms in women with SCIs. Table 5 describes the notable studies that have assessed the impact of orgasm in humans with SCIs. As the studies are numerous, only details regarding those reports that are most significant will be discussed (Table 5).

In the early 90's interest in the impact of SCIs on female sexuality and sexual response reemerged after previous discussion of “phantom orgasms”. During this time, a number of questionnaire studies
### Table 4. Effects of Centrally Active Drugs on Orgasm

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<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>N</th>
<th>Drugs</th>
<th>Conclusion</th>
<th>Level of evidence</th>
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</thead>
<tbody>
<tr>
<td>Shen &amp; Hsu (1995)</td>
<td>Retrospective reports</td>
<td>110 women</td>
<td>Fluoxetine, paroxetine, sertraline, bupropion</td>
<td>Few adverse effects with bupropion; similar inhibition of orgasm with the other 3</td>
<td>Clinic records</td>
</tr>
<tr>
<td>Lauerma (1995)</td>
<td>Retrospective reports</td>
<td>1 woman</td>
<td>Moclobemide</td>
<td>Hyperorgasmia with this MAO-A inhibitor (increased 5-HT and NE)</td>
<td>Single case, patient report</td>
</tr>
<tr>
<td>Feiger et al. (1996)</td>
<td>Prospective, randomized; 6 wks</td>
<td>143 men &amp; women</td>
<td>Sertraline, nefazodone</td>
<td>Sertraline impaired orgasm in both men &amp; women equally; nefazodone had no negative effects</td>
<td>Sexual function questionnaire</td>
</tr>
<tr>
<td>Montejo-Gonzalez et al. (1997)</td>
<td>Prospective, multicenter, open label; 17 mo</td>
<td>192 women, 152 men</td>
<td>Paroxetine, fluoxetine, fluoxetine, sertraline, moclobemide, amineptine</td>
<td>Paroxetine delayed orgasm more than fluoxetine, fluoxetine &amp; sertraline; few adverse effects with moclobemide or amineptine; women more severely affected; men more frequently affected</td>
<td>Descriptive, physician questioning</td>
</tr>
<tr>
<td>Modell et al. (1997)</td>
<td>Retrospective; open-label; patient population</td>
<td>57 women, 49 men</td>
<td>Bupropion, fluoxetine, paroxetine, sertraline</td>
<td>Greater duration and intensity of orgasm with bupropion; n.s. trend toward increased time to orgasm; fluoxetine and paroxetine decreased orgasm intensity, increased time to orgasm, and produced a n.s. trend to decreased duration of orgasm; sertraline decreased duration of orgasm, increased time to orgasm, and produced a trend to decreased intensity of orgasm</td>
<td>Descriptive; questionnaires mailed to patients in practices taking antidepressants; variable return rate</td>
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<tr>
<td>Authors</td>
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<td>Conclusion</td>
<td>Level of evidence</td>
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<tr>
<td>Piazza et al. (1997)</td>
<td>Prospective; open-label; 6 wks; no placebo</td>
<td>14 women, 11 men</td>
<td>Sertraline, paroxetine</td>
<td>No change in orgasm in women; other aspects of sexual function improved; impaired orgasm in men</td>
<td>5-item self-report scale; administered before and after 6 wk tx</td>
</tr>
<tr>
<td>Kavoussi et al. (1997)</td>
<td>Prospective randomized, double-blind, parallel group; 16 wks</td>
<td>119 women, 129 men</td>
<td>Bupropion, sertraline</td>
<td>Orgasm dysfunction more common with sertraline compared to bupropion</td>
<td>Investigator-conducted interview at each office visit</td>
</tr>
<tr>
<td>Labbate et al. (1998)</td>
<td>Prospective; 3-mo</td>
<td>19 women, 12 men w/ anxiety disorder; 18 women, 12 men w/ depression</td>
<td>Fluoxetine, sertraline, paroxetine</td>
<td>Decreased quality and longer delay in orgasm compared to baseline; anorgasmia more common in women than in men; similar effects of all 3 drugs on both patient groups at all 3 times</td>
<td>Descriptive, monthly rating on visual analog scales</td>
</tr>
<tr>
<td>Boyarsky et al. (1999)</td>
<td>Prospective, open-label, flexible dosing; 12 wks</td>
<td>18 women, 7 men</td>
<td>Mirtazapine</td>
<td>Ease/satisfaction with orgasm improved 48% with mirtazapine compared to baseline; 50% dropout rate</td>
<td>Questionnaire administered bimonthly</td>
</tr>
<tr>
<td>Kennedy et al. (2000)</td>
<td>Prospective, 8 or 14 wks</td>
<td>65 women, 42 men</td>
<td>Paroxetine, sertraline, moclobemide, venlafaxine</td>
<td>No difference between women and men in orgasm impairment; paroxetine and sertraline produced more dysfunction than moclobemide and vinlafaxine in women</td>
<td>Sexual Functioning questionnaire before and after antidepressant</td>
</tr>
<tr>
<td>Coleman et al. (2001)</td>
<td>Multicenter, randomized double-blind; 8 wks</td>
<td>288 women, 168 men</td>
<td>Bupropion SR, fluoxetine</td>
<td>~ 30% of fluoxetine-treated patients had orgasm dysfunction; bupropion SR- and placebo-treated patients had ~ 10%</td>
<td>Weekly questioning by physician</td>
</tr>
<tr>
<td>Authors</td>
<td>Design</td>
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<td>Drugs</td>
<td>Conclusion</td>
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<td>Montejo et al. (2001)</td>
<td>Multicenter, prospective open-label; total period 5 yrs (variable time per subject, from &lt;3 mo to &gt;1 yr)</td>
<td>610 women, 412 men; normal sexual function before tx</td>
<td>Fluoxetine, sertraline, fluoxetine, paroxetine, citalopram, venlafaxine, mirtazapine, nefazodone, amineptine, moclobemide</td>
<td>All SSRIs and venlafaxine produced more delayed orgasm or anorgasmia than mirtazapine, nefazodone, amineptine, or moclobemide; women had fewer but more severe dysfunctions than men</td>
<td>Psychotropic-Related Sexual Questionnaire at each office visit before and during tx</td>
</tr>
<tr>
<td>Michelson et al. (2001)</td>
<td>Multicenter, prospective; Acute phase: open-label 13 wks; Continuation phase: randomized, double-blind, 25 additional wks</td>
<td>342 women, 159 men</td>
<td>Fluoxetine</td>
<td>Acute phase: 44% of women reported improvement in orgasmic ability, 38% reported no change, 18% reported orgasmic impairment; both improvement and impairment in orgasmic ability associated with improvement and impairment, respectively, in depressive symptoms</td>
<td>Self-rated, 4-question before, at end of acute phase, and weekly in continuation phase; study conducted by Eli Lilly, manufacturer of fluoxetine</td>
</tr>
<tr>
<td>Bobes et al. (2002)</td>
<td>Prospective open-label; 6 mo tx</td>
<td>58 women, 43 men</td>
<td>Nefazodone, fluoxetine, paroxetine, venlafaxine</td>
<td>Orgasm improvement with nefazodone and orgasm impairment with paroxetine in women</td>
<td>Semistructured interview before and after treatment; funded by Bristol Myers Squibb, manufacturer of nefazodone</td>
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**II. Antipsychotics**

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<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>N</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>Ghadarian et al. (1982)</td>
<td>Retrospective open-label, ongoing tx</td>
<td>29 women, 26 men; random sample of outpatients</td>
<td>Fluphenazine</td>
<td>33% reported decreased quality of orgasm; 22% reported decreased ability to achieve orgasm; impairment in men, but not women, associated with elevated prolactin</td>
<td>Authors’ questionnaire</td>
</tr>
</tbody>
</table>
Table 4: Effects of Centrally Active Drugs on Orgasm (Ctd)

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<thead>
<tr>
<th>Authors</th>
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<tbody>
<tr>
<td>Hummer et al. (1999) [158]</td>
<td>Prospective open-label, ongoing tx; assessed weekly during 10-6 wks &amp; monthly thereafter</td>
<td>37 women, 116 men</td>
<td>Haloperidol, clozapine</td>
<td>0/12 women taking haloperidol reported orgasmic dysfunction, compared to 8/41 men (19.5%); 1/25 women (4%) taking clozapine reported orgasmic dysfunction, compared to 17/25 men (22.7%); fewer women reported dysfunction; no difference b/w drugs; authors note women may have under-reported effects</td>
<td>Observer-rated side effect rating scale</td>
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III. Phosphodiesterase inhibitors

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<th>Authors</th>
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<th>N</th>
<th>Drugs</th>
<th>Conclusion</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>Kaplan et al. (1999) [161]</td>
<td>Open-label nonrandomized; 12-wk</td>
<td>30 postmenopausal women</td>
<td>Sildenafil</td>
<td>Orgasm satisfaction improved 7.4%</td>
<td>Self-administered questionnaire</td>
</tr>
<tr>
<td>Caruso et al. (2001) [160]</td>
<td>Prospective double-blind, crossover; 12 wks</td>
<td>51 premenopausal women; arousal disorder</td>
<td>Sildenafil</td>
<td>25 and 50 mg sildenafil increased orgasm frequency, compared to placebo and baseline; placebo increased orgasm relative to baseline</td>
<td>Self-administered questionnaire, once/wk</td>
</tr>
<tr>
<td>Berman et al. (2001) [163]</td>
<td>Prospective open-label; 6 wks</td>
<td>7 women w/ history of sexual abuse; 24 w/o</td>
<td>Sildenafil</td>
<td>2/7 w/ history of childhood sexual abuse (CSA) reported improved orgasmic ability; 19/24 w/o CSA improved</td>
<td>5-item questionnaire at end</td>
</tr>
<tr>
<td>Berman et al. (2001) [162]</td>
<td>Prospective open-label; 6 wks</td>
<td>48 women; Sexual Arousal Disorder (SAD)</td>
<td>Sildenafil</td>
<td>67% improved orgasmic ability</td>
<td>Questionnaire at baseline &amp; end of study; psychological measures</td>
</tr>
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</table>
### Table 4. Effects of Centrally Active Drugs on Orgasm (Ctd)

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<tr>
<td>IV. Antihypersensives</td>
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<tr>
<td>Bulmire et al. (1989)</td>
<td>Retrospective questionnaire</td>
<td>1080 women, 1285 men</td>
<td>Hydralazine, beta-adrenergic antagonists, methyldopa</td>
<td>Women showed no increased difficulty achieving orgasm with any of the drugs</td>
<td>Self-administered questionnaire</td>
</tr>
<tr>
<td>Grinnan et al. (1997)</td>
<td>Prospective randomized, controlled, double-blind; 48 mo</td>
<td>345 women, 557 men</td>
<td>Acebutolol, amiodopine maleate, chlorothalidone, doxazosin maleate,</td>
<td>Women showed no increased difficulty achieving orgasm with any of the drugs</td>
<td>Questioning by physician at baseline and annually during tx</td>
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<td>enalapril maleate</td>
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<tr>
<td>Duncan et al. (2000)</td>
<td>Ambulatory medical record-based choice of subjects; case-control</td>
<td>104 mildly hypertensive women, 107 unmedicated healthy controls</td>
<td>ACE inhibitors, adrenergic blockers, Ca^2+ channel blockers, diuretics, combination drugs</td>
<td>No difference b/w medicated and unmedicated hypertensives; impaired orgasm in hypertensives compared to healthy women; less orgasm frequency in smokers compared to nonsmokers (not associated with age or hypertension)</td>
<td>Self-administered questionnaire and phone interview</td>
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<td>V. Anticonvulsants</td>
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<tr>
<td>Duncan et al. (1997)</td>
<td>Retrospective</td>
<td>243 women</td>
<td>Anti-epilepsy Drugs (AED)</td>
<td>159 epileptic women taking AEDs: less orgasm satisfaction compared to 48 healthy controls; no difference in no tx epileptic women</td>
<td>Validated questionnaire &amp; testosterone assay</td>
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<td>VI. Anticholinergics</td>
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<tr>
<td>Wagner &amp; Levin (1980)</td>
<td>Controlled laboratory study</td>
<td>11 women</td>
<td>Atropine, Methylatropine</td>
<td>Neither tx affected orgasm or vaginal blood flow; muscarinic cholinergic receptors do not appear important for orgasm or blood flow</td>
<td>Controlled laboratory study</td>
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Table 4. Effects of Centrally Active Drugs on Orgasm (Ctd)

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<tr>
<td>VI. Estrogens</td>
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<tr>
<td>Nathorst-Boos et al. (1992) [170]</td>
<td>Retrospective clinical study</td>
<td>66 oophorectomized, 35 hysterectomized with ovaries</td>
<td>Conjugated estrogens (ERT)</td>
<td>No improvement in orgasm ability in 33 oophorectomized women, compared to 33 oophorectomized no-ERT women</td>
<td>Questionnaire and structured interview</td>
</tr>
<tr>
<td>Eicher &amp; Mack (1996) [169]</td>
<td>Prospective open-label; 4 mo</td>
<td>188 women with sexual dysfunction</td>
<td>Estradiol transdermal patch</td>
<td>25% improved orgasmic ability</td>
<td>Uncontrolled clinical study</td>
</tr>
<tr>
<td>Kokcu et al. (2000) [171]</td>
<td>Prospective single-blind; 1 yr</td>
<td>50 postmenopausal women</td>
<td>Conjugated estrogens + medroxyprogesterone acetate (HRT), tibolone</td>
<td>No improvement in orgasm frequency (tibolone has estrogenic, androgenic &amp; progestogenic metabolites)</td>
<td>Questionnaire at baseline and after 1 yr</td>
</tr>
<tr>
<td>Wu et al. (2001) [172]</td>
<td>Prospective open-label; 3 mo</td>
<td>48 postmenopausal women</td>
<td>HRT, tibolone</td>
<td>Tibolone improved orgasmic ability compared to HRT</td>
<td>Questionnaire at end of 3 mo</td>
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<tr>
<td>VIII. Androgens</td>
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<tr>
<td>Sherwin &amp; Gelfand (1987) [173]</td>
<td>Prospective open-label; 1 mo (no hormone injection 8 wks pre-baseline)</td>
<td>44 oophorectomized &amp; hysterectomized women</td>
<td>E (8.5mg) + T (150mg), E alone (10 mg), no tx</td>
<td>Orgasm and coitus rates higher in E+T group during 1st 3 wks after monthly injection, compared to E or no tx controls and compared to baseline</td>
<td>Daily recording &amp; hormone assays at baseline and days 2, 4, 8, 15, 21, &amp; 28 of tx</td>
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<tr>
<td>Shifren et al. (2000) [174]</td>
<td>Prospective double-blind, counterbalanced; 9 mo</td>
<td>75 oophorectomized + hysterectomized women</td>
<td>Conjugated E plus either T (150 or 300 g/d transdermal) or placebo</td>
<td>300 g/d of T improved orgasm pleasure and frequency of sexual activity</td>
<td>Questionnaire &amp; sexual function and diary completed by phone</td>
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Table 4. Effects of Centrally Active Drugs on Orgasm (Cont)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Munarriz et al.</td>
<td>Retrospective</td>
<td>11 women</td>
<td>DHEA (50mg/d)</td>
<td>Greater orgasm frequency after DHEA tx; both DHEA and T increased to upper range of normal female levels</td>
<td>Questionnaires &amp; blood samples for hormone levels</td>
</tr>
<tr>
<td>Author</td>
<td>Design</td>
<td>N</td>
<td>Conclusion</td>
<td>Level of Evidence</td>
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<tr>
<td>Money (1960) [176]</td>
<td>Interview of hospitalized patients, no neurologic data</td>
<td>7 women with SCI, no controls</td>
<td>Coined the term “phantom orgasm” because patients reported orgasms in their sleep</td>
<td>Case Report</td>
<td></td>
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<tr>
<td>Sjostrom (1990) [177]</td>
<td>Structured questionnaire administered via interview, neurologic examination</td>
<td>13 women with SCI, no controls</td>
<td>33% unaltered orgasm, 25% orgasm decreased, 42% absent, 50% reported interest was unchanged, 33% interest decreased and 17% reported no interest</td>
<td>Uncontrolled questionnaire</td>
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</tr>
<tr>
<td>Kettl (1991) [178]</td>
<td>Mailed questionnaire, subjects reported neurologic data</td>
<td>74 mailings to women with SCI, 27 responses</td>
<td>52% orgasmic, 7 reported different orgasm, 3 exactly the same, 2 similar, 25% complete paraplegics and 25% complete quadriplegics orgasmic; women with complete quadriplegia related frequently of sexual activity as much less than others</td>
<td>Pre/post questionnaire</td>
<td></td>
</tr>
<tr>
<td>Charlifue et al. (1992) [179]</td>
<td>Telephone survey with neurologic data</td>
<td>293 subjects identified, 231 SCI women, No controls</td>
<td>“Approximately half of the women reported they had experienced orgasm since their injuries; stimulus generally genital or genital combined with breast”</td>
<td>Uncontrolled questionnaire</td>
<td></td>
</tr>
<tr>
<td>Sipski &amp; Alexander (1993) [180]</td>
<td>In person 80 item questionnaire, neurologic data provided</td>
<td>25 women with pre/post results; pre/post controls</td>
<td>44% reported ability to have orgasm; ability was not related to the degree of injury; frequency and satisfaction with sexual activity significantly decreased</td>
<td>Pre/post questionnaire</td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Studies of Orgasm in Women with Spinal Cord Injuries (Ctd)

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>N</th>
<th>Conclusion</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrison (1995)</td>
<td>Mailed questionnaire, no neurological data</td>
<td>Sent to 226 women, 85 answered</td>
<td>Pre injury 46% were orgasmic, post injury 36% were orgasmic, 7% were not orgasmic pre injury compared to 23% post, 33% reported this question was NA pre injury and 12% post, 14% did not pre injury and 28% did not post, frequency 55.6% report greater than once per week pre injury compared to 38% post</td>
<td>Pre/post questionnaire</td>
</tr>
<tr>
<td>Sipski et al.</td>
<td>Laboratory based analysis along with detailed American Spinal Injury Association (ASIA) exam, EMG, and SSEP, SCI questionnaire and DSFI; subjects self-stimulated (max 75 min) in any way they desired to orgasm; HR, BP, RR, rectal contractions, quality of and time to orgasm monitored</td>
<td>25 SCI subjects at 16 and above, 10 age-matched able-bodied controls</td>
<td>52% of SCI subjects achieved orgasm; degree and type of SCI did not affect ability to achieve orgasm; orgasmic subjects higher on the sexual information and sex drive subset of the DSFI</td>
<td>Controlled, laboratory study with physiologic testing</td>
</tr>
<tr>
<td>Kreuter (1996)</td>
<td>80-item questionnaire; subjects contacted by phone then completed a mail in questionnaire, neurologic data was included</td>
<td>264 subjects, 167 SCI and 97 age- and sex-matched randomly selected controls; 59% had partner</td>
<td>67% of SCI seldom or never experienced orgasm compared to 6% of controls</td>
<td>Controlled questionnaire study</td>
</tr>
<tr>
<td>Author</td>
<td>Design</td>
<td>N</td>
<td>Conclusion</td>
<td>Level of Evidence</td>
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<tr>
<td>Whipple et al.</td>
<td>Laboratory based study along with American Spinal Injury Association (ASIA) exam; subjects performed vaginal, cervical and hypersensitive area stimulation using fixed methodology; BP, HR, anxiety, sexual arousal, endogenous pain, and spasticity recorded</td>
<td>16 complete SCI at T6 and below, 5 able-bodied controls</td>
<td>Three SCI subjects and 1 able-bodied subject reported orgasms during the study</td>
<td>Controlled, laboratory-based study</td>
</tr>
<tr>
<td>(1996) [186]</td>
<td></td>
<td></td>
<td>------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Jackson (1999)</td>
<td>Pre-post injury questionnaire with neurologic data</td>
<td>478 subjects; multicenter study; 315 sexually active</td>
<td>54% reported orgasms, of those who were orgasmic 32% of injuries were cervical, 41% thoracic and 52% lumbar sacral; 32% had complete injuries and 41% had incomplete injuries</td>
<td>Pre-post questionnaire, multi-center study</td>
</tr>
<tr>
<td>[183]</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Sipski et al.</td>
<td>Laboratory-based study coupled with detailed neurologic assessment, SCI questionnaire, DSFI; HR, BP and RR monitored</td>
<td>69 SCI, 21 able-bodied controls; all levels of SCI represented</td>
<td>44% of SCI subjects were orgasmic in the laboratory vs. 100% of controls; subjects with complete lower motor neuron injuries affecting the sacral spinal segments were significantly less likely to achieve orgasm than all other SCI subjects</td>
<td>Controlled, laboratory-based study with physiologic testing</td>
</tr>
<tr>
<td>(2001) [189]</td>
<td></td>
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were published with larger sample sizes [177-182] and accompanying neurologic data was often included [177-180, 182]. Although some studies still suffered from a lack of controls [177, 179], others included pre-post injury data as a form of control [178, 180-181]. These studies documented that women with SCIs did experience orgasms and that, in general, approximately 50% of the women noted the ability to attain orgasm was present post-injury. Similar findings were also noted in the largest study of females with SCI to date. In a multicenter study, Jackson [183] reported on 478 subjects. Of these subjects, 315 were sexually active since their injuries and of this subgroup 54% reported achieving orgasm post-injury.

The next advance in the study of orgasm in women with SCIs has been the introduction of the laboratory-based assessment of women's orgasmic capacities. Sipski et al. [184] studied 25 women with SCIs at and above the level of T6 using standardized criteria [185] and compared them with 10 age-matched, able-bodied control subjects. Subjects were given 75 minutes to perform self-stimulation to orgasm in any way they chose. All able-bodied subjects achieved orgasm as compared to only 52% of SCI subjects. Degree and type of SCI were not found related to the SCI subject's ability to achieve orgasm. Orgasmic SCI subjects scored higher on the sexual information and sexual drive components of the Derogatis Sexual Functioning Inventory (DSFI).

Sixteen women with SCIs at and below the level of T6 were studied along with 5 able-bodied control subjects [186]. Subjects used a modified tampon to stimulate their cervix and vagina at monitored and specified levels of pressure. Three subjects with complete SCIs and one able-bodied subject had orgasms under these conditions; one for the first time. Based upon these data and other animal reports [187-188] the authors hypothesized that the vagus nerve conveys a sensory pathway from the cervix to the brain that is responsible for the preservation of the ability to achieve orgasm in women with SCIs.

More recently, Sipski et al. [189] expanded their study of orgasm to include women with all levels of injuries. Identical methodology was used to a previous study [185], thus data were combined. A total of 66 women with SCIs and 21 able-bodied controls were examined. Women with complete lower motor neuron injuries affecting their S2-S5 reflex arc were significantly less likely than other subjects to achieve orgasm. Overall, 55% of all SCI subjects reported orgasmic ability post-SCI whereas 44% were orgasmic in the laboratory. Subjects with SCIs took significantly longer (26.37 minutes) than able-bodied subjects (16.33 minutes) to achieve orgasm. Blood pressure, heart rate, and respiratory rate responses were similar between able-bodied and SCI subjects throughout the study. Moreover, subjective descriptions of sensations during orgasm were indistinguishable between able-bodied and SCI subjects. These authors reported the importance of an intact sacral reflex arc in the ability to achieve orgasm. Moreover, the presence of the urethrogenital reflex in spinalized rats [95, 104] that mimics orgasm in humans provides an animal model that is consistent with this hypothesis.

Overall, there is a strong level of evidence for the occurrence of orgasm in women with SCIs. There is also substantial evidence of the impact of specific injuries on orgasmic potential. Future human and animal studies are warranted to confirm the specific effects of spinal lesions on the ability to achieve orgasm. Women with spinal disorders other than SCIs would also be appropriate to study.

### III. PERIPHERAL NERVOUS SYSTEM INVOLVEMENT IN WOMEN’S ORGASM

In brief, the nervous supply of the genitalia is by the sympathetic and parasympathetic branches of the autonomic nervous system pelvic nerves, hypogastric nerve, paravertebral sympathetic chains and by somatic nerves (pudendal nerve from the pelvic splanchnic branches and sacral plexus). The nerves are either efferents that convey nervous impulses from the brain and spinal cord to control motor, secretory and vascular functions, or afferents that mediate sensation, usually by specialized nerve endings. The autonomic nerves regulate blood flow and the involuntary smooth muscle while the somatic nerves control the voluntary or striated muscles. Sensory nervous traffic can be mediated by both the somatic and autonomic systems. The nerves release a number of neurotransmitters, classically nor-adrenaline at the sympathetic nerve endings and acetylcholine at the parasympathetic and somatic. However, the former two systems become mixed in the pelvic plexus and with the recognition of NANC (non-adrenergic, non-cholinergic) nerves, many different transmitters and neuropeptides exist and are co-localized. Much of this knowledge comes from animal studies, usually rodent (rabbit/rat) studies; genital
data from women is sparse. While the studies using immunohistochemical techniques to identify and localize the various neurotransmitters give some insight as to what structures are innervated and by what chemicals, they unfortunately do not give any information of the exact functions of the nerves/neurotransmitters and therefore some degree of informed speculation has to be applied. Their proposed actions, together with those of secreted hormones, bring about the peripheral changes observed in sexual arousal and at orgasm.

1. VAGINA

The anterior wall, the area with the highest erotic sensitivity, has a denser innervation than the posterior wall and the distal area has more nerve fibers than the proximal [190]. According to Krantz [34] aggregated ganglion cells and nerve fibers were present in the adventitia surrounding the vagina. The fibers, filiform in shape, penetrated and supplied the muscularis and larger blood vessels. Hoyle, Stones, Robson, Whitey & Burnstock [191] showed that nerves were also closely applied to the papillary capillaries and were possibly “sensorimotor” nerves (sensory nerves stimulated by antidromic impulses giving them an efferent function).

The changes induced by sexual arousal for the vagina are summarized diagrammatically in Figure 3. Briefly, the unaroused human vagina has a low (acid) surface pH, minimal surface fluid, low blood flow and low surface pO2. A good sympathetic tone is probably maintaining this low flow by its constricting effect on the blood supply. Oral administration of the alpha-adrenoceptor blocker phentolamine to premenopausal women increased their vaginal blood flow indicative of a basal constrictive adrenergic tone, but whether the drug acted centrally or peripherally or both is unclear [192].

Effective sexual arousal causes a rapid increase in the blood flow activated by the release of VIP (Vasoactive Intestinal Peptide) from NANC-nerve endings, while NPY (Neuropeptide Y) probably constricts the venous drainage creating engorgement. The increased hydrostatic pressure in the capillaries forces a protein poor, plasma-like fluid into the tissues spaces (= tissue fluid) which then percolates through the Na+-absorbing epithelium onto the surface of the vagina as the increased surface fluid lubrication [35]. This neurogenic transudate (pH~7.4) can partially neutralize the acidity of the basal surface vaginal fluid (pH~4-6) and thus raise the vaginal pH [193]. The enhanced blood flow increases the vaginal surface pO2 facilitating the use of aerobic rather than anaerobic mechanisms to generate energy by any sperm when ejaculated into the vagina (see [1, 35, 194] for references). Laan et al. [195] provided evidence for a facilitatory effect of sildenafil (an inhibitor of phosphodiesterase 5, PDE5 influences male genital blood flow by controlled the level of cyclic GMP and nitric oxide [NO]) on vaginal photoplethysmograph measures of sexual arousal. Meston & Worcel [196] demonstrated a beneficial influence of the nitric oxide precursor L-arginine in combination with the alpha2 blocker yohimbine on genital engorgement in postmenopausal women. These findings lend support for a role of NO in the enhancement of vaginal blood flow, although very little NOS has been found in the vagina using immunohistochemistry [191].

Meston and colleagues provided evidence for a facilitatory role of peripheral adrenergic activation on sexual arousal in women. Ephedrine (50mg), an alpha and beta adrenergic agonist, facilitated vaginal photoplethysmograph measures of sexual arousal [197], and clonidine, an alpha2 adrenergic agonist which blocks peripheral sympathetic outflow, decreased these responses [198]. Increased sympathetic nervous system activity, induced via intense acute exercise, enhanced vaginal engorgement in women [199-201].

The pattern and density of innervation of the vaginal vasculature and microvasculature was described by Hoyle et al. [191] using immunohistochemistry in surgical specimens taken from five pre- and five postmenopausal women. They identified a number of neuropeptides in the papillae, subepithelial plexus, propria arteries and veins and the deep arteries and veins. These included Neuropeptide Y (NPY), Vasocative Intestinal Peptide (VIP), CGRP, Substance P (SP) and the enzyme NOS. The vasomotor properties of VIP (vasodilatation), NO (from NOS production- vasodilatation) and NPY (vasoconstriction) are well-known but the neuropeptides CGRP, NPY and SP (and also NO and VIP) are known to be involved in sensory nerve function and can influence the permeability of the capillaries. Orgasm is presumed to cause the decreased release of all of these and to enhance the release of the adrenergic system transmitters, thus effectively decreasing the blood flow and the production of vaginal lubrication. At present however, it should be said that our knowledge of the exact functions of these active agents lags far behind our knowledge of their locations.
Less attention has been paid to the longitudinal and circular smooth muscle coats of the vagina. They can contract spontaneously even in the non-pregnant woman and especially around menstruation, although the contractions are not perceived in consciousness [1, 202-203]. The muscles possess both alpha and beta adrenoreceptors: blockade of the alpha system inhibits spontaneous contractions of vaginal muscle strips while beta blockade induces greater adrenergic-mediated contractions [204]. The vepergic innervation (neurotransmitter = VIP) decreases both tone and induces relaxation. During arousal, the vepergic innervation is likely to be dominant by facilitating smooth muscle relaxation of the vaginal wall and thus not reducing the caliber of its blood vessels, thereby allowing the VIP-activated lubrication mechanism to operate. Contraction of the vaginal smooth muscle if it happens does not occur until the late excitation state just before orgasm (Figure 4).

2. Labia Minora

Although the neural mechanisms and the neurotransmitters creating the congestion and increased blood flow responses of the labia minora to sexual arousal have not been characterized, they are probably mediated through mechanisms similar or even identical to those described above for the vagina [35].

3. Clitoris

The most recent anatomical description from cadaveric dissections [205] is of a triplanar complex of erectile tissue with a midline shaft lying in the media sagittal approximately 2-4 cm long and 1-2 cm wide, which bifurcates internally into paired curved crura 5-9 cm long. Posterior to the shaft, on either side of the urethra are two separate vestibular bulbs (3-7 cm long of crescentric or triangular shape thought to be spongious tissue). The shaft is composed of two chambers, the corpora cavernosa, surrounded by a fibrous sheath (tunica albuginea). It is capped externally by the glans some 2-3mm long and wide consisting of cavernous spongious tissue coming from the vestibular bulbs [206] and is normally covered by a protective hood of skin formed from the fusion of the two labia minora. Its parasympathetic innervation comes from the lumbosacral segments L2-S2 while its sympathetic supply is from the hypogastric superior plexus. The pudendal and hypogastric nerves serve its sensory innervation. Sensory nerve terminations include Merkel tactile discs (touch), Pacinian (deep pressure ?) and genital nerve corpuscles, and free nerve endings (pain ?) [34, 207]. There was wide variation in the quantity, quality and location of the various nerve endings.

The clitoris also responds with increased blood flow and tumescence on being stimulated or through sexual arousal. Nitric oxide synthase (NOS), together with many neuropeptides, have been identified in the complex network of nerves in the clitoral tissue by immunohistochemical studies over the last few years. The list includes VIP, PHM (peptide histidine methionine), NPY, CPON (C-flanking peptide of NPY), CGRP (calcitonin gene-related peptide) and substance P [208-210]. The presence of the enzyme NOS in the nerves supplying the clitoral cavernous tissues and in the endothelial cells lining the cavernous tissue indicates that its vasodilating product NO is involved in the enhanced flow and tumescence while the presence of the vasoconstrictors NPY/CPON suggests that they could throttle venous drainage and facilitate the organ’s engorgement. VIP/PHM are known vasodilating neurotransmitters. The exact functions of the other neuropeptides are more problematic. It has been suggested that Substance P, CGRP, and even NO may have sensory roles or may be involved in influencing capillary permeability [210].

4. Uterus

The uterus was said to increase significantly in size during sexual arousal [14] when monitored by palpation, though limited MRI imaging has not confirmed this [28]. It may be that the latter needs better resolution. Odd contractions of the uterus can occur during arousal, but at orgasm a specific pattern of contractions occurs.

D. Psychological/Cultural Aspects of Women’s Orgasm

I. Psychosocial Factors Related to Women’s Orgasm

The psychosocial factors most commonly discussed in relation to female orgasmic ability include age, education, social class, religion, personality, and relationship issues. While no significant relation between education level and orgasmic ability with a
Figure 4: Summary diagram of the various changes that take place in the human vagina during coitus with and without orgasm.
partner, substantial differences between education level and ability to attain orgasm during masturbation have been reported. Approximately 87% of women with an advanced degree reported “always” or “usually” attaining orgasm during masturbation compared with 42% of women with a high school education.

A negative relation between orgasmic ability and high religiosity has been reported. Laumann et al. [211] reported a substantially higher proportion (79%) of women with no religious affiliation reported being orgasmic during masturbation compared with religious groups (53% - 67%). However, there were substantial differences in education levels between religious categories. A relation between improved orgasmic ability and decreased sexual guilt has also been reported [212]. Low orgasmic experience has been consistently related to childhood loss or separation from the father, fathers who had been emotionally unavailable, or fathers with whom the women did not have a positive childhood relationship. Reports of an association between early abuse and anorgasmia are inconsistent (e.g., [213-215]).

Orgasm consistency, quality, and satisfaction in women have been related to relationship factors such as marital satisfaction, marital adjustment, happiness, and stability (for review, see [4]) however rates of orgasm consistency in women are higher during masturbation than with a partner [211]. In summary, there are no consistent, empirical findings that psychosocial factors alone differentiate orgasmic from anorgasmic women. Research that systematically examines these factors among women who are more carefully diagnosed as either meeting or not meeting clinical criteria for Female Orgasmic Disorder is needed.

### II. ORGASM AS A GOAL OF WOMEN’S SEXUAL ENCOUNTERS

Perceived wisdom or a sex role stereotype is that men are goal-orientated to achieve orgasm; if it doesn’t occur in a sexual encounter, then they are supposedly dissatisfied and frustrated. For women, it is equally often stated that orgasm is not as highly prized as a goal in such encounters [216]. While some women consider coitus without achieving orgasm unfulfilling and frustrating, especially in relation to the lack of dissipation of their pelvic congestion, others have a high regard for coitus and its pleasures but pay low regard to orgasm per se [7, 217]. Women have been noted to appreciate the “afterglow” of sexual arousal and the body intimacy of being cuddled [218-219] as much as the orgasm itself.

In questionnaires administered to a self-selected rather than a statistically random population, it was reported that women, whether they experienced orgasm or not, gave affection, intimacy and love as major reasons for liking sexual intercourse, and their favorite experience was the act of penetration rather than orgasm itself [32]. All these studies and their conclusions were conducted over 25-40 years ago in America and sexual perceptions of societies and their individuals can change. Waterman & Chiauzzi [220] investigated the relationship between sexual enjoyment and orgasm in couples attending university. They reported “nothing in their data supports the cultural stereotype that orgasms are more important to men than to women”. A recent, statistically valid, national survey of British sexual behavior published in 1994 [221] asked both men and women to agree or disagree with the statement “Sex without orgasm cannot be really satisfying”. Although nearly half of all men (48.7%) agreed or strongly agreed that orgasm is necessary to male sexual satisfaction, a close 43.3% of all women also concurred.

In women, acute pelvic vasocongestion created by sexual arousal is extensive as it includes uterine, vaginal, clitoral, urethral and labial tissues, pelvic ligaments and possibly even the fallopian tubes [14, 55]. While it is dissipated by orgasm, the dissipation is not normally as rapid or as complete as in the male, and can even be only partial, needing a number of orgasms to occur before its complete resolution to the basal state. In the Masters & Johnson [14] laboratory study of human sexual female responses, the initial recruiting was from prostitutes (p. 10) who suffered from gross varicosities in the genital/pelvic region. The explanation was that their constant sexual arousal during their working day created chronic pelvic vasocongestion that was not dissipated by orgasm (pp. 119-122). Studies of the condition in prostitutes showed that it was accompanied by feelings of pelvic fullness, pressure, cramping, pain, low backache, irritability and sleeplessness, but relief could be instigated by self-induced orgasm. Prostitutes are of course extreme examples but they are illustrative of the condition. Chronic pelvic vasocongestion is an old, established condition first described and examined in the 1940’s [55, p. 49; 222-224]. Duncan & Taylor [225] undertook experiments to measure vaginal blood flow and showed that it
increased when subjects were made anxious, depressed and resentful. More recent laboratory studies have reported that female subjects viewing sexually arousing visual stimuli increase their vaginal “blood flow/congestion” as monitored by photoplethysmography without perception of it occurring, even if they subjectively report that they were not consciously sexually aroused or did not enjoy it [226]. The female genital sexual haemodynamic changes of hyperaemia and congestion thus are almost reflex responses even with a claimed negative central sexual arousal. Evidence that female genital sexual arousal is a reflex response is also provided by studies of women with complete SCI who demonstrate reflex genital vasocongestion [227-228]. While no studies have been published comparing the extent of pelvic varicosities in sexually active orgasmic and non-orgasmic women, a “prophylactic” role in their prevention can be envisaged for the female orgasm.

III. CULTURAL ASPECTS OF WOMEN’S ORGASM

Sexual arousal to orgasm through coitus is often thought of as a natural biological act, especially if linked to reproduction. A core concept of social constructionists however is that sexual behavior and identity are learned rather than intrinsic, and culture with its social and historical factors plays a large role in shaping, or at least trying to shape, an individual’s sexuality [229]. A very obvious involvement of culture/society on female sexuality has been the acknowledgement of female orgasms, which in reality means the acceptance of female sexual pleasure. Anthropologists have noted that in cultures that expect women to enjoy sex as men do the women have orgasms, while in those cultures that censor such a concept women have more difficulty attaining orgasm. Instances of societies that foster sexual pleasure for women and expect them to enjoy coitus include the Mundugumor [230] and the Mangaia [231]. Mangaian women are taught to have orgasms, hopefully two or three to her male partner’s one and to try to attain mutual orgasm. Mangaian males who are not able to give their partners multiple orgasms are not held in high esteem. At the other end of the spectrum are societies that assume women will have no pleasure from coitus and that the female orgasm does not exist. The Arapesh [232] are such a society, as they do not even have a word in their language for the female orgasm. In a similar vein, the Sambia people of the Highlands of New Guinea [233] accord the clitoris (lakandiku) no function or importance and it is never mentioned in public by men. Moreover men deny that there is a female orgasm (imbimboogu).

1. INTRODUCTION

Findings from the National Social and Health Life Survey conducted in the early 1990s [211] suggest that orgasmic problems are the second most frequently reported sexual problems in women. In this random sample of 1,749 US women, 24% reported a lack of orgasm in the past year for at least several months or more. This percentage is comparable to clinic-based data. Rosen et al. [234] noted 29% of 329 healthy women (ages 18-73) who attended an outpatient gynecological clinic reported orgasmic problems, and Read et al. [235] reported 23% of 104 women (18-65+) attending a U.K. general practice clinic reported anorgasmia. A precise estimate of the incidence of orgasmic disorder in women is however difficult to determine because few well-controlled studies have been conducted, and definitions of orgasmic disorder vary widely between studies depending on the diagnostic criteria used. The DSM-IV-TR [236], defines Female Orgasmic Disorder (302.73) using the following diagnostic criteria.

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 DSM-IV-TR uses the terms lifelong versus acquired and generalized versus situational. However, some studies of orgasm in women use the term “secondary” with little clarity as to whether this is an acquired inability to orgasm under any circumstances or is in fact a situational disorder possible acquired rather than lifelong. The International Statistical Classification of Diseases and Related Health
Problems (ICD-10) defines Orgasmic dysfunction (F52.3) simply as “Orgasm either does not occur or is markedly delayed”. Regarding women who can obtain orgasm during intercourse with manual stimulation but not intercourse alone, the clinical consensus is that she would not meet criteria for clinical diagnosis.

II. ORGASM IN MENOPAUSE

A critical period in the ageing process for women is the premenopausal-postmenopausal change. Compared to young women, the response to sexual stimulation in the laboratory in postmenopausal women showed delay in achieving full tumescence in the clitoris, marked decrease in breast volume engorgement, no engorgement of the uterus, delayed or absent vaginal lubrication and decreased vaginal expansion. At orgasm, there were fewer vaginal contractions and rarely any rectal ones. The reduced number of vaginal and anal contractions, possible indicators of the intensity of pleasure according to Masters & Johnson [14], suggested a “generalized reduction in the intensity of orgasm expression”. Unfortunately, their wording is ambiguous and could mean either a real decrease in the intensity of orgasm or a decrease in the physical expression of orgasm at various sites. This decrease in intensity of orgasm was also reported by Basson [237] in androgen deficient menopausal women. These women also had difficulty in trying to focus during arousal to orgasm.

In some menopausal women, pain can occur during and after the uterine/vaginal contractions of orgasm. Levin [194] suggested that in the premenopausal women, contractions of the vagina and uterus are induced by a neurotransmitter that has to overcome the inhibitory action of any released VIP. In the menopausal state, however, VIP is probably ineffective in relaxing smooth muscle [238] so that the contractions of the uterus/vagina induced by the neurotransmitter at orgasm is unopposed, leading to spasmodic type contractions creating anoxia and thus pain. Giving oestrogen and progesterone together causes relief, but neither is adequate separately [14].

III. TREATMENT

The treatment of anorgasmia has been approached from psychoanalytic, cognitive-behavioral, pharmacological, and systems theory perspectives [239]. Substantial empirical outcome research is available only for cognitive behavioral and, to a lesser degree, pharmacological approaches. Hence, this section will provide a review only of cognitive behavioral techniques and pharmacotherapy used to treat female anorgasmia. To this end, Tables 6, 7, and 8 provide a summary of controlled and uncontrolled studies by treatment techniques. Definitive recommendations for treatment are based solely on controlled outcome research. One of the difficulties in assessing treatment effectiveness for anorgasmia is the nebulous manner in which studies often define orgasmic dysfunction. While some studies use clinician interviews to determine whether women meet criteria for primary or secondary anorgasmia, others rely solely on participant verbal reports of orgasmic difficulty or the results of brief self-report inventories. For this reason, where possible, information on the way in which orgasmic dysfunction is defined is included in the Tables.

1. COGNITIVE-BEHAVIORAL APPROACHES

Cognitive-behavioral therapy for anorgasmia focuses on promoting changes in attitudes and sexually-relevant thoughts, decreasing anxiety, and increasing orgasmic ability and satisfaction. Behavioral exercises traditionally prescribed to induce these changes include directed masturbation, sensate focus, and systematic desensitization. Sex education, communication skills training, and Kegel exercises are also often included in cognitive-behavioral treatment programs for anorgasmia.

a) Directed masturbation

Given masturbation can be performed alone, any anxiety that may be associated with partner evaluation is necessarily eliminated. Related, the amount and intensity of sexual stimulation is directly under the woman’s control and therefore the woman is not reliant upon her partner’s knowledge or her ability to communicate her needs to her partner. Research that shows a relation between masturbation and orgasmic ability provides empirical support for this treatment approach [211].

Directed masturbation (DM) has been used to effectively treat anorgasmia in a variety of treatment modalities including group, individual, couples therapy, and bibliotherapy. As can be seen in Table 6, a number of outcome studies and case series report directed masturbation is highly successful for treating primary anorgasmia. In a controlled comparison of therapist-directed group masturbation training,
<table>
<thead>
<tr>
<th>Reference</th>
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<th>Definition of Anorgasmia</th>
<th>Treatment</th>
<th>Outcome</th>
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<tr>
<td><strong>DIRECTED MASTURBATION</strong></td>
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<tr>
<td>Controlled Outcome Studies</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Heinrich (1976) [240]</td>
<td>44</td>
<td>M age=25; 20 married, 24 with regular partner</td>
<td>Primary anorgasmia</td>
<td>DM (G) vs. DM bibliotherapy (I) vs. WL; DM: 10 sessions/5 wk; DM bibliotherapy: 1 session</td>
<td>2 mo: DM: 100% orgasmic with masturbation (om), 47% coital orgasmic (co); DM bibliotherapy: 47% om, 13% co; WL: 21% om, 0% co</td>
</tr>
<tr>
<td>Munjack et al. (1976) [247]</td>
<td>22</td>
<td>12 prim, 10 sec</td>
<td>Primary and secondary anorgasmia</td>
<td>SD, DM, assertiveness training, modeling, sexual edu (I/C) vs. WL; 22 weekly sessions</td>
<td>Tx &gt; WL orgasmic ability; no difference between prim and sec</td>
</tr>
<tr>
<td>Riley &amp; Riley (1978) [248]</td>
<td>SF (n=15)</td>
<td>M age=26; married</td>
<td>Primary anorgasmia, defined as orgasmic inability regardless of type of sexual stimulation</td>
<td>DM and SF (C) vs. SF (C); 6 weekly and 6 bi-monthly sessions</td>
<td>DM and SF: 18/20 orgasmic; SF: 8/15 orgasmic; 1 yr follow-up: gains maintained</td>
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<tr>
<td></td>
<td>DM + SF (n=20)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>McMullen &amp; Rosen (1979) [241]</td>
<td>DM (n=20)</td>
<td>M age=29; 30 married</td>
<td>Primary anorgasmia, defined as the orgasmic inability through any means of sexual stimulation; assessed via clinician interview, self-report, General Information Questionnaire and Sexual Behavior Inventory</td>
<td>DM Bibliotherapy (I) vs. DM Instructional videotape (I) vs. WL; 6 sessions/6 wk</td>
<td>Bibliotherapy: 65% orgasm with masturbation (om), 50% coital orgasmic (co); Instructional: 55% om, 30% co; WL: 0% om, 0% co; 1 yr follow-up: gains maintained/improved</td>
</tr>
<tr>
<td></td>
<td>WL (n=20)</td>
<td>30 single</td>
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</tr>
</tbody>
</table>
## Table 6. Psychological Treatment of Orgasmic Dysfunction (Ctd)

<table>
<thead>
<tr>
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<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reisinger (1979) [249]</td>
<td>3</td>
<td>M age = 33; married 8-15 yrs</td>
<td>Secondary anorgasmia, coitally and through masturbation</td>
<td>DM with erotic video 8-13 sessions; stimulation by partner w/o training 2-6 sessions; stimulation by partner w/ training 6-10 sessions; solitary stimulation w/o erotic aids 2-3 sessions; stimulation w/ partner 4-7 sessions</td>
<td>DM: 3/3 orgasmic ability through masturbation; limited orgasmic success w/o partner training; 67% orgasmic ability without partner training; 2, 6 mo follow-ups: 80% orgasmic ability with and without partner stimulation</td>
</tr>
<tr>
<td>Andersen (1981) [250]</td>
<td>30</td>
<td>M age = 25; 25 married, all with regular partners; some sexual aversion</td>
<td>Self-reported primary anorgasmia, also assessed via Sexual Interaction Inventory</td>
<td>SD (G) vs. DM (G) vs. WL; 10 sessions/5 wk</td>
<td>DM &gt; SD, WL on orgasmic response; 6 wk follow-up: DM &gt; SD on orgasmic response</td>
</tr>
<tr>
<td>Delehanty (1982) [251]</td>
<td>28</td>
<td>M age = 30</td>
<td>Preorgasmic: no history of orgasm within previous 5 yrs or primary anorgasmia; assessed via self-report and orgasm checklist</td>
<td>DM and assertiveness training in group co-therapy format for 10 wk vs. WL</td>
<td>82% orgasmic success with tx</td>
</tr>
<tr>
<td>Heiman &amp; LoPiccolo (1983) [252]</td>
<td>41</td>
<td>M age = 30; 25 prim, 16 sec, absence of severe marital distress</td>
<td>Primary and secondary anorgasmia</td>
<td>CBT, communication training, DM, SF, systems conceptualization (C) vs. WL; 15/1-hr sessions</td>
<td>Prim and Sec: Increased duration foreplay and si; Prim: increased frequency si, increased orgasmic response during masturbation and si; Sec: increased orgasmic response during si, increased initiation of sexual activity; 3 mo follow-up: Prim: gains maintained, Sec: orgasmic gains maintained, decreased duration foreplay and si</td>
</tr>
</tbody>
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Table 6. Psychological Treatment of Orgasmic Dysfunction (Ctd)

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<tbody>
<tr>
<td>Bogat, Hamernik, &amp; Brooks (1987) [253]</td>
<td>11</td>
<td>N/A</td>
<td>Self-reported preorgasmic (less than 10% of time) with desire to improve ability, also assessed with Women’s Orgasmic Efficacy and Comfort Scale</td>
<td>DM vs. no treatment (C); 10 sessions</td>
<td>80% Improvement in orgasmic success in tx vs. controls</td>
</tr>
<tr>
<td>Eichel, Eichel, &amp; Kule (1988) [254]</td>
<td>CAT (n=22) Control (n=43 men and women)</td>
<td>CAT: M age = 40; Control: M age = 39; interest in sexual enhancement</td>
<td>Orgasmic function assessed via orgasmic attainment criteria scale</td>
<td>Coital Alignment technique (CAT) (C) vs. no treatment (C)</td>
<td>CAT group: improvement in frequency of orgasm, simultaneous orgasm, &amp; orgasm satisfaction compared to controls; use of CAT by both groups correlated with improved frequency of all orgasm variables</td>
</tr>
<tr>
<td>Hurlbert &amp; Apt (1995) [242]</td>
<td>CAT (n=19) DM (n=17)</td>
<td>M age = 28; 36 sec; M yr married = 5 Secondary anorgasmia, assessed via self-report and sex diary</td>
<td>Coital alignment technique (CAT) I vs. DM 1 ; 4, 30-min sessions involving assertiveness training, communication skills, and SF plus 4, 10-min telephone contacts</td>
<td>CAT: 37% substantially improved, 58% moderately improved orgasmic ability during si; DM: 18% substantially improved, 35% moderately improved orgasmic ability during si</td>
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</tr>
</tbody>
</table>

No Control Outcome Studies

<p>| LoPiccolo &amp; Lobitz (1972) [255] | 8   | Married                  | Primary anorgasmia, assessment method not specified                                                                                     | DM (1) modeled after Masters &amp; Johnson; Kegel exercises; 15 sessions                                                              | 8/8 Orgasmic with masturbation, 6/8 coitally orgasmic; 6 mo follow-up: gains maintained                                           |
| Lobitz &amp; LoPiccolo (1972) [256]  | 13  | Married                  | Primary anorgasmia                                                                                                                          | DM (1 with partner participation); 15 sessions                                                                                    | 13/13 Orgasmic with masturbation, 13/13 coitally orgasmic 50% of time                                                             |</p>
<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Barbach (1974)</td>
<td>83</td>
<td>19-48 yo</td>
<td>Primary anorgasmia, defined as no orgasmic experience</td>
<td>DM (G); 10 sessions/5 wk</td>
<td>92% Orgasmic with masturbation</td>
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<tr>
<td>[257]</td>
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<tr>
<td>Wallace &amp; Barbach (1974)</td>
<td>17</td>
<td>M age =28; 11/17 married; all with partners</td>
<td>Primary anorgasmia</td>
<td>DM (G); 10 sessions/5 wk</td>
<td>100% Orgasmic with masturbation</td>
</tr>
<tr>
<td>[258]</td>
<td></td>
<td>(of 83 in Barbach, 1974)</td>
<td></td>
<td></td>
<td>87% orgasmic with partner; 8 mo follow-up; gains maintained</td>
</tr>
<tr>
<td>McGovern, Stewart, &amp; LoPiccolo (1975) [259]</td>
<td>12</td>
<td>6 prim, 6 sec</td>
<td>Primary anorgasmia and secondary anorgasmia</td>
<td>Sexual and communication skills training, anxiety re-education, DM; 15 sessions</td>
<td>Prim: 6/6 Increased orgasmic ability; Sec: no change in orgasmic ability</td>
</tr>
<tr>
<td>Schneidman &amp; McGuire (1976)</td>
<td>20</td>
<td>10 &lt; 35 yo, 10 &gt; 35 yo; 70% prim; some problems with male ejaculatory control</td>
<td>Primary anorgasmia (except nocturnal orgasms while dreaming)</td>
<td>Variation of Masters &amp; Johnson (sexual edu, group discussions, DM, couples tx) 1; 10 wk</td>
<td>&lt; 35 yo: 70% orgasmic during masturbation, 0/10 coitaly orgasmic; &gt; 30 yo: 40% orgasmic during masturbation, 0/10 coitaly orgasmic; 6 mo: &lt; 35 yo: 80% orgasmic during masturbation, none orgasmic during si; &gt; 30 yo: 60% orgasmic during masturbation, 1/10 orgasmic during si</td>
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<tr>
<td>[260]</td>
<td></td>
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<tr>
<td>Kirkpatrick et al. (1977)</td>
<td>4</td>
<td>Not available.</td>
<td>N/A</td>
<td>DM (G)</td>
<td>4/4 orgasmic during masturbation, 75% coitaly orgasmic</td>
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<tr>
<td>[261]</td>
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<tr>
<td>Leiblum &amp; Ersner-Hershfield (1977) [262]</td>
<td>16</td>
<td>23-43 yo; 12 married</td>
<td>Primary and secondary anorgasmia and general orgasmic dysfunction, assessed via General Information Questionnaire</td>
<td>DM, sensate focus, and sexual edu (G); 8 - 10 sessions/5-8 wk</td>
<td>88% orgasm with masturbation</td>
</tr>
<tr>
<td>Reference</td>
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<tr>
<td>Sotile, Kilmann, &amp; Follingsstad</td>
<td>6</td>
<td>3 prim, 3 sec; 15 previous SD sessions</td>
<td>Primary and secondary anorgasmia, assessed via Sexual Interaction Inventory</td>
<td>Sexual and communication skill training, sexual edu, SF, DM, Kegel ex, role-play orgasm (C); 6/1 _hr sessions</td>
<td>No change in orgasm</td>
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<tr>
<td>(1977) [263]</td>
<td></td>
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<tr>
<td>Ersner-Hershfield &amp; Kopel (1979)</td>
<td>22</td>
<td>M age=26; 14/22 married; 13 prim, 9 sec</td>
<td>Preorgasmic, defined as either no orgasmic experience or less than 10% success achieving orgasm in the past, assessed via Survey of Sexual Activities</td>
<td>DM: Spaced vs. massed sessions (G,I) vs. DM: spaced vs. massed sessions (G,C); 10 wk follow-up: 82% orgasmic with partner</td>
<td>91% Orgasmic with masturbation, 73% orgasmic with partner; no difference G1 vs. GC or spaced vs. massed sessions; 10 wk follow-up: 82% orgasmic with partner</td>
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<tr>
<td>[264]</td>
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<td></td>
</tr>
<tr>
<td>Barbach &amp; Flaherty (1980)</td>
<td>26</td>
<td>19 to 60 yo; follow-up on previous study</td>
<td>Secondary anorgasmia</td>
<td>DM, communication training (I); 10, 1 _hr sessions</td>
<td>1-2 yr follow-up: 60% increased orgasmic frequency with partners</td>
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<tr>
<td>[265]</td>
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</tr>
<tr>
<td>Kuriansky, Sharpe, &amp; O'Connor</td>
<td>19</td>
<td>M age=30; previous or current psychotherapy; 3/19 situationally orgasmic</td>
<td>Primary or secondary anorgasmia assessed via self-report and clinician interview; Orgasm Hierarchy Scale</td>
<td>SD, DM, assertiveness training (G,I), based on Barbach (1974), Lobitz &amp; LoPiccolo (1972), and LoPiccolo &amp; Lobitz (1972); 10 sessions/5 wk</td>
<td>18/19 Orgasmic; 68% orgasmic via self-stimulation; 21% orgasmic with partner; 2 yr follow-up: 16/19 orgasmic, 37% orgasmic via self-stimulation, 47% orgasmic with partner</td>
</tr>
<tr>
<td>(1982) [266]</td>
<td></td>
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<tr>
<td>Adkins &amp; Jehu, (1985) [267]</td>
<td>6</td>
<td>M age =28; M yr in relationship = 3.5</td>
<td>Self-reported primary orgasmic dysfunction</td>
<td>DM and bibliotherapy; 10 sessions/10 wk</td>
<td>3/6 Orgasmic success at partner-involvement with no intercourse phase; authors suggest use of vibrators aided orgasm success; 6 mo follow-up: 3/6 orgasmic success via masturbation or coitus with clitoral stimulation</td>
</tr>
</tbody>
</table>
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<tbody>
<tr>
<td>De Amicis et al. (1985) [268]</td>
<td>22</td>
<td>$M_{\text{age}}=34$; $M_{\text{yr married}}=13$; 13 prim, 9 sec</td>
<td>Primary and secondary anorgasmia</td>
<td>Sensual awareness, SF, DM, communication training, modification of sexual interactions (C); 15-20 sessions</td>
<td>No change in orgasmic ability, increased sexual satisfaction; 3 yr follow-up: Prim: increase in orgasmic ability with genital caress; Sec: increase in orgasmic ability during masturbation</td>
</tr>
<tr>
<td>Wakefield (1987) [269]</td>
<td>15</td>
<td>Reanalysis of data from Ersner-Hershfield &amp; Kopel (1979)</td>
<td>Self-reported primary anorgasmia, assessed via Survey of Sexual Activities</td>
<td>DM: spaced vs. massed sessions (GI) vs. DM: spaced vs. massed sessions (GC); 10 sessions/5 wk</td>
<td>80% orgasm via masturbation; 7% orgasm via partner stimulation; no coital orgasm; 10 wk follow-up: 93% orgasm via masturbation, 20% orgasm via partner stimulation; no coital orgasm</td>
</tr>
<tr>
<td>Kaplan (1992) [270]</td>
<td>21</td>
<td>Sexuality seminar participants; 21/30 attempted CAT</td>
<td>N/A</td>
<td>Coital alignment technique (CAT) for 1-3 sexual encounters/2 wk</td>
<td>1/21 Enhanced coital orgasm; 20/21 no enhanced or increased coital orgasm, nor increased simultaneous orgasm</td>
</tr>
</tbody>
</table>

**SYSTEMATIC DESENSITIZATION**

**Controlled Outcome Studies**

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Husted (1972; 1975) [271-272]</td>
<td>30</td>
<td>Mixed sexual dysfunction; all with partners; sexual anxiety</td>
<td>N/A</td>
<td>SD: Imaginal (I) vs. (C); vs. in vivo (I) vs. (C) vs. No-treatment control; Imaginal $M=8$ sessions, in vivo $M=13$ sessions</td>
<td>SD: Decreased anxiety, increased coital frequency and orgasmic ability with masturbation; no difference (I) vs. (C) or imaginal vs. in vivo</td>
</tr>
<tr>
<td>Obler (1973) [273]</td>
<td>37</td>
<td>Mixed sexual dysfunction; marital status matched across groups</td>
<td>N/A</td>
<td>SD with videotapes (I) vs. Psychoanalytic tx with videotapes (G) vs. WL; SD: 15 45-min sessions; Psychoanalytic: 10 75-min sessions</td>
<td>SD: 85% orgasmic; Psychoanalytic: 36% orgasmic WL: 23% orgasmic SD&gt; Psychoanalytic, WL on decreased anxiety</td>
</tr>
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<tbody>
<tr>
<td>Mathews et al. (1976) [274]</td>
<td>18</td>
<td>M age=28; 13 prim, 5 sec; 17/18 low sexual desire/arousal</td>
<td>Primary and secondary anorgasmia</td>
<td>SD, sexual tx (C) vs. SF, sexual tx (C) vs. SF, bibliotherapy (C); 10 sessions; 3 sessions and 10 wk mailing for SF, bibliotherapy</td>
<td>2/18 Increased orgasmic ability; no difference between groups; 4 mo follow-up; no difference between groups</td>
</tr>
<tr>
<td>Wincze &amp; Caird (1976) [275]</td>
<td>21</td>
<td>18-38 yo; 16 prim, 5 sec; 19/21 married; sexual anxiety</td>
<td>Frigidity, including “essential” sexual dysfunction</td>
<td>SD Imaginal (I) vs. SD video (I) vs. WL; M= 10 sessions/ 2-7 wk</td>
<td>SD: 40% orgasmic; no difference between imaginal/video groups; 1-3 mo follow-up: 25% orgasmic ability</td>
</tr>
<tr>
<td>Nemetz, Craig, &amp; Reith (1978) [276]</td>
<td></td>
<td>SD (I) (n=8)</td>
<td>21-39 yo; 7 prim, 15 sec; sexual anxiety; all with regular partners</td>
<td>Primary and secondary anorgasmia</td>
<td>SD (I) vs. SD (G) vs. Control; 5 sessions/3 wk</td>
</tr>
<tr>
<td>O’Gorman (1978) [277]</td>
<td>40</td>
<td>M age=36; low sexual desire/arousal, some dyspareunia/Vaginismus</td>
<td>Frigidity, including orgasm dysfunction</td>
<td>SD, sex edu (G), partner-only discussion groups vs. SD, intravenous methohxotone sodium to induce relaxation (1 with partner participation); SD (G) 20 1-hr sessions; SD (I) 15 10-min sessions/ 10 wk</td>
<td>SD, sex edu (G): 63% successful; SD, methoxitane sodium (I): 37% successful</td>
</tr>
<tr>
<td>Andersen (1981) [250]</td>
<td>30</td>
<td>M age=25; 25 married, all with regular partners; some sexual aversion</td>
<td>Self-reported primary anorgasmia, also assessed via Sexual Interaction Inventory</td>
<td>SD (G) vs. DM (G) vs. WL; 10 sessions/5 wk</td>
<td>DM &gt; SD, WL on orgasmic response; 6 wk follow-up: DM &gt; SD on orgasmic response</td>
</tr>
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<tr>
<td>Ober (1982) [278]</td>
<td>Integrated (n=8) Couples (n=8) No treatment (n=10)</td>
<td>18-36 yo; married or cohabiting for over 2 yrs; no previous psychotherapy</td>
<td>N/A</td>
<td>42 wk of Integrated hypnoanalytic/behavioral group vs. 16 wk of Cotherapist/Couples vs. No tx; 1 yr</td>
<td>Integrated: 7/8 self-reported orgasmic ability over 60% of time; Cotherapist/Couples: 2/8 self-reported orgasmic ability over 60% of time; No tx: no self-reported orgasmic ability</td>
</tr>
<tr>
<td>Fichten, Libman, &amp; Breder (1983) [279]</td>
<td>23</td>
<td>M age=33; sec; M yr married = 10; Orgasmic &lt; 25% of time</td>
<td>Secondary anorgasmia, defined as at least 1 orgasmic experience, dissatisfaction with orgasmic frequency, and narrow range of orgasmic stimulation</td>
<td>Sexual information, relaxation, Kegel ex, DM, SF, sexual communication training, ban on si: (C) vs. (G) vs. minimal contact bibliotherapy; 14 wk</td>
<td>No change in orgasm</td>
</tr>
</tbody>
</table>

#### Own Control or Wait-list Controlled Outcome Studies

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Munjack et al. (1976) [247]</td>
<td>22</td>
<td>M age =29; M age married=67; 12 prim, 10 sec; no women had experienced orgasm within 1 yr</td>
<td>Primary anorgasmia (except orgasm in sleep) or secondary anorgasmia</td>
<td>SD, DM, assertiveness training, modeling, sexual education (UC) vs. WL; 22 weekly sessions</td>
<td>Tx &gt; WL orgasmic ability; no difference prim vs. sec</td>
</tr>
<tr>
<td>Sotile &amp; Kilmann (1978) [280]</td>
<td>22</td>
<td>M age =28; 8 prim, 14 sec; all with partners; no partner sexual dysfunction; sexual anxiety</td>
<td>Primary and secondary anorgasmia, assessed via Sexual Behavior and Attitudes Questionnaire and self-report</td>
<td>Sexual education followed by SD (G) or WL for 16 sessions/8 wk</td>
<td>Increased noncoital orgasmic frequency; sec &gt; prim orgasmic frequency following tx; 6 wk follow-up: gains maintained</td>
</tr>
</tbody>
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<tbody>
<tr>
<td><strong>No Control Outcome Studies</strong></td>
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<tr>
<td>Cooper (1970) [281]</td>
<td>50</td>
<td>N/A</td>
<td>Coitally anorgasmic, assessed by clinical interview</td>
<td>* In vivo SD, sex education, psychotherapy (1); 21 sessions/1 yr</td>
<td>24/50 coitally orgasmic; 26/50 unchanged or worse</td>
</tr>
<tr>
<td>Jones &amp; Park (1972) [282]</td>
<td>55</td>
<td>Anxiety; sexual shame</td>
<td>Primary anorgasmia</td>
<td>SD with Brevital injections to induce relaxation (1 with partner participation); M=14 sessions</td>
<td>82% orgasmic success</td>
</tr>
<tr>
<td><strong>SENSATE FOCUS / OTHER</strong></td>
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<tr>
<td><strong>Controlled Outcome Studies</strong></td>
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</tr>
<tr>
<td>Mathews et al. (1976) [274]</td>
<td>18</td>
<td>M age=28; 13 prim, 5 sec; 17/18 low sexual desire/arousal</td>
<td>Orgasmic dysfunction, defined as failure to experience orgasm and assessed via clinician interview</td>
<td>SD, sexual tx (C) vs. SF, sexual tx (C) vs. SF, bibliotherapy (C); 10 sessions; 3 sessions and 10 wk mailing for SF, bibliotherapy</td>
<td>2/18 Increased orgasmic ability; no difference between groups; 4 mo follow-up; no difference between groups</td>
</tr>
<tr>
<td>Carrey, Bancroft, &amp; Mathews (1978) [283]</td>
<td>16</td>
<td>M age =29; sexual anxiety; Vaginismus or orgasm dysfunction as primary complaint excluded</td>
<td>Secondary anorgasmia assessed via self-report, clinician rating and independent assessor rating</td>
<td>SF weekly: testosterone, 10 mg daily (T) vs. diazepam, 10 mg daily (C) vs. SF monthly: T vs. diazepam (C); SF weekly: 16 sessions, SF monthly: 5 sessions</td>
<td>No difference in orgasm between weekly vs. monthly T &gt; diazepam frequency of orgasm; 6 mo follow-up (after drug discontinuation): gains maintained</td>
</tr>
<tr>
<td>Reference</td>
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<tr>
<td>Roughan &amp; Kunst (1981)</td>
<td>PC Group (n=14)</td>
<td>M age = 32; 14 participants met criteria for orgasmic dysfunction</td>
<td>Primary anorgasmia or secondary anorgasmia lasting over 2 yrs</td>
<td>PC (G): PC muscle exercises for 50 contractions, 5x daily for 12 wk vs. Relaxation (G): physical relaxation for 12 wk vs. no tx</td>
<td>No relationship between PC muscle tone and orgasmic ability in any group</td>
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<tr>
<td></td>
<td>Relaxation (n=12)</td>
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<td></td>
<td>Control (n=14)</td>
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<tr>
<td>Fichten, Libman, &amp; Breder (1983)</td>
<td>23</td>
<td>M age = 33; M yr married = 10</td>
<td>Secondary anorgasmia</td>
<td>Sexual information, relaxation, Kegel ex, DM, SF, sexual communication training, ban on si; (C) vs. (G) vs. minimal contact bibliotherapy; 14 wk</td>
<td>SF: No change in orgasm; increase in enjoyment of noncoital sexual caressing and si</td>
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<tr>
<td>Chambless et al. (1984) [285]</td>
<td>16</td>
<td>M age = 27</td>
<td>&lt; 30% orgasm success through coitus; assessed with Women’s Sexuality Questionnaire</td>
<td>Kegel ex vs. Attn. placebo (nonsexual imagery) vs. WL; 6 wk</td>
<td>No differences in coital orgasmic frequency despite improvement in each group; no change in perceived vaginal stimulation during orgasm in any group</td>
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<tr>
<td></td>
<td>(group n’s not specified)</td>
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<tr>
<td>LoPiccolo et al. (1985) [286]</td>
<td>31</td>
<td>M age = 35; 12 prim, 19 sec; M yr married = 13</td>
<td>Primary and secondary anorgasmia</td>
<td>CBT sexual therapy (LoPiccolo &amp; Hogan, 1979) vs. WL (C), both for 15 1-hr sessions</td>
<td>Prim and sec: Increase in orgasm with masturbation; 3 mo follow-up; gains maintained/improved</td>
</tr>
<tr>
<td>Kilmann et al (1986) [245]</td>
<td>55</td>
<td>M age = 33; 51 married; all with partners; no Dyspareunia or Vaginismus, no premature ejaculation in partners</td>
<td>Secondary anorgasmia for 5 mo through si or clitoral stimulation and dissatisfied with coital orgasmic ability; assessed via clinician interview and Sexual Behavior and Attitudes Questionnaire</td>
<td>2 2-hr sessions sex education followed by Communication skills (C/G) vs. Sexual skills (C/G) vs. WL vs. Attn-placebo</td>
<td>Communication and sexual skills &gt; controls in coital orgasm ability; no difference between groups; 6 mo follow-up; gains decreased, no difference between groups</td>
</tr>
<tr>
<td>Reference</td>
<td>N</td>
<td>Subject Characteristics</td>
<td>Definition of Anorgasmia</td>
<td>Treatment</td>
<td>Outcome</td>
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<tr>
<td>Morokoff &amp; LoPiccolo (1986) [287]</td>
<td>43</td>
<td><em>M</em> age = 30; prim; <em>M</em> yr married = 9; no male sexual dysfunction, no psychosis or depression</td>
<td>Primary anorgasmia, assessed via Sexual History Form</td>
<td>DM and Bibliotherapy in either Minimal therapist contact for 4 sessions (MTC; n=14) vs. Full therapist contact for 15 sessions (FTC; n=29)</td>
<td>Increased orgasmic ability with masturbation and si; MTC &gt; FTC on increased frequency orgasm with masturbation</td>
</tr>
<tr>
<td>Kilmann et al. (1987) [288]</td>
<td>11</td>
<td><em>M</em> age = 30; 10 married; no premature ejaculation in partners</td>
<td>Secondary anorgasmia, defined as 50% coital orgasmic success or less over 5 mo and dissatisfaction with orgasmic frequency, assessed via structured interviews, Sexual Interaction Inventory and Sexual Behavior and Attitudes Questionnaire</td>
<td>2 2-hr sessions sex education followed by communication and sexual skills vs. WL vs. Attn-placebo</td>
<td>Tx &gt; WL, Attn-placebo: increase in orgasmic ability with tx</td>
</tr>
<tr>
<td>Milan, Kilmann, &amp; Boland (1988) [289]</td>
<td>38</td>
<td><em>M</em> age = 33; sec; <em>M</em> yr relationship = 10; regular sexual partners with no sexual dysfunction; 9% orgasmic frequency pretreatment</td>
<td>Secondary anorgasmia, assessed via scale adapted from the Sexual Behavior and Attitudes Questionnaire</td>
<td>10 2-hr sessions/5 wk of sex education plus either: communication skills vs. sexual skills vs. condensed sex and communication skills vs. didactic lecture vs. WL</td>
<td>2-6 yr: No difference between tx groups, WL on sexual or relationship functioning</td>
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</table>
### Table 6. Psychological Treatment of Orgasmic Dysfunction (Ctd)

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<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Subject Characteristics</th>
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<th>Treatment</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Van Lankveld, Everaerd, &amp; Grotjohann (2001) [290]</td>
<td>Bibliotherapy (n=9)</td>
<td>M age =37; M sexual dysfunction duration= 8 y; Hyposexual Desire Disorder; Vaginismus; Dyspareunia</td>
<td>DSM-IV diagnosis of orgasmic dysfunction via structured interview, with no distinction between primary and secondary anorgasmia; assessed via self-report and Golombok Rust Inventory of Sexual Satisfaction</td>
<td>Bibliotherapy (including communication skills, sexual education, and SF) and CBT with telephone support vs. WL; 10 wk</td>
<td>No improvement in orgasm in tx vs. controls</td>
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<tr>
<td><strong>No Control Outcome Studies</strong></td>
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<tr>
<td>Lazarus (1963) [291]</td>
<td>16</td>
<td>M age =25; married; some decreased desire/arousal</td>
<td>Persistent orgasmic dysfunction, method of assessment not specified</td>
<td>SD (I), M=29 sessions over 6 mo</td>
<td>9/16 “nearly always achieve orgasm”; 15 mo follow-up (4 patients): gains maintained or improved</td>
</tr>
<tr>
<td>Masters &amp; Johnson (1970) [243]</td>
<td>342</td>
<td>193 prim; 11 masturbatory dys; 106 coital dys; 32 random</td>
<td>Primary and secondary anorgasmia</td>
<td>Sex education, SF, communication training, in vivo SD (C); 14 sessions/daily</td>
<td>Prim: 83% orgasmic; Masturbatory: 91% orgasmic; Coital: 80% orgasmic; Random: 63% orgasmic; 5 yr follow-up: Prim 1% relapse; Sec 2% relapse</td>
</tr>
<tr>
<td>Blakeney et al. (1976) [292]</td>
<td>38</td>
<td>10 prim, 28 sec; some male sexual dysfunctions</td>
<td>Primary and secondary anorgasmia</td>
<td>4-hr interview and 2 day workshops based on Masters &amp; Johnson (C)</td>
<td>Prim: 70% orgasmic; Sec: 57% orgasmic</td>
</tr>
<tr>
<td>Sotile, Kilmann, &amp; Follingstad (1977) [263]</td>
<td>6</td>
<td>3 prim, 3 sec</td>
<td>Primary and secondary anorgasmia</td>
<td>Sexual and communication skill training, sexual education, SF, DM, Kegel ex, role-play orgasm (C); 6/1 1-hr sessions</td>
<td>Decreased sexual anxiety, increased sexual communication</td>
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<tr>
<td>Reference</td>
<td>N</td>
<td>Subject Characteristics</td>
<td>Definition of Anorgasmia</td>
<td>Treatment</td>
<td>Outcome</td>
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<tr>
<td>Golden et al. (1978) [293]</td>
<td>17</td>
<td>M age =27; 14/17 married</td>
<td>Secondary anorgasmia as primary diagnosis, assessed via Gondis for Sexual Therapy: Female form</td>
<td>Couples assigned SF, sexual skills, and communication skills in either a tx (G) vs. tx (C) format; 12 wk</td>
<td>Couple and group tx improved orgasm satisfaction (data suggests group tx slightly more beneficial)</td>
</tr>
<tr>
<td>Jankovich &amp; Miller (1978)</td>
<td>17</td>
<td>19–38 yo</td>
<td>Primary anorgasmia assessed via interview</td>
<td>Therapy and audiovisual sexual education over a single week (G)</td>
<td>7/17 experienced orgasm within a week; 4 via masturbation, 2 via partner manual stimulation, 1 via manual stimulation and si</td>
</tr>
<tr>
<td>Dodge, Glasgow, &amp; O’Neill (1982) [295]</td>
<td>13</td>
<td>M age = late 20s</td>
<td>Primary or secondary anorgasmia (orgasmic mainly through masturbation), Sexual Interactions Inventory and Sexual Arousal Inventory</td>
<td>Tx of minimal-contact bibliotherapy in 3-4 h therapy sessions vs. delayed treatment group given information on human sexuality</td>
<td>Tx increased coital orgasm; 2/3 prim attained orgasm with tx vs. 0/2 orgasm in prim controls; no change orgasm via masturbation for tx or control; 6 wk follow-up: increase in coital orgasmic ability with tx</td>
</tr>
<tr>
<td>Costan-Huston &amp; Wheeler (1983) [296]</td>
<td>70</td>
<td>M age of treatment group=34; M age of control group=31; both groups with organic dysfunction</td>
<td>Primary or secondary anorgasmia, method of assessment not specified</td>
<td>Combination of group and sex therapy approaches vs. no tx</td>
<td>Increased masturbation and orgasm through masturbation in tx vs. controls</td>
</tr>
<tr>
<td>Kilham et al. (1983) [297]</td>
<td>48</td>
<td>M age =33; M yr married= 10; 8.4% coital orgasm frequency; M dysfunction persistence of 9.6 yr</td>
<td>Secondary anorgasmia, with orgasm frequency less than 50% for 5 mo, assessed in interview; orgasmic ability also assessed via Sexual Behavior and Attitudes Questionnaire</td>
<td>Sex education during 2, 2-hr sessions within a single wk</td>
<td>Increases in orgasmic frequency subscale; increases in coital, noncoital, and masturbatory orgasm frequency</td>
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</table>
Table 6. Psychological Treatment of Orgasmic Dysfunction (Ctd)

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<thead>
<tr>
<th>Reference</th>
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<tbody>
<tr>
<td>Trudel &amp; Saint-Laurent (1983) [298]</td>
<td>PC Group (n=6)</td>
<td>N/A</td>
<td>Orgasmic ability via clitoral stimulation, not coitus (assessed through interview)</td>
<td>PC group: 20 m daily PC exercises for 8 wk; Relaxation group: 20 m daily exercises in sexual awareness, relaxation, and breathing for 8 wk</td>
<td>No differences between groups in coital orgasm ability; in the Relaxation group, 1 orgasmic woman during tx, 1 woman orgasmic post-tx (not attributed to tx effects)</td>
</tr>
<tr>
<td>Libman et al. (1984) [299]</td>
<td>Couple (n=7)</td>
<td>M age 33; M yr married 10; 25% orgasmic frequency</td>
<td>Secondary androgynasia assessed via interview and Jewish General Hospital Sexual Behavior Questionnaire</td>
<td>15, 1-hr sessions over 14 wk (G) vs. all-female groups for 15, 1.5 hr sessions over 14 wk (G) vs. Minimal Contact; Bibliotherapy: 2 sessions at beginning and end of 14 wk period</td>
<td>Therapy (C) and bibliotherapy &gt; therapy (G) in orgasm with manual stimulation; Therapy (C) &gt; other groups in orgasm via giving and receiving manual stimulation; overall gains in orgasm via masturbation, receiving manual stimulation, giving and receiving manual stimulation, receiving oral stimulation across conditions</td>
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<tr>
<td></td>
<td>Group (n=8)</td>
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<td></td>
<td>Bibliotherapy (n=8)</td>
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<tr>
<td>De Araincet et al. (1985) [268]</td>
<td>22</td>
<td>M age 34; M yr married 13; 13 prim, 9 sec; low arousal and desire, Vaginismus, and/or Dyspareunia</td>
<td>Primary and secondary anorgasmia, assessed with diagnostic criteria of Schorer et al. (1982) and Sexual History Form</td>
<td>Sensual awareness, SF, DM, communication training, modification of sexual interactions (C), 15-20 sessions</td>
<td>No change in orgasm: 3 yr follow-up; Prim: increase in orgasm with genital exercises; Sec: some increase in orgasm during masturbation</td>
</tr>
<tr>
<td>Sarver &amp; Durlak (1997) [300]</td>
<td>34</td>
<td>Couples ages 20-60 yr; married</td>
<td>DSM-III-diagnosis of inhibited orgasm</td>
<td>Behavioural treatment: involved SF for 30 min, video, lecture, and sex education material over 7 wk of weekly sessions of 4 hr</td>
<td>65% resolved orgasm dysfunction by end of tx</td>
</tr>
<tr>
<td>Billups et al. (2001) [301]</td>
<td>32</td>
<td>Pre- and post-menopausal women with and without FSD</td>
<td>Orgasmic function assessed with Female Intervention Efficacy Index</td>
<td>6 at-home sessions of clitoral vacuum therapy; 5-15 m with or without partner</td>
<td>FSF: 55% Increased orgasm; non-FSD: 42% increased orgasm</td>
</tr>
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</table>
Table 6. Psychological Treatment of Orgasmic Dysfunction (Ctd)

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<tr>
<th>Reference</th>
<th>N</th>
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<th>Treatment</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>McCabe (2001)</td>
<td>36</td>
<td>$M$ age =36; low sexual interest; sexual arousal disorder;</td>
<td>Orgasm dysfunction, assessed via Sexual</td>
<td>CBT, SF, interpersonal communication; sexual skills; alleviating sexual</td>
<td>Anorgasmia decreased from 66.7% to 11.1% post-tx; increase in positive sexual attitudes</td>
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<td></td>
<td></td>
<td>Vaginismus</td>
<td>Dysfunction Scale</td>
<td>anxiety</td>
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<tr>
<td>Zajecka et al.</td>
<td>CBASP (n=140)</td>
<td>$M$ age =43; 65% of sample female; depression; 48%</td>
<td>Difficult, less intense, or lack of</td>
<td>Cognitive Behavioral Analysis System of Psychotherapy (CBASP) 2x weekly,</td>
<td>N.s. improvement in orgasm with CBASP, nefazodone and combination tx</td>
</tr>
<tr>
<td>(2002) [303]</td>
<td>Nefazodone (n=144)</td>
<td>women reported baseline sexual dysfunction</td>
<td>orgasm</td>
<td>nefazodone (200-600 mg/d), or combination for 12 wk period</td>
<td>groups at 12 wk compared to baseline</td>
</tr>
<tr>
<td>Combined (n=155)</td>
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Note: SD = systematic desensitization, DM = directed masturbation, SF = sensate focus, CBT = cognitive-behavioral therapy; WL = wait-list, (I) = individual therapy, (C) = couples therapy, (G) = group therapy (GI) = group/individual therapy, (GC) = group/couples therapy, prim = primary orgasmic dysfunction, sec = secondary orgasmic dysfunction, si = sexual intercourse.
### Table 7. Pharmacological Treatments for Non-Antidepressant-Induced Orgasmic Dysfunction

<table>
<thead>
<tr>
<th>References</th>
<th>N</th>
<th>Subject Characteristics</th>
<th>Definition of Anorgasmia</th>
<th>Treatment</th>
<th>Outcome</th>
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<tbody>
<tr>
<td><strong>ArginMax</strong></td>
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<tr>
<td>Ito, Trant, &amp; Polan (2001)</td>
<td>77</td>
<td><em>M</em> age =43; 6 subjects with previous sexual dysfunction</td>
<td>Orgasm function assessed with Female Sexual Functioning Index</td>
<td>ArginMax herbal supplement for 4 wk vs. placebo</td>
<td>47.1% of ArginMax tx improvement in orgasm function at 4 wk vs. 30.2% in placebo group</td>
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<td><strong>Bupropion</strong></td>
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<tr>
<td>Modell, May, &amp; Katholi (2000)</td>
<td>20</td>
<td>21-54 yo; healthy</td>
<td>Self-reported secondary anorgasmia as inability to achieve or delay of orgasm in appropriate time frame; orgasm function also assessed with modified sexual satisfaction questionnaire</td>
<td>3 wk placebo dose, 3 wk bupropion-SR (150 mg) once daily plus placebo dose, 3 wk bupropion-SR (150 mg) 2x daily</td>
<td>No improvement in orgasm, satisfaction, or intensity beyond placebo with either 150 or 300 mg doses</td>
</tr>
<tr>
<td><strong>Nefazodone, Psychotherapy</strong></td>
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<tr>
<td>Zajeczka et al. (2002)</td>
<td></td>
<td><em>M</em> age =43; 65% of sample female: depression; 48% women reported baseline sexual dysfunction</td>
<td>Difficult, less intense, or lack of orgasm</td>
<td>Nefazodone (200-600 mg/d), Cognitive Behavioral Analysis System of Psychotherapy (CBASP) 2x weekly, or combination for 12 wk period</td>
<td>Improvement in orgasm in nefazodone, CBASP, and combination tx groups at 12 wk vs. baseline</td>
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</table>
Table 7. Pharmacological Treatments for Non-Antidepressant-Induced Orgasmic Dysfunction (Ctd)

<table>
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<tr>
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<th>Outcome</th>
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<tbody>
<tr>
<td><strong>Sildenafil</strong></td>
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<tr>
<td>Kaplan et al. (1999) [161]</td>
<td>12</td>
<td>M age =52; postmenopausal</td>
<td>Self-reported orgasm difficulty or inability via Index of Female Sexual Function</td>
<td>Sildenafil (50 mg) 1 h before sexual activity</td>
<td>At 12 wk, 7.4% improvement in orgasm function</td>
</tr>
<tr>
<td><strong>Berman et al. (2001) [162]</strong></td>
<td>44</td>
<td>M age =46; all women with Female Sexual Arousal Disorder; hypoactive sexual desire disorder</td>
<td>Difficulty or inability to achieve orgasm, assessed via Brief Index of Sexual Functioning (BISF-W) and Female Intervention Efficacy Index (FIEI)</td>
<td>Sildenafil (100 mg) at second visit and 6-wk home supply</td>
<td>BISF-W: Increase in orgasm; FIEI: 67% increased orgasmic ability</td>
</tr>
<tr>
<td><strong>Testosterone</strong></td>
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<tr>
<td>Carney, Bancroft, &amp; Mathews (1978) [283]</td>
<td>Testosterone (n=16)</td>
<td>M age =29; sexual anxiety; Vaginismus or orgasm dysfunction as primary complaint excluded</td>
<td>Secondary anorgasmia assessed via self-report, clinician rating and independent assessor rating</td>
<td>Sensate Focus (SF) weekly: testosterone, 10 mg/d (T) vs diazepam, 10 mg/d (C) vs SF monthly; T vs diazepam (C); SF weekly: 16 sessions, SF monthly: 5 sessions</td>
<td>No difference in orgasmic ability between weekly vs. monthly T&gt;diazepam frequency of orgasm; 6 mo follow-up (after drug discontinuation): gains maintained</td>
</tr>
<tr>
<td></td>
<td>Diazepam (n=16)</td>
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<tr>
<td>Davis et al. (1995) [306]</td>
<td>Estradiol, Testosterone (n=16) Estradiol (n=17)</td>
<td>E&amp;T: M age =57; E: M age =51; postmenopausal; 13/32 hysterectomy; 2/32 oophorectomy</td>
<td>Self-reported orgasmic dysfunction, assessed via Sabbatsberg self-rating scale</td>
<td>Estradiol (50 mg) plus testosterone (50 mg) (E&amp;T) vs estradiol (50 mg) (E), administered 3x monthly for 2 yr; checkups ever 6 mo</td>
<td>Both E&amp;T and E tx increased orgasmic function; E&amp;T &gt; E greater orgasmic response</td>
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*Note: SF=Sensate Focus*
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<th>Reference</th>
<th>N</th>
<th>Subject Characteristics</th>
<th>Antidepressant</th>
<th>Definition of Anorgasmia</th>
<th>Treatment</th>
<th>Outcome</th>
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<td><strong>Placebo Controlled Outcome Studies</strong></td>
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<tr>
<td>Bupropion</td>
<td>Bupropion (n=15)</td>
<td>Impairment of sex drive, arousal and/or vaginal lubrication</td>
<td>N/A</td>
<td>Impairment in orgasm and orgasm satisfaction assessed via Arizona Sexual Experiences Scale</td>
<td>Bupropion SR (150 mg) daily for 3 wk vs. placebo daily for 3 wk</td>
<td>No change in bupropion tx in orgasm/organism satisfaction; no difference bupropion vs. placebo</td>
</tr>
<tr>
<td>Masand et al. (2001)</td>
<td>Placebo (n=15)</td>
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<td>[312]</td>
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<tr>
<td><strong>Buspirone</strong></td>
<td>Buspirone (n=16)</td>
<td>MDD; decreased libido; orgasmic dysfunction (n=19)</td>
<td>Citalopram (min 40 mg/d) or paroxetine (min 30 mg/d)</td>
<td>Orgasm dysfunction assessed in interview via Udvalg for Klinaisk Undersogelser scale</td>
<td>Buspirone (20 mg/d) for 4 wk vs. placebo; SSRI continued during tx</td>
<td>Change in orgasm function not specified</td>
</tr>
<tr>
<td>Landen et al. (1999)</td>
<td>Placebo (n=11)</td>
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<td>[308]</td>
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<td><strong>Buspirone, Amantadine</strong></td>
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<tr>
<td>Michelson et al. (2006)</td>
<td>Buspirone (n=19)</td>
<td>Depression; anxiety disorder; OCD; premenstrual syndrome; premenopausal and postmenopausal replacement; decreased arousal and pleasure</td>
<td>Fluoxetine dosage by group: B (31.4 mg/d), A (28.4 mg/d), and P (25.7 mg/d)</td>
<td>Impaired orgasm assessed by clinician, self-report, daily diary, and interview Rating of Sexual Function scale</td>
<td>Baseline and 4-wk dose, respectively: amantadine (50, 100 mg/d) buspirone (20,30 mg/d) vs. placebo; fluoxetine continued during tx</td>
<td>Improved orgasm in tx and placebo; no difference tx vs. placebo</td>
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<tr>
<td>Amantadine (n=18)</td>
<td>Placebo (n=20)</td>
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<td><strong>Ephedrine</strong></td>
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<tr>
<td>Meston (2003)</td>
<td>19</td>
<td>Female Sexual Arousal Disorder with complaints of decreased orgasm</td>
<td>Fluoxetine, sertraline, or paroxetine; min. 10 wk</td>
<td>Orgasmic ability, intensity/pleasure assessed via self-report</td>
<td>Two wk baseline, 8 wk crossover design placebo vs. 50 mg ephedrine 1 hr prior to sexual activity</td>
<td>Improved orgasm intensity/pleasure in ephedrine tx and placebo; no difference in orgasm tx vs. placebo</td>
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<tr>
<td>Reference</td>
<td>N</td>
<td>Subject Characteristics</td>
<td>Antidepressant</td>
<td>Definition of Anorgasmia</td>
<td>Treatment</td>
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<td>Ginkgo Biloba</td>
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<tr>
<td>Kang et al. (2002)  [310]</td>
<td>Ginkgo (n=4)</td>
<td>Ginkgo group: M age= 47; placebo group: M age=46; depressive or anxiety disorders</td>
<td>Fluoxetine (20 mg/d), paroxetine (20-40 mg/d), or nortriptyline (30 mg/d)</td>
<td>DSM-IV diagnosis of sexual dysfunction; orgasm satisfaction and frequency via self-report and clinical interview</td>
<td>Ginkgo biloba at 120 mg/d for 2 wk, 160 mg/d for following 2 wk, 240 mg/d for final 4 wk vs. placebo doses on same schedule</td>
<td>No improvement in orgasm frequency or satisfaction in ginkgo vs. placebo; 8 wk orgasm satisfaction improvement in placebo</td>
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<tr>
<td>Mirtazapine, Yohimbine, and Olanzapine</td>
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<tr>
<td>Michelson et al. (2002) [309]</td>
<td>Mirtazapine (n=36)</td>
<td>M age =36; depression; decreased vaginal lubrication</td>
<td>Fluoxetine (20 mg/d or greater)</td>
<td>Self-reported orgasmic inhibition, at least moderate in severity</td>
<td>Random assignment to mirtazapine (15-30 mg/d), yohimbine (5-10.8 mg/d), olanzapine (2.5-5 mg/d), or placebo, to be taken 1-2 h before sexual activity</td>
<td>No differences drug vs. placebo in diary or self-report ratings of orgasm function</td>
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<td></td>
<td>Yohimbine (n=35)</td>
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<td></td>
<td>Olanzapine (n=38)</td>
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<td></td>
<td>Placebo (n=39)</td>
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<td>No Control Outcome Studies</td>
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<tr>
<td>Bupropion</td>
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<tr>
<td>Walker et al. (1993)  [313]</td>
<td>22</td>
<td>M age =45; depressed; libido decrease since fluoxetine tx</td>
<td>Fluoxetine (M dose= 25 mg/d)</td>
<td>Assessment of delayed or impaired orgasm via interview and self-report</td>
<td>2 wk washout followed by bupropion (75 mg b.i.d. = 150 mg b.i.d. daily) for 8 wk</td>
<td>84% complete and 10% partial resolution of orgasm dysfunction (results of female and male participants presented together)</td>
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</table>
Table 8. Pharmacological Treatments for Antidepressant-Induced Orgasmic Dysfunction (Ctd)

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Subject Characteristics</th>
<th>Antidepressant</th>
<th>Definition of Anorgasmia</th>
<th>Treatment</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Ashton &amp; Rosen (1998) [314]</td>
<td>28</td>
<td>M age =42; affective or anxiety disorders; desire and arousal complaints</td>
<td>Paroxetine, fluoxetine, sertraline, venlafaxine, fluoxetine</td>
<td>Delayed orgasm or anorgasmia, assessed via clinical interview</td>
<td>Bupropion (75-150 mg/d 1-2 h before sexual activity; if no response, 75 mg t.i.d./d for 3 days, 75 mg b.i.d./d for 3 days, and 75 mg t.i.d./d for 2 w). (longest tx period, 9 mo); SRI continued during tx.</td>
<td>Improvement in 71% of orgasm complaints</td>
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<tr>
<td>Clayton et al. (2001) [315]</td>
<td>4</td>
<td>22-52 yo; MDD; decreased desire, arousal, and libido</td>
<td>Paroxetine (M dose=35 mg/d), sertraline (M dose=94 mg/d), fluoxetine (M dose=12.5 mg/d), and venlafaxine (M dose=225 mg/d)</td>
<td>Orgasmic ability via Changes in interview form of Sexual Functioning Questionnaire</td>
<td>Bupropion 150 mg at start, 345 mg average ending dose) daily or twice daily, for 8 wk; SSRI discontinuation by 4 wk.</td>
<td>4 wk: Improvement in orgasm subscale scores after discontinuation of SSRI</td>
</tr>
<tr>
<td>Gitlin et al. (2002) [316]</td>
<td>15</td>
<td>M age =41; History of MDD, dysthymic disorder, or depressive disorder NOS; not currently depressed</td>
<td>Fluoxetine (M dose=33 mg/d), sertraline (M dose=106 mg/d), paroxetine (M dose=31 mg/d), or citalopram (M dose=20 mg/d)</td>
<td>Self-reported orgasmic ability and satisfaction via Arizona Sexual Experiences Scale</td>
<td>Bupropion SR (100-150 mg) 2x daily for 7 w.</td>
<td>Improvement in ease of reaching orgasm, n.s. improvement in orgasm satisfaction</td>
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<td>Reference</td>
<td>N</td>
<td>Subject Characteristics</td>
<td>Antidepressant</td>
<td>Definition of Anorgasmia</td>
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<td><strong>Ginkgo Biloba</strong></td>
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<tr>
<td>Cohen &amp; Bartlik (1998)[317]</td>
<td>33</td>
<td>Decreased libido and orgasm dysfunction</td>
<td>Fluoxetine, nefazodone, bupropion, sertraline, paroxetine, venlafaxine, phenelzine, or vivaactil</td>
<td>Delayed or inhibited orgasm through clinical interview or self-report</td>
<td>Ginkgo Biloba (40–60 mg) 2x daily up to 120 mg b.i.d. for 4 wk; antidepressants continued during tx</td>
<td>Improvement in orgasmic functioning assessed via clinical interview and self-report</td>
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<td><strong>Granisetron, Sumatriptan</strong></td>
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<td>Berk et al. (2000)[318]</td>
<td>16</td>
<td>M age =37; diagnoses include major depression, OCD, bulimia, social phobia, bipolar II disorder, panic disorder, trichotillomania, and/or borderline personality disorder</td>
<td>Clomipramine (125-250 mg/d), paroxetine (20-40 mg/d), sertraline (50-150 mg/d), fluvoxamine (100-300 mg/d), fluoxetine (20-40 mg/d), citalopram (20-60 mg/d)</td>
<td>Self-reported orgasm difficulty, frequency of difficulty, satisfaction, and intensity via Feiger scale</td>
<td>Sequential course of granisetron (1 mg) and sumatriptan (100 mg) 1 h before sexual activity</td>
<td>Improvement in orgasm difficulty and frequency of difficulty with granisetron; n.s. improvement with sumatriptan</td>
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<td><strong>Mianserin</strong></td>
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<tr>
<td>Aizenberg et al. (1999)[319]</td>
<td>16</td>
<td>M age ~47; MDD, OCD, panic disorder, bipolar I disorder</td>
<td>Fluoxetine (20-40 mg/d), paroxetine (20-40 mg/d), fluvoxamine (200 mg/d), clomipramine (75-150 mg/d)</td>
<td>Self-reported that orgasm function had “markedly decreased”</td>
<td>Mianserin (15 mg/d) at bedtime; SRI continued during tx</td>
<td>62% improvement in orgasm function: 7/16 restored normal orgasm function and 3/16 improved orgasm function to a minor disturbance</td>
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<tr>
<td>Reference</td>
<td>N</td>
<td>Subject Characteristics</td>
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<td><strong>Mirtazapine</strong>&lt;br&gt;Gelenberg et al. (2000) [320]</td>
<td>12</td>
<td>M age ~47; improvement in MDD with SSRIs; 12/19 female in total sample</td>
<td>Fluoxetine (20 – 80 mg/d), sertraline (50 – 150 mg/d), paroxetine (20 mg/d)</td>
<td>Orgasmic dysfunction diagnosed by clinician via DSM-IV interview and self-reported through Arizona Sexual Experiences Scale</td>
<td>1 – 2 wk washout; Mirtazapine (7.5 mg h.s. - 45 mg/d) for 3-6 wk</td>
<td>6 wk: Improvement in orgasm function but not satisfaction (results of males and females reported together)</td>
</tr>
<tr>
<td><strong>Sildenafil</strong>&lt;br&gt;Nurnberg et al. (1999) [321]</td>
<td>7</td>
<td>M age ~37; MDD, panic disorder, bipolar disorder; decreased libido and arousal; pain during intercourse</td>
<td>Fluoxetine (20–50 mg/d), sertraline (50–200 mg/d), nefazodone (150 mg/d), valproate (1 gm/d), trazodone (100 mg/d)</td>
<td>Anorgasmia or delayed/less intense orgasm, assessed by clinicians</td>
<td>Sildenafil (50–100 mg) 1-2 h before sexual activity</td>
<td>7/7 orgasm (less delay, more intense)</td>
</tr>
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<td><strong>Salerian et al.</strong>&lt;br&gt;(2000) [322]</td>
<td>31</td>
<td>Dissatisfaction with libido, arousal, orgasm and lubrication</td>
<td>64% of sample receiving SSRIs; other drug types include: TCAs, other antidepressants, benzodiazepines, mood stabilizers, stimulants, narcotics, antipsychotics</td>
<td>Satisfaction with orgasm assessed with Salterian Sexual Satisfaction Survey</td>
<td>Sildenafil (12.5 – 100 mg); duration of tx: 1 – 36 wk</td>
<td>Improved orgasm satisfaction; similar response regardless of psychotropic meds</td>
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*Note: OCD=Obsessive Compulsive Disorder; MDD=Major Depressive Disorder; SRI=Serotonin Reuptake Inhibitor; SSRI=Selective Serotonin Reuptake Inhibitor; TCA=Tricyclic Antidepressants.*
self-directed masturbation training (bibliotherapy) and wait-list control, Heinrich [240] reported a 100% success rate for treating primary anorgasmia using therapist DM training at 2 month follow-up. Forty-seven percent of the bibliography subjects reported becoming orgasmic during masturbation compared with 21% of wait-list controls. The effects of self-directed masturbation training were further investigated in a randomized trial comparing written versus videotaped masturbation assignments [241]. After 6 weeks, 65% of subjects using a text and 55% of women using videotapes had experienced orgasm during masturbation and 50% and 30%, respectively, were orgasmic during intercourse. None of the control women had attained orgasm. More recently, Hurlbert & Apt [242] compared the effectiveness of DM with coital alignment technique in 36 women with secondary anorgasmia. Coital alignment is a technique in which the woman assumes the supine position and the man positions himself up forward on the woman such that clitoral contact is maximized during coitus. Thirty-seven percent of woman receiving instructions on coital alignment technique versus 18% of those receiving DM reported substantial improvements (> 50% increase) in orgasmic ability during intercourse after only four 30-min sessions.

In summary, DM has been shown to be an empirically valid, efficacious treatment for women diagnosed with primary anorgasmia. For the woman with acquired anorgasmia who is averse to touching her genitals, DM may be beneficial. If, however, the woman is able to attain orgasm alone through masturbation but not with her partner, issues relating to communication, anxiety reduction, safety, trust, and ensuring the woman is receiving adequate stimulation, either via direct manual stimulation or engaging in intercourse using positions designed to maximize clitoral stimulation (i.e., coital alignment technique) may prove more helpful.

b) Anxiety reduction techniques

Anxiety can serve as a distraction that disrupts the processing of erotic cues by causing the woman to focus instead on performance related concerns, embarrassment, and/or guilt. It can lead the woman to engage in self-monitoring during sexual activity, an experience Masters & Johnson [243] referred to as “spectatoring”. Some researchers have speculated that the increased sympathetic activation that accompanies an anxiety state may impair genital vasocongestion via inhibition of parasympathetic nervous system activity. Others have argued that SNS activation plays more of a facilitatory than inhibitory role in sexual arousal [244].

As originally conceived by Masters & Johnson [243], sensate focus involves a step-by-step sequence of body touching exercises, moving from non-sexual to increasingly sexual touching of one another's body. Components specific for treating anorgasmic women often include non-demand genital touching by the partner, female guidance of genital manual and penile stimulation and coital positions designed to maximize pleasurable stimulation. Sensate focus is primarily a couples’ skills learning approach designed to increase communication and awareness of sexually sensitive areas between partners. Conceptually, however, the removal of goal-focused orgasm which can cause performance concerns, the hierarchical nature of the touching exercises, and the instruction not to advance to the next phase before feeling relaxed about the current one, suggest sensate focus is also largely an anxiety reduction technique and could be considered a modified form of in vivo desensitization.

The success of using anxiety reduction techniques for treating anorgasmia is difficult to assess because most studies have used some combination of anxiety reduction, sexual techniques training, sex education, communication training, bibliotherapy, and Kegel exercises, and have not systematically evaluated the independent contributions to treatment outcome. Of the controlled studies that have included anxiety reduction techniques, few have differentiated between treatment outcomes for lifelong versus acquired female orgasmic disorder. As can be seen in Table 6, across studies women have reported decreases in sexual anxiety and, occasionally, increases in frequency of sexual intercourse and sexual satisfaction with systematic desensitization, but substantial improvements in orgasmic ability have not been noted. Similarly, of the few controlled studies that have included sensate focus as a treatment component, none have reported notable increases in orgasmic ability. These findings suggest that, in most cases, anxiety does not appear to play a causal role in anorgasmia and anxiety reduction techniques are best suited for anorgasmic women only when sexual anxiety is coexistent.

c) Other Behavioral techniques

Ignorance about female anatomy and/or techniques for maximizing pleasurable sensations can certainly contribute to orgasm difficulties. Killmann and associates [245] compared the effectiveness of various
sequences of sex education and communication skills versus wait-list control on orgasmic ability in women with secondary anorgasmia. The authors found sex education to be beneficial for enhancing coital ability at post-test but not at 6-month follow-up. In a comparison study of the effectiveness of sex therapy versus communication skills training for secondary anorgasmia, Everaerd & Dekker [246] found both treatments were equally effective in improving orgasmic ability. As can be seen in Table 6, treatment comparison studies have generally found no differences in orgasmic ability between women whose therapy included using Kegel exercises versus those whose therapy didn't. To the extent that Kegel exercise may enhance arousal and/or help the woman become more aware and comfortable with her genitals, these exercises may enhance orgasm ability [239]. In summary, there is no direct empirical evidence to suggest that sex education, communication skills training, or Kegel exercises alone are effective for treating either primary or secondary anorgasmia. A review of studies suggests they may serve as beneficial adjuncts to therapy.

d) Pharmacological Approaches

There have been few placebo-controlled studies examining the effectiveness of pharmacological agents for treating Female Orgasmic Disorder. Of the few published, most examine the efficacy of agents for treating antidepressant-induced anorgasmia. Whether pharmacological agents would have the same treatment outcome effect on non-drug- versus drug-induced anorgasmia is not known.

• Non drug-induced anorgasmia

Using a single-blind design, Modell and associates [304] reported no significant effect beyond placebo of either 150 mg/day or 300 mg/day bupropion-SR on orgasm in 20 women with delayed or inhibited orgasm. Ito et al. [305] conducted a double-blind, placebo-controlled study of ArginMax, a nutritional supplement comprised of ginseng, Ginkgo biloba, Damiana leaf and various vitamins, on sexual function in 77 women with unspecified sexual function and reported a marginally significant group difference. It cannot be determined from the report how many women would meet a clinical diagnosis for anorgasmia. To date, there have been no published placebo-controlled studies on sildenafil for female anorgasmia (Table 7).

• Antidepressant-induced anorgasmia

As can be seen in Table 8, a number of case reports and open label studies report success in alleviating SSRI-induced anorgasmia with various agents. Findings from the few placebo-controlled studies published are less optimistic. Michelson et al. [307] examined the comparative effects of 8 weeks of treatment with either buspirone (20 mg/day; n=19), amantadine (50 mg/day; n=18), or placebo (n=20) on fluoxetine-induced sexual dysfunction in premenopausal women reporting either impaired orgasm or sexual arousal. The authors reported all groups experienced an improvement in orgasm during treatment, but neither buspirone nor amantadine was more effective than placebo in restoring orgasmic function. At a higher dose level (mean daily dose = 47 mg), buspirone showed a marginally significant alleviation of sexual side effects in women taking either citalopram or paroxetine compared with placebo [308]. The authors did not distinguish between orgasm and desire disorders in either the classification of patients or treatment outcome. In a randomized, double-blind, parallel, placebo-controlled study of mirtazapine (15 mg/day), yohimbine (5.4 mg/day), olanzapine (25 mg/day) or placebo for fluoxetine-induced sexual dysfunction, Michelson et al. [309] found no significant improvement in orgasmic ability beyond placebo in 107 women with either impaired orgasm or vaginal lubrication. Kang et al. [310] reported no significant effect of Gingko-biloba beyond placebo in a small group of women with SSRI-induced sexual dysfunction. Meston [311] reported no significant effect of ephedrine (50 mg 1-hr prior to intercourse) beyond placebo on orgasmic function in 19 women with sexual side effects secondary to either fluoxetine, sertraline, or paroxetine treatment (Level 1 evidence).

In summary, to date there are no pharmacological agents proven to be beneficial beyond placebo in enhancing orgasmic function in women. Placebo-controlled research is needed to examine the effectiveness of agents with demonstrated success in case series or open-label trials (i.e., granisetron, and sildenafil) on orgasmic function in women.
We conclude that Directed Masturbation is an empirically valid and efficacious treatment for Lifelong Female Orgasmic Disorder (Grade A). To date, there are no empirically validated treatments for Acquired Female Orgasmic Disorder. Anxiety reduction techniques such as Sensate Focus and Systematic Desensitization have not been shown to be efficacious for treating either Lifelong or Acquired Female Orgasmic Disorder (Grade A). Anxiety reduction techniques may serve as beneficial adjuncts to therapy if the woman is experiencing a high level of anxiety (Grade B). There is no direct empirical evidence to suggest that sex education, communication skills training, or Kegel exercises alone are effective for treating either Lifelong or Acquired Female Orgasmic Disorder (Grade B). Of the few studies examining the effects of pharmaceutical agents for Female Orgasmic Disorder, none have been shown to be more effective than placebo (Grade A). Placebo-controlled research is essential to examine the effectiveness of agents with demonstrated success in case series or open-label trials (i.e., sildenafil, testosterone) on orgasmic function in women.

We recommend that future studies on women with orgasm difficulties conduct more careful classification of the disorder and better discriminate between women with Lifelong versus Acquired, and Generalized versus Situational Female Orgasmic Disorder: There is a paucity of research on the role of psychological, interpersonal, and social factors in the development of orgasm difficulties in women. Research is needed to examine the impact of learning and sexual scripts, relationship history, partner views, sexual experience, need to please partner, attitudes and beliefs toward sexuality and orgasm, and religious and cultural norms and expectations on orgasmic ability in women.

In order to better understand the physiology of women's orgasm, future studies are needed to:

1. Further examine the differential brain activation during orgasm and during sexual arousal without orgasm.
2. Examine which specific serotonin receptor subtype(s) mediate the inhibitory effects of SSRI antidepressants on women's orgasm.
3. Assess whether prolactin secretion is a true specific indicator of orgasm in females and whether it serves as a biological “off switch” for sexual arousal in women.
4. Record uterine contractions during orgasm to better understand their role in women's orgasm and their relation with vaginal and rectal contractions.
5. Assess whether the vagus nerve is a real mediator of afferent supply from the human cervix/uterus.
6. Assess the physiological functions of the identified neuropeptides (e.g., VIP, Substance Y, CGRP, NO) in women's genitals.

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CHAPTER 22

Committee 16

Women’s Sexual Desire and Arousal Disorders and Sexual Pain

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Vice-Chair

W.C.M. WEIJMAR SHULTZ (THE NETHERLANDS)

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G. WYATT (USA),
L. WYATT (USA),
S. LEIBLUM (USA),
S.E. ALTHOF (USA),
G. REDMOND (USA)
A. INTRODUCTION

B. WOMEN’S SEXUAL DESIRE AND INTEREST : DISORDERS OF DESIRE AND INTEREST

C. WOMEN’S SEXUAL AROUSAL AND AROUSAL DISORDERS

D. BIOLOGICAL BASIS OF AROUSAL AND DESIRE

E. ASSESSMENT OF WOMEN’S SEXUAL DYSFUNCTION

F. PSYCHOLOGICAL ETIOLOGICAL FACTORS INVOLVED IN AROUSAL AND DESIRE DISORDERS

G. MANAGEMENT OF DESIRE AND COMORBID AROUSAL DISORDERS IN WOMEN

H. MANAGEMENT OF GENITAL AROUSAL DISORDER

I. MANAGEMENT OF ORGASMIC DYSFUNCTION

J. THE ROLE OF ANDROGENS IN WOMEN’S SEXUAL FUNCTION AND DYSFUNCTION

K. THE ROLE OF ESTROGEN IN WOMEN’S SEXUAL RESPONSE AND DYSFUNCTION

L. CONTEXTUAL NATURE OF WOMEN’S SEXUALITY AND DYSFUNCTION

M. CHILD SEXUAL ABUSE AND SEXUAL DYSFUNCTION

N. FEMALE GENITAL MUTILATION AND SEXUAL DYSFUNCTION

O. MANAGEMENT OF ANTIDEPRESSANT-ASSOCIATED SEXUAL DYSFUNCTION

P. SEXUAL PAIN AND ITS MANAGEMENT

Q. NEUROBIOLOGY OF THE PELVIS

R. CHRONIC PAIN PHYSIOLOGY AND SEXUAL PAIN DISORDERS

S. CLINICAL PRESENTATION OF SEXUAL PAIN DISORDERS

T. PSYCHOLOGICAL ASPECTS OF SEXUAL PAIN DISORDERS

U. PELVIC FLOOR AND SEXUAL PAIN DISORDERS

V. MUCOUS MEMBRANES AND SEXUAL PAIN DISORDERS

W. MANAGEMENT OF SEXUAL PAIN DISORDERS

X. CONCLUSIONS RE SEXUAL PAIN

Y. CONCLUSIONS TO REPORT OF COMMITTEE 16
In countries and cultures where women are freely able to acknowledge their own sexual needs and sexual pleasure and expect freedom from pain with sexual activity, the prevalence of self-reported sexual difficulties (“disabilities”) as opposed to clinician’s careful diagnosis, appears high, [1, 2] (level 4 evidence). Lack of interest in being sexual or sexual dysfunction - the term used when the expected physiological and/or psychological sexual response to sexual stimulation does not occur - may or may not be seen as a problem causing distress and reducing sexual satisfaction [3, 4]. Data suggest that of 33% of women in a nationally representative randomized study, who reported reduced sexual interest, 43% considered this to be a problem and of those, 87% reported sexual dissatisfaction [1]. When lubrication is absent or there is sexual pain, more (63% and 70%) find this a problem, causing sexual dissatisfaction in more than 80% of them. Another nationally representative community study confirmed more than 50% of women wanted professional help for the sexual problems self-disclosed in 41% of them [5].

Dysfunction may be associated with medical disease, (level 3b evidence) e.g. neurological conditions affecting the autonomic nervous system [6], with pharmacological treatment, e.g. serotonergic antidepressants [7], with medical therapies, e.g. pelvic radiation, or with surgical procedures, e.g. radical hysterectomies for cancer of the cervix whereby damage to the autonomic nerves between the bladder and anterior vaginal wall is possible [8]. Dysfunction may also be associated with past or current psychological factors that may have influenced psychosexual development. Interestingly, despite medical factors, mood and psychological entities may more strongly correlate with sexual dysfunction. This has been shown to be true for women with diabetes [9], (level 3b) and women with gynecological surgery [10] (2b). It is possible women have variable proneness to sexual excitement and to sexual inhibition that is genetically and/or societally programmed. Early research is suggesting women have more proneness to sexual inhibition than do men [11]. This inhibition may be more about possible untoward consequences at sexual behaviour (including pregnancy) than about fear of sexual failure. Finally, dysfunction may be largely related to contextual factors - evidence of something psychologically or biologically amiss within the woman herself, being absent. Her sexual “dysfunction” is logical and adaptive [4, 11] It is nevertheless possibly highly distressing to her. It is therefore strongly recommended that in addition to considering which aspects of response are dysfunctional and causing distress, clinicians also routinely note the presence of associated factors:

- Predisposing factors in the woman’s past affecting her psychosexual development, e.g. past abuse [12], (level 3b),
- Precipitating and perpetuating factors in the current context which are disrupting to, and/or consequences of her sexual difficulties [4, 11, 12] (level 2b, 4)
- Past and present medical/surgical entities [6-8] (Level 3b).

If phase(s) of the sex response cycle are the only major criteria governing the diagnosis of dysfunction, scientific proof of benefit of therapeutic intervention will be unlikely - put very simply, medication, for instance, will not ameliorate a problematic context.
In countries and cultures where women are freely able to acknowledge their own sexual needs and sexual pleasure and expect freedom from pain with sexual activity, the prevalence of self-reported sexual difficulties (“disabilities”) as opposed to clinician's careful diagnosis, appears high, [1, 2] (level 4 evidence). Lack of interest in being sexual or sexual dysfunction - the term used when the expected physiological and/or psychological sexual response to sexual stimulation does not occur - may or may not be seen as a problem causing distress and reducing sexual satisfaction [3, 4]. Data suggest that of 33% of women in a nationally representative randomized study, who reported reduced sexual interest, 43% considered this to be a problem and of those, 87% reported sexual dissatisfaction [1]. When lubrication is absent or there is sexual pain, more (63% and 70%) find this a problem, causing sexual dissatisfaction in more than 80% of them. Another nationally representative community study confirmed more than 50% of women wanted professional help for the sexual problems self-disclosed in 41% of them [5].

Dysfunction may be associated with medical disease, (level 3b evidence) e.g. neurological conditions affecting the autonomic nervous system [6], with pharmacological treatment, e.g. serotonergic antidepressants [7], with medical therapies, e.g. pelvic radiation, or with surgical procedures, e.g. radical hysterectomies for cancer of the cervix whereby damage to the autonomic nerves between the bladder and anterior vaginal wall is possible [8]. Dysfunction may also be associated with past or current psychological factors that may have influenced psychosexual development. Interestingly, despite medical factors, mood and psychological entities may more strongly correlate with sexual dysfunction. This has been shown to be true for women with diabetes [9], (level 3b) and women with gynecological surgery [10] (2b). It is possible women have variable proneness to sexual excitement and to sexual inhibition that is genetically and/or societally programmed. Early research is suggesting women have more proneness to sexual inhibition than do men [11]. This inhibition may be more about possible untoward consequences at sexual behaviour (including pregnancy) than about fear of sexual failure. Finally, dysfunction may be largely related to contextual factors - evidence of something psychologically or biologically amiss within the woman herself, being absent. Her sexual “dysfunction” is logical and adaptive [4, 11] It is nevertheless possibly highly distressing to her. It is therefore strongly recommended that in addition to considering which aspects of response are dysfunctional and causing distress, clinicians also routinely note the presence of associated factors:

- Predisposing factors in the woman’s past affecting her psychosexual development, e.g. past abuse [12], (level 3b),
- Precipitating and perpetuating factors in the current context which are disrupting to, and/or consequences of her sexual difficulties [4, 11, 12] (level 2b, 4)
- Past and present medical/surgical entities [6-8] (Level 3b).

If phase(s) of the sex response cycle are the only major criteria governing the diagnosis of dysfunction, scientific proof of benefit of therapeutic intervention will be unlikely - put very simply, medication, for instance, will not ameliorate a problematic context.
Until recently, it has been accepted that women’s sexual response is similar to men’s such that women’s sexual dysfunction mirrors categories of men’s sexual dysfunction. This is not confirmed by empirical evidence - see Table 1.

1. TRADITIONAL CATEGORIES

The traditional model of Masters, Johnson and Kaplan depicts a sexual desire phase and a subsequent phase of arousal characterized by genital congestion. A plateau of higher arousal continues the response on to an experience of high intensity arousal and orgasmic release, lasting some many seconds. A phase of resolution with physical and psychological well being completes the experience. This work was originally based on a subset of women who were willing to be monitored in great detail while they were sexually active in a laboratory and who were reliably orgasmic with intercourse. A phase of sexual desire initiating any sexual responding - such desire characterized by sexual thoughts and sexual fantasies, was later added by Kaplan given many women were voicing their sexual distress in terms of low sexual desire. The traditional categories of women’s dysfunction have been based on this linear progression of discreet phases - desire, genital focused arousal, plateau of arousal, orgasmic release and resolution.

2. EVIDENCE OF INACCURACIES OF TRADITIONAL MODEL OF HUMAN SEX RESPONSE AND SUBSEQUENT DEFINITIONS OF DYSFUNCTION

The following evidence-based table lists facets of women’s sexual function and dysfunction which contradict the traditional model of human sexual responding that underlies the existing definitions of women’s sexual dysfunction.

Both the International Statistical Classification of Disease and Related Health Problems (ICD-10) and the American Psychiatric Association Diagnostic and Statistical Manual (DSM-IVTR) assumes that it is possible to distinguish between organic and psychogenic etiology [56, 57]. However, not only is the precise etiology of women’s sexual dysfunction frequently unclear, there is no evidence that the majority are either biological or psychological. Rather, there is growing evidence of mechanisms by which the mind influences the various systems in the body - immunological, neurological and hormonal. We note the emerging fields of psychoneuroendocrinology and psychoneuroimmunology. Sexual function would appear to be a prime example of the mandatory blending of mind and body. A recent community study of 987 women in the United States provided data supporting the possibility that relationship disharmony may cause impaired sexual response rather than the opposite [4].

3. ALTERNATIVE MODEL OF SEXUAL RESPONSE

The following model (Figure 1) of women’s sexual response attempts to reflect the features of women’s sexual response itemized in Table 2.

The model (on page 862) shows a woman’s sexual response may begin for one of a number of reasons (incentives) [58]. At that stage, there may be no awareness of sexual desire. A willingness to be receptive to sexual stimuli in appropriate context allows her potential sexual arousal - both subjective excitement and physical responding. Many psychological and biological factors influence this information processing in her mind and determine her arousability. Once arousal is experienced, if it continues sufficiently long and is enjoyed, sexual desire may be accessed [58-60, 62]. This has been termed a responsive form of desire [15]. A psychologically and physically rewarding outcome need not necessarily involve orgasmic release(s). The wanting or motivation to be sexually active again is increased if the outcome is positive and decreased if it is either emotionally or physically dissatisfying.

4. INCORPORATION OF SPONTANEOUS OR INNATE DESIRE INTO MODEL

Sexual desire that appears to be “innate” or “spontaneous”, as reflected by sexual thinking/fantasizing/a wanting of sexual sensations per se, may or may not augment or override the cycle based on other motivations. See Figure 2. Women typically are far more aware of this type of desire early on in relationships. For some, it continues decades with the same partner, for the majority, it is infrequent [16-21]. Whether this apparent “innate” or “spontaneous” desire is truly so - is not able to be established. It has been argued that there is no such thing as spontaneous desire [63]. Based on motivation theory, motivation to engage in sex will be influenced by 1) an internal
Table 1: Facets of women's sexual function and dysfunction which are at variance with traditional views of women's sexual response

<table>
<thead>
<tr>
<th>Facets of Women's Sexual Function/Dysfunction</th>
<th>References</th>
<th>LOE Cited</th>
</tr>
</thead>
<tbody>
<tr>
<td>An awareness of sexual desire is not the most frequent reason women accept or initiate sexual activity.</td>
<td>16, 17, 18, 19, 20, 21</td>
<td>2b, 3b, 4, 5</td>
</tr>
<tr>
<td>Sexually healthy women in established relationships are frequently unaware of spontaneous sexual thoughts.</td>
<td>4, 22, 23</td>
<td>4</td>
</tr>
<tr>
<td>Sexual fantasies are often deliberate means to focus on the sexual stimulus rather than an indication of sexual desire.</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>The sexual, and the larger context is integral to women’s sexual function/dysfunction</td>
<td>4, 24, 25, 26, 27, 28, 29, 30</td>
<td>2b, 4</td>
</tr>
<tr>
<td>The couple, rather than the woman, is the correct focus for assessing dysfunction.</td>
<td>4, 24, 29, 31-34</td>
<td>2b, 4</td>
</tr>
<tr>
<td>The phases of women’s sexual response are not discreet and comorbidity of dysfunction is common.</td>
<td>29, 31, 34-171</td>
<td>1b, 2b, 3b, 4</td>
</tr>
<tr>
<td>Women’s experience of sexual arousal is not primarily to do with genital vasocongestion/ vaginal lubrication/perception of genital swelling.</td>
<td>4, 42-50</td>
<td>3b, 4</td>
</tr>
<tr>
<td>Women’s subjective sexual arousal is strongly modulated by emotions and cognitions.</td>
<td>36, 42, 51-54</td>
<td>2b, 3b, 4</td>
</tr>
<tr>
<td>There is no demonstrable lack of genital congestion in the majority of women (with or without arousal disorder), who watch erotic videos and disclaim any subjective arousal.</td>
<td>42, 53, 54</td>
<td>3b, 4</td>
</tr>
<tr>
<td>The musculature of the vagina or around the vagina has not been shown to go into spasm.</td>
<td>55</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 2: Evidence supporting an alternative model (figure 1) of women’s sexual response

<table>
<thead>
<tr>
<th>Facets of Women's Sexual Function/Dysfunction</th>
<th>References</th>
<th>LOE Cited</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are many reasons a woman initiates or agrees to sexual activity.</td>
<td>16, 17, 18, 19, 20, 21</td>
<td>2b, 4</td>
</tr>
<tr>
<td>For one or more reasons, women choose to be receptive to sexual stimuli (or to provide them) and subsequently become sexually aroused.</td>
<td>16, 17, 18, 19, 20, 21, 22</td>
<td>2b, 4</td>
</tr>
<tr>
<td>Emotional intimacy with the partner is often a motivating force and influences her arousability to sexual stimuli.</td>
<td>4, 17, 20, 21</td>
<td>2b, 4</td>
</tr>
<tr>
<td>Various psychological and biological factors influence the woman’s arousability, i.e. the processing of sexual stimuli in her mind potentially on to a state of subjective sexual arousal.</td>
<td>36, 42, 51, 52</td>
<td>2b, 3b, 4</td>
</tr>
<tr>
<td>If the subjective sexual arousal is enjoyed, if the stimulation continues sufficiently long, and if she remains focused on the stimuli, then the arousal becomes more intense and an urge or “desire” for more of the sexual sensations is accessed.</td>
<td>58, 59, 60</td>
<td>5</td>
</tr>
<tr>
<td>Sexual desire and arousal continue together – each reinforcing the other.</td>
<td>58, 59, 60, 61</td>
<td>5</td>
</tr>
<tr>
<td>A positive outcome, emotionally and physically, increases the woman’s motivation (reasons/incentives) to be sexual again in the future.</td>
<td>58, 61</td>
<td>5</td>
</tr>
</tbody>
</table>

Figure 2. Blended sex response cycle showing many motivations to be sexual, spontaneous desire and responsive desire accessed during the experience. Copied with permission from Elsevier. Basson R. Obstet. Gynecol 2001; 98:350-3
state, disposition, or “sexual response system”; 2) stimuli in the environment; 3) rules for access or transgression that regulate the acting out of sexual tendencies. So, desire is part of arousal, triggered by a stimulus that has sexual meaning. It is facilitated or inhibited by situational and sexual partner variables. As such, sexual motivation will occur only when there are appropriate sexual stimuli present (given a sufficiently sensitive sexual response system). The occurrence of sexual motivation, including fantasies, must therefore be the result of sexual information processing of some kind, even though, in some or even most cases, it may not be clear what the initiating sexual stimulus was [63]. For most people, their sexual response system reacts with sexual stimuli in an automatic, unreflected and effortless way. This results in experiences that were not consciously intended, which may explain why so many people experience sexual desire “as if” it were spontaneous.

Based on this alternative model of women’s sexual response, revised and expanded definitions of dysfunction have been proposed by an international panel and will be described in this chapter [64].

### B. WOMEN’S SEXUAL DESIRE AND INTEREST: DISORDERS OF DESIRE AND INTEREST

#### I. DEFINITIONS OF DISORDERED SEXUAL DESIRE AND INTEREST

Given the broad range of awareness of “spontaneous” sexual desire (additional to desire experienced during sexual activity once sexual arousal has been accessed), across women [2, 16, 18, 22], it is quite unclear when any woman should be diagnosed with hypoactive sexual desire disorder. Moreover, given sexual desire is an uncommon reason women in established relationships give for having sex [16-21] focusing on this aspect of sexual response is not clinically helpful. However this is the focus of exiting definitions.

#### 1. CURRENT DEFINITIONS OF HSDD

**a) DSM-IV Definition:**

Persistent or recurrent deficiency (or absence) of sexual fantasies and desire for sexual activity. This disturbance causes marked distress or interpersonal difficulty [57].

**b) ICD-10:**

Loss of Sexual desire is the principal problem and is not secondary to other sexual difficulties, such as erectile failure or dyspareunia.

**c) Frigidity**

Hypoactive Sexual Desire Disorder [56].

#### 2. RECOMMENDED DEFINITION OF WOMEN’S SEXUAL INTEREST/DESIRE DISORDER (BASED ON EVIDENCE IN TABLES 1 AND 2)

The word “interest” was chosen to cover the spectrum of motives/reasons underlying women’s decision to agree to or instigate sexual activity. 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 have sexual arousal are scarce or absent. The lack of interest is considered to be beyond the normative lessening with lifecycle and relationship duration [64].

#### II. PREVALENCE OF SELF-PERCEIVED LOW SEXUAL DESIRE/LOW SEXUAL INTEREST IN WOMEN

Using the criteria of experiencing sexual desire only occasionally, rarely or never, the percentage of women affirming they have “low sexual desire” could be as high as almost 80% - only 22% of 1,335 women in a Scandinavian community study experienced sexual desire more than occasionally [1]. This percentage would drop to 14% in the same cohort of women if the criteria used for diagnosing low sexual desire is experiencing sexual desire only rarely or never.1 Some authors report on “low sexual interest” and others on “low sexual desire”. In the aforementioned study, women with reduced sexual interest amounted to 33% of the sample and almost half of those women perceived it to be a problem associated with sexual dissatisfaction. Previous randomized nationally representative surveys suggest from 8-33% of women self-report or are assessed to have via questionnaire +/- interview, low sexual interest or desire - see Table 3. Few studies ask about both desire and interest. Moreover, what the women interpret these words to mean, is often unclear.

Overall, age seems to have a fairly minimal effect on
the concern of low sexual interest or the concern of low sexual desire. However, two studies [1, 66] show increasing prevalence of low desire after the early 50s. In contrast, other studies show a marked [68] or mild [2] decrease with age. Modest increase with age but less distress about it, characterizes other studies [4, 67]. Complicating all of this is the lessening of desire with relationship duration [21].

### III. THE PARADOX OF THE CRUCIAL ROLE OF SEXUAL AROUSAL AND THE HIGH PREVALENCE OF COMPLAINTS RE LOW DESIRE COMPARED TO COMPLAINTS RE LOW AROUSAL

The crucial role of sexual arousal is apparent from the alternative models, Figures 1 and 2. However, complaints of low interest or low desire far outnumber arousal complaints. Careful history-taking from women complaining of low sexual desire frequently identifies a difficulty with becoming aroused. Women find it hard to separate the two problems. The comorbidity of arousal and desire disorder is well documented [31, 35, 36, 38, 39]. It is recommended that women able to be aroused and have rewarding experiences but lacking apparently “spontaneous” sexual thinking and fantasizing be considered to be sexually healthy given the wide variability across women of this latter aspect of their sexuality. This is in contrast to the existing definitions of hypoactive sexual desire disorder which suggest otherwise. In view of the evidence to date, acceptance of the aforementioned revised definition of low sexual interest is strongly advocated. The innate or spontaneous component of sexual desire may be in part hormonally based [70], specifically related to androgen levels and sensitivity of the androgen receptor. It is also known to relate to relationship duration [1, 21, 71] and to life cycle with reports suggesting lower levels in the 25 to 34-year-old women (as compared to those immediately younger and older) and in women over 49 years of age [1, 66, 72].

### Table 3: Level 4 studies of more than 200 women in nationally representative samples giving prevalence of low sexual desire/interest

<table>
<thead>
<tr>
<th>Study</th>
<th>Criterion</th>
<th>Age</th>
<th>Prevalence in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garde,1982 [23]</td>
<td>Lacked or had no desire</td>
<td>40</td>
<td>21</td>
</tr>
<tr>
<td>Béjin,1982 [65]</td>
<td>No or insufficient sexual desire</td>
<td>18-69</td>
<td>8</td>
</tr>
<tr>
<td>Kontula,1995 [66]</td>
<td>Quite often were with decreased sexual interest</td>
<td>18-74</td>
<td>32</td>
</tr>
<tr>
<td>Hawton,1994 [67]</td>
<td>Impaired sexual interest (only women with partners)</td>
<td>35-59</td>
<td>17</td>
</tr>
<tr>
<td>Ventegodt,1998 [68]</td>
<td>Reduced sexual desire</td>
<td>38-88</td>
<td>17</td>
</tr>
<tr>
<td>Fisher,1999 [69]</td>
<td>Sexual desire “often” lower than they would like it to be</td>
<td>18-45</td>
<td>39</td>
</tr>
<tr>
<td>Laumann,1999 [2]</td>
<td>Lacking interest in sex</td>
<td>18-59</td>
<td>33</td>
</tr>
<tr>
<td>Fugl-Meyer,1999 [1]</td>
<td>Sexual desire never or rarely</td>
<td>18-74</td>
<td>14</td>
</tr>
</tbody>
</table>

The past focus on just one aspect of women’s sexual arousal, namely, genital vasocongestion, specifically the increase in lubrication fluid resulting at least in part from that increase in vasocongestion, has led to misunderstanding of women’s complaints of low sexual arousal [73]. In the clinical setting, if the difficulty is absent lubrication, the woman will typically complain of vaginal dryness or discomfort with intercourse. In contrast, when she speaks in terms of absent sexual arousal, she is referring to subjective
sexual excitement in her mind [53]. When she speaks of overall sexual satisfaction or sexual distress, data suggests impaired vaginal lubrication to be a non-significant predictor [4].

Even recently developed questionnaires may not contain questions regarding subjective arousal, whereas other questionnaires have included this domain [75-77]. It is apparent that the lack of inclusion of subjective arousal in definitions of dysfunction has moved the focus of diagnosis away from women's subjective experience.

1. PSYCHOPHYSIOLOGICAL STUDY OF SUBJECTIVE SEXUAL AROUSAL AND INCREASES IN VAGINAL VASOCONGESTION

The evidence to follow, shows that the vast majority of women diagnosed with “female sexual arousal disorder” over the past 25 years, under laboratory conditions of viewing erotic videos (which frequently fail to subjectively arouse them and may cause negative emotions), nevertheless, show prompt genital vasocongestion comparable to sexually healthy women. In three studies genital responsiveness to sexual stimuli, measured by vaginal pulse amplitude (VPA) as assessed with vaginal photoplethysmography, was compared between premenopausal women with and without sexual problems [42, 46, 78]. A fourth study using the same measure compared responses between pre- and postmenopausal women with and without sexual arousal disorder diagnosed according to DSM-IV criteria [54]. Interestingly women with dyspareunia were found to respond with equal VPA increases to visual sexual stimuli as do women without dyspareunia [78]. No differences were found in VPA between a group of 12 women with hypoactive sexual desire, a group of 12 anorgasmic women, and a control group of 12 women [46]. Similarly, Morokoff and Heiman [42] failed to find differences in VPA between 11 women with sexual arousal disorders who presented for sex therapy, and a control group of 11 women. Twenty-nine medically healthy women with sexual arousal disorder (15 premenopausal; 14 postmenopausal), diagnosed according to DSM-IV criteria, showed no evidence of impaired genital congestion [54]. These women responded with an increase in vaginal vasocongestion to visual sexual stimuli, an increase that did not deviate from that of 30 age- and menopausal status-matched women without sexual problems. In addition, these women's VPA response did not occur at a slower rate. The women with sexual arousal disorder were carefully diagnosed, using strict and unambiguous criteria of lack of awareness of genital responsiveness, and in a similarly careful way it was established that the other women did not have any sexual dysfunction. It seems plausible that with respect to sexual function, these groups were more homogeneous, and differences between groups were greater, than was the case in the three studies mentioned above. Despite that, this study again failed to find differences in vaginal vasocongestion between women with and without sexual arousal disorder. Thus women's complaints of lack of genital responding may be conceptualized at least in part as an inattention to, or disconnection from physiologically healthy vasocongestion.

2. COMPONENTS OF SEXUAL AROUSAL

The following two tables show the various components of women's sexual arousal. Table 4 lists conscious components. Table 5 lists aspects organized by the woman's involuntary (autonomic) nervous system that are outside of conscious awareness.

<table>
<thead>
<tr>
<th>Components</th>
<th>Characteristics</th>
<th>Reference</th>
<th>LOE Cited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective sexual arousal/ sexual excitement.</td>
<td>Correlates with appraisal of stimulus and its context. Often poor correlation with genital vasocongestion. Modulated by thoughts and by emotions. Not necessarily increased by performance demand.</td>
<td>49, 42,43,44,45,46, 47,48,49, 36,41,51,52, 79</td>
<td>4, 3b, 4, 2b, 3b, 4, 4</td>
</tr>
<tr>
<td>Direct awareness of genital engorgement, throbbing, tingling.</td>
<td>Correlates poorly with subjective arousal. Highly variable amongst women.</td>
<td>80</td>
<td>4</td>
</tr>
<tr>
<td>Sexual sensations and sexual excitement from stimulating engorged structures.</td>
<td>This provides an indirect confirmation of genital engorgement. Repetitive sexual stimulation to non-engorged structures leads to irritation, discomfort.</td>
<td>73</td>
<td>5</td>
</tr>
</tbody>
</table>
3. Model of Women's Sexual Arousal

The following model attempts to show the two parallel processes - one conscious and one unconscious. It also shows how variable modulation of subjective arousal by genital feedback and robust modulation by the woman's concurrent thoughts and emotions (Figure 3).

4. Brain Imaging in Women During Sexual Arousal

Magnetic resonance imaging of sexually healthy women willing to be imaged during sexual arousal from watching an erotic video, delineates areas of the brain active during sexual arousal. Of interest, the activation in the areas concerned with organizing and receiving afferent input from the genital reflexes, including the hypothalamus correlates very poorly with the women's rating of their subjective arousal. This is in contrast to men where there is high correlation between activation these areas and their rating of sexual arousal. Again, the rather minimal importance of genital feedback in women as they rate their overall subjective experience of arousal is emphasized [89].

II. Women's Sexual Arousal Disorders

1. Current Definitions of Women's Sexual Arousal Disorders

a) DSM-IV

Female Sexual Arousal Disorder (FSAD)

Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity adequate lubrication, swelling response of sexual excitement. This disturbance causes marked distress or interpersonal difficulty.

b) ICD-10

Failure of genital response.

In women, the principle problem is vaginal dryness or failure of lubrication.

Female Sexual Arousal Disorder

2. Recommended Definitions of Women's Sexual Arousal Disorders (Based on Evidence in Tables 4 and 5)

a) Combined Genital and Subjective Arousal Disorder

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).

b) Genital Sexual Arousal Disorder

Complaints of 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 sensations.
from caressing genitalia. Subjective sexual excitement still occurs from non-genital stimuli.

c) Subjective Sexual Arousal Disorder

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.

3. Psychophysiological Data to Support Clinical Subtyping

Clinical subtyping of women complaining of lack of sexual arousal allowed further investigation of 34 women meeting the criteria for genital arousal disorder. These were postmenopausal estrogenized women who maintained healthy sexual interest and arousal from non-genital sexual stimulation. Since genital stimulation had been their former means of reaching orgasm, most were currently anorgasmic or experienced markedly delayed and reduced intensity orgasms. Psychophysiological studies with vaginal photoplethysmography showed markedly reduced genital vasocongestion in 13 women, moderately reduced in 8, and normal vasocongestion in 11 women. Interestingly, the double-blind placebo-controlled use of 50mg sildenafil under laboratory settings improved the orgasmic experience only in those women with markedly abnormal psychophysiological testing [88]. Thus clinical subtyping produced a heterogeneous group. This study contrasts to the previously mentioned study whereby none of 29 women with DSM-IV diagnosed arousal disorder (i.e. also genitally focused disorder), showed abnormal vasocongestive response [54]. Of note, the study showing heterogeneity included only women with acquired genital loss - within the previous 6 years. Of these women with acquired genital sexual arousal disorder, some clearly had abnormal vasocongestion demonstrable by currently available methods. Others may have had vascular deficit observable by more sensitive methods in the future. However, it may well be that factors other than the degree of vasocongestion, e.g. to do with sexual sensitivity of the engorging structures, underlie the loss of genital responsibility in some of this clinical subgroup of acquired genital arousal disorder. A very recent study of 31 sexually healthy women and 31 with arousal disorders - subtypes, acquired genital, long term subjective and combined, identified reduced vasocongestive response to erotic stimuli only in the subgroup with acquired genital arousal disorder [43].

Figure 3. Model of women's sexual arousal
D. BIOLOGICAL BASIS OF AROUSAL AND DESIRE

I. CENTRAL NEUROENDOCRINE BASIS

The neuroendocrine basis of arousal is poorly understood. A limited understanding stems in part from sexual effects of medication with known or partially known mechanisms of action. It is suggested that more than 30 neurotransmitters, peptides and hormones are involved - the most clinically relevant being noradrenaline, dopamine, oxytocin, serotonin acting via 5HT1A, 5HT2C receptors, being "pro-sexual", prolactin, GABA and serotonin acting via other receptors tending to be sexually negative. These neurotransmitters and peptides in turn are modulated by sex hormones - estrogens, androgens and progesterone. Work with brain imaging of women during sexual arousal points to some areas of the brain being involved in cognitive appraisal, namely, the frontal orbital and anterior cingulate areas, and others being involved in the emotional response to arousal, including the rostral anterior cingulate. Other areas involved in the organization and perception of genital reflexes include the rostral anterior cingulate and posterior hypothalamus [89].

II. GENITAL CONGESTIVE RESPONSE

1. AUTONOMIC INNERVATION

The genital arousal (i.e. vasocongestion), response involves the sympathetic and parasympathetic nerves. It is thought that pelvic sympathetic postganglionic neurons primarily release noradrenaline and adenosine triphosphate ATP, but some release acetylcholine (ACh), NO and VIP. Nerves from the more caudal sympathetic ganglia release noradrenaline and probably neuropeptide Y to produce expected vasoconstriction. However, sympathetic fibers in the hypogastric nerve pass through the ganglionic relay stations in the pelvic plexus and can produce vasoilation of vulval congestion as well as the opposite [90]. Parasympathetic nerves from S2,3,4 release neurotransmitters including NO mediating vasodilation, and ACh blocking noradrenergic vasocongestive mechanisms pre or post junctionally and acting on the endothelium to release NO.

This autonomic neuroanatomy is based on comparable nerves in the man. How accurate all of this is for women is currently unclear. There is some recent clarification of the parasympathetic input to vaginal vasocongestion. Stimulating the second and third sacral anterior nerve roots in a conscious young woman who was paraplegic, by using an intradural implanted Finetech/Brindley stimulator activated by radio signals, caused significant increases in vaginal congestion as measured by vaginal photoplethysmography [91]. Stimulating the fourth sacral root failed to increase the vaginal congestion. Women with spinal cord injury below the T10 to L2 spinal cord levels where the sympathetic nerves leave the cord, are able to vasocongest from psychogenic sexual stimuli [92].

2. NEUROTRANSMITTERS OF THE GENITAL RESPONSE

Nitric Oxide, ACh, VIP appear to be prime neurotransmitters contributing to clitoral engorgement [81]. The results of female genital tract smooth muscle cell cultures suggest a role of cAMP dependent pathways via Prostaglandin E1, VIP and beta-adrenergic receptors. The uncongested vulval structures are perceived to be under a tonic control via adrenergic and possibly peptidergic sympathetic vasoconstrictor mechanisms. Functional α1 and α2 adrenergic receptors in human clitoral and vaginal smooth muscle are present [93]. Hormones influence vascular function by genomic and non-genomic means, by endothelial dependent and independent means.

Regarding vaginal smooth muscle relaxation, there is a neurotransmitter, the identity of which remains illusive. Although it is thought that VIP and possibly NO are involved [82, 83] in vaginal smooth muscle relaxation, there remains a non-nitrergic NANC response - not associated with any known neuropeptides or purines [84]. Also, the agent for contraction of nonvascular vaginal smooth muscle involved in orgasm is not known.
The woman's detailed account of her sexual difficulties is crucial as many different types of problems give rise to sexual symptoms. This comprehensive history is summarized in Table 6. Note there are predisposing, precipitating and maintaining etiological factors.

1. COMPONENTS OF SEXUAL ENQUIRY

- Establish the sexual difficulties in the woman's own words (e.g. cannot become aroused, always has pain with intercourse).
- Clarify the context when activity is attempted, including the adequacy of sexual stimulation, the woman's feelings towards her partner at that time, the safety and privacy of the situation.
- Enquire if the problem(s) is lifelong or acquired: i.e. was there a time when the sexual problems were not present. Lifelong dysfunction necessitates more detailed psychosexual enquiry regarding childhood, adolescence and past relationships.
- Acquired dysfunction necessitates careful enquiry into the context (psychological and medical), surrounding the onset of the dysfunction.
- Establish if the problems are situational or generalized (e.g. arousal may be minimal with her partner but prompt with her own self-stimulation/masturbation). Situational problems suggest an absence of organic disruption of the sexual response.
- Situational problems may be adaptive - logical to the problematic context and this has obvious therapeutic relevance.
- Establish the rest of her sexual response cycle (sexual interest, arousal, orgasm, satisfaction, and distress).

Table 6: Components of a comprehensive sexual, medical, psychosocial history
freedom from pain associated with sexual stimulation or intercourse).

- Establish *her partner’s sex response cycle*.
- Enquire about *the reaction of both partners* to the sexual difficulties.

### 2. Components of Medical Enquiry

Assessment of the current and past medical background is strongly recommended for all sexual dysfunctions - even when the concern is situational.

1. Establish current general health with systems enquiry.
2. Establish current mood and mental health: note impact of any anxiety/depression on sexual dysfunction.
3. Clarify current medications/substance abuse.

### 3. Components of Psychosocial History

Assessment of the psychosocial and psychosexual history is strongly recommended for all sexual dysfunctions:

- Nature and duration of current relationship.
- Dynamics of current interpersonal relationship.
- Clarify any negative/coercive/abusive experiences (physical, sexual or emotional).
- Societal values/beliefs that are impacting on the sexual problems.
- For most sexual problems, especially those that are lifelong, the following further components are necessary:
  
  - Identify any past pattern of sexual relationships.
  - Clarify the woman's sexual experiences as a teenager (alone/partnered).
  - Clarify developmental history, particularly relationships with parental figures, siblings, traumas and losses.

### II. Components of Enquiry for Individual Dysfunctions

#### 1. Sexual Interest Disorder/Hypoactive Sexual Desire

Enquire re possible etiological factors:

- Interpersonal issues
- Lack of useful sexual stimuli
- Lack of useful sexual context
- Psychological issues within the woman herself, e.g.: - past negative experiences or abuse
  - negative self-image
  - feelings of shame, guilt
- Expectation of negative outcome, e.g.: - partner sexual dysfunction
  - poor sexual skills
  - dyspareunia
  - emotionally negative outcome

The following nine questions in Table 7 may be helpful for the initial assessment of low desire/interest:

<table>
<thead>
<tr>
<th>Table 7: Questions to clarify the complaint of low sexual interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>- How long have you had these concerns with respect to your sexual desire/interest?</td>
</tr>
<tr>
<td>- Currently would you feel some interest in sex from something that was potentially erotic to you, e.g. a picture, book, movie, dancing?</td>
</tr>
<tr>
<td>- For many women, feeling emotionally close and able to trust their partner is as important to them as sensing their partner is physically sexually attractive. How is the emotional intimacy with your partner - the trust, ability to be honest, ability to share feelings?</td>
</tr>
<tr>
<td>- Especially in longer-term relationships, women often start out a sexual experience without any feelings of sexual desire. However, they can respond to their partner or to other sexual stimuli. So I need to ask you about the circumstances when you consider being sexual, or when your partner is instigating. Can you describe the circumstances?</td>
</tr>
<tr>
<td>- Can you in time, respond to the sexual touching and stimuli and then feel some desire to continue?</td>
</tr>
<tr>
<td>- Can you stay focused and are you able to guide your partner as to what pleases you - does anything negative happen (the situation is not what you want or intercourse is attempted too soon, or there is pain).</td>
</tr>
<tr>
<td>- Do you sometimes have positive sexual thoughts, sexual daydreams and fantasies (even though you may not act on them)?</td>
</tr>
<tr>
<td>- Many women self-stimulate – is that something you still do from time to time?</td>
</tr>
<tr>
<td>- What would your answers have been to the above questions previously?</td>
</tr>
</tbody>
</table>
2. AROUSAL DISORDERS

Evaluate the following components of arousal:

- Mental sexual excitement
  - e.g. from reading, viewing, hearing erotica
  - stimulating the partner
  - receiving sexual stimulation to non-genital and genital areas
  - deliberate sexual fantasy or recall of sexual memories

- Direct awareness of genital congestion
  - tingling, pulsing, throbbing in response to the above stimuli, vaginal lubrication

- Indirect evidence of genital congestion
  - progressively intense sexual sensations from direct massaging of vulval structures with her fingers, partner's fingers, partner's body, oral stimulation, dildo, penile vulval contact.

- Cognitive and Affective Evaluation:
  - Clarify her thoughts (Is she distracted, feeling sexually substandard, worried the outcome would be negative, aware that the situation is not safe from STDs or pregnancy or will confirm again her infertility, is she feeling used, not being considered)
  - Clarify her emotions (Is there sadness, embarrassment, guilt, awkwardness, displeasure [e.g. from the giving of stimulation to the partner], are there feelings of attraction to the partner?)

3. ORGASMIC DISORDER (FOD)

- Clarify exactly what is unsatisfactory: its absence, delay, reduced intensity.
- Are there also concerns with arousal, i.e. is this arousal disorder by definition?
  (If so - evaluate as above)
- Is there fear of letting go control?
- Is the degree of trust and safety she needs to let go control present?
- What does she fear may happen?

4. DYSPAREUNIA AND VAGINISMUS

The detailed assessment follows in the section on sexual pain.

III. PHYSICAL EXAM

A careful focused pelvic exam is needed in the circumstances listed below. However, it must be remembered such an examination is intrusive and may elicit emotions linked to past coercive, abusive and/or painful sexual experiences. It is highly recommended that the procedure is explained in detail, what will and will not occur and the woman's understanding and consent obtained. She may prefer her partner or a nurse to be present. Details of the nature of examination are given in Chapter 16 under the heading of "Sexual Pain Disorders".

- For women with dyspareunia - an educational exam is often recommended - see section on "Pain Disorders".
- For women diagnosed with vaginismus, done in progressive stages once fear of vaginal entry has lessened with therapy an educational exam is recommended.
- For women with genital arousal disorder. Information will, of course, be limited because the genitalia are in non-aroused state but estrogen deficiency or more rarely, disease such as connective tissue disorder, can be identified.
- For women with combined arousal disorders. Likely there will be no abnormality - nothing arouses these women 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 vulval 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 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 therapeutic value).
Physical examination may not be needed on some occasions, e.g. the woman with low sexual desire or interest for sex but who is otherwise completely healthy. The complete physical exam is necessary for the woman who has symptoms additional to those sexual, e.g. fatigue, irregular menses. For women with chronic medical conditions, a general exam will be necessary to address mobility requirements for sexual activity, and also cardiac and respiratory status, given the physical demands of orgasm and intercourse. The presence of stomas, catheters, urinary diversions, or parts of the body that are giving rise to chronic pain and influencing sexual enjoyment can also be identified.

**IV. LABORATORY INVESTIGATIONS**

These are frequently unnecessary, but need to be done when there are relevant symptoms or findings in the general medical assessment. However, investigations may be needed specifically for sexual symptoms, e.g. the vaginal discharge may need to be examined with microscopy and culture and sensitivity when dyspareunia is considered to be potentially due to infection. If sensitive and accurate assays for androgens are available, they can be ordered to support a clinical diagnosis of insufficient androgen activity.

If psychophysiological investigation is available, this may be very helpful especially in identifying the common inattention to apparently healthy genital response [64]. However, the role of psychophysiological testing in the clinical arena is currently unclear.

**V. ESTABLISHING THE DIAGNOSES**

Comorbidity of sexual dysfunction in women is common, especially sexual interest disorder (hyposexual desire) and sexual arousal disorders. The following algorithm, Figure 4, parts 1 and 2, is recommended to aid diagnoses.

In addition:

a) Clarify if the Dysfunction is Lifelong or Acquired - see page (859).

b) Clarify if a Dysfunction is Situational or Generalized - see page (859).

c) Clarify Contextual Factors:

• PAST: negative upbringing/losses/trauma (physical, sexual, emotional), past interpersonal relationships, cultural/religious restrictions.

• CURRENT: interpersonal difficulties, partner sexual dysfunction, inadequate stimulation and unsatisfactory sexual emotional contexts.

• MEDICAL: surgical, psychiatric conditions, medications, substance abuse.

Given that women's sexuality is contextual, there is some difficulty with the concept of diagnosing a woman as having a sexual dysfunction when the primary problem appears to be the “sexual context” in which the sexual exchange occurs. However, she is reporting that dysfunction is present even though factors other than her own sexuality need to be highlighted. It is therefore strongly recommended to include contextual descriptors within each diagnosis.

d) Clarify the Degree of Distress

*Mild, moderate, marked*: in the absence of distress, a disruption of sexual response (or lack of interest) still has epidemiological but rather little clinical importance.

**VI. FORMULATION OF SEXUAL PROBLEMES**

Construction of the woman's sex response cycle noting the problematic areas is highly recommended (for example, see Figure 5).
Figures 4a

Detailed Sexual Inquiry

- Persistent lack of sexual interest, inability to sense desire at any time during the sexual experience?
  - Yes
  - Sexual interest/desire disorder
  - No

- Persistent inability to become aroused?
  - Yes
  - Sexual arousal disorder
  - No
  - Recurrent pain from attempted or completed intercourse?
    - Yes
    - Dyspareunia
    - No
    - Orgasm disorder

- Difficulty with vaginal entry, variable fear, avoidance, muscle tightening?
  - Yes
  - Vaginismus

Figures 4b

Further assessment of Arousal Disorder

- Stimuli which allow subjective excitement?
  - None
  - Awareness of lubrication?
    - Yes
    - Subjective Sexual Arousal Disorder
    - No
    - Combined Sexual Arousal Disorder
  - Many, but not genital
    - Genital Arousal Disorder
This section will focus on certain psychological factors potentially involved in the etiology of desire and arousal disorders. The focus here will be on depression, anxiety and personality factors. By focused inquiry into past and current psychological states, the clinician elucidates the predisposing, precipitating, and perpetuating factors implicated in the woman’s sexual difficulties, and is able to formulate a case conceptualization. It must be noted at the outset that there is a paucity of prospective, randomized controlled trials in this area, largely attributable to the ethical limitations involved in doing such research. In addition, two seemingly orthogonal research streams have focused on the impact of psychological factors in this way: one has employed controlled, laboratory investigations that typically involve an experimental manipulation; the other involves quasi-experimental clinical investigations of individuals with the psychological feature of interest. An attempt will be made to integrate the findings from these two streams of research. Studying psychological and personality factors may lead to a better understanding of the mechanisms involved in the development of sexual dysfunction. Such understanding also has major treatment implications and may guide a comprehensive, multidimensional treatment approach.

I. PSYCHOLOGICAL DEVELOPMENT

The development of personality and psychological profile begins before birth and continues life-long, involving a complex interplay between biological, psychological, and socio-cultural forces. One might consider a diathesis-stress model in which psychological factors present early in development interact with life events to influence a particular sexual profile. Alternatively, it is possible that the order of causation is reversed such that a particular sexual difficulty may trigger or exacerbate psychological distress. Given that the predominance of research examining the relationship between psychological factors and sexual dysfunction relies on correlational analyses, determining the order of causation is not possible.

II. GENERAL PSYCHOLOGICAL FEATURES

Studies that have examined general psychological profiles have consistently found higher rates of psy-
chological distress in women with sexual dysfunction [95-100] as shown in Table 8. Where conflicting findings arise, these can usually be attributed to different methodologies employed, as interview assessment results in higher prevalence compared to paper-and-pencil tests.

III. THE ROLE OF ANXIETY IN SEXUAL FUNCTION AND DYSFUNCTION

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 [102]. 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 [103], 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. 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.

IV. CLINICAL STUDIES ON ANXIETY IN WOMEN WITH SEXUAL DYSFUNCTION

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, as shown in Table 9. One review found high levels of anxiety in sexually dysfunctional individuals [104], however, there was a high degree of variability in the amount and quality of anxiety across individuals with different sexual disorders [117, 118]. Sexual aversion tends to correlate highly with acute anxiety [106]. More recent studies on women with general sexual dysfunction [107] as well as those with low sexual desire [108] find higher rates of depression and anxiety compared to sexually healthy women. 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 problems in nonclinical populations [109].

V. CLINICAL STUDIES ON SEXUAL FUNCTION IN WOMEN WITH ANXIETY DISORDERS

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 women with anxiety disorders - see Table 9. 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 [110, 111] and obsessive compulsive disorder [111] show lower sexual desire than healthy controls. Women with OCD are more likely to experience sexual difficulties, in particular avoidance of sexual activity, than women with generalized anxiety [112]. 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 [114]. However, in a very large sample of college students [113], as well as in a clinical sample of 40 socially phobic women [115] social anxiety was very strongly related to sexual difficulties, fewer sexual partners, and greater unhappiness in sexual encounters.

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. 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 [119]. 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 [116].
Table 8. Studies investigating general psychological features and sexual dysfunction in women. SD = sexual dysfunction, LOE = level of evidence

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Type of sample</th>
<th>LOE</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derogatis, Meyer, King, 1998 [95]</td>
<td>N = 325 male and female patients (n = 110 with inhibited orgasm, n = 8 with dyspareunia, n = 8 with vaginismus) seeking treatment for SD</td>
<td>4</td>
<td>Individuals completed the Symptom Check List-Revised 90 (SCL-R-90) and participated in psychiatric evaluations</td>
<td>50% of women with inhibited orgasm and 88% of women with dyspareunia or vaginismus met criteria for psychiatric diagnoses according to the SCL-90</td>
<td>Primary psychiatric symptoms were depression, interpersonal sensitivity, and psychosomatic. Unable to determine order of causation.</td>
</tr>
<tr>
<td>Schreiner-Engel, Schiavi, 1986 [96]</td>
<td>N = 46 married couples with inhibited desire compared to 36 control subjects</td>
<td>2a</td>
<td>Individuals participated in a clinical interview (the Schedule for Affective Disorders and Schizophrenia-Lifetime Version) and completed the SCL-R-90</td>
<td>Women with ISD had elevated lifetime prevalence rates of affective disorder, especially major depression; strong correlation between depression and inhibited desire onset</td>
<td>They speculate that the psychiatric disorder may be contributing to the development of low sexual desire but this is a correlational study.</td>
</tr>
<tr>
<td>Fagan, Schmidt, Wise, Derogatis, 1988 [97]</td>
<td>N = 65 women with SD</td>
<td>4</td>
<td>Full DSM-III criteria for various psychiatric disorders were assessed</td>
<td>5% with substance abuse; 9% affective disorder; 6% anxiety disorder; 3% adjustment disorder; 5% another Axis I disorder; 15% personality disorder</td>
<td>No control group included.</td>
</tr>
<tr>
<td>Osborn, Hawton, Gath, 1988 [98]</td>
<td>Community survey of 436 women aged 35-59 in a general medical setting</td>
<td>4</td>
<td>Questionnaire completion assessing prevalence of sexual dysfunction and other contextual factors</td>
<td>33% of the sample met criteria for SD; of these, 13% had significant psychiatric issues vs. 3% of women without SD; when comparing women who complain of sexual problems vs. those who do not, 31% of the former had significant psychiatric issues vs. 7% of the latter</td>
<td>No difference in women meeting criteria for SD vs. those that do not in psychiatric disorder; significant differences were found in women complaining of any sexual problem, especially prominent in those complaining of low desire</td>
</tr>
</tbody>
</table>
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</tr>
</thead>
<tbody>
<tr>
<td>Catalan, Hawton, Day, 1990 [99]</td>
<td>200 couples seeking treatment for SD</td>
<td>4</td>
<td>All couples took part in standardized assessments</td>
<td>0% had current psychiatric disorder – predominately depression and anxiety; 51% had lifetime psychiatric disorder</td>
<td></td>
</tr>
<tr>
<td>Donahue, Carroll, 1993 [100]</td>
<td>N = 47 male and N = 22 female patients seeking treatment for hypoactive sexual desire disorder</td>
<td>4</td>
<td>Completed the Sexual History Form, the Symptom Check List-Revised-90, the Dyadic Adjustment Scale, and the Stress Inventory.</td>
<td>Women showed symptom profiles similar to outpatients; also twice as much psychological distress than men with HSDD. Women reported experiencing twice as much stress as men</td>
<td>Most of the women had a primary sexual arousal disorder as well. Absence of a control group.</td>
</tr>
<tr>
<td>Van Lankveld, Grotjohann, 2000 [101]</td>
<td>Controlled study of N = 181 male and N = 201 female consecutive patients seeking bibliotherapy. (120 women with HSDD, 18 with orgasm disorder, 31 with vaginismus, and 32 with dyspareunia)</td>
<td>4</td>
<td>Took part in a composite international diagnostic interview; rates were compared to data from a large incidence study of a general population.</td>
<td>Significantly higher prevalence of anxiety disorder in women with SD compared to general population; prevalence of current affective disorder was higher than general population, but not statistically; compared to the general population, those with HSDD and dyspareunia had higher rates of depression and anxiety; women with vaginismus had higher rates of anxiety, and women with orgasmic disorder did not show any particular psychiatric profile</td>
<td>Limitation: only included individuals in a stable, heterosexual relationship, thus rates may be underestimated.</td>
</tr>
</tbody>
</table>
Table 9. Clinical studies investigating anxiety and sexual dysfunction in women. SD = sexual dysfunction, LOE = level of evidence

<table>
<thead>
<tr>
<th>Authors/year</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Norton, Jchu, 1984</td>
<td>Review of empirical studies on anxiety in individuals with SD</td>
<td>3a</td>
<td>Studies that compare anxiety in those with SD to those without; studies that examine efficacy for anxiety reduction procedures; studies that examine anxiety-related stimuli in SD</td>
<td>Anxiety is common among individuals with SD, but the level and nature of the anxiety varies greatly among individuals.</td>
<td>Most of the studies reviewed are Level 4 or 5</td>
</tr>
<tr>
<td>Murphy, Sullivan, 1981</td>
<td>Women with sexual aversion disorder compared to sexually healthy women</td>
<td>2b</td>
<td>Individuals completed the Social Sexual History Questionnaire, the State-Trait Anxiety Inventory, and the Sexual Response Questionnaire</td>
<td>Women with sexual aversion had higher levels of acute anxiety in sexual and non-sexual situations; also had higher rates of difficulty with identity, self-acceptance, and feelings of inadequacy.</td>
<td></td>
</tr>
<tr>
<td>Kaplan, 1995</td>
<td>N = 414 women with sexual aversion disorder over 20 years</td>
<td>4</td>
<td></td>
<td>35% of those with aversion disorder met criteria for anxiety disorder vs. 10% of those with other sexual dysfunctions</td>
<td></td>
</tr>
<tr>
<td>Campo, Bravo, Carmona, Perales, Calderon, 1999</td>
<td>N = 200 women with SD; N = 184 sexually healthy women</td>
<td>2b</td>
<td>Compared anxiety and depression levels in OB/GYN patients with and without SD</td>
<td>Higher levels of trait anxiety and depression in women with SD</td>
<td></td>
</tr>
<tr>
<td>Trudel, Landry, Larose, 1997</td>
<td>N = 20 couples.</td>
<td>4</td>
<td>Examined role of depression, anxiety, and marital adjustment in couples with low sexual desire</td>
<td>Low levels of depressed mood and moderate levels of anxiety</td>
<td></td>
</tr>
<tr>
<td>Katz, Jardine, 1999</td>
<td>N = 138 College undergraduates</td>
<td>4</td>
<td>Questionnaire study</td>
<td>Weak relationship between worry and low sexual desire, as well as between worry and sexual aversion.</td>
<td></td>
</tr>
</tbody>
</table>
Table 9. Clinical studies investigating anxiety and sexual dysfunction in women. SD = sexual dysfunction, LOE = level of evidence

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<tbody>
<tr>
<td>Ware, Emmanuel, Johnson, Brawman-Miatzer, Knapp, Crawford-Harrison, Lydiard, 1996 [110]</td>
<td>Women with social phobia, panic disorder, and generalized anxiety disorder</td>
<td>2b</td>
<td></td>
<td>Higher rates of low sexual desire specifically in women with panic disorder</td>
<td></td>
</tr>
<tr>
<td>Van Minnen, Kampman (2000) [111]</td>
<td>Female inpatients with panic disorder (n = 27) and OCD (n = 7) were compared to 34 sexually healthy women</td>
<td>2b</td>
<td>Administered the Questionnaire for Screening Sexual Dysfunction, Maudsley Marital Questionnaire, and Symptom Check-list</td>
<td>Women with OCD and panic had lower sexual desire and frequency of intercourse; 76% of OCD patients, 44% of panic patients, and 17% of controls met criteria for sexual dysfunction; OCD patients more impaired than panic– showed lower sexual satisfaction</td>
<td>No differences in sexual arousal or orgasm; patients with anxiety disorder may be more likely to develop SD which allows them to avoid potentially “dangerous” situations</td>
</tr>
<tr>
<td>Aksaray, Yelken, Kaptanoglu, Olu, Ozlutin, 2001 [112]</td>
<td>Consecutive cases of N = 23 outpatients with OCD compared to n = 26 outpatients with generalized anxiety disorder</td>
<td>2b</td>
<td>Administered Maudsley OC inventory, State-Trait anxiety inventory, and GRISS</td>
<td>Women with OCD more sexually nonsensical, avoidant, and anergic than women with GAD</td>
<td>OCD may be a risk factor for SD</td>
</tr>
<tr>
<td>Leary, Dobbins, 1983 [113]</td>
<td>260 college students</td>
<td>4</td>
<td>Completed questionnaires on sexual experience and level of heterosexual anxiety</td>
<td>Those with high heterosexual anxiety had fewer sexual partners, lower frequency of sexual intercourse, higher incidence of sexual difficulties, greater unhappiness in sexual encounters</td>
<td>Social anxiety leads to reduced opportunities for social interaction, therefore less dating, romantic and sexual partners, and therefore end up less sexually experienced</td>
</tr>
</tbody>
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Table 9. Clinical studies investigating anxiety and sexual dysfunction in women. SD = sexual dysfunction, LOE = level of evidence

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<tbody>
<tr>
<td>Figueira, Possidente, Marques, Hayes, 2001 [114]</td>
<td>Retrospective review of male and female patients (n = 14 women with panic disorder, n = 11 women with social phobia)</td>
<td>4</td>
<td>Authors developed a semi-structured interview to assess for DSM-IV SDs</td>
<td>Sexual aversion disorder was the most common SD in panic disorder patients (50% of 14). FSAD, orgasm disorder, dyspareunia, and vaginismus did not differ</td>
<td>Patients reported sexual aversion developed because of panic; Small sample and retrospective design limit the generalizability</td>
</tr>
<tr>
<td>Bodinger, Hermesh, Aizenberg, Valevski, Marom, Shiloh, Gothelf, Zemishlany, Weizman, 2002 [115]</td>
<td>N = 40 male and female patients with social phobia compared to N = 60 anxiety-free individuals.</td>
<td>2b</td>
<td></td>
<td>Women with social phobia had significantly higher impairment in desire, arousal, sexual activity, and subjective satisfaction, and fewer sexual partners</td>
<td>Attributed to difficulty with sexual interaction</td>
</tr>
<tr>
<td>Van den Hout, Barlow, 2000 [116]</td>
<td>Review of the literature</td>
<td>2a</td>
<td>Reviewed clinical and experimental studies on sexual disorders and anxiety disorders to explore any relationship</td>
<td>Provide a theoretical framework for understanding the relationship between anxiety and sexual dysfunction: increasing threat narrows attention that for individuals with SD forces them to focus on nonsexual, task-irrelevant performance concerns whereas for sexually healthy individuals, attention is more efficiently focused externally on erotic material</td>
<td>Although most of the literature cited to substantiate their theory is based on research with men, they do not distinguish between men and women when proposing this theory</td>
</tr>
</tbody>
</table>
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, as shown in Table 10.

In sexually healthy women, anxiety-inducing techniques have been found to significantly increase psychophysiological sexual arousal [79, 120, 121, 123]. Specifically, it appears as though anxiety’s mechanism of action may be via increased sympathetic nervous system (SNS) activity given that exercise [86] and other methods of SNS-facilitation [45] enhance physiological sexual arousal. Subjective sexual arousal, however, has been shown to be increased [79] decreased [121], and unaffected [45-47, 86] by these techniques. In women with heterogeneous sexual difficulties, anxiety significantly improved genital sexual congestion [121, 123, 124]. In contrast, heightened SNS activity facilitated genital sexual congestion in women with low sexual desire, but impaired it in women with orgasm disorder, and there was no effect on subjective sexual arousal [46]. Taken together, these results suggest that techniques which facilitate SNS activity may have promise for improving genital congestion - but not subjective sexual arousal.

Whereas anxiety historically has been linked to impaired sexual function, more recent laboratory evidence suggests potential enhancement of the physical response, at least by some types of anxiety. However, high levels of clinical anxiety are related to impaired sexual function in the real life situation. Clearly, investigations that aim to clarify the mechanisms by which acute and chronic anxiety affect sexual function are needed. Moreover, research must aim to identify the precise cognitive, affective, and/or physiological processes by which anxiety and women’s sexual function are related. The ongoing work by Janssen & Bancroft exploring a dual-control model of sexual excitation and inhibition in women as well as men, may clarify any role of anxiety in women’s predisposition to sexual inhibition and to sexual excitement [11].

Loss of interest or pleasure is a hallmark feature of depression. By extension, sexual interest is vulnerable to the effects of depression, and impaired sexual desire has been found in the majority of patients with depressed mood since the mid-1960s [125]. The opposite may also be true in that disruption in sexual function may affect mood. As with anxiety, two streams of research, one conducted in a laboratory and other in clinical samples, has attempted to explore the relationship between depression and sexual function - see Table 11.

Derogatis and colleagues administered the Symptom Check-List Revised 90 (SCL-90R) to 325 male and female outpatients seeking treatment for sexual dysfunction [95]. Of the 126 women, 50% were assigned a psychiatric diagnosis. Specifically, major depression was found to be a feature of women with orgasm disorder and sexual pain disorder. Schreiner-Engel and Schiavi [96] compared women with impaired sexual desire to sexually healthy controls on current and lifetime affective symptoms. 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.

VII. CONCLUSIONS: ANXIETY AND SEXUAL FUNCTION IN WOMEN

VIII. THE ROLE OF DEPRESSION IN SEXUAL FUNCTION AND DYSFUNCTION

IX. CLINICAL STUDIES ON DEPRESSION IN WOMEN WITH SEXUAL DYSFUNCTION
Table 10. Laboratory studies investigating anxiety and sexual dysfunction in women. SD = sexual dysfunction, LOE = level of evidence

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Type of sample</th>
<th>LOE</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoon, Wincze, Hoon, 1977 [120]</td>
<td>Sexually functional women in a controlled laboratory setting</td>
<td>2b</td>
<td>Women viewed an anxiety-elicitting video prior to an erotic film</td>
<td>Anxiety pre-exposure led to significantly higher VBV</td>
<td>Confounds of testing in an artificial laboratory environment.</td>
</tr>
<tr>
<td>Luan, Everaerd, van Anholt, Rebe, 1993 [79]</td>
<td>49 sexually healthy university students</td>
<td>2b</td>
<td>Women were given specific instructions that induced performance demand during conditions of film and erotic fantasy</td>
<td>Performance demand resulted in significantly higher genital arousal, especially during the fantasy condition. It also significantly facilitated overall subjective arousal, strongest genital sensations</td>
<td>Confounds of testing in an artificial laboratory environment.</td>
</tr>
<tr>
<td>Palace, Gorzalka, 1990 [121]</td>
<td>16 women diagnosed by physician with psychogenic sexual dysfunction (3 HSDD, 8 orgasmic disorder, 3 dyspareunia; 10 of these had low sexual desire and 4 had arousal secondary arousal disorder) compared to 16 sexually healthy women</td>
<td>2b</td>
<td>All women viewed an erotic film that was preceded by an anxiety film and a neutral film; photoplethysmography and a self-report film scale measured genital and subjective sexual arousal, respectively</td>
<td>Significant facilitation in genital arousal with the anxiety-elicitting film in women with and without SD. Significant reduction in subjective sexual arousal with anxiety pre-exposure in all women</td>
<td>Heterogeneous groups of women limit clear conclusions to be drawn</td>
</tr>
<tr>
<td>Palace, 1995a [122]</td>
<td>Review of the literature</td>
<td>2a</td>
<td>Reviews the laboratory studies of anxiety in sexual arousal and provides a theoretical framework for understanding</td>
<td>Describes an additive model in which the effects of a physiologically based intervention to enhance autonomic arousal combine with a cognitively based intervention to facilitate labeling of genital cues</td>
<td>Suggests that treatment of sexual dysfunction may benefit from using techniques that enhance physiological activation as well as modify negative cognitions</td>
</tr>
<tr>
<td>Palace, 1995b [123]</td>
<td>Laboratory study of 64 women with SD</td>
<td>1b</td>
<td>Randomly assigned to one of four conditions based on autonomic activation vs. neutral pre-exposure, and false feedback vs. no feedback</td>
<td>Anxiety film and positive false genital arousal feedback significantly increased genital arousal, with the combination eliciting the highest amount. Positive false feedback also increases subjective sexual arousal.</td>
<td>Sexual dysfunction may be modified through the repeated pairing of autonomic arousal and feedback</td>
</tr>
</tbody>
</table>
Table 10. Laboratory studies investigating anxiety and sexual dysfunction in women. SD = sexual dysfunction, LOE = level of evidence

<table>
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<tr>
<th>Authors/ year</th>
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</tr>
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<tbody>
<tr>
<td>Meston, Gorzalka, 1995 [86]</td>
<td>Laboratory study of 35 sexually healthy women</td>
<td>2c</td>
<td>Viewed neutral and erotic films during an exercise and no exercise conditions. Genital and subjective sexual arousal measured.</td>
<td>Exercise significantly facilitated VPA, and had no effect on subjective arousal.</td>
<td>It is possible that the effects of anxiety occur through heightened sympathetic nervous system activity.</td>
</tr>
<tr>
<td>Meston, Gorzalka, 1996 [46]</td>
<td>Laboratory study of N = 12 women with orgasmic disorder, N = 12 women with low desire, and N = 12 sexually healthy women</td>
<td>2c</td>
<td>Viewed neutral and erotic films during an exercise and no exercise conditions. Genital and subjective sexual arousal measured.</td>
<td>Exercise significantly facilitated VPA in sexually healthy women and women with low sexual desire, but impaired it in women with orgasmic difficulties. Exercise had no effect on subjective arousal in any group.</td>
<td>Women with SD did not meet diagnostic criteria for SD, but rather, self-reported sexual difficulties. Unclear to what extent the current findings generalize to women with sexual dysfunction.</td>
</tr>
<tr>
<td>Meston, Heiman, 1998 [45]</td>
<td>Laboratory study of N = 20 sexually healthy women</td>
<td>2b</td>
<td>Viewed neutral and erotic films during an ephedrine and during a placebo condition. Genital and subjective sexual arousal measured.</td>
<td>Ephedrine significantly facilitated genital arousal but had no effect on subjective arousal.</td>
<td>Findings are limited to young, sexually healthy women.</td>
</tr>
<tr>
<td>Brocco, Gorzalka, 2002 [47]</td>
<td>Laboratory study of sexually healthy women, N = 25 young, premenopausal; N = 21 perimenopausal; N = 25 older, postmenopausal</td>
<td>2b</td>
<td>Viewed neutral and erotic films during a condition of laboratory-induced hyperventilation and the control condition. Genital and subjective sexual arousal measured.</td>
<td>The SNS-enhancing technique significantly increased genital arousal only in young premenopausal women, and had no effect on subjective arousal in any group of women.</td>
<td>Possible that the effects of anxiety and SNS activity are most prominent only in young, premenopausal women.</td>
</tr>
<tr>
<td>Authors/ year</td>
<td>Type of sample</td>
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<tr>
<td>Derogatis, Meyer, King, 1981 [95]</td>
<td>N=325 male and female patients (n = 110 with inhibited orgasm, n = 8 with dyspareunia, n = 8 with vaginismus) seeking treatment for SD</td>
<td>4</td>
<td>Patients were administered the SCL-90R and received a psychiatric evaluation.</td>
<td>Depression was a feature of women with orgasmic disorder and sexual pain disorder.</td>
<td>Difficult to determine order of causation.</td>
</tr>
<tr>
<td>Schreiner-Engel, Schiavi, 1986 [96]</td>
<td>Compared 24 female and 22 male patients seeking treatment for desire disorder with 36 sexually healthy individuals. None met criteria for affective disorder at study entry.</td>
<td>2b</td>
<td>Each individual completed the SCL-90, a clinical interview, and an instrument assessing lifetime affective and schizophrenic disorders.</td>
<td>Women with sexual desire disorder were twice as likely as controls to have a history of major depressive disorder. In 100% of these women did the major depressive episode either coincide with or precede the sexual dysfunction onset.</td>
<td>Argued for a common biological etiology, or that affective psychopathology may be contributing to pathogenesis of sexual desire problems.</td>
</tr>
<tr>
<td>Kivela &amp; Pahkala, 1988 [126]</td>
<td>Exploration of mood and sexuality variables in a sample of elderly Finnish men and women.</td>
<td>4</td>
<td>Completed the Hamilton Rating Scale for Depression and symptoms of sexual dysfunction.</td>
<td>Loss of libido was a feature of depressed women only in the 60-year age group but not the 70-year age group.</td>
<td>Did not use validated instruments to assess sexual difficulties.</td>
</tr>
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</table>
Table 11. Clinical studies investigating depression and sexual dysfunction in women. SD = sexual dysfunction, LOE = level of evidence

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<thead>
<tr>
<th>Authors/ year</th>
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<tbody>
<tr>
<td>Dunner, Dwyer, Fieve, 1976 [128]</td>
<td>Examined sexual symptoms in men and women with uni- and bipolar depression</td>
<td>4</td>
<td>Methodology</td>
<td>Significant reduction in libido in most patients with uni- and bipolar depression.</td>
<td>Data were not broken down by gender.</td>
</tr>
<tr>
<td>Kennedy, Dickens, Eisfeld, Bagby, 1999 [129]</td>
<td>Consecutive series of N = 79 women with Major Depression</td>
<td>4</td>
<td>Completed the Sexual Function Questionnaire which asked about sexual function in the preceding month</td>
<td>Only 50% of women reported sexual activity in the preceding month. Over 50% of women reported decreased sexual desire. 40-50% of the women reported difficulties with arousal, and 15-20% reported problems with orgasm. Age of depression onset and number of depressive episodes correlated with sexual dysfunction whereas severity of depression did not.</td>
<td>Absence of non-depressed comparison group.</td>
</tr>
<tr>
<td>Frohlich, Meston, 2002 [130]</td>
<td>N = 47 college-age women without depressed mood were compared to N = 47 college-aged women with clinical depression.</td>
<td>2b</td>
<td>Women completed the Brief Index of Sexual Functioning for Women in the laboratory.</td>
<td>The depressed group had significantly higher levels of desire for sexual activity alone than the non-depressed group. No differences in the two groups in desire for sexual activity with a partner. Women with depression had significantly higher levels of problematic arousal, orgasm, pain, less satisfaction, and less pleasure.</td>
<td>Speculated that the higher level of sexual desire alone may reflect the fact that this is a reliable form of pleasure compared to sexual activity with a partner. Study limited by the sole use of the Beck Depression Inventory to diagnose depression.</td>
</tr>
</tbody>
</table>
X. CLINICAL STUDIES ON SEXUAL FUNCTION IN DEPRESSED WOMEN

The literature on sexual function of depressed individuals is complicated by the effects of antidepressant medication. Bartlik and colleagues reviewed the literature on sexual dysfunction secondary to depressive disorders, concluding that loss of desire is a consistent consequence of major depression, regardless of antidepressant use [131]. Kivela found a strong association between low sex drive and depression in Finnish women in their 60s [126]. Decreased libido was also found to be a key feature in depressed patients with Bipolar disorder [125, 128]. 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 [129].

XI. LABORATORY STUDIES ON DEPRESSED MOOD IN WOMEN WITH SEXUAL DYSFUNCTION

Frohlich and Meston compared depressed to non-depressed 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 [130].

XII. CONCLUSIONS : DEPRESSION AND SEXUAL FUNCTION IN WOMEN

Compared to the literature on anxiety and sexual function, a strong, and clear relationship exists between depressed mood and sexual dysfunction in women. 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. This literature is complicated by the high number of medicated depressed patients, thus precluding clear conclusions.

XIII. PERSONALITY VARIABLES AND WOMEN’S SEXUAL FUNCTION

Compared to the research on psychiatric disorders and women’s sexual dysfunction, much less attention has focused on the role of personality disorders - see Table 12. An extensive exploration into the role of personality factors in female orgasm failed to find any major associations [132]. With respect to hypoactive sexual desire disorder, Hartmann and colleagues studied 52 consecutive women diagnosed with HSDD, and found significant disturbance with emotional stability and self-esteem [31].

Some authors have speculated that such 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 [133]. 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 [134].

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 [135]. In an extensive review which included individual differences pertaining to women's sexuality, Andersen and Cyranowski [136] 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 [137] whereas in younger women, the trait of Extraversion was more prominent [138].
<table>
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<tr>
<th>Authors/year</th>
<th>Type of sample</th>
<th>LOE</th>
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<tbody>
<tr>
<td>Hartmann, Heiser, Ruffer-Hesse, Kloth, 2002 [31]</td>
<td>Two samples of N = 52 and N = 66 women with HSDD (30-70% also had arousal difficulties) were compared to a sexually healthy group.</td>
<td>2c</td>
<td>Women in the first sample took part in detailed clinical interviews and completed self-report questionnaires addressing several aspects of physical and psychological functioning. Women in the second sample completed personality inventories.</td>
<td>Older women had significantly more depressed episodes, more psychosomatic symptoms, and a higher frequency of psychological therapy. More than 2/3 experienced a significant lack of self-esteem and feelings of guilt. Elevated scores on neuroticism and lower scores on extraversion and openness.</td>
<td>Women seeking treatment for desire disorder have significant mood instability, and a low and fragile self-regulation and self-esteem. Unable to determine direction of causality in this study.</td>
</tr>
<tr>
<td>Apt, Hurlbert, 1994 [133]</td>
<td>Compared a sample of women with histrionic personality disorder to non-histrionic women</td>
<td>2b</td>
<td>Completed a battery of questionnaires.</td>
<td>Women with HPD were found to have significantly lower sexual assertiveness, greater erotophobic attitudes toward sex, lower self-esteem, and greater marital dissatisfaction. They were also found to evidence significantly greater sexual preoccupation, lower sexual desire, more sexual boredom, greater orgasmic dysfunction, and were more likely to enter into an extramarital affair. Despite these impairments, this group was found to have higher sexual esteem.</td>
<td>Sexual behavior in this group varies widely from non-responsive to sexually promiscuous.</td>
</tr>
<tr>
<td>Authors/ year</td>
<td>Type of sample</td>
<td>LOE</td>
<td>Methodology</td>
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<tr>
<td>Hurlbert, Apt, White,</td>
<td>Compared women with borderline personality disorder to a matched sample of non-</td>
<td>2c</td>
<td>Completed the Hurlbert Index of Sexual Assertiveness, the Sexual Opinion</td>
<td>50% of the women with borderline personality reported history of abuse vs. 15% of controls; women with borderline had higher sexual assertiveness, erotophilic attitudes, and higher self esteem. They had greater sexual depression and sexual dissatisfaction.</td>
<td></td>
</tr>
<tr>
<td>1992 [134]</td>
<td>personality disordered women, aged 23-33</td>
<td></td>
<td>Survey, the Sexuality Scale, and the Index of Sexual Satisfaction.</td>
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<tr>
<td>Apt &amp; Hurlbert,</td>
<td>Nonclinical population of married women. Comparisons were made between matched</td>
<td>2b</td>
<td>Zuckerman’s Sensation Seeking Scale.</td>
<td>High sensation seekers had higher sexual desire, arousability, but less sexual satisfaction.</td>
<td></td>
</tr>
<tr>
<td>1992 [135]</td>
<td>samples of high and low sensation seekers</td>
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<td></td>
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<tr>
<td>Andersen, Cyranowski,</td>
<td>Systematic review of cohort studies examining individual differences in women’s</td>
<td>2a</td>
<td>Costa et al., 1992</td>
<td>Older women seeking treatment for sexual dysfunction had high Neuroticism Younger women with sexual complaints had higher Extraversion.</td>
<td>Validated instruments for sexual dysfunction were not used.</td>
</tr>
</tbody>
</table>
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. 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.

Given the links between low desire/impaired subjective arousal, with depression, clinical anxiety disorders and certain personality attributes, the following components of the psychological assessment are recommended. As the studies reviewed are mostly levels 2b and 4, the grade of recommendation is B-C.

- Assessment of women's sexual function should always take into account psychological and personality factors that might affect or be affected by the current sexual difficulty.
- Regardless of antidepressant use, depression is consistently related to sexual dysfunction, in particular low sexual desire. The clinician must assess mood, and associated symptoms of depressive disorder, in women presenting with sexual difficulties.
- The temporal relationship between psychiatric symptom and sexual difficulty should be assessed in order to determine cause or effect.
- Given the conflicting data on the role of chronic versus acute anxiety in women's sexual dysfunction, a clear assessment of the severity, chronicity, and degree of anxiety is necessary to understand what role, if any, anxiety plays in maintaining the current sexual complaint.
- In order to distinguish if a personality or psychological feature is influencing a given sexual concern, and thus amenable to change, the clinician should assess if such features are reflective of deep-rooted personality factors (i.e., trait), or short-term reactions (i.e., state).

Psychological therapy remains the mainstay of management of women's sexual dysfunction. Making deliberate changes in thoughts and attitudes and in behaviour can lead to not only changes in the mind (feelings and emotions) but changes in the body's physiology - including sexual response. Psychological management contains various elements. **Sensate focus techniques originate** from the work of Masters and Johnson [139] and consist of **exchanging physical touch, moving from non-sexual to sexual touching**. They resemble the systematic desensitization approach common to behaviour therapies, in that anxiety-reduction is incorporated throughout the process. **Sex therapy** may also address the woman's distractions during sexual stimulation, promote more varied and/or more prolonged sexual stimuli, and encourage the couple to guide each other as to their required sexual stimulation. Safety, privacy, optimal timing of sexual contacts can also be addressed. **Cognitive-behavioural therapy (CBT) adds attention to cognitive restructuring of distortions and myths** that may be related to the sexual difficulty, and places a heavy emphasis on “in session” and homework assignments. The behavioural changes may include addressing the lack of required sexual stimuli and/or addressing the sexual context, including privacy, safety, what has occurred prior to attempting sexual activity, what will follow, as well as concurrent demands, e.g. sleep, care of children. **Couple therapy is commonly a component of, or adjunct to sex therapy, and focuses on interpersonal issues such as communication training** that affect the sexual relationship. **Psychodynamic therapy** has also received much attention as it relates to female sexuality. This therapy tends to **focus on issues in the woman's past developmental period** that influence current sexual function, especially her arousability (factors governing the information processing of the sexual stimuli). Particular attention to family of origin as well as the parental relationship can often provide important insights into the current sexual difficulty. Schnarch proposes that as part of **systemic therapy**, **sexual differentiation** (i.e., ability to balance desire
for contact with desire for uniqueness) is important for relationship and sexual health [140].

II. REVIEW OF EFFICACY OF PSYCHOLOGICAL THERAPY

This section will review psychological treatments for hypoactive sexual desire disorder and combined desire and arousal disorders, including studies cited in the review by Heiman and Meston [141] as well as additional investigations that have been published since 1997. Most are of Levels 3, 4, and 5 evidence. A literature search resulted in only one relevant randomized controlled trial.

1. DIFFICULTIES WITH OUTCOME RESEARCH

Research on efficacy of sex therapy is challenged by a number of factors that make this type of research difficult and inconclusive. (1) Women's sexual complaints may take the form of formal DSM-IV diagnoses such as lack of, or diminished sexual desire or interest, or pain during both genital and non-genital sexual activities [142, 143]. However, women's sexual complaints also include dissatisfactions that do not involve observable or perceived physical impairment but rather, unobservable factors related to pleasure, enjoyment, satisfaction, or passion. The International Classification of Diseases - 10, acknowledges this by noting the "anhedonia/lack of sexual enjoyment" category [56]. Although these components are recognized by the treating clinician, they tend not to receive detailed attention in efficacy research. As such, our outcome research may be targeting and/or detecting changes in aspects of the sexual response that are less important for women than these more ubiquitous aspects. (2) Given the biopsychosocial complexity of the sexual response, it is difficult for researchers to agree on what endpoint variables should be assessed as indicators for response to treatment. (3) Researchers also have not reached consensus on the degree of change which denotes improvement versus no change. Historically intercourse frequency was the gold-standard indicator of sexual function; however, exclusive focus on this variable ignores the rich complexity of sexuality that cannot be captured by a simple frequency count of one particular act. In their review, Heiman and Meston (1997) criticize this literature for employing small sample sizes, failing to include adequate control groups, lacking randomization, unclear descriptions of diagnostic criteria which prohibit replication, failing to include long-term follow-up data, and incomplete descriptions of the therapy technique utilized, again prohibiting replication [141]. This research area also has not historically employed treatment manuals or assessment instruments with good psychometric properties. Lack of recognition of this topic as a high priority by major granting agencies, and minor incentive for pharmaceutical companies to fund psychological efficacy studies may explain the paucity of well-controlled randomized trials of psychological therapy.

2. MASTERS AND JOHNSON SEX THERAPY

In 1970 Masters and Johnson published their efficacy studies conducted on 500 couples seen in their institute [139]. Briefly, treatment was administered 2-3 times/week by a male-female therapist duo, and outcome was assessed with one item (i.e., success or not) by these clinicians. Success rates reached 72% for female anorgasmia and 98% for vaginismus, with a mere 5% relapse rate after five years. Given the expensive, intensive, and unfeasible nature of Masters and Johnson's model of sex therapy, there has been no replication of their findings. However, this body of research stimulated an attempt at exploring which component(s) of their therapy were responsible for improving sexual function. In a large clinical trial of 365 married couples presenting to a sex therapy clinic with heterogeneous sexual complaints, 65% of the couples responded to behavior therapy with improved outcomes. Specifically, the amount of sensate focus was most strongly predictive of a positive outcome [144]. However, it is unclear which sexual complaints specifically benefited from treatment and the outcome measure was simply a clinician-judgement of the primary sexual complaint.

III. SEXUAL DESIRE DISORDERS

Most women complaining of low desire are in fact suffering from a concomitant arousal disorder [35, 36, 38-40]. However, with a model of lubrication difficulties as the central focus in arousal complaints, lack of wanting sexual experience, for whatever reasons, has been termed low sexual desire. In fact, as reviewed in Basson (2002), the data support the conclusion that women can enjoy healthy and rewarding sexual lives, despite minimal awareness of desire, and the latter is not typically their primary
incentive for seeking sexual activity [61]. Few published efficacy studies exist for sexual desire disorder. Numerous published descriptions of treatments for this condition exist, but few meet criteria for evidence-based treatment [140].

Crowe and colleagues compared traditional sex therapy with marital therapy and relaxation training in 48 couples presenting with erectile dysfunction, low sexual desire, and anorgasmia. Although results suggest that the sex therapy improved self-reported desire, data were not examined by gender or by individual diagnosis [146]. The outcome data of Zimmer (1987) faced similar confounds in that although their treatment showed benefit of sex therapy over relaxation training, data were not examined separately by presenting problem [147]. Hawton employed a modified Masters and Johnson approach in his prospective, non-controlled study of a community sample of couples. Sexual desire difficulties were significantly improved in 56% of the couples following treatment, however 75% of the sample relapsed at 1-6 years post-treatment [148]. Hurlbert investigated the efficacy of orgasm consistency training for the treatment of female desire disorder [149]. Women received either standard sex therapy or sex therapy plus orgasm consistency training (directed masturbation) in addition to sensuality exercises, communication training and education. Both groups demonstrated greater sexual arousal, assertiveness, and satisfaction, but the combination group experienced greater overall improvement. The efficacy of CBT in women with sexual desire disorder has been examined in two studies [150]. McCabe found that CBT in a sample of women seeking treatment for mixed sexual dysfunction resulted in 54% of the sample retaining this complaint following treatment. However, the findings are limited in that a large number of the women had multiple sexual dysfunctions, and there was the absence of a comparison control group. In the only published study testing the efficacy of a psychological treatment for impaired desire against a control group, CBT was adapted to specifically target relevant causal factors implicated in impaired desire [151]. Only 26% of women with HSDD randomized to the CBT condition met diagnostic criteria for this disorder at post-treatment, and this stabilized to 36% at one-year follow-up. Compared to the control group, CBT also led to significant improvements in: the quality of the sexual and marital life, sexual satisfaction, perception of sexual arousal, dyadic adjustment and cognitions, sexual repertoire and pleasure, sexual self-esteem, motivation, depression, and anxiety, and fewer dysfunctional negative cognitions - see Table 13.

Basson (1996) reviewed important factors to consider when treating low desire that appears to be beyond the common lessening with relationship duration [152]. She highlighted the importance of attention to the emotional intimacy and other contextual factors that historically promoted healthy responsive sexual desire. In addition, management should address the cause of the non-rewarding outcome of the sexual encounter. Once these factors have been identified, they can receive focused attention and intervention. These claims are based on level 4 and 5 evidence [153].

IV. SEXUAL AROUSAL DISORDERS

There are no published outcome studies focusing on the psychological treatment of arousal disorders in women. This may largely be attributable to the previously mentioned high degree of comorbidity between desire and arousal disorders, as well as desire and orgasm disorders.

Recently, attention to one aspect of dysfunctional sexual arousal has increased. The success of vasoactive agents in the treatment of male sexual arousal (i.e., erectile disorder), has prompted a focus on women's genital congestion and the testing of similar vasoactive products. Lack of recognition of the need to distinguish impaired genital congestion from absence of subjective arousal (despite genital congestion) has limited progress in this area - see section on “Genital Arousal Disorder”.

V. NON-HORMONAL PHARMACOLOGICAL TREATMENT OF LOW SEXUAL DESIRE

The place of pharmacological management for women's complaint of low desire is unclear. Given the broad normative range of women's appreciation of “sexual desire” in sexually content women and the importance of subjective arousal once sexual stimulation has begun, which then generates sexual desire, the appropriate outcome criteria for any “desire drug” remain to be determined. Two studies have been reported - both with bupropion hydrochloride. A 12-week double-blind placebo controlled study
<table>
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<tr>
<th>Authors, year</th>
<th>Type of sample</th>
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<tr>
<td>Masters, Johnson, 1970 [139]</td>
<td>500 couples attending the Masters and Johnson Institute seeking treatment for SD.</td>
</tr>
<tr>
<td>Sarwer, Durlak, 1997 [144]</td>
<td>Field trial of behavioral sex therapy in 365 couples presenting with a range of SD.</td>
</tr>
<tr>
<td>Crowe, Gillan, Golombok, 1981 [146]</td>
<td>Compared traditional sex therapy with marital therapy and relaxation training in 48 couples presenting with erectile dysfunction, low sexual desire, or anorgasmia.</td>
</tr>
<tr>
<td>Zimmer, 1987 [147]</td>
<td>Controlled comparison of (1) relaxation and information then sex therapy, (2) marital therapy then sex therapy, and (3) wait-list control group.</td>
</tr>
</tbody>
</table>

### LOE

- 2b All couples received 12 weeks of treatment. |
- 4 Intensive 2-3/week sex therapy; endpoint measure was one clinician-determined judgment of improved vs. not improved. |
- 4 Outcome defined dichotomously as successful vs. unsuccessful. |

### Results

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>LOE</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masters, Johnson, 1970 [139]</td>
<td>4</td>
<td>Intensive 2-3/week sex therapy; endpoint measure was one clinician-determined judgement of improved vs. not improved.</td>
<td>Success rates were: 98% vaginismus, 96% premature ejaculation, 78% secondary erectile dysfunction, 72% female anorgasmia, 67% primary erectile dysfunction. Relapse rates after 5 years were 5.1%.</td>
</tr>
<tr>
<td>Sarwer, Durlak, 1997 [144]</td>
<td>4</td>
<td>Outcome defined dichotomously as successful vs. unsuccessful.</td>
<td>63% success rate across entire sample, with little effect of diagnosis, gender, or abuse history. Strongest predictor: amount of sense of focus in last week of treatment. 70% of women maintained gains at one year follow-up.</td>
</tr>
<tr>
<td>Crowe, Gillan, Golombok, 1981 [146]</td>
<td>2c</td>
<td>Compared traditional sex therapy with marital therapy and relaxation training in 48 couples presenting with erectile dysfunction, low sexual desire, or anorgasmia.</td>
<td>Sex therapy improved self-reported sexual desire.</td>
</tr>
<tr>
<td>Zimmer, 1987 [147]</td>
<td>2b</td>
<td>Controlled comparison of (1) relaxation and information then sex therapy, (2) marital therapy then sex therapy, and (3) wait-list control group.</td>
<td>Both treatment groups showed clinical and statistical improvement, but treatment gains were more pronounced in those who received combined marital and sex therapy.</td>
</tr>
</tbody>
</table>

**Table 13. Efficacy studies investigating effects of psychological therapy on female sexual desire disorder. SD = sexual dysfunction; LOE = level of evidence.**
Table 13. Efficacy studies investigating effects of psychological therapy on female sexual desire disorder. SD = sexual dysfunction; LOE = level of evidence.

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Type of sample</th>
<th>LOE</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawton, Catalan, Martin, Fagg, 1986 [148]</td>
<td>Uncontrolled prospective study of a modified Masters and Johnson approach in 140 outpatients seeking treatment for SD.</td>
<td>4</td>
<td>Independent assessors rated degree of improvement on a 5-point scale.</td>
<td>Entire group: immediate post treatment response: 26% resolved, 32% resolved with some difficulties, 18% some improvement, 22% no change, 2% worse. Success rate in women with hypoactive desire was 56%. 75% of the total sample relapsed at 1-6 year follow-up.</td>
<td>75% relapse rate 1-6 years post-treatment.</td>
</tr>
<tr>
<td>Hurlbert, 1993 [149]</td>
<td>Randomized comparison of standard group intervention compared to standard group intervention plus orgasm consistency training in 39 women with hypoactive sexual desire disorder.</td>
<td>1b</td>
<td>Specificity of sexual change in arousal, assertiveness, and satisfaction were assessed.</td>
<td>All women responded positively to treatment. Women in the combined group reported greater sexual arousal and assertiveness following treatment.</td>
<td></td>
</tr>
<tr>
<td>McCabe, 2001 [150]</td>
<td>CBT was assessed in 54 women presenting to a sexual behaviour clinic with complaints of SD.</td>
<td>4</td>
<td>Patients completed the Sexual Function Scale and the Sexual Dysfunction Scale at pretreatment and after 10 sessions of CBT.</td>
<td>54% of the women retained their sexual complaints following treatment, although overall levels of sexual dysfunction were reduced, positive attitudes towards sex increased, perception that sex was enjoyable increased, and likelihood of perceiving self as a sexual failure decreased.</td>
<td>No comparison group makes interpretation difficult. Many women had significant comorbidity.</td>
</tr>
<tr>
<td>Authors, year</td>
<td>Type of sample</td>
<td>LOE</td>
<td>Methodology</td>
<td>Results</td>
<td>Comments</td>
</tr>
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</tr>
<tr>
<td>Trudel, Marchand, Ravart, Aubin, Turgeon, Fortier, 2001 [151]</td>
<td>Randomized comparison of 12-week cognitive-behavioural group treatment versus control group in 74 couples with hypoactive sexual desire disorder.</td>
<td>1b</td>
<td>Subjects completed a battery of self-report questionnaires at pre- and post treatment.</td>
<td>Of 100% of women who met criteria for HSDD at pretreatment, 26% continued to meet criteria at post treatment, and 36% met criteria at one-year follow-up. CBT group experienced significant improvements on quality of sexual and marital life, sexual satisfaction, perception of sexual arousal, dyadic adjustment and cognitions, better self-repertoire and pleasure, perceived self-esteem, motivation, depression, and anxiety.</td>
<td>Gains maintained at one-year follow-up.</td>
</tr>
<tr>
<td>Basson, 2001 [153]</td>
<td>Case series of 47 heterosexual couples whereby the referring physician questioned low androgen as a probable etiology for the woman’s low desire</td>
<td>4</td>
<td>An intimacy-based model of the sexual response cycle was used in the assessment of women and their partners to examine the extent to which they could relate to, and incorporate it.</td>
<td>At least 2 factors interrupted women’s sexual cycles: Insufficient emotional intimacy (n = 24), factors related to the sexual stimuli (n = 25), psychological (n = 40) and biological (n = 30) factors influencing processing of stimuli, unsatisfactory sexual outcome related to partner’s sexual dysfunction (n = 7).</td>
<td>Findings based on uncontrolled consecutive case-studies.</td>
</tr>
</tbody>
</table>

Table 13. Efficacy studies investigating effects of psychological therapy on female sexual desire disorder. SD = sexual dysfunction; LOE = level of evidence.
showed statistically significant benefit for non-depressed women with a spectrum of sexual complaints, including sexual aversion, low sexual desire, “low sexual excitement” and impaired orgasm. Whereas 19 of the 30 women with active drug improved - only one did so on placebo. Analysis was not performed separately according to diagnostic group [154]. Of a group of non-depressed women diagnosed with hypoactive sexual desire receiving bupropion hydrochloride in single-blinded manner, 29% responded. None had responded to an initial four-week placebo phase [155]. Larger placebo-controlled randomized trials of bupropion or other molecules altering the neurotransmitters known to influence desire, or more importantly, subjective arousability to sexual stimuli, including dopamine, serotonin and noradrenaline, are awaited.

VI. FACTORS ASSOCIATED WITH GOOD PROGNOSIS IN SEX THERAPY

Based on clinical observation and experience, as well as a few empirical studies [156, 157], there are several factors that appear to be related to successful treatment outcome. These are summarized in Table 14.

VII. CONCLUSIONS AND RECOMMENDATIONS

Traditional sex therapy (with sensate focus) has been the most widely investigated psychological approach to treating hypoactive sexual desire disorder in women, and although efficacy rates are not as impressive as those from Masters and Johnson’s data, there is still some empirical support for this treatment. Additionally, there appears to be good data supporting the use of CBT in couples with hypoactive sexual desire. Clearly these results require replication. Partially due to the inherent difficulty in testing its efficacy, there are no randomized controlled trials of psychodynamic treatment, despite the clinical experience of its need and efficacy. There is very modest evidence of benefit from the use of bupropion HCl in some women with low sexual desire. Acknowledgement that sexual desire per se (as in sexual thinking, fantasizing, or needing to masturbate, awareness of sexual desire before any sexual stimulation begins), has a broad normative range amongst women is important. What may have greater therapeutic benefit is a focus on women’s distress around having little sexual interest/motivation/incentives for sexual activity. Lastly, there are

<table>
<thead>
<tr>
<th>Factors associated with positive outcome in sex therapy trials</th>
<th>Study</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall quality of the couple’s non-sexual relationship</td>
<td>Hawton &amp; Catalan, 1986 [158]</td>
<td>4</td>
</tr>
<tr>
<td>Couple’s motivation to enter treatment</td>
<td>Whitehead &amp; Mathews, 1986 [159]</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Hawton, Catalan, &amp; Fagg, 1991 [160]</td>
<td>2c</td>
</tr>
<tr>
<td>Degree of physical attraction between partners</td>
<td>Hawton, 1995 [156]</td>
<td>5</td>
</tr>
<tr>
<td>Absence of major psychiatric disorders</td>
<td>Hawton, 1995 [156]</td>
<td>5</td>
</tr>
<tr>
<td>Evidence of early homework compliance</td>
<td>Hawton, 1995 [156]</td>
<td>5</td>
</tr>
<tr>
<td>Attention to systemic issues in the relationship</td>
<td>Besharat, 2001 [161]</td>
<td>2a</td>
</tr>
<tr>
<td></td>
<td>Milan, Kilmann, &amp; Boland, 1988 [162]</td>
<td>2c</td>
</tr>
<tr>
<td>Male partner’s motivation to obtain a successful outcome</td>
<td>Hawton, Catalan, &amp; Fagg, 1991 [160], Hirst &amp; Watson, 1997 [163]</td>
<td>2c</td>
</tr>
<tr>
<td>Amount of sensate focused completed in the last week of treatment</td>
<td>Sarwer &amp; Durlak, 1997 [144]</td>
<td>2c</td>
</tr>
</tbody>
</table>
no published psychological efficacy studies for women with any type of arousal disorders. It is recommended that the focus on loss of subjective sexual arousal is made in future studies.

In summary :

• Benefit from psychological treatment has been unclear in part due to outcome measures that reflect male sexual desire but show a broad normative range across sexually healthy women

• Improvement in subjective arousal and excitement is rarely addressed despite the data confirming its importance relative to genital congestion.

• Cognitive-behavioural techniques show efficacy in women with low desire - Grade B-C and deserve research attention in the treatment of women with subjective arousal disorder.

• Despite the frequent clinical occurrence of non-sexual psychodynamic factors negatively influencing women's sexual arousal and interest and the frequent recommendation for psychodynamic treatment, due to inherent difficulty in testing efficacy, there have been no randomized controlled trials. The recommendation for this treatment is thus - Grade D.

• Techniques that improve homework compliance early-on may lead to better outcomes with sex therapy - Grade D.

• Prognostic factors related to the interpersonal relationship such as quality of the non-sexual relationship, couple’s motivation for treatment, degree of physical attraction, and systemic issues in the relationship are important predictors of positive response to treatment in sex therapy - Grade B-C.

H. MANAGEMENT OF GENITAL AROUSAL DISORDER

I. USE OF PHOSPHODIESTERASE INHIBITORS FOR GENITAL AROUSAL DISORDER

Delineation of the likely small subgroup of estrogen replete women complaining of difficulty with genital congestion is only recent [35, 43, 88, 164, 165]. Early evidence suggests that history alone may not delineate which women will respond to phosphodiesterase inhibitors [88]. Whereas benefit is expected in some women with autonomic nerve damage [166], women with presumed vascular etiology are difficult to identify. A small recent laboratory based placebo-controlled study of women clinically diagnosed with physical/genital arousal disorder suggested only some might benefit from Sildenafil [88].

The use of the vaginal photoplethysmograph appeared to identify those women. Of 34 postmenopausal estrogenized women with acquired genital arousal disorder only those with clearly abnormal vasocongestive response to an erotic visual stimulus appeared to show benefit in terms of ease of genital arousal and orgasm under laboratory conditions [88].

Sildenafil has not been shown to be of benefit to women with broad spectrum sexual dysfunction including arousal disorder, in either large [35] or small [167] studies. Women identified as having DSM-IV arousal disorder (note: the focus is on absent lubrication and swelling, i.e. the subgroup now classified as having genital arousal disorder) but no DSM-IV diagnosis of hypoactive sexual desire disorder did show benefit beyond placebo in a very recent study [164]. The Table 8 summarizes studies to date (Table 15).

II. USE OF TIBOLONE FOR GENITAL AROUSAL DISORDER

Studies of women who were not identified as having sexual dysfunction do show benefit over placebo (and some studies show benefit over other forms of HRT) in terms of sexual satisfaction, genital responsiveness, coital comfort, subjective arousal and sexual desire/interest - see Table 9.

III. THE USE OF ESTROGEN FOR GENITAL AROUSAL DISORDER

For women who are estrogen deficient, local estrogen treatment is highly recommended as first line treatment for genital arousal disorder - please see section on “Estrogen Treatment”.
Table 15: Pharmacotherapy for women’s genital arousal disorder: use of sildenafil

<table>
<thead>
<tr>
<th>Study</th>
<th>LOE</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basson, McInnis, 2002 [130] Double-blind parallel group – 3 mos (10-100 mg)</td>
<td>1b</td>
<td>No benefit over placebo on CSFQ*; daily diaries, 2 GEQ**; (on any parameter including arousal, vaginal lubrication).</td>
<td>557 estrogenized women with broad spectrum sexual dysfunction.</td>
</tr>
<tr>
<td>Basson, McInnis, 2002 [130] Double-blind parallel group – 3 mos (10-100 mg)</td>
<td>1b</td>
<td>No benefit over placebo on CSFQ*; daily diaries, 2 GEQ**; (on any parameter including arousal, vaginal lubrication).</td>
<td>204 estrogen deficient women with broad spectrum sexual dysfunction.</td>
</tr>
<tr>
<td>Sipski, Rosen, 2000 [114] Double-blind crossover. Two separate days (50 mg)</td>
<td>1b</td>
<td>VPA increase of borderline significance. Subjective arousal statistically significantly increased beyond placebo – of doubtful clinical significance (on scale of 1-10 subjective arousal 4.08 with placebo, 4.68 with drug).</td>
<td>Lab-based proof of principle. Thirteen of the 19 SCI*** women were complete and 5 of the 19 had sacral cord injury – unclear if these 5 were complete and unlikely to benefit from PDEI.</td>
</tr>
<tr>
<td>Caruso, Intelisano, 2001 [155] Double-blind crossover (0.25,50 mg each for 4 weeks)</td>
<td>1b</td>
<td>Arousal and orgasm improved more than with placebo. Note: significantly increased orgasmic experiences beyond baseline with placebo. Thirty-six of 53 wished to continue.</td>
<td>53 otherwise healthy women, median age 29 with healthy sexual desire but minimal genital response and no orgasm. Pathophysiology unclear. Clinical benefit uncertain since questionnaire used had no item of subjective sexual arousal.</td>
</tr>
<tr>
<td>Kaplan, Reis, 1998 [147] Open label – 3 months.</td>
<td>4</td>
<td>18% had significant improvement in IFSF**** 21% developed clitoral discomfort.</td>
<td>33 postmenopausal women (14 on HRT) with broad spectrum sexual dysfunction.</td>
</tr>
<tr>
<td>Berman, 2003 [134] Double-blind parallel group. 12 weeks (25-200 mg).</td>
<td>1b</td>
<td>Vaginal lubrication and ability to have orgasm and overall sexual experience increased significantly in women without concomitant desire disorder.</td>
<td>202 postmenopausal estrogenized women with DSM-IV arousal disorder. 54 with comorbid desire disorder.</td>
</tr>
<tr>
<td>Basson, Brott, 2003 [180] Double-blind placebo-controlled use of sildenafil to increase arousal and orgasmic experience from vibro and visual erotic stimulation.</td>
<td>1b</td>
<td>Latency to orgasm ↓, intensity of subjective arousal and perception of genital engorgement ↑ by sildenafil only in those with minimal increase in VPA from erotic and subjectively arousing stimulus.</td>
<td>34 postmenopausal estrogenized women clinically diagnosed with genital arousal disorder.</td>
</tr>
</tbody>
</table>

**Key:**
* SFQ Thirty-one item sexual function questionnaire.
** GEQ Global efficacy question
*** SCI Spinal cord injury
**** IFSF Index of female sexual function
**Table 16. Pharmacotherapy for women’s genital arousal disorder: tibolone**

<table>
<thead>
<tr>
<th>Study</th>
<th>LOE</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castelo-Branco, Vincent, 1999 [160]</td>
<td>1b</td>
<td>Sexual satisfaction, responsivity, orgasmic frequency increased compared to placebo. Dyspareunia decreased compared to placebo. Responsivity also higher than with estrogen.</td>
<td>96 women post-surgical menopause not identified as having sexual dysfunction. Those receiving tibolone or androgen had low bone densities.</td>
</tr>
<tr>
<td>Palacios, Menendez, 1995 [169]</td>
<td>2b</td>
<td>Sexual excitement and orgasm intensity increased, coital discomfort decreased.</td>
<td>28 women postnatural menopause not identified as having sexual dysfunction.</td>
</tr>
<tr>
<td>Nathorst-Boos, Hammar, 1997 [170]</td>
<td>2b</td>
<td>Improvement in arousal and vaginal dryness in both groups.</td>
<td>315 women post-natural menopause not identified as having sexual dysfunction.</td>
</tr>
<tr>
<td>Laan, van Lunsen, 2001 [171]</td>
<td>1b</td>
<td>Arousability and vaginal lubrication increased compared to placebo. VPA during fantasy increased compared to placebo but not during visual erotic stimulation.</td>
<td>38 naturally post-menopausal women not identified as having sexual dysfunction.</td>
</tr>
<tr>
<td>Köökçü, Mehmet, 2000 [172]</td>
<td>2b</td>
<td>Vaginal Dryness improved in both groups. Tibolone group showed improved sexual desire.</td>
<td>50 naturally post-menopausal women, not identified as having sexual dysfunction. No question re subjective arousal.</td>
</tr>
<tr>
<td>Rymer, Chapman, 1994 [173]</td>
<td>3</td>
<td>Improvement in vaginal dryness (vaginal cytology). Increased sexual enjoyment, decreased vaginal dryness compared with placebo.</td>
<td>91 naturally post-menopausal women not identified as having sexual dysfunction. No question re subjective arousal.</td>
</tr>
<tr>
<td>Mendoza, Suárez, 2000 [174]</td>
<td>2b</td>
<td>Vaginal dryness improved in both groups.</td>
<td>76 women post-surgical menopause not identified as having sexual dysfunction. No question re subjective arousal.</td>
</tr>
</tbody>
</table>
I. MANAGEMENT OF ORGASMIC DYSFUNCTION

In clinical practice most women complaining of lack of orgasm have comorbid lack of subjective arousal [40]. However, high/adequate arousal that is not released with orgasm(s) may cause distress to the woman. It frequently causes distress to the partner.

For situational orgasm disorder (orgasm with masturbation but not with the partner):
- the focus of therapy is on the relationship, especially the issues of trust and safety such that the woman can be vulnerable. The partner may need information regarding the woman’s sexual function. Both may need to hear that women usually need to guide the partner as to the stimulation they need.

For generalized orgasm disorder:
- Cognitive behavioural therapy is recommended. This focuses on promoting changes and attitudes in sexually relevant thoughts. Behavioural exercises traditionally prescribed include direct masturbation, sensate focus and desensitization - Grade B.
- Anxiety reduction techniques are best suited for anorgasmic women only when sexual anxiety is coexistent - Grade C.
- Components of treatment programs including education, communication skills, Kegel exercises are recommended only as adjuncts to CBT - Grade C.
- No pharmacological agents can be recommended. (Only open labeled studies have suggested benefits e.g. with bupropion, granisetron) - Grade B.

Table 18 summarizes studies investigating short-term sexual benefit of testosterone treatment. A much quoted early study used testosterone enantate producing total T levels several times the upper female normal -- comparable to those seen in severe polycystic ovary syndrome or hyperthecosis [180]. Several other studies have reported improvement in a variety of parameters related to sexual activity and satisfaction. Though the doses used were more moderate, all produced blood levels which were supraphysiological or for a few, close to the upper end of the normal range for premenopausal women-- which may be definitely supraphysiological for postmenopausal women. Note a biologically optimal testosterone range for postmenopausal women has not been established.

Another early study employed implants of testosterone and estradiol which produced high normal total T levels [181]. However, a recent study used a testosterone matrix patch to administer transdermal testosterone to women already receiving CEE. This delivery method has the advantage of producing relatively steady-state levels and avoids the initial very

I. RANDOMIZED CONTROLLED STUDIES OF SHORT TERM TESTOSTERONE THERAPY

J. ROLE OF ANDROGENS IN WOMEN’S SEXUAL FUNCTION AND DYSFUNCTION

Hormones are of obvious critical importance for sexual and reproductive function. Follicle maturation, ovulation and pregnancy maintenance depend on pituitary and gonadal hormones. Puberty does not occur in the absence of the normal rise in levels of these hormones and the onset of conscious sexual feelings occurs at puberty. Mood and well being are substantially affected in many women by cyclic shifts in estrogen and progesterone [175]. In contrast, though testosterone levels fluctuate substantially in men during the day, these have not been clearly related to changes in libido or well being, though chronic deficiency of testosterone has.

The impetus for treating women who complain of decreased libido with testosterone comes from the assumption that this hormone will play a similar role in women’s sexuality as it does in men’s. Cross-sectional and cohort studies of sexual function and testosterone levels are inconclusive - see Table 17. Experimental evidence of sexual benefit from testosterone administration is suggestive but not conclusive - see Table 18. It is not clear from any human data if sexual benefit from testosterone is via the androgen receptor or solely via the estrogen receptor from aromatization of testosterone to estradiol. The major effect of testosterone, therefore, could simply be to decrease SHBG and thereby make estrogen more available. This remains an unanswered question. To add further complexity, it is of note that women with complete androgen insensitivity syndrome mostly report healthy desire and response [176].
high levels produced by testosterone enanthate and other esters as well as the oral preparation, testosterone undecanoate. In the patch study, the delivery of 300 $\mu$g T daily showed sexual benefit and produced elevated total T levels and free T levels near the top of the menstrual age normal range [182]. Of interest, later data analysis found that in women aged up to 48, outcome did not differ between active and placebo whereas in the over 48 age group, the difference was significant. A possible interpretation would be a greater contribution of purely biological factors in diminished sexual interest in women after the fifth decade. Further investigations of the interaction of age and other factors with women's diminished sexual interest to better define differences in etiology, are needed. In another recent study using testosterone undecanoate, testosterone levels were clearly supraphysiological [183].

The combination of methyl testosterone and esterified estrogens has been the most widely used preparation in the United States, though studies reporting efficacy re improved sexual function are recent. This preparation compared to estrogen alone was studied in an RCT which found improvement in sexual functioning with the combination [184].

A very recent level 1b 4-month trial of 1.25mg methyl testosterone plus 0.625mg esterified estrogen showed increase in the total score for desire/interest in a new validated questionnaire (SIQ) (measuring level of desire, distress re low desire). The women were naturally or surgically menopausal and their low desire dated from menopause. An increase in frequency of desire did not reach statistical significance, sexual arousability was not measured and scores in the BISF-W responding to interest/desire did not change significantly. There were, however, highly significant correlations between changes in bioavailable testosterone and changes in interest using the SIQ. The unmeasured androgenic activity of the methyl testosterone itself, as well as borderline high bioavailable testosterone levels are the major concerns precluding any recommendation regarding clinical use of this formulation based on this study. Moreover, the women with natural menopause were not receiving a progestin for the duration of the study [185].

A recent study reported the beneficial results of administration of transdermal testosterone administration to premenstrual age women complaining of diminished sexual interest for which neither psychological nor contextual cause had been found [70]. However both total testosterone and free testosterone index were elevated in the treatment group. The study population appears to have been somewhat heterogeneous. Hirsutism ratings increased only slightly, however the insensitivity of such ratings is discussed below in reference to Shifren, et al. Metabolic safety parameters (lipids, insulin, glucose) were not reported - see Table 18.

**In summary, though an effect of testosterone administration to women complaining of diminished sexual interest and satisfaction to improve these**

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DETAILS</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cawood,1996 [22]</td>
<td>141 women aged 40-60 in representative community survey.</td>
<td>4</td>
</tr>
<tr>
<td>Dennerstein, 2002 [72]</td>
<td>No hormonal parameter correlated with any measurements of sexual desire and response</td>
<td></td>
</tr>
<tr>
<td>438 women observed over 8 years across the menopause transition.</td>
<td>Sexual response and desire correlated with estradiol levels and not with testosterone.</td>
<td>2b</td>
</tr>
<tr>
<td>Leiblum, Bachmann, 1981 [177]</td>
<td>59 women aged 60-70 not identified as having sexual problems.</td>
<td>4</td>
</tr>
<tr>
<td>Nathorst-Boos, 1992 [178]</td>
<td>700 women with hysterectomy +/- or minus BSO +/- ERT.</td>
<td></td>
</tr>
<tr>
<td>Conaglen, 2003 [179]</td>
<td>29 hirsute women given cyproterone acetate and estradiol for 12 months.</td>
<td>2a</td>
</tr>
</tbody>
</table>

Table 17: Level 4 evidence from cross sectional and cohort studies of sexual response and testosterone values note: limitations of testosterone assays in these studies
Table 18: studies examining short-term benefit of testosterone therapy

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DETAILS</th>
<th>LOE</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shearin, 1985</td>
<td>53 women at time of BSO – 1 year</td>
<td>150 mg testosterone IM q 4 weeks + 1 IM estradiol increased desire more than ET alone or placebo.</td>
<td>2b</td>
</tr>
<tr>
<td>Burg, 1984</td>
<td>17 women postmenopausal with low desire despite URT</td>
<td>100 mg testosterone implants + estradiol increased desire and sexual enjoyment compared to previous oral ERT</td>
<td>4</td>
</tr>
<tr>
<td>Burg, 1987</td>
<td>20 postmenopausal women with low desire despite ERT – 6 months</td>
<td>Implants of 50 mg testosterone with estradiol increased desire and enjoyment of sex more than estradiol alone.</td>
<td>2b</td>
</tr>
<tr>
<td>Davis, 1995</td>
<td>34 naturally postmenopausal women (women with low desire excluded) single blind 2 years</td>
<td>Sexual desire and response (but not desire) in women with combined hormones significantly greater improvement than estradiol alone.</td>
<td>2b</td>
</tr>
<tr>
<td>Sarrel, 1998</td>
<td>20 postmenopausal (natural and surgical) women “dissatisfied with HRT” – 8 weeks</td>
<td>2.5 mg methyl testosterone + CEE improved desire and sexual sensation more than CEE alone.</td>
<td>2b</td>
</tr>
<tr>
<td>Flotter, 2002</td>
<td>50 women at BSO</td>
<td>URT vs. oral testosterone undecanoate + ERT caused improved enjoyment of sex and sexual interest.</td>
<td>2b</td>
</tr>
<tr>
<td>Shifren, 2000</td>
<td>75 women on URT with low desire some years post BSO – 12 weeks</td>
<td>300ug transdermal testosterone daily but not 150ug, increased sexual pleasure, orgasm, frequency but not desire compared to placebo. Benefit only in women older than 48 years</td>
<td>2b</td>
</tr>
<tr>
<td>Barrett-Conner, 1999</td>
<td>311 women with previous BSO not identified as having sexual dysfunction.</td>
<td>Women with methyl testosterone 1.25 mg or 2.5 mg with CEE 0.625 and 1.25 mg improved in sexual desire and response comparable to those using CEE alone.</td>
<td>2b</td>
</tr>
<tr>
<td>Goldstadt, 2003</td>
<td>45 premenopausal women with low desire – 12 months</td>
<td>A 10% testosterone cream improved sexual desire, pleasure, orgasm satisfaction beyond placebo.</td>
<td>2b</td>
</tr>
<tr>
<td>Lobo, 2005</td>
<td>218 women post-natural or surgical menopause with low interest/desire since menopause.</td>
<td>Women given methyl testosterone 1.25 mg with esterified estrogen 0.625mg had increased sexual desire on new validated SAT but not on BISE-W, compared to those on estrogen alone.</td>
<td>2b</td>
</tr>
</tbody>
</table>
outcomes has been found by most, though not all, RCTs, this constitutes level 2b evidence in view of use of different preparations, low numbers, short duration, different outcome measures between studies and statistical significance on only some of multiple measures. It is not known if short-term therapy could allow long-term benefit and there is zero long-term safety data.

II. RANDOMIZED CONTROLLED STUDIES OF DHEA THERAPY

Despite documented progressive loss of DHEA and DHEAS in women (as well as men) [190], from late 30s onwards, results of DHEA supplementation to improve sexual health have been conflicting - see Table 19. Measurement of adrenal androgens in otherwise healthy women with and without sexual dysfunction is needed.

III. ANDROGEN DEFICIENCY SYNDROME

Although an “androgen deficiency” syndrome in women has been described, this does not meet usual criteria in endocrinology for establishment of a deficiency state, which may be formulated as follows:

1) Symptoms regularly associated with low levels of the hormone as determined by measurement of hormone levels.
2) Relationship of symptoms to the established biological actions of the hormone.
3) Reversal of symptoms upon administration of the hormone in doses which establish normal blood levels. Effects at pharmacological doses do not establish a deficiency state.

None of these criteria are fully met with testosterone administration to women with diminished sexual interest or other sexual dysfunction.

A specific level of testosterone in women which can be considered diagnostic of androgen deficiency has not been established. While some studies have claimed that women with diminished interest are more likely to have low testosterone levels than women without this complaint [196, 197], these are limited by the fact that results on women with diminished libido were compared to laboratory normal ranges rather than to a matched control group i.e. this is level 4 evidence. Other studies have found no correlation between androgen levels and sexual interest or activity [22, 179, 198]. A study of women in their twenties and thirties presenting with complaints of low desire compared to control women, also did not find a difference in free testosterone levels [199]. In premenopausal hirsute women, treatment with the antiandrogen cyproterone acetate combined with CEE, though it lowered free testosterone levels did not alter sexual parameters other than being associated with increased coital frequency. This was based on comparison to baseline [200]. A recent study has shown similar androgen and SHBG values in sexually healthy naturally menopausal women and women with surgical menopause complaining of low sexual desire [201].

Table 19: Placebo controlled trials of DHEA

<table>
<thead>
<tr>
<th>Study</th>
<th>Details</th>
<th>LoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arlt, 1999</td>
<td>[191] 24 women with androgen insufficiency.</td>
<td>1b</td>
</tr>
<tr>
<td>Lovas, 2003</td>
<td>[192] 39 women with Addison’s disease.</td>
<td>1b</td>
</tr>
<tr>
<td>Hunt, 2000</td>
<td>[193] 24 women with Addison’s disease.</td>
<td>1b</td>
</tr>
<tr>
<td>Barnhart, 1999</td>
<td>[194] 66 perimenopausal women with reduced well being and reduced sexual desire.</td>
<td>1b</td>
</tr>
<tr>
<td>Baulieu, 2000</td>
<td>[195] 140 women 60-79 years old with general aging symptoms</td>
<td>1b</td>
</tr>
</tbody>
</table>
One further study did show lower free testosterone levels in women with lifelong absence of sexual interest [202]. Unfortunately, hormones were measured only once; the relation to a lifelong problem is therefore uncertain. Evidence for lower testosterone in women with diminished sexual interest does not meet even level 4 criteria in view of inconsistent results, diversity of populations studied as well as absence of controls in some studies.

To some degree conflicting data may be due to problems in measuring testosterone including lack of assay specificity and circadian variation. Free testosterone, preferably measured by equilibrium dialysis -- unfortunately rarely available in clinical settings -- correlates more closely with the biological effects of the hormone than does the total because most of the circulating testosterone is bound to SHBG which prevents diffusion into tissues. Accordingly the free fraction should be measured. Analogue assays for free-testosterone are unreliable and not recommended. Free testosterone can be estimated from the SHBG, albumin and total testosterone. However, the measurement of total testosterone is also problematic. Whatever method is chosen, it must be adequately validated. There are, unfortunately, no simple assays of total testosterone that have been shown to produce reliable results at the low levels found in many women. Direct immuno assays are not problem free either, particularly because of cross-reactivity with other steroids, markedly so at low testosterone concentrations.

It is difficult to make these direct amino assays both accurate (by various techniques) and cost effective. The preferred method is liquid chromatography with mass spectrometry. Weakly bound testosterone, ie “bioavailable testosterone” may correlate slightly better with hormone action than the free testosterone but it is less widely used and no specific relevance to evaluation of women's sexual complaints has been established.

A further major complicating factor is that much testosterone activity is derived from intracellular production of testosterone from ovarian and adrenal precursors [190]. This intracellular testosterone cannot be measured. Estimating testosterone activity from the measurement of testosterone metabolites (glucuronides) is not yet standardized.

Free testosterone is reduced by about 50% by many oral contraceptives and may also be reduced by concomitant administration of glucocorticoids. In the case of oral contraceptives, this reduction has not been convincingly shown to result in reduced sexual desire or activity [203-205].

The RCTs reporting that some women do report higher sexual desire with administration of testosterone in controlled studies did not establish that the women who responded had lower testosterone levels than non-responders or than women without sexual complaints. Of equal importance, studies have not so far clarified what factors predict response, other than age over 48 years [182].

The question as to whether testosterone levels are lower in ovariectomized women throughout postmenopausal life, continues. There is level 2b evidence on both sides [201, 206]. The belief that levels are indeed lower has led to an assumption that removal of the ovaries peri or post menopause is associated with decreased libido, however, this has not been validated in appropriate studies. Nor has it been determined whether women who have undergone surgical removal of their ovaries are more likely to respond to exogenous testosterone than those with natural menopause.

As no studies have established that testosterone blood level is predictive of response, patient selection is problematic. Furthermore, many women with diminished desire who are treated with testosterone do not respond. This is in contrast to treatment of recognized deficiency syndromes in which virtually all treated individuals respond. In women under age 48 in the patch study, response to placebo and testosterone were identical [182].
At this time, knowledge is simply the observation reviewed above, statistically significant in some relatively short term studies, that some women who complain of low sexual interest and response do show increases in related study endpoints on testosterone regimens which produce slightly or overtly supraphysiological levels. This observation is important, considering the high incidence of reported low sexual interest and loss of arousability and the subjective distress it sometimes, though not always [1], produces. However at this time, evidence-based criteria for patient selection do not exist.

1. ENDOGENOUS HIGH LEVELS OF TESTOSTERONE

A variety of conditions such as polycystic ovary syndrome, congenital adrenal hyperplasia and others are associated with testosterone excess in women [207]. In these conditions, testosterone levels vary from borderline to severely elevated. Experience with these conditions demonstrates potential adverse effects of androgens on women. The changes in the appearance of hair and skin are direct effects of testosterone and the resulting effects are particularly disturbing for women. Greater sebum production, is the initial event leading to acne. Testosterone also alters hair follicle activity, inhibiting it in the case of scalp hair and stimulating it on specific areas of face and body including upper lip, chin, sideburns and cheeks, midline of chest and abdomen, periareolar area, lower back and legs. Axillary and pubic hair appear in girls at puberty as a direct result of increased adrenal and ovarian production of testosterone. Increased testosterone action can stimulate extension of pubic hair down the thighs and up toward the umbilicus. Differences in scalp and body hair are important determinants of perception of gender.

2. DERMATOLOGICAL EFFECTS OF EXOGENOUS TESTOSTERONE

Unfortunately, published studies have not used adequate methodology to assess the incidence and severity of the effects of administered testosterone on women's skin and hair. For example, the study reported by Shifren, et al [182] found no difference in hirsutism ratings but did find significantly more frequent removal in treated as compared to placebo women, suggesting that the rating system was insufficiently sensitive. Crossover design further complicated safety assessments as all subjects received active for 6 out of 9 months and the skin and hair changes may be permanent. A further limitation of such studies is that they have generally lasted only several months while appearance of these testosterone effects can be gradual over a period of years. That many women who present for medical evaluation of acne, hirsutism and androgenic alopecia have testosterone levels at the high normal range indicates that a small increase in blood level might engender such changes to a distressing degree.

3. METABOLIC EFFECT OF EXOGENOUS TESTOSTERONE

In PCOS and other clinical syndromes, testosterone excess has been associated with hyperinsulinemia, with unfavorable lipid changes, with hypertension and with an increased later risk of cardiovascular disease. Generally these complications are observed in women who are significantly obese. While it appears that hyperinsulinemia is usually the cause of hyperandrogenism, there are some reports of situations in which hyperandrogenism causes insulin resistance [208]. Further research is needed to be certain that testosterone administration does not increase the risk of these metabolic dysfunctions in some women.

4. EXOGENOUS TESTOSTERONE IN ESTROGEN DEPLETE WOMEN

An important safety issue which has not been addressed in any studies is the effect of testosterone administration to menopausal or otherwise estrogen deficient women without concomitant administration of estrogen (and progesterone if uterus is intact). This issue has particular urgency in light of the recent report of the Women's Health Initiative (WHI) finding increased risk in women on a fixed dose combination of conjugated equine estrogens and medroxyprogesterone acetate. The wide publicity which these results received has resulted in many women discontinuing estrogen replacement [209]. Thus some women may want to receive testosterone without estrogen replacement. There are several areas of potential concern. First, the safety of replacing
androgens but not estrogens in women deficient in both, is entirely unknown, as no studies have used this regimen. Second, if we assume hypothetically that sexual activity will be increased by the testosterone, it is not clear that atrophic vaginal tissues will permit comfortable and safe intercourse. With the availability of vasoactive agents such as sildenafil, there is the possibility that more frequent intercourse with partners with firmer erections may tear or otherwise damage an atrophic vaginal mucosa.

5. Conclusions Re risks and safety of exogenous testosterone

In view of intracellular conversion to estrogen, long term safety re venothrombotic events, breast cancer and cardiovascular disease, is unknown.

Since adverse effects on the lipid profile can be seen with orally administered progestins possessing androgenic activity, methyl testosterone may have the same potential. Despite the availability of the preparation for many years, safety data is quite limited. The dose of MeT used in a recently reported study [185] was found in another study to lower HDL cholesterol [210].

In the patch study [182] lipid parameters, fasting glucose and insulin were unaltered. However, effects of administration of exogenous testosterone to women, particularly long-term, on metabolic safety parameters such as lipids, glucose and insulin need further study. Such effects may be specific for preparation and route of administration. Accordingly evidence on safety is level 4 in view of short follow-up, inconsistencies between studies and incomplete or inadequate safety outcome measures.

X. Algorithm for assessing and managing investigational androgen therapy

Current knowledge regarding treatment of low desire or response with testosterone is not sufficient to permit patient selection on evidence-based criteria. However, given that some affected women urgently request treatment and the observation that testosterone is sometimes efficacious, it is appropriate to offer tentative recommendations. However, these can only be considered for post menopausal estrogenized women, and only in the short term. Definitive guidelines cannot be formulated in the present state of knowledge. Accordingly, these recommendations should be regarded as provisional and subject to revision as research proceeds and are only Grade C-D. A major intent is avoidance of harm and inappropriate patient selection. The recommendations are given as an algorithm, progressing from one question to the next only if the previous answer is “yes”. The purpose is to assess the suitability of short-term androgen therapy.

First, does the patient understand and accept that in the absence of studies longer than several months, long-term safety is currently unknown and the treatment that is about to begin cannot currently be extended beyond one year ? If so :

1) Does the patient complain of persistently decreased sexual interest, response and satisfaction and is she postmenopausal ?
2) Is she using systemic ERT?

3) Has patient and clinician taken into account normative changes with relationship duration, life cycle and the broad range of sexual interest and desire across women?

4) Did the patient previously have a higher level of desire and feel satisfaction with sexual activity?

5) Is there absence of psychosocial causes of the sexual dysfunction? This would include issues within the woman herself, e.g. the need for control, or suppressed anger or difficulty feeling any emotions, interpersonal difficulties with the partner as well as contextual problems such as lack of privacy or safety, lack of appropriate erotic stimulation and atmosphere?

6) Is the history negative for factors which might limit sexual response such as fatigue, medication effect, chronic illness, chronic non-sexual pain, dyspareunia or mood disorder?

7) If the woman has a partner, is he or she free of sexual dysfunction? Partner dysfunctions should be addressed before considering androgens for the woman.

8) Are total and free testosterone levels well below the upper limit of normal by a reliable assay?

9) Is she free of androgenic skin and hair changes - seborrhea, acne, hirsutism or alopecia?

10) Is she willing to accept possible risk of such changes and the need for discontinuation of testosterone therapy should they occur?

11) Is she willing to come for regular visits to monitor testosterone therapy?

12) Will the condition of genital tissues permit comfortable intercourse?

Note: Biological factors such as removal of the ovaries or what exactly constitutes “low” free and/or total testosterone levels are not included in the algorithm. This is because such have not been convincingly shown to predict response to treatment.

Further data are needed before there can be any recommendations regarding testosterone therapy for premenopausal women.

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**K. THE ROLE OF ESTROGEN IN WOMEN’S SEXUAL RESPONSE AND DYSFUNCTION**

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**I. ESTROGEN AND VULVOVAGINAL HEALTH: SEXUAL SYMPTOMS OF DEFICIENCY**

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**1. Estrogen Effects on Epithelia, Blood Vessels and Glands**

Estrogen has been demonstrated to have effects on all tissue components of the vulvovaginal area, including epithelia (skin, vaginal), skin appendages, blood vessels, nerves, and specialized glands. In summary, estrogen is a growth-promoting hormone and thus stimulates activity in all the above tissues. Estrogen promotes maturation and proliferation of the epithelia, enhances vascularity and increases blood flow, and stimulates glandular secretions (e.g., Bartholin’s gland).

In turn, the decline in estrogen levels as occurs postmenopause, is associated with reversal of the above effects. This is evidenced as thinning of vulvovaginal epithelium, diminished blood flow, and reduced activity of specialized glands. The prevalence of vaginal dryness is estimated to range from 12% to 34%, largely dependent on age. Factors other than vascularity (e.g., permeability of vaginal epithelial cells) may influence lubrication and/or dryness. Nerve endings releasing CGRP and other neurotransmitters are found on vaginal epithelial cells [82]. Although their function is unclear, they may potentially alter permeability.

The vaginal epithelium is an exquisite bioassay for estrogen levels (an observation starting over 60 years ago with Papanicolaou). Thus, the vaginal smear utilized as a measurement of estrogenicity by its effect on the ratio of parabasal to intermediate to superficial cells [82], as in the Maturation Index, is confirmed by its direct correlation with estrogen levels [213].

**2. Sexual Symptoms from Estrogen Lack in Genital Tissues**

These physical changes can lead to sexual symptoms. These include vaginal dryness, dyspareunia,
reduced or absent pleasure from direct genital stimulation, urinary symptoms (especially urgency, frequency, and possibly incontinence), and predisposition to vulvar, vaginal, and lower urinary tract infections [214].

The extent of vulvovaginal atrophy can vary from mild to extremely severe. The latter results in vaginal shortening and narrowing, and can also lead to introital stenosis. The result of this atrophy is to prevent penetration or at least to be a cause of significant pain and/or bleeding from attempted penetration. This can, in turn, result in escalation of problems for the woman and her partner. The woman with atrophy might avoid genital touch or intercourse even in the presence of subjective arousal for fear of experiencing pain or discomfort. Fear of hurting his partner or physical difficulty from introital stenosis or vaginal narrowing could exacerbate erectile dysfunction in the male partner. Needing to move quickly onto intercourse for fear of losing any erection further exacerbates the woman's difficulty. Either vulvovaginal atrophy or urinary dysfunction could reduce the woman's sense of attractiveness and, therefore, interest in sex [171]. Similarly, fear of incontinence or of urinary tract infection could also trigger the same avoidance response or lead to lack of subjective arousal and anorgasmia.

3. Complexities of Relationship between Genital Sexual Congestion and Estrogen Activity

Despite evidence for the above symptoms in estrogen-deplete women, factors other than estrogen levels are involved. The percentage of estrogen-deplete women without any of these symptoms even in the presence of easily observable atrophy is unknown. Possibly frequent sexual arousal and activity promotes continued genital health [177]. Psychophysical studies show similar increases in vaginal congestion in response to sexually arousing erotic stimulation in both estrogen deficient and replete women [215]. Recent MRI studies suggest similar increases in clitoral volume in response to arousing erotic stimuli in pre and postmenopausal women [216].

Conclusion: There is excellent basic and clinical research to confirm a direct relationship between estrogen and vulvovaginal health, and sexual symptoms related to deficiency in some women. However, other poorly researched factors may prevent the presence of sexual symptoms despite estrogen deficiency.

II. Estrogen Levels and General Menopausal Symptoms

The majority of menopause-related studies have not utilized well-validated symptom profiles. The only symptoms that have been specifically related to the menopause transition are increasing vasomotor symptoms (VMS), vaginal dryness, and insomnia, and decrease in breast tenderness [217] (1b level evidence). Also, sleep disturbance is probably related to decline in estradiol levels [218, 219] (2b).

There are remarkably few well-documented studies that have investigated changes in estradiol (E2) and estrone (E1) levels in relation to the final menstrual period (FMP) and/or symptoms [219-222]. Good data on estrogen and symptoms are anticipated from the Study of Women Across the Nation (SWAN), a multicenter, community-based, cohort study of US women and the menopause transition [221].

The Melbourne Women's Health Project (MWHP) has reported that sexual functioning (including sexual responsivity, frequency of sexual activities, and libido) declines concurrently with the decline in levels of estradiol, but not androgen, from the early to the late menopause transition [72] (2b). On the other hand, the Massachusetts Health Study II (MHS II) concluded that menopause status, but not estradiol levels, is related to some, but not all, aspects of sexual functioning. This could be due to menopause per se or to another factor, such as aging [223]. Indeed, the MWHP has also found sexual responsivity to decline with age.

Conclusion: Current evidence suggests specific menopausal symptoms are related to changing estrogen levels.

III. Estrogen Levels and Skin Sensitivity

An extremely common and distressing symptom beyond menopause is an intolerance or reduced awareness of sensual touching to all areas of the body. No scientific study has investigated this phenomenon. Nor is there data to support the clinical findings that in women of reproductive age, two-point discrimination is directly correlated to the stage of the reproductive cycle. That is, as estrogen levels escalate toward ovulation, two-point discrimination nar-
rows, and then widens as estrogen levels drop premenstrually. This would imply a direct effect of estrogen on peripheral neural activity.

**Conclusion:** Estrogen probably plays a major role in neural sensitivity. Research is necessary on other factors as well, such as androgen.

### IV. ESTROGEN RECEPTORS IN THE BRAIN

Estrogen effects on the brain can be mediated through receptor and/or nonreceptor mechanisms. These mechanisms have been well reviewed and can explain potential impact on well being, mood, and sleep [224]. The characterization and understanding of specific receptor activity has, for obvious reasons, been better defined in animals than humans [225].

### V. ESTROGEN AND WELL BEING, MOOD AND SLEEP

There are several impediments to examining the literature relating menopause and sense of well being, enhancement of mood, and relationship to sleep. These include poor definition of menopause status in study groups, failure to distinguish spontaneous from surgical menopause, lack of baseline hormone levels, disregard for concomitant medications, and variability in detail on combinations and permutations of replacement exogenous steroids. Instruments for measurement of domains of quality of life (QOL), mood, and sleep patterns are also usually poorly defined. For example, subtle changes in mood are difficult to extrapolate from the customarily utilized standard measures of depressive symptoms. Finally, it is not always apparent whether well being (QOL), mood, and sleep are enhanced by the well-established estrogenic effects on relief of hot flashes and night sweats. That is, studies need to control for hot flashes in analyses to determine any direct effect of menopause on mood [226-231].

Despite these difficulties, there is level 1a evidence demonstrating enhancements of mood with estrogen therapy [232], and level 1b level of evidence of improved quality of life and well being [233]. It can only be speculated that these effects, in turn, mediate a response in terms of enhanced desire or arousability [230].

Vasomotor symptomatic postmenopausal women suffer more sleep disturbances during the night [231]. In turn, estrogen therapy in symptomatic women reduces hot flash frequency and nighttime awakenings [234] (1b) There is evidence that estrogen increases rapid eye movement (REM) sleep [234].

One major, level 1b, randomized study has reported no benefit of continuous-combined estrogen plus progestogen therapy (EPT) on mood and sexuality. The large WHI trial of healthy postmenopausal women, found in its EPT arm of 16,608 women (aged 50-79 years) with an intact uterus that continuous-combined EPT (Prempro) did not have a clinically meaningful effect on health-related QOL [235]. However, this study has major design weaknesses (e.g., the average age of 63 is 12 years older than the menopause median age of 51; women with moderate or severe symptoms were discouraged from study participation; and no validated QOL instrument was utilized). Thus, investigators relied on surrogate biophysical tests with severe limitations (e.g., only one question was used to determine sexuality, the Modified Mini-Mental State Examination is too crude to measure cognition, the menopause symptom profile was unvalidated, and the Rand-36 is a symptom profile not covering acceptable QOL domains). Recognizing potential deficiencies, a post-hoc intent-to-treat analysis was performed on symptomatic women aged 50 to 54. The intent-to-treat analysis is satisfactory for the WHI primary objectives (i.e., cardiovascular and breast cancer outcomes), but it is unacceptable when evaluating a drug’s mental effect to conclude lack of drug benefit in women not on the actual drug. This was an intent-to-treat study, and almost half of the women in the study group discontinued therapy, although they remained in the treatment arm for determination of QOL results. The authors admitted in the text that “it is possible that differences were not significant at 3 years because of poorer adherence to assigned therapy” [235].

**Conclusion:** Estrogen probably enhances mood, sense of well being, and sleep.

### VI. RISKS AND BENEFITS OF LOCAL AND SYSTEMIC ESTROGEN

Sex-related symptoms from low levels of estrogen may be treated with estrogen, provided potential...


benefits outweigh potential risks. Based on level 1a evidence, clinicians are advised to prescribe the lowest dose of estrogen for the shortest duration consistent with treatment goals, benefits, and risks for the individual woman, taking into account quality of life issues [236] - Grade A. Effects may vary, not only among estrogens and mode of administration, but also from woman to woman.

Vulvovaginal symptoms from local deficiency of estrogen may be treated with low-dose estrogen (1a. 1b & 2b) - Grade A. All estrogen types and modes of administration (pill, patch, vaginal preparation) are effective for this use. Vaginal estrogen preparations at doses used to treat atrophic vaginitis are unlikely to demonstrate any systemic effects. However, the possibility of systemic effects cannot be entirely excluded [237-240]. There is also 1b evidence of significant reduction and significance of urinary tract infection with an estradiol releasing vaginal ring [241]. Evidence suggests that the 17β-estradiol vaginal ring (estring), may be less likely to deliver systemic levels than the estradiol hemihydrate vaginal tablet (Vagifem) or the estrogen vaginal creams.

Other sexual sequelae of low estrogen levels, including poor sleep, dislike of sensual touching, and lack of well being, can also be treated with low-dose estrogen - Grade C. Theoretically, transdermal estrogen may be a more appropriate choice than oral therapy, given the less effect on sex hormone-binding globulin and androgen activity. However, there is no scientific evidence to support this premise.

It is well documented that systemic estrogen therapy (ET) can dramatically increase the risk of developing endometrial hyperplasia and carcinoma. Adding progestogen to ET (EPT) reduces that risk to the level of taking no hormones [242] (1b) - Grade A.

The WHI study found that continuous combined EPT increased risks for breast cancer, coronary heart disease, thromboembolism, and stroke after 5 years [242]. The ET-only arm continues. Evaluating these results and those from other significant trials, The North American Menopause Society issued its Hormone Therapy Advisory Panel Report [236] which included among its basic recommendations for clinical practice that these data cannot be directly extrapolated to symptomatic perimenopausal women or to women experiencing early menopause (i.e., 40-50 years of age) or premature menopause (i.e., < 40 years), and that treatment of menopause symptoms (including urogenital symptoms) remains the prima-

ry indication for ET and EPT(1a). The US Food and Drug Administration (FDA) has subsequently generalized these data on Prempro to all estrogen-progestogen and estrogen-only preparations. A very recent multi-centred case controlled study of 155 consecutive cases of venous thromboembolism showed that oral but not transdermal ET was associated with risk of thromboembolism in post menopausal women [243]. Another very recent study, albeit nonrandomized, has confirmed the increased risk of both incident and fatal breast cancer with current use of estrogen therapy with a substantially greater effect for estrogen/progestin combinations. The progestins involved included medroxyprogesterone acetate, norethisterone and norgestrel/levonorgestrel [244].

The memory study of WHI (WHIMS) has concluded that continuous-combined EPT in women over age 65 (average age 71) demonstrates no cognitive value and may increase the rate of dementia [245, 246]. However, the absolute involvement in dementia is low, and the role of estrogen alone on cognition and dementia is still under investigation.

All types and modes of administration of estrogen therapy and estrogen-progestogen therapy, that allow systemic absorption, including vaginal estrogen, are contraindicated in women with known or suspected pregnancy, history of hormone-sensitive carcinoma, unexplained uterine bleeding, liver disease (especially applies to oral estrogen), history of coagulopathies, and confirmed cardiovascular disease - Grade A. However, individual women, fully understanding the potential risks and benefits, may choose hormone therapy.

Several studies, (levels 2a & 3b), have failed to demonstrate tumor recurrence in breast cancer patients on ET/EPT [247, 248]. A few studies in women previously diagnosed with breast cancer have actually suggested that ET/EPT may have beneficial effects [248-249]. However, a recent open randomised trial was stopped after 2.1 years due to increased numbers of new cancers in women on ET/ EPT [250].

Potential side effects of systemic ET include uterine bleeding, breast effects (e.g., mastalgia), skin effects (e.g., rash, melasma), headache, and psychological effects (e.g., mood swings, irritability, fatigue, depression). By tailoring the hormone type, dosage, or route of administration, an appropriate therapy can typically be found for each woman.

Conclusion : As with all prescription drugs, estro-
gen therapy offers potential benefits but also carries potential risks. The decision to prescribe should be based on an individualized risk-benefit profile and the wishes of the woman herself.

VII. SELECTIVE ESTROGEN RECEPTOR MODULATORS

One of the consequences of the WHI findings has been increased interest in selective estrogen receptor modulators (SERMs). These are chemically diverse substances without the steroid structure of estrogen but containing a tertiary structure that allows binding to α and β estrogen receptors. The exact mechanisms of the tissue selective, mixed agonist/antagonist action of SERMs is currently being clarified. These molecules potentially could retain estrogen's benefits and avoid most of the adverse effects. Of the two in current use - raloxifene and tamoxifen, unfortunately, there are no reported sexual benefits. There is no evidence of reversal of estrogen deficiency associated vulvar and vaginal changes. Increased well being/sleep/mood and decreased vasomotor symptoms attributable to estrogen are not seen. Future SERMs will hopefully have both the apparent benefits of raloxifene (antagonistic action on the endometrium, breast, along with absence of pro inflammatory effects and estrogen agonist action on bone), will also have estrogen agonist action on vulval and vaginal tissues and the ability to ameliorate vasomotor symptoms [251].

VIII. TIBOLONE

This synthetic steroid with tissue selective estrogenic, progestogenic and androgenic actions has been shown to relieve sexual symptoms from vaginal atrophy, although the women studied were not those identified as having sexual dysfunction (recruitment was regarding bone density or vasomotor symptoms) [168-174]. Just a few studies [168, 170] reported significant improvement in sexual desire/interest in the women receiving tibolone. Of note, these prospective randomized trials have compared tibolone to placebo or to various formulations of estrogen and progestin therapy. The very recent million women study on breast cancer and hormone therapy [244] reported a significant excess of breast cancer for women currently using tibolone, as well as those using various estrogen and progesterone combinations. The study was nonrandomized but in order to isolate the effects of tibolone alone (as opposed to using tibolone at baseline and other hormone preparations previously), analyses were restricted to women whose reported duration of use of tibolone was the same as the reported total duration of any type of therapy. The relative risk of breast cancer was 1.48 - the relative risk for other estrogen/progestosterone combinations ranged between 1.53 and 1.97 (and between 1.19 and 1.65 for estrogen alone therapy).

IX. EVIDENCE REGARDING PROGESTOGENS ON SEX AND MOOD

While the evidence for a positive impact of estrogen on sex and mood is more substantial, progestogens (or more strictly progestins), on the other hand appear to have a negative impact. When a progestin is added to oppose estrogen therapy in women with an intact uterus, negative effects on sex and mood can occur. Although not all progestogens have the same effect, data are inadequate to recommend specific progestogens or estrogen-progestogen regimens that will minimize this effect [252-256].

Conclusion: Progestogens do not appear to offer added benefit to sexual function and some may have a negative impact on mood.

L. CONTEXTUAL NATURE OF WOMEN’S SEXUALITY AND DYSFUNCTION

Contextual factors which influence women's sexual function can be considered the framework within which sexuality is experienced, and are important aspects for the clinician to consider. Previous sections have highlighted the roles of interpersonal, societal, and mental health contexts. Two further contextual dimensions are the sexual health of the partner and chronic illness. The National Health and Social Life Survey clarified that women reporting sexual difficulties also experienced higher rates of poor health and low physical well being [2]. In this section we consider the role of pelvic and breast cancer, diabetes, multiple sclerosis (MS), spinal cord injury (SCI), and heart disease. Finally, despite a relatively small literature, we address the entity of resilience to sexual dysfunction.
Interpersonal factors play a key role in several theoretical explanations for women's sexual desire difficulties [145, 257-261]. A partner's sexual health is one specific interpersonal factor that has received recent attention. In a large, nationally representative sample of Swedish women (n = 1335) and men (n = 1475) aged 18-74, the male partner's early ejaculation and/or erectile dysfunction were found to significantly predict sexual well being [30], sexual disability [29], and the more global aspect of quality of life in the female partner. Interestingly, a longitudinal Australian study of determinants of sexual outcome in women transitioning menopause, showed increased “libido” - as in autoerotic practices, in the women whose frequency of sexual activity with their partner was reduced due to his sexual dysfunction [33]. This is reminiscent of another cross-sectional study of perimenopausal women which found a similar result - in that study the man was stated to have “physical limitations which restricted sexual activity” [223]. Table 20 illustrates the findings from these analyses.

Low sexual desire is a common complaint among women with chronic illness. Although low sexual desire may be present before the diagnosis of a chronic illness, the more typical picture is one of a global decrease in desire associated with the diagnosis or treatment of the medical illness. Moreover, the effects of a chronic illness on sexual function may be mediated directly by physiological mechanisms, or by psychological factors related to the illness. When considering the effects of chronic disease on women's sexual function, the following areas are deemed important:

1. Is there evidence of a biological disruption of the sexual response?
2. Is there evidence of psychological consequences of the illness affecting the sexual response?
3. Does the chronic illness increase fatigue or involve chronic pain?
4. Have psychological reactions triggered a depressive episode?
5. Has treatment for the chronic illness influenced the sexual response?
6. Does the chronic illness limit the mobility necessary for caressing, self-stimulating, or engaging in intercourse?
7. Is there evidence of cardiovascular or respiratory compromise such that orgasm or movements of intercourse might be dangerous?
8. Is the chronic illness associated with incontinence or stomas?

Despite the importance in obtaining such information, a well-established literature on each of these factors is scarce, in part due to difficulties inherent in recruitment. For example, in a study designed to investigate the effects of aortic surgery on female sexual function, 100 consecutive patients that had undergone aortic grafting 1-6 years earlier were mailed a questionnaire assessing recent sexual activity [263]. Thirty-nine patients had died, 15 were recently widowed, 15 reported being too unwell to participate, and of the remaining 31, only 7 completed the questionnaire. Age, patient life circumstances, and social stigma discouraging open discussion of sexuality, may be limiting research on the topic of sexual function in chronic illness.

1. Pelvic cancer

Whereas general physical health may be minimally affected by pelvic cancer, specific inquiry into sexual health reveals deleterious effects of the cancer and in particular, of its treatment - see table 21. Havenga et al reviewed the literature on sexual function after conventional surgery for rectal cancer and found that 24% of women reported reduced desire for sex, 38% had dyspareunia, and 28% noted difficulty reaching orgasm [265]. After a nerve-sparing mesorectal incision, few women report any new sexual dysfunction compared to pretreatment [265, 266]. Gynecological surgery (i.e., hysterectomy) for benign conditions does not significantly impair sexual desire [18]. However, for the treatment of cervical cancer, hysterectomy has been found to result in reduced vaginal lubrication, a shortened vaginal canal, lack of vaginal elasticity, and reduced pleasure from genital stimulation, in a retrospective Swedish study [8]. It is possible that these complaints were not exclusively due to the surgery given that many of these women also received intracavity or external beam irradiation. This group of authors also found that dyspareunia was more common for women who had external beam irradiation, and similar rates of
Table 20. Studies examining the role of partner sexual health in women’s sexual function and dysfunction. SD = sexual dysfunction; LOE = level of evidence. ED = erectile difficulties.

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Type of sample</th>
<th>LOE</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fugl-Meyer, 1998 [30]</td>
<td>Nationally representative sample of n = 1335 Swedish women and n = 1475 Swedish men aged 18-74.</td>
<td>2b</td>
<td>Individuals completed structured questionnaires and checklists, in addition to a face-to-face interview.</td>
<td>74% of women who had partners with erectile dysfunction experienced this as a problem for themselves. Of this group, 82% reported not being satisfied with their sexual lives.</td>
<td>Causation unclear; it is possible that a dissatisfaction with sexual life, due to psychosocial issues, may lead to sexual difficulties.</td>
</tr>
<tr>
<td>Fugl-Meyer, 2002 [29]</td>
<td>Nationally representative sample of n = 1335 Swedish women and n = 1475 Swedish men aged 18-74.</td>
<td>2a</td>
<td>Individuals completed structured questionnaires and checklists, in addition to a face-to-face interview.</td>
<td>Men with ED: 50% of women with a partner with ED had low sexual interest, 44% of these women had insufficient lubrication, 52% of these women had low orgasmati, 17% of these women had dyspareunia. Men with ejaculation difficulties: 50% of women with a partner with ejaculatory difficulties had low sexual interest, 24-36% of these women had insufficient lubrication, 42-50% of these women had low orgasmati, 14-19% had dyspareunia. Men reported consistently less often than women that their own sexual disability co-occurred with that of the partner. Men experienced the female partner having a sexual disability as less than the woman. Odds Ratio = 2 for a broad spectrum sexual disability being associated with a non-satisfying sex life – especially high for problems due to low interest or partner’s early ejaculation.</td>
<td>Recommend that in the context of treatment for SD, the role of the sexual partner must be addressed.</td>
</tr>
<tr>
<td>Wagner, Fugl-Meyer, Fugl-Meyer, 2000 [262]</td>
<td>Nationally representative sample of n = 1335 Swedish women and n = 1475 Swedish men aged 18-74.</td>
<td>2a</td>
<td>Attempted to extract information from their large-scale epidemiological study on the impact of ED on the couple.</td>
<td>Women who reported that their partner had ED reported their own sexual dysfunction significantly more often than those with sexually healthy male partners.</td>
<td>It is important to assess quality of life in a couple, as men and women are negatively affected by male erectile difficulties.</td>
</tr>
<tr>
<td>Dennerstein, Lehert, 1999 [33]</td>
<td>Longitudinal study n = 354; annual interview and McCoy Sexuality Questionnaire.</td>
<td>2a</td>
<td>Structural modelling equations to depict sexual outcome factors.</td>
<td>Partner sexual dysfunction leading to reduced frequency of sexual activity increased women’s “libido” – autocrine practices.</td>
<td>Support for the clinical observation that sufficient time to look forward to sexual activity allows awareness of sexual desire.</td>
</tr>
</tbody>
</table>
Table 21  Studies examining the role of pelvic cancer and its treatment in women's sexual function and dysfunction.  SD = sexual dysfunction;  LOE = level of evidence.

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Type of sample</th>
<th>LOE</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stewart, Wong, Duff, Melancon, &amp; Cheung, 2001 [264]</td>
<td>200 women with ovarian cancer without active disease, and who have not received treatment for two years recruited from university cancer clinics, community support groups, and a network newsletter.</td>
<td>2b</td>
<td>Women completed an anonymous mail-back survey inquiring into physical, psychological, social, and spiritual well being.</td>
<td>89% regarded health as good or excellent and reported better mental health and equivalent energy levels to the general population. 37% reported their sexual lives were negatively affected. Younger women (under age 55) reported more a sense of loss about sexual function and fertility than older women.</td>
<td></td>
</tr>
<tr>
<td>Havenga, Maas, DeRuiter, Welvaart, Trimbos, 2000 [265]</td>
<td>Literature review on investigations into sexual effects of conventional surgery and nerve-sparing surgery for rectal cancer.</td>
<td>2a</td>
<td>Generated 7 studies on women using conventional surgery (6 retrospective and 1 prospective).</td>
<td>Decreased libido in 24%, dyspareunia in 38%, and diminished or no orgasm in 28%.</td>
<td>Few studies conducted on women; only 1 prospective study.</td>
</tr>
<tr>
<td>Pocard, Zinzindohoue, Haub, Caplin, Parc, Tirost, 2002 [266]</td>
<td>Prospective study of 7 women who had autonomic nerve-sparing surgery for rectal cancer</td>
<td>2b</td>
<td>Standardized questionnaires assessing sexual function pre- and postoperatively were administered.</td>
<td>No difference in pre- vs. postoperative urinary function. Sexual activity and ability to achieve orgasm was unchanged in those women who were sexually active before surgery. No dyspareunia was reported.</td>
<td>Small study, n = 7</td>
</tr>
<tr>
<td>Galver, Conaglen, Hare, Conaglen, 1999 [18]</td>
<td>Retrospective study of women who had undergone hysterectomy for benign reasons compared to women whose nongynecological surgery was of a similar status.</td>
<td>2b</td>
<td>Women completed the Sexual Desire Questionnaire, the Hurlbert Index of Sexual Desire, and the Sexual Desire Inventory.</td>
<td>No significant differences in sexual desire between women receiving gynecological vs. nongynecological surgery. No relationship between androgen levels and sexual desire.</td>
<td>Surgery undergone for benign reasons; difficult to generalize to cancer patients.</td>
</tr>
<tr>
<td>Bergmark, Avall-Lundqvist, Dickman,</td>
<td>Retrospective study of 256 women who were treated with radical or</td>
<td>2b</td>
<td>Women completed an anonymous questionnaire assessing various aspects</td>
<td>26% of cancer patients vs. 11% of controls reported impaired vaginal lubrication; 26% of cancer patients</td>
<td>No effect of type of treatment.</td>
</tr>
</tbody>
</table>
Table 21  Studies examining the role of pelvic cancer and its treatment in women's sexual function and dysfunction.  SD = sexual dysfunction;  LOE = level of evidence.

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Type of sample</th>
<th>LOE</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henningsohn, Steineck, 1999 [8]</td>
<td>Simple hysterectomy for cervical cancer compared to 350 control women.</td>
<td></td>
<td>of sexual function.</td>
<td>and 3% of controls reported a shortened vagina; 23% of cancer patients and 4% of controls reported an insufficiently elastic vagina; 26% of cancer patients vs. 8% of controls reported significant distress due to vaginal changes.</td>
<td></td>
</tr>
<tr>
<td>Bergmark, Avall-Lundqvist, Dickman, Henningsohn, Steineck, 2002 [267]</td>
<td>Retrospective study of 256 women who were treated with radical or simple hysterectomy for cervical cancer compared to 350 control women.</td>
<td>2b</td>
<td>Symptom-induced distress compared in hysterectomy only patients (HYS) to women receiving combined hysterectomy plus intracavitary radiotherapy (COMB).</td>
<td>Distress over reduced orgasm frequency found in 23% of HYS and 23% of COMB women. Distress from dyspareunia found in 24% of COMB group and 19% of radiotherapy only group.</td>
<td>Recommend that sexual symptoms from cancer treatment are important part of patient satisfaction.</td>
</tr>
<tr>
<td>Grumann, Robertson, Hacker, Sommer, 2001 [268]</td>
<td>Prospective study of n = 20 women undergoing radical hysterectomy for cervical cancer, n = 18 women undergoing hysterectomy for a benign condition, and n = 26 gynecologically healthy women.</td>
<td>1b</td>
<td>Tested at 0, 4, and 8 months postoperatively on standardized questionnaires assessing sexual function, relationship satisfaction, psychiatric symptoms, physical and mental well being.</td>
<td>No statistically significant worsening or improvement in any of 15 domains of sexual function in the cervical cancer group compared to pre-treatment, though notable trends for a gradual decline over the course of treatment that did not reach significance. Orgasmic function improved in this group.</td>
<td>Low sample size may be obscuring true effects from being observed.</td>
</tr>
<tr>
<td>Jensen, Groenvold, Klee 2004 [269]</td>
<td>Prospective study of 173 women with early stage cervical cancer receiving nerve sparing radical hysterectomy</td>
<td>2b</td>
<td>Assessed 6 times during 2 post operatoire years</td>
<td>Many sexual dysfunctions in first few months. Little difference from controls at 24 months</td>
<td>All received between class II-III procedure, avoiding the most lateral aspects of cardinal and utero sacral ligaments</td>
</tr>
</tbody>
</table>
orgasmic difficulties and trouble having intercourse were seen in women having surgery alone vs. those also exposed to intracavity radiotherapy [267]. Prospective studies, on the other hand, have failed to find any major persistent sexual dysfunction caused by radical hysterectomy for cervical cancer [268, 269], whereas radiation therapy was found to induce long-term sexual problems. Although vascular damage following radiation therapy is a common consequence of pelvic cancer in men, this has not been well studied in women. In general, vascular damage following radiation therapy in women has been associated with sexual pain [267, 270-271]; and impaired vaginal lubrication [272]. Determining if these effects are due to vascular damage versus hormonal loss is complicated by the fact that such radiotherapy also leads to permanent ovarian failure. Chemotherapy-induced ovarian failure may decrease sexual desire and increase vaginal dryness. However, given that cancer faces women with a life-threatening condition, it is unlikely that these effects can be attributed only to hormonal changes [273]. Across studies, it appears that relationship happiness plays a more important role than physical factors in response to cancer treatment.

The fear of diminishing orgasm with hysterectomy has led to the development of either supracervical [274] or “nerve-sparing hysterectomy” [275]. The detailed neuroanatomy of autonomic fibers in the lateral aspects of the cardinal and uterosacral ligaments has recently been clarified and should enable preservation of genital sexual function whenever possible [276]. Nerve-sparing hysterectomy has been shown to improve rates of post-surgical incontinence, controlled studies examining effects on sexual function remain are beginning [269].

2. BREAST CANCER

Difficulties with sexual function following treatment for breast cancer are the most likely areas of distress to persist a year after diagnosis [277]. It appears that chemotherapy during treatment for breast cancer is responsible for most of the resulting sexual difficulties, such as loss of desire, trouble getting subjectively aroused, vaginal dryness, and pain with intercourse - see table 22. Twenty-eight percent of women who had undergone breast reconstruction or partial mastectomy without chemotherapy, versus 37% of women who received one of these surgeries with chemotherapy, met criteria for hypoactive sexual desire disorder [278]. In one of the largest longitudinal follow-up studies of 817 women 5-10 years after breast cancer diagnosis, sexual activity decreased despite overall higher quality of life [277]. Specifically chemotherapy-induced ovarian failure, rather than a genital toxicity of chemotherapy, is responsible for these effects. These same authors developed a predictive model for sexual interest, sexual dysfunction, and sexual satisfaction after breast cancer in two very large independent groups of breast cancer survivors [279]. They found that the most important predictors of sexual health in sexually active cancer survivors were: absence of vaginal dryness, emotional well being, body image, quality of the relationship, and partner’s sexual problems, accounting for 33% of the variance.

3. DIABETES

In a systematic review of women with diabetes, reports of problematic desire, arousal, and orgasm experience vary widely from study to study and do not appear to have a simple correlation with degree of complication of their disease [280]. These authors speculated that difficulties with orgasm may be secondary to decreased sexual desire and arousability, rather than a primary problem with orgasmic function, per se. In the laboratory setting, neither subjective nor psychophysiological sexual arousal was found to differ between 24 women with diabetes mellitus type I and 10 control women [281]. However in the clinical setting, a large outpatient sample of 120 women attending a diabetes clinic, higher rates of overall sexual dysfunction were found compared to a normal control sample of 180 women [9], but a significant effect was found only for the complaint of decreased lubrication. Depression was found to be a significant predictor of these sexual complaints, and lower overall quality of marital relationship was also a factor in those women with sexual dysfunction [9, 282]. Across studies, there was evidence that psychological, as opposed to somatic, factors largely accounted for these sexual complaints in women with diabetes - see Table 23.

4. MULTIPLE SCLEROSIS

Compared to the literature on men, relatively few empirical investigations into the sexual health of women with MS are available. Across investigations, there appears to be a significant amount of variability in the prevalence of sexual dysfunction in this group, and this is partially attributed to the failure to include control comparison groups. Recent data comparing women with MS to the general popula-
Table 22  Studies examining the role of breast cancer and its treatment in women’s sexual function and dysfunction.  SD = sexual dysfunction;  LOE = level of evidence

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Type of sample</th>
<th>LOE</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganz, Desmond, Leedham, Rowland, Meyerowitz, Belin, 2002 [277]</td>
<td>Longitudinal study of 817 breast cancer survivors who were 5-10 years after initial diagnosis.</td>
<td>1b</td>
<td>Mailed a large pack of questionnaires assessing quality of life and survivorship concerns.</td>
<td>Physical and emotional well being were excellent; sexual activity with a partner significantly declined.</td>
<td>Authors attribute declines to age-related changes. Difficult to reach this conclusion without a control group.</td>
</tr>
<tr>
<td>Schover, Yetman, Tuason, Meisler, Esselstyn, Hermann, Grundfest-Broniatowski, Dowden, 1995 [278]</td>
<td>Retrospective study of sexual and psychological function in women who had either breast conservation (n=72) or reconstruction (n=146) for breast cancer treatment.</td>
<td>2b</td>
<td>Questionnaires were completed 4 years after surgery.</td>
<td>Advantage of partial mastectomy over breast reconstruction in terms of maintaining pleasure and frequency of breast caressing during sexual activity. 28% of women undergoing breast conservation or reconstruction without chemotherapy vs. 37% of women receiving chemotherapy met criteria for hypoactive sexual desire disorder.</td>
<td>Chemotherapy significantly predicted greater psychosocial distress.</td>
</tr>
<tr>
<td>Ganz, Desmond, Belin, Meyerowitz, Rowland, 1999 [279]</td>
<td>Two large, independent groups (n = 863 and 1094) of breast cancer survivors.</td>
<td>2b</td>
<td>Explored a conceptual framework for predictors of sexual health in breast cancer, then tested this model in the 2nd sample.</td>
<td>Important predictors of sexual health were: absence of vaginal dryness, emotional well being, body image, quality of the relationship, and partner’s sexual problems, accounting for 33% of the variance.</td>
<td>Retrospective, correlational study only. Order of causation cannot be determined.</td>
</tr>
</tbody>
</table>
Table 23  Studies examining the role of diabetes in women's sexual function and dysfunction.  SD = sexual dysfunction;  LOE = level of evidence.

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Type of sample</th>
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<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spector, Leiblum, Carey, Rosen, 1993 [280]</td>
<td>Systematic review of research on biological, psychological, and dyadic correlates of sexual dysfunction in women with diabetes.</td>
<td>3a</td>
<td>Systematic review of literature.</td>
<td>Hypoactive sexual desire disorder: equivocal findings on rates of impaired sexual desire in diabetic versus control group. Sexual arousal disorder: equivocal findings on rates of physiological sexual arousal between diabetic and control women. Orgasm disorder: studies are equivocal comparing diabetic to control women. Dyspareunia: rates range from 1-5% across studies; one study found high rates of dyspareunia in diabetes type II, but no difference in dyspareunia between diabetes type I and controls.</td>
<td>Authors speculate that equivocal findings are due to: (1) not delineating type of diabetes, (2) failing to include obesity and menopause status, and (3) predictor descriptions such as neuropathy, retinopathy, and nephropathy.</td>
</tr>
<tr>
<td>Sloh, Koster, Raadker, van der Werff ten Bosch, 1990 [281]</td>
<td>Laboratory study comparing n = 24 women with diabetes mellitus type I and n = 10 control women</td>
<td>2b</td>
<td>Psychophysiological (i.e., labia temperature) and subjective (i.e., self-report questionnaire) sexual arousal were compared in response to audio-visual erotic stimuli.</td>
<td>No significant group differences in subjective sexual arousal or in psychophysiological sexual arousal.</td>
<td>Lack of difference may be due to a non-representative sample lacking serious neuropathy and angiopathy.</td>
</tr>
</tbody>
</table>
Table 23: Studies examining the role of diabetes in women's sexual function and dysfunction. SD = sexual dysfunction; LOE = level of evidence.

<table>
<thead>
<tr>
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<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzlin, Mathieu, Van den Bruel, Bosteels, Vanderschueren, Demyttenaere, 2002 [9]</td>
<td>120 diabetic women attending a diabetes outpatient clinic compared to an age-matched control group of 180 healthy women.</td>
<td>2b</td>
<td>Completed questionnaires assessing psychological factors, marital satisfaction, depression, and sexual function.</td>
<td>27% of women with diabetes vs. 15% of controls reported sexual dysfunction specifically for decreased lubrication; sexual function was not related to duration of diabetes, HbA1c, medications, or complications; sexual dysfunction related to lower quality of life and depression.</td>
<td>Sexual function deserves more clinical attention in women with diabetes.</td>
</tr>
<tr>
<td>Enzlin, Mathieu, Van den Bruel, Vanderschueren Demyttenaere, 2003 [282]</td>
<td>97 diabetic women and 95 diabetic men attending a diabetes outpatient clinic.</td>
<td>4</td>
<td>Completed questionnaires assessing sexual function and medical records used to evaluate HbA1c and diabetic complications.</td>
<td>SD reported by 27% of diabetic women; SD related to depression and quality of partner relationship.</td>
<td>Conclude that in women psychological factors predict SD but in men a combination of somatic and psychological factors predict SD in diabetes.</td>
</tr>
</tbody>
</table>
tion showed more difficulty masturbating and a lack of sensations or numbness - difficulties related to the nerve damage of MS [283]. Men and women as a group had higher levels of overall sexual dysfunction, and lower levels of sexual activity, relationship satisfaction, and sexual satisfaction than the general population. Face-to-face interviews of women with MS suggest more problematic sexual function with 73% of women reporting a sexual dysfunction compared to 39% of other chronic disease samples, and 12% of controls in an Italian sample of women [6]. These authors speculate that sexual dysfunction in women with MS is attributable to both physical (e.g., sphincteric dysfunction, fatigue, sensory loss) and psycho-social (e.g., depression, anxiety) factors [284]. In a qualitative study, Koch and colleagues found that sexuality was regarded as an important part of life in their sample, despite the acknowledgement of specific sexual difficulties and strongly advocate for health care professionals to reject the myths surrounding the “asexual” status of women with MS [285] - see Table 24.

5. Spinal Cord Injury

Problems with vaginal lubrication are common even in premenopausal women with spinal cord injury, since depending on the level of injury, the peripheral autonomic nervous system may not respond to central nervous system sexual arousal - see Table 25. In women with SCI, difficulties with orgasm are common, as are reports of unusual experiences, such as having a sensation of orgasm at the anatomical area where sensation begins to be present [286]. In a laboratory study comparing sexual arousal and orgasm in women with SCI to able-bodied women, only 44% of women with SCI, vs. 100% of able-bodied women, were able to reach orgasm in the laboratory; however, the experience of orgasm was the same in the two groups [287]. In a group of 85 SCI women, sexual dysfunction was reported to significantly increase post-injury, whereas importance of sex was unchanged [288]. Interestingly, there was an inverse relationship between sexual dysfunction and the importance of sex, such that women reporting higher levels of sexual dysfunction tended to place less importance on sex. Body satisfaction, which was higher than for eating disorder patients and comparable to volunteers, was not associated with sexual frequency or dysfunction. Tepper and colleagues conducted a qualitative study on the psychosocial, emotional, and relationship aspects of sexuality in women with SCI [289]. They described a sexual rediscovery that takes place some years following the injury.

5. Brain Injury

When brain injury is involved, Oddy [290] notes that the effects of the injury on sexual function may be attributable to direct neurological or endocrinological effects, from prescribed drugs, from psychological factors related to loss of confidence or motivation, and partner-related changes such as withdrawal.

Past studies of sexual effects of stroke have suggested lesions in the right hemisphere to be more frequently associated with low desire and sexual dysfunction. However this was not the case in a recent series of 46 men and 16 women [291]. These authors found sexual hesitancy was common and due to both partners’ fear of provoking another stroke and partner’s dislike of the idea of “having sex with a sick person”.

6. Cardiac Disease

The literature suggests that women are treated less seriously and aggressively than men when presenting with symptoms of heart disease. However, statistics indicate that the number of female deaths surpasses the number of male deaths due to heart disease. With respect to sexual function, the Myocardial Infarction Onset Study group interviewed 1774 patients approximately one week after a myocardial infarction to understand possible triggers for the event, including sexual activity [292]. They found that the relative risk for having a myocardial infarction (MI) two hours after sexual intercourse was small and transient (2.9). Moreover, physical exercise decreased the risk of MI onset two hours after sexual activity from 3.0 to 1.2, for individuals who exercised 3 or more times/week. An effort has also been made to examine the resumption of sexual activity following MI. Hamilton and colleagues mailed questionnaires to 54 women and 110 men who survived an MI from a medical center in New England [293]. Of those who returned their questionnaires, 20 women and 42 men, all resumed sexual activity after the MI, with an average time to resume of 8.3 weeks. Thirty-nine percent reported that information regarding sexual activity from their health provider was either insufficient (15%) or not discussed at all (24%). Compared to men, women significantly reduce the frequency of sexual activity following the MI.

Westlake attempted to understand the sexual
Table 24. Studies examining the role of multiple sclerosis (MS) in women’s sexual function and dysfunction. *Q* = qualitative; *SD* = sexual dysfunction; *LOE* = level of evidence.

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Type of sample</th>
<th>LOE</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCabe, 2002 [283]</td>
<td>237 female and 144 male patients with MS registered with the MS Society of Victoria, compared to 190 females and 101 males drawn from the general population.</td>
<td>2b</td>
<td>Completed the Index of Sexual Satisfaction, the Kansas Marital Satisfaction Scale, the Sexual Dysfunction Scale, and the Ways of Coping Questionnaire</td>
<td>Women with MS experienced more difficulties with masturbation, and lack of sensation numbness than controls. Men and women with MS, as a group, had higher levels of sexual dysfunction and lower levels of sexual activity, relationship satisfaction, and sexual satisfaction, compared to male and female controls as a group. Predictors of better sexual satisfaction in women with MS were: capacity for more involvement with partner, and cognitive variables (e.g., focusing on the positive, problem-focused coping, and higher cognitive functioning).</td>
<td>Sexual dysfunction in women with MS is limited to those physiological symptoms of MS.</td>
</tr>
<tr>
<td>Zorzon, Zivadinov, Buseo, Bragadin, Moretti, Bonfigli, Morassi, Iona, Cazzuto, 1999 [6]</td>
<td>Case-control study of 108 MS patients, 97 patients with chronic disease, and 110 healthy individuals</td>
<td>4</td>
<td>Face-to-face interviews assessing MS, cognitive performance, psychiatric/psychological profile, and sexual function.</td>
<td>73.1% of MS, 39.2% of chronic disease, and 12.7% of controls had a sexual dysfunction. Most common complaints were anorgasmia (37.1%), decreased vaginal lubrication (35.7%), and decreased libido (31.4%).</td>
<td>Sexual dysfunction may be attributed to physical structures involved in sexuality, or to psychiatric status, given the higher rate of depression and anxiety in the MS sample. Analyses were not computed separately for males and females with MS.</td>
</tr>
<tr>
<td>Zivadinov, Zorzon, Buseo, Bragadin, Moretti, Bonfigli, Iona, Cazzuto, 1999 [284]</td>
<td>Case-control study of 108 MS patients, 97 patients with chronic disease, and 110 healthy individuals</td>
<td>4</td>
<td>Face-to-face interviews assessing MS, cognitive performance, psychiatric/psychological profile, and sexual function.</td>
<td>Sexual dysfunction correlated with physical disorders, disability, age of onset, sphincteric dysfunction, depression, anxiety, fatigue, cognitive deterioration, neurological impairment, marriage.</td>
<td></td>
</tr>
<tr>
<td>Koch, Krafl, Eastwood, 2002 [285]</td>
<td>Qualitative study involving 5–5 hr sessions with 12 women with MS.</td>
<td>Q</td>
<td>Feminist principles guided the research and analysis with the aim of understanding the experiences of women who live with MS, to consider constructions of sexuality when MS intervenes.</td>
<td>Women acknowledged specific sexual difficulties (e.g., masturbation, decreased sensuality, desire, and arousal). However, their sexuality evolved, and the ability to communicate and share with a partner became central. Women with MS continued to regard sexuality as an important part of life.</td>
<td>Qualitative study.</td>
</tr>
</tbody>
</table>
Table 25  Studies examining the role of spinal cord injury (SCI) in women's sexual function and dysfunction.  Q = qualitative; SD = sexual dysfunction; LOE = level of evidence.

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Type of sample</th>
<th>LOE</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tepper, Whipple, Richards, Komisaruk, 2001 [289]</td>
<td>15 women with complete SCI volunteered for a physiological study on SCI.</td>
<td>Q</td>
<td>Qualitative semi-structured interviews focusing on the meaning of sexuality and on recollection of specific instances of sexuality.</td>
<td>Women identified a loss of sexual identity with SCI; based on the assumption that sexual pleasure was no longer possible, women described a cognitive-genital dissociation (i.e., shutting out of sexuality); described being deprived of their sexuality; with time and experience women developed improved self-esteem.</td>
<td>General self-esteem may return to normal quickly after the SCI, but sexual self-esteem may be delayed. Ability to experience pleasure follows reinstatement of sexual self-esteem.</td>
</tr>
<tr>
<td>Sipski, Alexander, Rosen, 2001 [287]</td>
<td>Two samples: (1) 68 women with SCI and 21 able-bodied women, and (2) 66 women with SCI and identical control subjects</td>
<td>2b</td>
<td>Neurological assessment, sphincter EMG, Vaginal photoplethysmography, Psychiatric Diagnostic Interview-Revised, and questionnaires.</td>
<td>Women with low sensory scores had impaired genital arousal compared to SCI women with higher sensory scores. SCI and able-bodied women showed similar subjective arousal to audio-visual stimuli, but women with SCI showed impaired subjective arousal to audio-visual-manual stimuli. 100% of able-bodied vs. 44% of SCI women were orgasmic in the lab; orgasmic experience of the two groups were similar. No effect of type or level of SCI on orgasmic ability in the laboratory.</td>
<td>Possible that fewer SCI women reaching orgasm is due to psychological factors; therefore, education is necessary.</td>
</tr>
<tr>
<td>Harrison, Glass, Owens, Soni, 1995 [288]</td>
<td>85 women with SCI</td>
<td>4</td>
<td>Completed questionnaires assessing affect, body satisfaction, sexual function pre- and post-injury, including satisfaction.</td>
<td>Sexual dysfunction increased after SCI. Importance of sex was unaffected by SCI. Body satisfaction unrelated to any measure of sexual function; body satisfaction higher than for women with eating disorders but decreased as level of disability increased.</td>
<td>No comparison group</td>
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</table>
concerns of patients and partners with advanced heart failure [294]. They found that dissatisfaction with the sexual relationship (55%) and loss of sexual interest (63%) were significant complaints among the partners of individuals with advanced heart failure. They advocate for more attention to the partners when providing counseling to individuals with heart failure - see Table 26.

IV. FACTORS ASSOCIATED WITH SEXUAL RESILIENCE

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 enhanced ability to confront and master future adversity. This is an important area to study because many of the chronic illnesses discussed in this section carry with them the potential to further impair physical health. Adversity has been studied in various groups of survivors to severe physical or psychological stressors. For example, women with ovarian cancer who were studied after they had been without treatment for two years reported excellent mental health and quality of life, despite ongoing physical difficulties such as sexual dysfunction [264]. Women with MS [35] and SCI [289] who were able to redefine their experience of sexuality due to physical limitation are further examples of resilience in the face of adversity. Such women were able to continue to enjoy satisfying sexual encounters because resilience enabled them to focus on new aspects of sexuality. Women with MS who showed problem-focused coping, focused on the positive, and those with better cognitive functioning had better sexual satisfaction and function [283]. With the advent of state-of-the-art treatments for even the most serious physical and psychological illnesses, research must begin to focus more on survivorship. In this way, the role of resilience as a contextual factor in women's sexual function will be clarified.

V. GENERAL EMOTIONAL WELL BEING AND SEXUAL FUNCTION

Well being, a similar psychological attribute that is considered to cover a broader range of affect than positive or negative mood, has also been studied in the context of women's sexuality. Recent large scale population-based studies find that well being plays a more important role than traditional markers of physical sexual arousal in predicting sexual distress [4], and low emotional satisfaction and happiness are associated with all categories of women's sexual dysfunction [2].

The relationship between well being and hormones has also received a significant amount of attention over the past ten years [22]. Whereas earlier studies may be criticized for using unvalidated measures of well being, even well-validated measures of well being, such as those employed in the Melbourne Women's Midlife Health Project fail to find associations of well being and hormone levels [72, 295]. Against this background of large prospective and cross sectional studies failing to find a correlation between endogenous levels of estrogen, androgen and well being, RCTs of supplementation have been conflicting. The addition of testosterone undecanoate to estrogenized women failed to find effects on well being [183]. The WHI study of CEE plus medroxyprogesterone to asymptomatic postmenopausal women failed to show a relationship between hormones and well being [235]. Recently, there was some evidence that transdermal testosterone improved well being in women with sexual dysfunction after bilateral oophorectomy (i.e. the women achieving high normal testosterone levels showing improvement on one of the two measures) [182].

Whereas hormone levels were not shown to play a key role in the Australian study, well being significantly increased from early to late/postmenopause, and this was significantly affected by life events such as having a partner, work satisfaction, and life hassles [296]. Having positive feelings for the partner has been shown to strongly positively influence sexual desire, responsivity, well being and protect against menopausal symptoms [33]. Similarly, the health of the emotional relationship with the partner during sexual activity was a robust indicator of sexual distress in the recent large population based study [4].

Taken together, the epidemiological literature plus the empirical literature on hormones, suggest that well being is an important contextual factor to be considered in women's sexual function. Moreover, it is likely much more robustly related to life events, than to hormones, and it affects women's sexual health more strongly than traditional physical markers of the human sexual response.
Table 26  Studies examining the role of ischemic heart disease in women’s sexual function and dysfunction. LOE = level of evidence; MI = myocardial infarction.

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Type of sample</th>
<th>LOE</th>
<th>Methodology</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muller, Mittleman, Macleure, Sherwood, Tufler, 1996 [280]</td>
<td>Interviewed 1774 patients (n = 1236 men and n = 538 women) approximately one week after myocardial infarction.</td>
<td>4</td>
<td>Asked about last time of sexual intercourse prior to MI, and frequency of intercourse. Also asked about frequency of physical exertion and outbursts of anger prior to the MI. Data from the 2 hour period immediately before the MI were compared to data from the last year.</td>
<td>48% of patients reported being sexually active in the past year; among those, 9% reported sexual activity in the 24 hours prior to the MI, and 3% reported sexual activity in the 2 hours prior to MI. Heavy physical exertion and exercise exerted a significant protective effect.</td>
<td>Data were not examined separately for men and women. Only intercourse data were gathered.</td>
</tr>
<tr>
<td>Hamilton, Seidman, 1993 [293]</td>
<td>164 questionnaires (n = 54 women and n = 110 men) mailed to survivors of MI that were treated at a medical center in New England</td>
<td>4</td>
<td>Questionnaires assessed areas related to returning to work, cardiac rehabilitation, and sexual activity.</td>
<td>Of those who were sexually active before the MI, 82% reported resuming sexual activity gradually and 18% reported doing so with the same frequency as prior to the MI; the mean time to resume sexual activity was 8.3 weeks. 39% reported that issues around sexual activity were either not discussed at all or in enough detail by their health providers. Compared to men, women reported significantly decreasing frequency of sexual activity after MI.</td>
<td>Small sample size and lack of validated questionnaires.</td>
</tr>
<tr>
<td>Westlake, Dracup, Walden, Fonarow, 1999 [294]</td>
<td>126 patients and spouses recruited from a university-affiliated heart failure outpatient center. 69% patients were men, 74% of partners were female</td>
<td>4</td>
<td>Sexual relationship issues were assessed with the Psychosocial Adjustment to Illness Scale</td>
<td>62% of respondents reported a significant decrease in frequency of sexual activity, and 30% reported sexual activity had stopped; 44% of partners reported no change in sexual satisfaction, 31% reported marked loss of pleasure, and 24% reported sexual pleasure had stopped. With respect to sexual interest, 37% of partners reported no change, 44% reported marked loss of interest, and 19% reported no sexual interest.</td>
<td>No comparison of male partners with female partners.</td>
</tr>
</tbody>
</table>
VI. SUMMARY

Considering the role of context in women's sexual function is an essential component of assessment and treatment. Here we provided a brief review on the literature on (1) role of partner's sexual health, (2) role of various chronic illnesses, and (3) role of resilience and well being, in affecting women's sexuality.

- A partner's sexual health significantly affects a woman's sexual well being, sexual disability, and quality of life. The effects are complex.
- Chronic illness may impact sexual function via physiological and/or psychological factors, making it important to consider both.
- Treatment of the chronic illness itself can affect sexual function.
- It is difficult to differentiate the separate contributions - vascular, neurological, hormonal, and psychological to dysfunction associated with pelvic cancer. Results after nerve sparing surgery are encouraging.
- It appears that chemotherapy induced ovarian failure during treatment for breast cancer is responsible for most of the resulting sexual difficulties.
- Studies on sexual function in women with diabetes are inconclusive, with laboratory studies failing to find significant differences in genital congestion between women with and without diabetes, whereas some clinical studies find significantly higher rates of sexual dysfunction in the former. Despite the presence of potentially relevant physical factors, it is clear psychological factors have more impact.
- Questionnaire and interview studies on women with multiple sclerosis suggest impairments in sexual desire, arousal and orgasm compared to healthy women
- Laboratory and clinical investigations of women with spinal cord injury clarify preservation and impairment of sexual function.
- Qualitative methodology in women with multiple sclerosis and spinal cord injury suggest that the experience of sexuality evolves over the course of their illness and is no longer focused on intercourse.
- Dissatisfaction with the sexual relationship and loss of sexual interest are common complaints among partners of individuals with chronic heart failure, and deserve more attention by the health care provider.

VII. RECOMMENDATIONS

- The clinician must assess sexual function of the partner.
- When considering the role of physical illness in sexual function, the clinician must include a multidimensional assessment that considers:
  - The role of biological factors that might impact sexual response
  - Effects of the chronic illness, such as fatigue or chronic pain
  - Psychological reactions to the illness that may reach clinically significant levels (e.g., a depressive episode)
  - The effects of treatment of chronic illness on sexual response
  - Mobility restrictions that may limit the range of sexual practices
- For women who have faced significant physical or psychological adversity, encouragement of her resilience (through psychotherapy, support groups, education) may facilitate better long-term adjustment to the illness itself and to related sexual difficulties.
- Sexual well being should be fostered by focusing on life events that promote emotional health. For the otherwise healthy woman, less attention should be placed on physical response, when addressing sexual distress.

M. CHILD SEXUAL ABUSE AND SEXUAL DYSFUNCTION

I. INTRODUCTION

Factors influencing the etiology of sexual dysfunction are multifaceted and often poorly understood. One area receiving increasing attention is the role that early sexual abuse plays in later sexual functio-
ning for women. Child sexual abuse (CSA) and sexual dysfunction both occur frequently and are usually not reported. While significant associations between CSA and HIV-risk behaviors [297, 298] have been documented, more understanding of many other sequelae including effects on sexual function and behaviours is needed.

II. THE DEFINITION OF CHILD SEXUAL ABUSE

Definitions of CSA vary according to the types of sexual behavior included in the definition, the upper limit placed on the victim's age at the time the abuse occurred, and the criteria used to define the incident as abusive [299]. Wyatt [300, 301], initially defined CSA as sexual body contact prior to age 18 by someone of any age and relationship to the victim. Two additional exclusion criteria were used to distinguish CSA from exploratory sexual experimentation before age 12 or consensual sexual activity with peers [302, 303]. Incidents were considered to be sexual abuse if: (a) the age difference between the alleged perpetrator and victim was more than 5 years; or (b) the age difference was less than 5 years, but the contact was not desired or was coercive. National and international definitions of CSA need to consider the age of legal consent to engage in sexual activities so that non-consensual incidents can be evaluated for their coercive and explorative effects.

III. THE TYPES AND PREVALENCE OF CHILD SEXUAL ABUSE

Researchers have confirmed that many more children are sexually abused than are reported to authorities [300, 304]. Wyatt and associates [303] reported contact abuse incidents ranging in severity from those that were less severe (fondling and frottage) to very severe (digital penetration and attempted or completed oral sex, anal sex, or rape). A commonly reported estimate of the prevalence of CSA in the United States is approximately 33% in community samples of girls under the age of 18 [303] and approximately 5% in boys under 18 years of age 14 [305]. Research examining the stability of prevalence rates suggests that the prevalence of CSA among girls has remained stable over time [303, 306].

IV. CHILD SEXUAL ABUSE AND SEXUAL DYSFUNCTION

The limitations in sampling and methods of the research make it difficult to understand how CSA influences sexual dysfunction. Most studies are level 2b or 4. The trauma of CSA may result in psychological disturbances that affect sexual function [307]. Because they were powerless to make their own decisions about sex as children or adolescents, women may not develop adequate sexual communication and decision-making needed to interact with sexual partners.

Sex can also become associated with pain and trauma, anxiety and thus, sexual dysfunction [308]. Flashbacks or intrusive thoughts of sexual abuse may compromise sexual function and enjoyment [308].

Although race and ethnicity have not received adequate attention with regard to CSA [309], the sociocultural context in which CSA occurs influences initial reactions to the abuse, the effects of disclosure, and associated symptomatology [300, 306]. Epidemiological studies with female CSA survivors have been primarily limited to European American women [306]. Less is known about sexual dysfunction within various ethnic and cultural groups.

Few differences in prevalence rates among African American, Latina, American Indian and European American women with histories of CSA have been documented [300-302]. Similarities in prevalence rates suggest that ethnic background is not a risk factor for CSA. However, the circumstances surrounding abuse incidents and how families respond to them can differ by ethnicity [309].

The inclusion of a more comprehensive sampling of women of a variety of ethnic groups and nationalities is also necessary to understand issues pertaining to possible ethnic differences in sexual consequences of CSA.

V. ABUSE, ETHNICITY, CULTURE AND SEXUAL DYSFUNCTION
VI. ASSOCIATION OF CSA AND ADOLESCENT SEXUAL FUNCTIONING

Sexual abuse research has focused primarily on children and adult women. Less attention has been given to adolescent girls. Evidence suggests that psychological and biological processes of pubertal development may add increased stress to this phase of development [310].

Physical complaints of sexually abused girls and adolescents include genital abnormalities (e.g., discharge, bleeding, pruritis, skin lesions, and trauma), genital infections, sexually transmitted infections, recurrent urinary tract infections, abdominal pain, and pregnancy [310]. These symptoms and diseases may affect body image and sexual function [311]. However, these findings need to be replicated with more representative samples, in order to better understand how CSA might influence a cumulative history of sexual dysfunction beginning in adolescence [312].

VII. ASSOCIATION OF CSA AND SEXUAL FUNCTIONING IN ADULT WOMEN

It is important to examine sexuality in the context of interpersonal functioning and to understand the relationship between CSA and long term individual and relationship adjustment [313]. Several studies have reported increased difficulties with sexual function and orgasm in women with past CSA, especially if the abuse involved incest and/or sexual penetration and force [313]. Multiple incidents of CSA also increased the chance of difficulty with desire, arousal and orgasm [314].

Other links between CSA and sexual dysfunction have been noted. Laumann, Paik, and Rosen [2] reported associations between sexual dysfunction and prior negative sexual experiences, including CSA. Women's sexual victimization in childhood was associated with difficulties in becoming aroused and lubricated.

In a prospective study of African American women with documented histories of CSA, those who experienced revictimization in adulthood reported more painful intercourse, vaginal infections, and STIs than those who experienced only CSA [315].

In a nationally representative sample of 1,335 Swedish women, 12% of respondents had been sexually abused at least once in their life times - half of them abused more than once. Two-thirds of those abused had at least one sexual dysfunction compared to two-fifths of non-sexually abused women. Importantly, the sexually abused women had a significantly higher number of sexual dysfunctions. The majority of types of sexual abuse were significantly associated with orgasmic dysfunction. When there had been vaginal penetration, genital manipulation, forced giving or receiving oral stimulation, there were lower levels of sexual interest. Additionally, forced giving of oral stimulation and genital manipulation were associated with a higher prevalence of vaginismus. In this study, no significant difference was found in levels of sexual function between those violently as opposed to non-violently abused [12].

Interpretations of these findings are inconsistent due to sampling limitations. Some investigators have found that childhood and adult sexual abuse (ASA) similarly disrupt sexual functioning. Others report that associations with CSA are different than those of ASA [316]. Becker, Skinner, Abel, and Treacy [317] noted that women who had experienced incest as children were likely to have orgasm dysfunction, but this did not occur for women who experienced only adult sexual assault. Additional research is needed with more representative samples and control groups of non-abused women.

Much of the research on women's sexual dysfunction focuses on measures of sexual performance, examining symptoms, including low sexual desire or arousal, orgasmic dysfunction, and vaginismus. However, a focus on symptoms alone, without an examination of their context as well as other etiological factors, reveals only limited information about the possible effects of sexual abuse on sexual functioning. It is recommended that future studies also examine the context of the wanted sexual function.

In summary, the association of CSA with sexual dysfunction is more pronounced for women who experience severe abuse (i.e., penetration, force, incest, multiple incidents), report family dysfunction or other types of child abuse, or who experience revictimization in adulthood. Other emotional problems or stressors can also increase the probability of sexual dysfunction. These findings highlight the importance of examining the context of a person's past and present sexual experiences when examining the influence of CSA.
VIII. CSA AND RELATIONSHIP SATISFACTION

Compared to women without a CSA history, CSA survivors face greater difficulties in their relationships, including less relationship satisfaction, more high risk sexual behavior, more intrusive thoughts and partner violence [312]. Women who reported multiple types of childhood abuse described greater fears of intimacy, and intrusive experiences than those who experienced no abuse and those who experienced either physical or sexual abuse alone [318].

*In summary, CSA can have lasting effects in the area of adult sexual relationships.*

IX. ASSESSMENT OF SEXUAL DYSFUNCTION IN THE WOMAN WHO DISCLOSES CSA

- Assessment of recovery from the abuse (with or without past therapy):
  - history of recurrent depression
  - history of substance abuse, self-harm
  - history of promiscuity
  - unable to trust especially persons of the same gender as the perpetrator
  - exaggerated need for control
  - exaggerated need to please (and inability to say no)
- When recovery is incomplete further assessment of the abuse is necessary. However, its timing is important - therapy for the abuse should follow any detailed questioning:
  - circumstances of the abuse including woman's age and perpetrator's age
  - what sexual behaviours occurred
  - if there were forces or threats made
  - if there was reflexive genital responding and if so, did the perpetrator compound her distress by stating such a response meant she “enjoyed or wanted it”. Does she understand now why that can happen?
  - if she reported the incident to anyone and that person's reaction
  - her knowledge of the whereabouts of the perpetrator currently.

X. TREATMENT FOR SEXUAL DYSFUNCTION IN THE CONTEXT OF PAST ABUSE

- Treatment for sexual trauma should be addressed before treatment for sexual dysfunction can begin.
- Therapy should help women understand any possible connections between past and current sexual functioning, particularly re feelings of trust and being sexually vulnerable.
- Important aspects of therapy include:
  - Encouragement that women can be in control of their sexual encounters.
  - Learning to mentally and physically relax prior to receiving sexual stimulation.
  - Recognition that women need only engage in encounters with which they are fully comfortable.
  - Help to develop verbal and non-verbal communication with sexual partners to limit further sexual stimulation when feeling overwhelmed, “numb” or fearful.
  - Assistance to develop relationships where there is a healthy balance of power.
  - When relevant, explanation of the reflexive (automatic) physiological genital responding that sometimes occurs during abusive/coercive sex.

It is clear that when sexual dysfunction has its roots in childhood trauma, a pharmacological intervention is likely to prove ineffective in resolving sexual symptoms. A more extensive exploration and confrontation of the psychological, emotional, and relational issues that impact women's sexuality, is needed. Berman and associates examined the efficacy of sildenafil (Viagra), a drug used to treat arousal disorders in men, for women with and without a history of CSA seeking treatment for sexual dysfunction [319]. This drug was effective in increasing sexual arousal (including lubrication, genital sensation, satisfaction with intercourse, and orgasm) for women who had no history of CSA, but not for women with those histories. These findings illustrate the importance of obtaining complete sexual histories when treating female sexual dysfunction with medications.
Abuse is common and enquiry re its occurrence must be a routine part of the assessment of women's sexual dysfunction.

Given internal pelvic examinations can provoke emotions associated with the abuse, these should not be considered simply “routine” for all women with sexual complaints, but rather there must be a reason for such an examination and its nature and purpose explained to the woman ahead of time - see page 871.

The evidence is that sexual dysfunctions, especially orgasm dysfunction, is correlated with a past history of sexual abuse.

Given poorer general relationship satisfaction is also associated with past sexual abuse and women's sexual function is closely linked to relationship satisfaction, sexual sequelae of abuse can be severe.

Once the history of sexual abuse is elicited, there must then be an assessment of the woman's recovery.

When recovery is incomplete, it is necessary to advise that the abuse itself is addressed rather than moving onto any definitive treatment for sexual dysfunction per se [320].

The parts of the external female genitalia involved in female circumcision are:

1) Mons Pubis: the area where the labia majora join together at the top of the vulva.
2) Perineum: the skin between the anus and the opening of the vagina.
3) Labia majora: two easily seen elliptical folds of skin extending between the pubis and the perineum.
4) Labia minora: two smaller folds of skin beneath the labia majora. They extend from the perineum to meet and surround the clitoris.
5) Clitoris: structure similar to the penis but much smaller, located about one-half inch above the urethral opening at the point where the labia minora meet. Clitoral tissue is extensive - the visible, palpable part being less than 10%. It extends under the pubic bones and connects with similar tissue around the vaginal opening under the thin superficial perineal muscles - “bulbs of the clitoris”.

Literature on sexual functioning after female circumcision is limited and most of what is to follow has been accumulated from clinical practice and group discussions between the author and girls and women who have been excised. Dyspareunia, orgasmic delay and lack of orgasm are not uncommon [322]. One study found approximately half the women...
reported lack of sexual desire. Similarly, half reported lack of sexual pleasure and 60% lack of orgasm [323]. The imposed infertility from infection of these procedures can indirectly affect the woman's sexual functioning as the psychosocial consequences of infertility in communities practicing genital circumcision, can be extreme. Moreover, emotional distress and physical pain during sexual stimulation and intercourse diminishes enjoyment for the man also, impairing the intimacy of their relationship and again indirectly, therefore reducing the woman's sexual function.

The types of female circumcision are [321, 324]:

1. TYPE I : EXCISION OF ALL OR PART OF THE CLITORIS AND ITS PREPUCE OR SKIN.

Removal of the visible part of the clitoris, its covering (frenulum below and prepuce above formed by the labia minora) and perhaps its suspensory ligament, will also involve cutting its blood supply (branch of the internal pudendal artery) and innervation (branch of the pudendal nerve). This can lead to chronic referred pain over the lower back and groin. Dyspareunia with diminished or absent arousal, orgasm and sexual satisfaction can occur.

2. TYPE II : EXCISION OF THE CLITORIS WITH PARTIAL OR TOTAL REMOVAL OF BOTH LABIA MINORA.

When the labia minora have been partially or totally removed along with the clitoris additional blood vessels (pudendal branches from the femoral artery and vein) and nerves (branches of the ilioinguinal, pudendal and genito-femoral) are cut. Referred pain is to the vagina. This can heighten or exaggerate the female sexual dysfunction described with type I.

3. TYPE III : EXCISION OF ALL EXTERNAL GENITALIA, CLOSURE OF THE VAGINAL OPENING EXCEPT FOR A MATCH TIP SIZE AREA FOR URINE AND BLOOD TO ESCAPE.

Removal of all external genitalia is accomplished with this excision. Not only is there a greater chance for more pronounced sexual dysfunction but placement of sutures and binding the legs together leads to higher rates of infection and known findings of nerve entrapment and scarring. This procedure may result in dyspareunia and/or vaginismus. Women may report low sexual desire due to fear of pain upon penetration.

4. TYPE IV : PRICKING, PIERCING OR INCISING THE CLITORIS AND OR LABIA.

Depending on the extent of the excision the effect of Type IV excisions may be marginal to extreme. Hypersensitivity to direct clitoral contact may lead to dyspareunia and/or decrease in sexual desire to avoid the pain associated with vaginal penetration.

Procedures performed in type IV circumcisions include a) stretching of the clitoris and/or labia, b) cauterizing the clitoris and/or surrounding tissue, c) scraping the tissue surrounding the vaginal opening (angurya cuts), d) cutting into the vagina (gishiri cuts) and e) inserting corrosive substances or herbs into the vagina to tighten or narrow it.

These procedures are usually associated with less painful intercourse but can be associated with psychological problems that affect sexual functioning. Type I is performed 80% of the time. Type III is performed 15% of the time.

Female circumcision is commonly performed prior to puberty but can be done as early as 7 days after birth [326]. Female circumcision can be performed more than once especially in some women who request re-suturing of the vagina after childbirth. The most common reasons given for this procedure, are to [327]:

1) maintain chastity and virginity until marriage
2) maintain fidelity during marriage
3) increase the man's sexual pleasure
4) heighten the woman's sexual desire.
5) help keep the genitalia clean and pleasing to the eye.
6) follow the cultural tradition of initiating girls into womanhood
7) follow religious tradition
8) enhance fertility and child survival

Less common myths are: men prefer circumcised women; a man can get sick or even die if his penis comes into contact with an uncircumcised woman's genitals; circumcision prevents cancer; men cannot
match an uncircumcised woman's unbridled sex drive; circumcision prevents masturbation; and without circumcision the clitoris may grow to an enormous size and hang between the woman's legs.

**V. IMMEDIATE EFFECTS OF FEMALE CIRCUMCISION/FEMALE GENITAL MUTILATION**

Immediate effects of female circumcision are severe. Pain, bleeding and shock may occur. It is ironic that in some cultures circumcision is performed on the 7th day of birth to “lessen” the amount of pain. Unfortunately there is tremendous pain and occasionally bleeding and shock leading to death. As the site of surgery heals swelling (congestion) and infection are common since the technique is carried out with non-sterile instruments and the circumcised person may be forced to remain with legs bound together for 40 days.

**VI. LONG TERM EFFECTS OF FEMALE CIRCUMCISION/FEMALE GENITAL MUTILATION**

The combination of scar tissue, trapped nerves, compromised blood supply and formation of neuromas increase the chance of continued pain at the point of circumcision, the surrounding area and the abdomen. Although the underlying pathophysiology is poorly understood dyspareunia is an unwanted side effect of female circumcision.

Since pain is an unpleasant experience it is also an emotional experience. There is no direct relationship between the amount of tissue damage and the degree of pain perceived. Factors such as:

1) the amount of distress experienced as a result of the excision;
2) traumatic memories;
3) family dysfunction;
4) financial status;
5) a history of substance abuse and
6) relationship problems, all influence perceptions of pain and sexual dysfunction. Even with similar procedures and stimuli individuals will have different perceptions of the amount of pain.

**VII. ASSESSMENT OF SEXUAL FUNCTION IN WOMEN WHO HAVE SURVIVED “GENITAL CUTTING”**

Assessing the sexual health of girls and women should be carefully and respectfully conducted. Women have reported feeling betrayed by mothers, husbands and other family members when forced to undergo excision [326]. “Routine examination” is rarely an appropriate concept for women with these histories - rather physicians must be aware that such procedures may trigger flashbacks, especially in those suffering from post-traumatic stress disorder associated with the genital cutting Psychotherapy is recommended to help those who report traumatic experiences with female circumcision. Therapy should include assessment of any sexual dysfunction. While not all women report sexual problems as a result of female circumcision, it is important to offer them an opportunity to discuss feelings and learn skills to increase self-esteem and sexual satisfaction. Caution is recommended to remember that many of these women may well be well adjusted and have no sexual complaints [328].

Before history and physical examination are performed, both male and female physicians should ensure that trust and rapport is well established. Often but not always, the presence of a female chaperone is helpful. Initially a discussion defining sexual dys- function and how it can affect relationships and sexual satisfaction is necessary. The following question can be asked, “Do you have any sexual concerns you need to discuss?” During the physical examination care should be taken to thoroughly inspect and palpate the genital and pelvic anatomy. This should include an anorectal exam, demonstration of control of vaginal muscles and strength of pelvic floor muscles. The type of female circumcision should be pinpointed. The examiner should note the amount and site of pain. Pain can be graded on the cardinal score of zero to ten with zero for no pain and ten for the worst pain. Each site of pain should be noted anatomically and a score placed on its location. Any consideration for sex therapy should include the continuum of pain a woman describes. A woman's partner and family may need to be included in counseling sessions in order to educate families about the effects of female circumcision on the woman's psychological well being and physical health. Additional treatment for sexual dysfunction may range from recommending vaginal lubricants and pelvic floor strengthening exercises to surgical correction and should be individualized.
1. Ways to facilitate change of beliefs within the communities practising excision are urgently needed.

2. Laws prohibiting female circumcision need to be enforced.

3. Further investigation is necessary to fully understand all circumstances surrounding this spectrum of “surgeries”, especially the claim of genital rejuvenation and increased sexual pleasure.

4. Girls and women who have undergone genital circumcision should be encouraged to seek out support groups for FGC survivors. They should be informed about the surgical options for repair including the release any constricting sutures, reconstruction of the vagina and improving or correcting any blockage of urine or menstrual blood. Again, it is recommended to be aware that such a surgical intervention may bring back acute awareness of the original trauma.

5. Psychotherapy should be available and outcome studies conducted.

6. Aside from laws prohibiting female circumcision under the age of 18 in most countries, on an ethical basis, excision cannot be condoned.

IX. CONCLUSION

It is recommended that health practitioners do not take a judgmental role. There needs to be close liaison between Sexual Medicine, Primary Care, Pediatrics, Obstetrics, Psychiatry and Psychology and importantly, the immigrant communities when women are being seen in western countries.

The challenge to change attitudes is immense and must continue as a major focus of human rights and other international non-governmental organizations.

It is important to always be aware that even for those women who have relocated to the west, these seemingly abhorrent practices may, nevertheless, serve as a confirmation of their cultural identity. For some, it may be extremely important to preserve their traditions and cultures [328].

O. MANAGEMENT OF ANTIDEPRESSANT-ASSOCIATED SEXUAL DYSFUNCTION

Adequate systematic studies of medication (antidepressant medication in particular) associated sexual dysfunction in women, have not published. Clinically, the most common concerns are with selective serotonin reuptake inhibitors reducing sexual responsiveness. This is thought to be possibly due to increasing the serotonergic tone, thereby reducing dopamine mediated activation of sexual response, and augmenting the descending inhibitory serotonergic pathways. Despite apparent benefit of the 5HT1A agonist buspirone, and the dopaminergic agonist amantadine in uncontrolled studies, neither drug was statistically superior to placebo in a two-month RCT [329]. Sexual pleasure, psychological arousal, overall sexual function was reviewed, as well as sexual interest/desire, lubrication and orgasm.

A case series of 106 women treated in a nonrandomized manner with either moclobemide, paroxetine, sertraline or venlafaxine, were followed for sexual complications [330]. There was somewhat less reduction of desire/interest for those on moclobemide and to a lesser extent for those on venlafaxine and there was less reduction of arousal with these two drugs. Lubrication difficulties were rare only with moclobemide and interestingly, no women taking moclobemide reported orgasm difficulties.

A randomized controlled trial of augmentation therapy with placebo, mirtazapine, yohimbine or olanzapine for 6 weeks given to women with fluoxetine-associated sexual dysfunction, did not support the previous uncontrolled reports of efficacy with these agents in women [331].

Although numerous open label studies suggested bupropion combined with SSRIs ameliorated the SSRI-induced sexual dysfunction, a placebo-controlled bupropion add-on study of SSRI-associated sexual dysfunction showed no significant difference compared to placebo. It is of note that the dose of bupropion was fixed at 150 mg without any titration [332]. It is highly recommended that further randomized controlled studies are done given the high prevalence of sexual dysfunction associated with SSRIs and the frequent noncompliance that ensues with subsequent risk for relapse/recurrence of major depressive disorder.
Treatment for sexual pain disorders in the healing professions has always been a tricky matter. This is well-illustrated by a comment made by Robert Latou Dickinson in 1933:

“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 pre-marital examination and instruction” [333].

This section on the various aspects of sexual pain will review pathophysiology, psychopathology, treatments, prognostic factors but interestingly there are no studies on prevention. Everyone who regularly encounters the complaint of dyspareunia knows that women are inclined to continue with coitus, if necessary, with their teeth tightly clenched. The repercussions on the woman sexually and emotionally plus the distancing and misunderstanding between the two partners can make the treatment of sexual pain disorders difficult and frustrating for patients and clinicians.

1. Terminology

Vulvar vestibulitis syndrome (VVS) is thought to account for the vast majority of chronic dyspareunia currently identified in some 3 -20% of nationally representative community studies [1, 2, 69]. The syndrome includes painful penile-vaginal intercourse or pain upon touching the vulvar vestibule and signs limited to variable vestibular erythema.

Interestingly, hyperesthesia of the vulva, which features prominently in women with VVS, was a well-described entity in American and European gynecological textbooks more than 100 years ago [334, 335].

Surprisingly, despite early detailed reports, chronic vulvar dysesthesia disappeared to a large extent from the medical literature until the early 1980s. In 1982 the International Society for the Study of Vulvar Disease (ISSVD) formed a task force to survey vulvar pain syndromes. This task force coined the term “vulvodynia” as chronic vulvar discomfort, characterized by the patient’s complaint of burning (and sometimes stinging, irritation or rawness) in the vulvar area [336]. The term vulvodynia (the symptom) is often loosely used as a somewhat composite “diagnosis” covering several disorders, all of which result in chronic vulvar pain; VVS, dysesthetic vulvodynia, vulvar dermatosis, cyclic vulvovaginitis, vulvar papillomatosis [337].

At the 1999 World Congress of the ISSVD a new classification system for vulvar dysesthesia was proposed, namely a division into two broad categories: (1) generalized vulvar dysesthesia, (2) localized vulvar dysesthesia - vestibulodynia, clitorodynia and other. This new classification is based on location of pain (recognizing, that we know little about the etiology of pain in vulvodynia), in contrast the initial classification system focused on possible etiologies. However, as of June 2003 this new classification system has not been published in the peer-reviewed literature.

This review highlights the clinical presentation of two categories of sexual pain disorders, dyspareunia and vaginismus. As discussed earlier in this chapter, the ICD-10, and the DSM IV view sexual dysfunction as involving either psychological or somatic components or a combination, suggesting these are separate entities and that etiologies are usually known [56, 57]. However, sexual function is a supreme example of the mandatory blending of mind and body. Moreover the precise etiology of dysfunction is often unclear. Frequently, sexual pain is or becomes associated with lack of subjective arousal (and orgasm) and lack of desire/interest. Reduced genital congestion is frequently reported but is as yet not scientifically documented [78]. Whereas a lack of sexual arousal is one certain etiological factor, others are currently extremely unclear. We therefore do not recommend the specification of a biological or psychological etiology.

2. Overlap of Pain Syndromes

Current diagnostic systems also rely heavily on the sexual response cycle. However, the categories of pain disorders, vaginismus and dyspareunia are not part of the sexual response cycle. Also, the assumption that dyspareunia and vaginismus are distinct types of sexual pain disorders, have recently been challenged [338-342]. Research has demonstrated persistent problems with the sensitivity and specificity of the differential diagnosis of these two pheno-
mena. Both complaints may comprise, to a smaller or larger extent:

1. Problems with muscle tension (voluntary, involuntary, limited to vaginal sphincter, or extending to pelvic floor, adductor muscles, back, jaws, or entire body);

2. Fear of sexual pain (either specifically associated with genital touching/intercourse or more generalized fear of pain), or fear of intercourse for reasons other than pain;

3. Propensity for behavioral approach or avoidance. Despite painful experiences with genital touching/intercourse, a subgroup of women continues to be receptive to sexual partner initiatives or to self-initiate sexual interaction. Avoidance of opportunity and/or avoidance specifically of touch between the labia minora is characteristic of others.

So, for example, complaints of pain upon genital touching, superficially located at the vaginal introitus during sexual activity, sometimes associated with other types of vulvar/vaginal/pelvic pressure (e.g., sitting, riding horse or bicycle, wearing tight trousers), are typical of VVS. However the above phenomena typical of “vaginismus”, may also be present. 

Despite the above, in this chapter, the independent existence of dyspareunia, VVS and vaginismus is a priori accepted to allow the use of the existent scientific literature based on this nosological distinction.

For the present review in the etiology of sexual pain disorders, dyspareunia is defined as: recurrent or persistent genital pain associated with sexual intercourse [64]. It can be subdivided into deep and superficial pain. Superficial (introital) pain, dyspareunia may either be or not be identified as VVS.

Vaginismus has been defined as recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with vaginal penetration, which causes personal distress. As knowledge of etiology and treatment of sexual pain disorders advances, these definitions are being modified. An international consensus committee recently recommended the following definition [64].

The persistent or recurrent difficulties of the woman 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, involuntary pelvic muscle contraction and anticipation/fear/ experience of pain. Structural or other physical abnormalities must be ruled out/addressed.

3. Sexual pain and evidence based reporting

The Oxford system of levels of evidence unfortunately, is poorly adapted for this literature. There are very few empirical studies and the overall quality of evidence is poor.

The evidence that does exist is usually linked to one laboratory or investigator and has rarely, if ever, been independently replicated. By definition, therefore, most of the evidence is level 2b or below.

Q. 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 [343].

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 [344].

This section provides a detailed description of the female external reproductive system and pelvic floor musculature. It also contains a brief overview of the current knowledge of the relevant neurochemical basis for regulatory functions and sensory processing.

It is important to note that the 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 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 [345].
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. 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 6). 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 [346-352].

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 [353,354]. 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).

I. NEUROANATOMY OF THE PELVIS AND PELVIC FLOOR

The inferior hypogastric plexus

Within the pelvis, the inferior hypogastric plexus is regarded to be the major neuronal integrative center. Neuroanatomical 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 [355-357]. 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 [358]. 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 are situated in the parametrium lateral to the cervix and the upper part of the vagina, and distribute nerve fibers to the corpora cavernosa of the clitoris, vagina and periurethral tissues [359].

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. Preganglionic 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 preganglionic 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) [360]. 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 [361, 362]. Parasympathetic afferents have cell bodies located in the S2-S4 dorsal root ganglia and course also within the pelvic splanchnic

Figure 6: The neuroanatomy of the pelvis and the pelvic floor
nerve. In addition to its parasympathetic efferent and afferent component the pelvic splanchnic nerve also receives postganglionic axons from the caudal sympathetic chain ganglia [90].

2. Pelvic Autonomic Innervation

A distinctive distribution of pelvic autonomic innervation 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 [354, 363]. 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* [363]. The exact course of the nerves piercing the urogenital diaphragm to supply the vulvar tissues which engorge with sexual arousal is currently being delineated. The cavernosal or autonomic neural anatomy is microscopic and difficult to define consistently. It appears to be a network of nerves rather than discrete nerves.

3. 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 [364]. Central projections of somatic afferents overlap with pelvic nerve afferents within the spinal cord, which theoretically allows coordination of somatic and visceral motor activity [360].

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 between an initial division of sacral nerves and a subsequent division of fibers that intermingle with autonomic pelvic nerves coursing to the inferior hypogastric plexus [365-369]. The pudendal nerve also receives postganglionic axons from the caudal sympathetic chain ganglia. In general, the pudendal nerve runs medial to the internal pudendal vessels along the lateral wall of the ischiorectal fossa dorsal to the sacrospinous ligament. The pudendal nerve divides into upper and lower trunks [366]. The lower trunk of the pudendal nerve gives rise to the inferior rectal nerve innervating the external anal sphincter and perianal skin. The *dorsal nerve of the clitoris* is derived from the upper trunk of the pudendal nerve. The clitoral and perineal neurovascular bundles are paired terminations of the pudendal neurovascular bundles. They arise at the pelvic sidewall. The clitoral neurovascular bundle ascends along the ischiopubic ramus to meet the neurovascular bundle from the other side close to the midline. Where the crura join to become the joined corpora (the body of the clitoris) the clitoral neurovascular bundles pass to the superior surface of the clitoral body to pass along that surface, supplying the clitoris but also largely passing as an intact large neural trunk into the clitoral glans. The perineal neurovascular bundle supplies the urethra and bulbs and is seen passing under the pubic arch to gain access to this area. *These neurovascular bundles are very large, visible to the naked eye and the nerves are 2mm in diameter even in the infant.*

The remaining branch of the pudendal nerve, the *perineal nerve*, arises either from the upper or 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 [366]. Many well-regarded 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 [370-372]. However, a recent study in female cadavers 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: iliococcygeal, pubococcygeal and puborectal muscles [366]. 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 scrotal (or labial) skin [369].

4. Innervation of the Vulvar and Vaginal Area - Clinical Relevance

Most studies on vulvar/vaginal innervation have been derived from animal studies [343, 373]. 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. Recent evidence showing that in addition the vagus may innervate all components of the female reproductive tract may be important [374].** 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 [375-378]. Fibers innervating the vagina are activated by both gentle and intense mechanical stimulation, including noxious stimuli [375, 379]. Mechanical probing (non-noxious stimuli) of the vagina and/or cervix has produced antinociceptive effects in rats and analgesia in women [380, 381]. 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 [382-385]. The human vulvar vestibule contains free nerve endings but has no specialized nerve endings such as Meissners or Pacinian corpuscles [386]. The first survey of the innervation pattern in the human vagina using a pan-axonal marker was published in 1995 [363]. 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 [387]. Interestingly, two independent studies reported vestibular neural hyperplasia in women with vulvodynia, which might provide a morphological explanation for the vestibular hyperalgesia reported by these patients [384, 388].

### II. 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 [364, 389, 390].** 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 postganglionic, 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 [389]. In fact, neuropeptides, purines, kinins, monoamines, and amino acids, as well as local factors such as prejunctional muscarinic receptors and non-neural endothelins, may all serve as cotransmitters 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 recently been documented in P2X3 knockout mice [391].

#### 1. GENITAL ORGAN BLOOD ENGORGEMENT

Clitoral and vaginal vasocongestion is generally associated with parasympathetic vasodilator mechanisms, among which acetylcholine, VIP and nitric oxide appear to be contributing neurotransmitters [8, 82]. Flaccid genital organ states appear to be tonically governed by adrenergic and possibly peptidergic sympathetic mechanisms [392]. 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 [390, 393, 394]. Somatic nerves also exert a significant role in activating bulbospongious and ischiocavernous muscles as well as other muscles of the pelvic floor. Contraction of these perivaginal muscles during sexual stimulation contributes to intravaginal pressure effects [394].

#### 2. NOCICEPTION AND PAIN

Nociception and pain arising from within the pelvis and pelvic floor also 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 origins**
Receptive fields in the perineum are understood to be carried out primarily by sensory-motor discharges associated with pudendal nerve afferents [395,389]. While the interactions of sensory afferents are quite complex, likely possibilities by which these pathways exert effects on autonomic efferent function include mediatory effects on spinal cord reflexes and modulatory effects on efferent release in peripheral autonomic ganglia and in peripheral organs.

Afferent nerve distributions within the vascular and nonvascular smooth muscle of the vagina contain the neuropeptides, galanin and substance P, [82, 390] while extensions into the epithelium and between epithelial cells primarily contain substance P and CGRP [82].

R. CHRONIC PAIN
PHYSIOLOGY AND SEXUAL PAIN DISORDERS

I. NEUROGENIC INFLAMMATION

It is of interest, that there are several urogenital and pelvic pain syndromes, where the chronic pain syndrome seems to be related to an inflammatory etiology: loin pain/hematuria syndrome, interstitial cystitis, irritable bowel syndrome, prostatodynia (prostatitis), VVS. However, despite numerous research efforts, no causes for these inflammatory changes have been identified so far. It is possible that neurogenic inflammation plays a role. It is generally accepted that noxious stimuli can increase the level of pain-producing substances by damage to local tissue. It is important to realize, that substances contributing to nociception are actually present in the terminals of primary afferent nociceptors and that these substances can be released by those terminals when the nociceptor is stimulated. The observation that sensory fibers mediate not only afferent function but also efferent function through the release of modulatory factors dates back to Bayliss (1901), who showed that antidromic conduction in afferent fibers caused vasodilatation [396]. When sensory fibers are stimulated electrically near the spinal cord, electrical impulses will travel from the site of stimulation in both directions: towards the spinal cord (the normal - orthodromic - direction for sensory axons) and towards the periphery (opposite to normal - antidromic direction). When the antidromic impulses arrive in the periphery in the area innervated by the activated primary afferent nociceptors, neurogenic inflammation is produced, characterized by reddening (vasodilatation), edema (plasma extravasation) and hyperalgesia. This neurogenic inflammation is produced by diffusible substances or substances released from the terminals of primary afferent neurons (neuropeptides and probably other autoacoids). The primary afferents involved are thought to be mainly C-fibers, although A-delta fibers also play a role. Although the efferent action of primary afferent fibers is often attributed to axon reflexes, recent studies have indicated that also dorsal root reflexes play a major role in neurogenic inflammation [397]. Neurogenic inflammation has been described in numerous tissues including skin, the joints, the eye, the middle ear, the respiratory, reproductive and digestive system, the dura mater, and most importantly in the context of interstitial cystitis in the genitourinary system [398-400]. Under normal conditions neurogenic inflammation seems to be an adaptive response, promoting rapid increases in tissue substrates, activating cells for local defense and enhancing fluid transport to isolate and dilute invading bacteria and toxins. However, in other settings, due to reasons that are not clear and are the subject of intense research, neurogenic inflammation can become maladaptive. There is increasing evidence for the role of neurogenic inflammation in the pathophysiology of several diseases including asthma, arthritis, migraine and more recently the involvement of neurogenic inflammation has also been suggested in the development of interstitial cystitis [401-403]. In visceral pain conditions neurogenic inflammation does not only play a role in pain and inflammation at the site of the viscus, but also appears to be an important mechanism in referred pain [404]. For example, pain of acute myocardial infarction may sometimes induce a left scapulohumeral periarthritis, an inflammatory condition in the referred zone [405]. It could be hypothesized that neurogenic inflammatory mechanisms in the referred zone might play a role in patients who present with interstitial cystitis and vulvodynia, or pelvic pain and vulvodynia where 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 [400].
II. NEUROPATHIC PAIN: CENTRAL AND PERIPHERAL MECHANISMS

There is experimental evidence from several psychophysical studies, suggesting that neuropathic pain mechanisms might be involved in VVS [406-408]. There is general consensus today that both peripheral and central nervous system mechanisms play a role in neuropathic pain [409]. Briefly, neuropathic pain is typically characterized by spontaneous paraesthesias, dysesthesias and by evoked pain (for example pain evoked by mechanical stimuli, such as the pain evoked by tampon insertion or sexual intercourse in patients with VVS). 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 hyperalgiesia”, thus the pain sensation no longer matches the painful stimulus. The clinical phenomena of alldynia and hyperalgesia can also be due to abnormal signal amplification in the CNS, a process called “central sensitization”. In the presence of “central sensitization” signals entering the CNS via non-nociceptive A-beta touch afferents may evoke pain. The cause of increased descending excitatory signals and/or decreased inhibitory signals to allow this central sensitization of dorsal horn cells is unclear. Never the less, the typical initiation and exacerbations of VVS after times of severe stress fits this model of central sensitization. Various medical regimens (tricyclic anti-depressants, venlafaxine, anti-convulsants - usually carbamazepine or gabapentin) have aimed therapy at nerve hyperesthesia. Some offer some pain relief, although total pain resolution with these drugs appears infrequent [410].

S. CLINICAL PRESENTATION OF SEXUAL PAIN DISORDERS

I. PREVALENCE

Prevalence estimates for dyspareunia range from 3% to 43% and varies with culture (the lower estimates are from Northern European countries whereas the higher ones are from the U.S), but also with the setting (3 to 18% in the general population, 3 to 46% in the general practice, 0 to 30% in sexuality clinic settings and 10 to 20% in gynecological clinics) and the gynecologist’s initiative to bring up the matter. Several authors found a major difference in the incidence of sexual complaints between self-reported data by the patients and data obtained during a discussion about sexuality initiated by the gynecologist [411-413]. Therefore, in order to detect sexual problems and sexual dysfunctions, explicit questions will have to be asked.

Prevalence rates for vaginismus are scant, without the benefit of multiple studies on specific populations. Prevalence estimates for vaginismus range from 1 to 6% (see Table Fugl-Meyer).

II. PHYSICAL CONDITIONS ASSOCIATED WITH PAIN ON ATTEMPTED OR COMPLETED VAGINAL ENTRY

The following table summarizes various conditions that may be associated with varying degrees of chronic dyspareunia (Table 27).

III. 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 on her experience of sexuality (and that of her partner). It therefore seems advisable for physicians addressing gynecological concerns to ask each (new) patient about the existence of sexual problems and possible negative sexual experiences prior to procedures and treatments. It is very important that the physician makes it clear to the patient in the way he/she formulates his/her questions that he/she is not making any a priori assumptions about the existence of a sexual relationship, not expressing a heterosexual preference, or making judgments about various aspects of sexuality, sexual behaviour or sexual experience. Sexual problems are imbedded in a somatic, psychological, relational and social context which must be assessed in order to make adequate decisions regarding diagnosis, treatment or referral.
Table 27 Physical conditions associated with chronic dyspareunia

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<td>- atrophy</td>
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<td>- vulvitis, vulvovaginitis</td>
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<td>- interstitial cystitis</td>
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<td>- condylomata</td>
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<td>- non-infectious inflammations</td>
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<td>- epithelial defects</td>
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<td>- anatomic variations</td>
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<td>- hymenal remnants</td>
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<th>Deep</th>
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<td>- estrogen deficiency</td>
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<td>- vaginitis</td>
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<td>- chronic PID</td>
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<td>- forshortened vagina</td>
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<td>- endometriosis</td>
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<td>- vaginal septum</td>
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<td>- urethritis, cystitis</td>
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<td>- fibroid uterus</td>
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<td>- irritable colon syndrome</td>
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<td>- hemorrhoids</td>
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In order to detect or exclude physical illness or abnormalities that cause pain on (attempted) vaginal entry (Table 28), the non-physician and physician will have to work together. Especially in the case of dyspareunia or vaginismus, it is not always desirable or practical to perform a medical examination straight away. The patient and care provider together must make decisions about timing, who is present, and the extent of the examination.

Table 28. [414]

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 your partner’s ejaculation, after withdrawal, with subsequent micturition?
Do you find your body is tensing when you or your partner attempts to insert his penis? What are your thoughts and feelings at this time?
How long does the pain last? Does touching elsewhere in the genital area 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? (Continue/stop intercourse/continue to make love without intercourse?)
Do you currently 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 relationship?

5. BIOMEDICAL ANTECEDENTS

When and how did the pain start? What tests have been done? What treatment have you received

The examination technique to search for the cause of dyspareunia is more detailed and requires much more finesse than a routine pelvic examination. 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 can correct misinformation and resultant negative self-image, and can clarify how any physical changes relate to sexual problems. If not precluded by her pain, additional transvaginal sonographic assessment for deep dyspareunia, increases both the sensitivity and specificity of the exam, especially any ovarian abnormality [415].

It is extremely important that the patient knows in advance that she has total control over the situation, knows exactly what is going to happen and that she is the one who decides who is going to be there and who is not, and that she knows that during the examination, her personal boundaries will be respected and safe-guarded [416]. Through this examination, the foundations are laid 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 is recommended to lessen the common occurrence of women having to seek multiple health care providers before an accurate diagnosis is made.

1. THE CONTEXT

When a component of vaginismus is indicated by the history, the patient is told ahead of time that the use of speculum or other means of internally examining the pelvis will not be part of this 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 on what is happening. The physician is seated comfortably on a low stool and the examination couch adjusted for the woman to be sitting so she may see in a hand mirror, but her wish not to will be respected. Verbally checking how the woman is coping with the exam from time to time is recommended. Non-verbal communication - the patient's behaviour and that of her partner during the examination are noted, and the physician, too, must be aware of his or her non-verbal signals.
2. ADEQUATE SPREADING

Permission is asked to gently spread the vulva or the patient is asked to spread the vulva 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 labia minora, majora and the crease between, 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 bud (Q-tip) applying the stimulus of touch along the outer edge of the hymen which is also the inner edge of the inner surfaces of the labia minora. The skin at the opening of Skene's ducts must also be tested for allodynia as it is commonly involved in vulvus vestibulitis.

3. INTERNAL EXAM

It may be possible to proceed to the internal exam on this first visit when the characteristic features of vaginismus were not present in the history and are not present during this exam. With the woman bearing down, the insertion of physician's finger or if necessary, something smaller such as Q-tip, with her permission, confirms vaginal entry without any pain. (Even with VVS, if the woman is opening the introitus and the finger is carefully placed without pressure on the edge, especially the posterior fourchette, the procedure is painless).

4. MEASUREMENT OF ALLODYnia IN VVS

The cotton-swab test is widely used [382, 417]. As the Q-tip is repeatedly placed on the edge of the vestibule in a clockwise fashion, the woman's verbal and physical reactions are noted and she may be asked to grade the pain (e.g. out of 1-4). However, the cotton swab test is prone to measurement error when used for experimental purposes or to measure treatment outcome [407]. Therefore a new simple mechanical devise, the vulvalgesiometer (Figure 7) has been developed [418].

The vulvalgesiometer is cost- and time-effective and easy to use. It can be used as a diagnostic tool capable of differentiating among women with different types of genital pain, and because of its large range of exertable pressures, it may aid in quantifying the severity of pain (mild, moderate, severe) experienced by these women. This device also has applications in quantifying changes in vestibular sensitivity as a result of treatment.

5. THE PELVIC FLOOR

Involuntary contraction on the gynecology couch does not infer that this is also necessarily present at home. Conversely, some women can undergo a gynecological examination without any problem, but have vaginistic reactions in other circumstances, depending on what they find threatening. 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. The physician places his or her finger between the woman’s labia just in front of the vaginal opening and applies very gentle pressure. The woman is asked to bear down whilst 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 again as the patient bears down. The use of a lubricant will facilitate the examination and also prevent tissue damage.

V. QUESTIONNAIRE ASSESSMENT OF PATIENTS WITH DYSPAREUNIA

It is worthwhile to administer a questionnaire before and after treatment - see Chapter 5. With the aid of such a measurement instrument, possible comorbidity can be detected and the effect of the intervention can be evaluated. Questionnaires in the English lan-
guage have the advantage that they are well-known in the international literature, which facilitates comparisons of international publications, and that they have been used often in research, which facilitates comparisons between results and populations. However, for local use these questionnaires have to be translated and validated again. This is recommended because of cultural differences.

A simple and effective instrument to obtain measurement data is the Visual Analogue Scale. From time to time during the treatment, the woman marks a score on a sliding scale to represent the amount of progress that has been made.

T. PSYCHOLOGICAL ASPECTS OF SEXUAL PAIN DISORDERS

I. OVERVIEW AND DATABASE

The following psychological factors in the causation and/or maintenance of sexual pain disorders will be discussed:

a. individual psychological characteristics of the women, resulting in increased vulnerability for sexual pain: personality traits, personality disorders, psychiatric comorbidity
b. characteristics of the woman's sexual relationship
c. psychological processes
d. psychological variables enabling prediction of treatment outcome.

As to the establishment of causative vs. correlational relationships between psychological factors and the origin and maintenance of sexual pain, empirical evidence of the highest level available is needed. Confidence in the hypothesized relationships is highest, and causal inferences can more safely be made, when based on the results of (replications of) prospective, randomized, and controlled trials, in which the factors under scrutiny are kept under strict experimental control. No causal inferences can be made from correlational, cross-sectional, and retrospective studies, or from treatment studies, although these types of evidence provide circumstantial support and may suggest directions for future controlled research.

Evidence for psychological factors involved in the causation or maintenance of the sexual pain disorders is grouped into the following categories:

I. Psychometric data, showing differential presence of psychopathology in patients and non-patient comparison groups (Table 28) [5, 101, 419-421];

II. Psychometric data, showing differences on measures of personality traits between patients and non-patient comparison groups (Table 29) [78, 95, 340, 407, 420-432];

III. Experimental data on psychological processes (Table 30) [78, 407, 424, 433-437];

IV. Psychometric data successfully predicting treatment outcome (Table 31) [438-442].

A summary of findings from this database follows:

(**: If more than one study with results pointing in the same direction are retrieved; *: if only single study results were retrieved; see Table 32 for summary of these findings.) Note, psychopathology and impaired psychological functioning may be caused as well as effect of the various forms of sexual pain.

II. VULV AR VESTIBULITIS

Vulvar vestibulitis is thought to underlie the vast majority of superficial (introital) dyspareunia.

1. INDIVIDUAL PSYCHOLOGICAL AND PERSONALITY CHARACTERISTICS

Higher rates of psychopathology in women with VVS were found with regard to depression** and anxiety disorders* (see Tables 28 & 32).

On self-report measures (see Tables 29 & 32), scores on neuroticism of women with VVS are found to be in the normal range**. 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.

Trait anxiety scores are consistently found to be elevated**.

The personality trait of shyness was found higher*. Results with regard to hostility scores and paranoid ideation in women with VVS are left unresolved, with studies both finding higher* and equal** scores. The personality trait of psychoticism has
Table 29. Psychopathology in women with sexual pain disorders  Refs: 5, 101, 419-423

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<sup>a</sup> Dysf. Type: VAG = Vaginism, DYS = Dyspareunia, VVS = Vaginism/Vaginism.

<sup>b</sup> Instrument: SPAIIQ, SCL-90, SCL-90-R, Derogatis.


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<td>VVS</td>
<td>BSI</td>
<td>Gates, 2001</td>
<td>2b</td>
<td>VVS</td>
<td>BSI</td>
<td>van Lankveld, 1996</td>
<td>2b</td>
</tr>
<tr>
<td></td>
<td>VAG</td>
<td>SCL-90-R</td>
<td>van Lankveld, 1995</td>
<td>2b</td>
<td>VAG</td>
<td>BSI</td>
<td>Reissing, 2003</td>
<td>2b</td>
</tr>
<tr>
<td>Psychological characteristic</td>
<td>Dysf. Type</td>
<td>Instrument</td>
<td>Author's, year</td>
<td>LOE</td>
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<tr>
<td>Hysterical personality</td>
<td>VAG</td>
<td>CESI</td>
<td>Kennedy, 1995</td>
<td>1a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perfectionism</td>
<td>VVS</td>
<td>MPS</td>
<td>Janot, 1997</td>
<td>2b</td>
<td></td>
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<td></td>
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<tr>
<td>Low self-esteem</td>
<td>VAG</td>
<td>SEI</td>
<td>Kennedy, 1995</td>
<td>3b</td>
<td></td>
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<tr>
<td>Harm avoidance</td>
<td>VVS</td>
<td>TCI</td>
<td>Danielson, 2001</td>
<td>2b</td>
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<tr>
<td>Erotophobia</td>
<td>VVS</td>
<td>SOS</td>
<td>Meana, 1997</td>
<td>2b</td>
<td></td>
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<tr>
<td>Positive sexual self-schema</td>
<td>VAG</td>
<td>SSS</td>
<td>Reissing, 2003</td>
<td>2b</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(positive sexual self-schema lower than no-pain control women)</td>
<td></td>
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<tr>
<td>Negative sexual self-schema</td>
<td>VVS</td>
<td>SSS</td>
<td>Reissing, 2003</td>
<td>2b</td>
<td></td>
<td></td>
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<tr>
<td>Catastrophizing thoughts</td>
<td>VVS</td>
<td>PCS</td>
<td>Pukall, 2002</td>
<td>2b</td>
<td></td>
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<tr>
<td>Marital problems</td>
<td>VVS</td>
<td>MMQ</td>
<td>Reissing, 2003</td>
<td>2a</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>DYS</td>
<td>LW-MAS</td>
<td>van Lankveld, 1996</td>
<td>2b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LW-MAS</td>
<td>DAS</td>
<td>Meana, 1997</td>
<td>2b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less sexual self-stimulation</td>
<td>VAG</td>
<td>SHF</td>
<td>Reissing, 2003</td>
<td>2b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual desire problems</td>
<td>VVS</td>
<td>SHF</td>
<td>Reissing, 2003</td>
<td>2b</td>
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</table>
Table 30. Psychological characteristics of women with sexual pain disorders

<table>
<thead>
<tr>
<th>Psychological characteristic</th>
<th>Dysf. Type</th>
<th>Instrument</th>
<th>Author(s), year</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual arousal problem/sexual interaction</td>
<td>VVS</td>
<td>QSD</td>
<td>van Lankveld, 1996</td>
<td>2b</td>
</tr>
<tr>
<td></td>
<td>DYS</td>
<td>Spec. Quest.</td>
<td>Reising, 2003</td>
<td>3b</td>
</tr>
<tr>
<td></td>
<td>VAG</td>
<td>Campion Q</td>
<td>Reising, 2003</td>
<td>3b</td>
</tr>
<tr>
<td>Lubrication problem/sexual interaction</td>
<td>VVS</td>
<td>SHF</td>
<td>Reising, 2003</td>
<td>2b</td>
</tr>
<tr>
<td>Sexual arousal problem/masturbation</td>
<td>VVS</td>
<td>SHF</td>
<td>Reising, 2003</td>
<td>2b</td>
</tr>
<tr>
<td>Lubrication problem during masturbation</td>
<td>VVS</td>
<td>SHF</td>
<td>Reising, 2003</td>
<td>2b</td>
</tr>
<tr>
<td>Lack of sexual pleasure</td>
<td>VVSV</td>
<td>SHF</td>
<td>Reising, 2003</td>
<td>2b</td>
</tr>
<tr>
<td>Negative feelings about sexual interaction</td>
<td>VVS</td>
<td>Campion Q</td>
<td>Reising, 2003</td>
<td>2b</td>
</tr>
</tbody>
</table>

References:
<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Dys-Func -tion type</th>
<th>N</th>
<th>Design</th>
<th>Assessment</th>
<th>Psychological process</th>
<th>Level of evidence (Oxford system)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granot, Friedman, Yarnitsky &amp; Zimmer, 2002</td>
<td>VVS</td>
<td>N(VVS)=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 Analogue Scale of perceived pain intensity and unpleasantness</td>
<td>Heat pain threshold lower in VVS vs. controls (42.2°C ± 2.5 vs 43.6°C ± 1.9). Unpleasantness threshold lower in VVS 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 84.5 ± 14.8).</td>
<td>2b</td>
</tr>
<tr>
<td>Meana, Binik, Khallifé &amp; Cohen, 1998</td>
<td>DYS, VVS</td>
<td>N=76; N(VVS)=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>Gynecological examination; pain rating (MPQ), depression &amp; anxiety (BDI); marital adjustment (LW MAS)</td>
<td>Significant correlations of pain ratings with anxiety (r = -0.36; p &lt; .01), marital adjustment (r = -0.35; p &lt; .01), and depression (r = -0.25; p &lt; .05); pain rating in VVS predicted by marital adjustment (r = 0.24; p &lt; .02); pain rating in DYS predicted by depression (r = 0.26; p &lt; .03)</td>
<td>2b</td>
</tr>
<tr>
<td>Pukall, Binik, Khallifé, Amsel &amp; Abbott, 2002</td>
<td>VVS</td>
<td>N=26; N(VVS)=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>Tactile thresholds for tactile sensitivity, pain, pressure-pain tolerance</td>
<td>Tactile thresholds were lower in VVS at all vestibular sites, labium minus and deltoid. Lowered tactile sensitivity was stable over time in VVS. Pain thresholds were lower in VVS, at all vestibular sites, labium minus, deltoid and forearm. VVS women gave higher distress ratings for sustained suprathreshold pressure. Women with VVS tolerated less pressure than controls.</td>
<td>2b</td>
</tr>
<tr>
<td>Payne, Binik, Amsel, Khallifé &amp; Lahalle, 2002</td>
<td>VVS</td>
<td>N=34; N(VVS)=17</td>
<td>Controlled comparison of context-specific hypervigilance with non-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 word tasks</td>
<td>Interference effect was found of pain words, with state and trait anxiety (STAI) explaining this effect.</td>
<td>2b</td>
</tr>
</tbody>
</table>
Table 31. Psychological processes in sexual pain disorders in women: Results of experimental investigations  Refs 78, 407, 424, 428, 433-437

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Dysfunction type</th>
<th>N</th>
<th>Design</th>
<th>Assessment</th>
<th>Psychological process</th>
<th>Level of evidence (Oxford system)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wouda, Hartman, Bakker, Bakker, van de Wiel, Weijmar Schultz, 1998</td>
<td>DYS</td>
<td></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>2b</td>
</tr>
<tr>
<td>Meana, Binik, Khalife &amp; Cohen, 1999</td>
<td>DYS</td>
<td>N(DYS)=100, N(Contr.)=43</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, psychosocial, and lower on marital adjustment.</td>
<td>2b</td>
</tr>
<tr>
<td>Van der Velde &amp; Everaerd, 1999</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>2b</td>
</tr>
<tr>
<td>Van der Velde &amp; Everaerd, 2001a</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>
<td>2b</td>
</tr>
<tr>
<td>Van der Velde &amp; Everaerd, 2001b</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>
<td>2b</td>
</tr>
</tbody>
</table>

Dysfunction type: DYS = dyspareunia; VVS = vulvar vestibulitis syndrome; 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.
been found to be both higher* and equal** as has the personality trait of somatization. As to the extraversion trait, women with VVS did not have higher scores than normative groups**. Women with VVS, however, did appear to be more perfectionistic*, and harm avoiding*, particularly fearing of negative evaluation by others*.

2. SEXUAL RELATIONSHIPS OF WOMEN WITH VVS
With regard to personality traits assumed to be directly related to the domain of sexuality, they are found to score higher on erotophobia*, and to have more self-reported difficulties with sexual arousal and vaginal lubrication during partner interaction** as compared to functioning during masturbation*. They were also found to lack sexual pleasure more often*, and to have more negative feelings about sexual interaction*. Their marital satisfaction was equal to normative groups** as was the strength of positive sexual self-schema*.

3. PSYCHOLOGICAL PROCESSES
As to psychological processes causing or maintaining dyspareunia (see Tables 29 and 31), the level of pain ratings in VVS patients is predicted by their level of marital adjustment*, where lower marital adjustment is associated with higher pain ratings.

Heat pain thresholds, and unpleasantness thresholds, in women with VVS are lower in comparison with asymptomatic women*, while perceived pain during suprathresholds heat stimulation is higher in women with VVS*. The thresholds for tactile (pressure) sensitivity at several vestibular sites, labia minora, and deltoid muscles are lower in women with VVS*, compared with asymptomatic women. This lowered sensitivity is stable over time. Pressure pain thresholds at vestibular sites, labia minora, deltoid and volar forearm are lower in women with VVS*. Women with VVS report higher distress for sustained suprathreshold pressure, and tolerate less pressure than controls*. Attentional bias for pain-related stimuli is demonstrated in women with VVS*, as compared with normal controls, leading to hypervigilence for pain-related stimuli*. The level of hypervigilence is largely accounted for by state and trait anxiety levels.

4. PSYCHOLOGICAL VARIABLES AND OUTCOME
The psychological treatment of vulvar vestibulitis has been evaluated in three controlled trials [429, 444, 445]. Significant improvement in experienced pain, and in intercourse frequency and other measures of sexual functioning were reported, which results were found to be maintained over time.

Prediction of treatment by means of psychological or psychosocial variables (see Table 30) has been investigated in VVS in three studies. Psychosocial variables predictive for better outcome were: higher socioeconomic status*, lower education*, and childlessness*. Psychological factors at pain 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 vestibulecтомy*, as was cooperation of patient in postoperative counseling*. High scores on instruments measuring fear of negative evaluation by others, phobia re vaginal entry and the Personality Assessment Screener have been associated with poor outcome. No replications of prediction models have been reported.

5. CONCLUSIONS RE WOMEN WITH DYSPAREUNIA FROM VESTIBULITIS
In sum, in women with vulvar vestibulitis, elevated comorbid psychopathology was found (depression and anxiety disorders). The self-report findings on psychological characteristics, however, were not unequivocally found to support psychopathology findings. Both more problematic psychological functioning and unaffected functioning have been reported, possibly reflecting differences in study samples and instrumentation or true heterogeneity of women with VVS.

Increased trait anxiety in women with VVS, however, has been found in two studies, and may represent a stable characteristic. Single study findings of women with VVS included elevated rates of shyness, perfectionism, the temperament trait of harm avoidance, increased tendency to have catastrophizing thoughts and negative feelings towards sexual interaction, erotophobia, and problems with subjective sexual arousal and lubrication during sexual interaction with partner, but not during masturbation. Psychopathology and impaired psychological functioning may be cause as well as effect of vulvar vestibulitis. Women with VVS have been found to be more sensitive to thermal and tactile stimulation, reflected in lowered thresholds for sensitivity and the experience of pain on stimulation. An etiological element may be the attentional bias of hypervigilence for pain-relation stimuli. These latter experimental findings have not yet been replicated.
<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Dysfunction type</th>
<th>N</th>
<th>Design</th>
<th>Assessment</th>
<th>Psychological and psychosocial predictors</th>
<th>Level of evidence (Oxford system)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scull, 1998</td>
<td>VAG</td>
<td>N(VAG)=33</td>
<td>Variables associated with positive treatment outcome were assessed in a behavioral treatment of anal/digital disinterest, employing increasing anal dilators, Kegel exercises, relaxation exercises, and bimanual intercourse.</td>
<td>Dichotomous assessment of intercourse success: unvalidated interview ratings of predictor variables.</td>
<td>Length of therapy was related to duration of acquisition, patient's past history of sexual abuse, history of sexual treatment, motivation factors, partner acceptance of sexual therapy, previous treatment, desire to sustain therapy, and sexual relationship.</td>
<td>3b</td>
</tr>
<tr>
<td>Hawco &amp; Carlin, 1990</td>
<td>VAG</td>
<td>N(VAG)=33</td>
<td>Treatment provided was sex therapy, vaginal self-examination (first with mirror, then with fingers and Kegel exercises. Later: digital examination with partner's fingers before pelvic-vaginal examination was reintroduced.</td>
<td>Four-point rating of outcome: excellent (no change), poor (no change), acceptable (improvement in intercourse), and poor (no change).</td>
<td>Treatment outcome was positively related to therapist-rated compliance to homework assignment by the patient and to therapist-rated distress in the relationship.</td>
<td>3b</td>
</tr>
<tr>
<td>Schuyler, Schuyler, Stinnett, &amp; Blau, 1998</td>
<td>VAG</td>
<td>N(VAG)=44</td>
<td>Behavioral sex therapy involving daily home exercises with insertion of vaginal dilators after demonstration of insertion by therapist (no visible therapist's visual examination only on video), participants randomized to treated conditions.</td>
<td>Dichotomous assessment of intercourse success: unvalidated interview ratings of predictor variables.</td>
<td>Success tended to occur more often in the absence of sexual anxiety. No correlations were found between success and patient's sexual history variables.</td>
<td>4</td>
</tr>
<tr>
<td>Schover, Young, &amp; Cusato, 1992</td>
<td>VVS</td>
<td>N(VVS)=45</td>
<td>Uncontrolled prospective study. Treatment: local vasoactive therapy, vaginal dilation, and couple therapy.</td>
<td>Outcome measures rated on 5-point scale: very much improved to very much worse. Predictor variables: Sex History Form, Dyadic Adjustment Inventory, Brief Symptom Inventory, and structured interview for DSM-IV disorders and sexual history.</td>
<td>Predictive for better outcome were: higher socioeconomic status, relationship status, and sexual function.</td>
<td>2b</td>
</tr>
<tr>
<td>Bergeron, Brown, Lund, Oda, Blau, &amp; Kladis, 2002</td>
<td>VVS</td>
<td>N(VVS)=35</td>
<td>Retrospective study: physical therapy (pelvic floor muscle rehabilitation and biofeedback), provided with a mean of 7 sessions. Length of follow-up = 2-44 months; mean = 16 months.</td>
<td>Telephone assessment of sexual dysfunctions, outcome of anxiety disorder (5-point scale from a lot worse to complete relief), current pain during intercourse, and sexual functioning.</td>
<td>Successful responses were less affected than nonrespondents.</td>
<td>3b</td>
</tr>
</tbody>
</table>

Dysfunction type: VVS = vulvar vestibular syndrome; VAG = vaginismus.
III. DYSPAREUNIA NOT IDENTIFIED AS VVS

1. INDIVIDUAL PSYCHOLOGICAL AND PERSONALITY CHARACTERISTICS

Higher rates of psychopathology in women with dyspareunia not stated to be due to VVS were found with regard to depression**, anxiety disorders*, more specifically: generalized anxiety disorder*, simple phobia*, obsessive-compulsive disorder*, and social phobia*. Equal rates of psychopathology in women with dyspareunia, compared with healthy controls, were found with regard to posttraumatic stress disorder*, and eating disorder* (see Tables 28 and 32).

In women with dyspareunia equal frequency of childhood sexual trauma has been found*, when compared with the general female population.

On self-report measures (see Tables 29 and 32), women with dyspareunia are found to have higher scores on neuroticism*, depression**, and state anxiety**. Phobic anxiety in women with dyspareunia is found higher**, as are obsessive-compulsive behaviors**, and social phobia (interpersonal sensitivity)**. Women with dyspareunia also report more symptoms of hostility**, more (psychosomatic complaints (somatization)*, higher paranoid ideation*, and more psychotic symptoms*.

2. SEXUAL RELATIONSHIPS OF WOMEN WITH DYSPAREUNIA

With regard to personality traits assumed to be directly related to the domain of sexuality, they are found to score higher on erotophobia*, and to have more negative feelings about sexual interaction*.

With regard to sexual functioning, they appear to have more problems with sexual arousal**.

They are shown to be suffering from increased relationship discord**.

3. PSYCHOLOGICAL PROCESSES

As to psychological processes causing or maintaining dyspareunia (see Tables 30 and 32), 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. Compared with nonsymptomatic women, genital respon-
<table>
<thead>
<tr>
<th>Clinical psychopathology</th>
<th>Dyspareunia</th>
<th>VVS</th>
<th>Vaginismus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety disorder</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Depression</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychological characteristics assessed with psychometric instruments</th>
<th>Dyspareunia</th>
<th>VVS</th>
<th>Vaginismus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroticism</td>
<td>+</td>
<td>-</td>
<td>+/ -</td>
</tr>
<tr>
<td>Depression</td>
<td>++</td>
<td>++/ -</td>
<td>++/ -</td>
</tr>
<tr>
<td>State anxiety</td>
<td>++</td>
<td>++/ -</td>
<td>++/ -</td>
</tr>
<tr>
<td>Trait anxiety</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phobic anxiety</td>
<td>++</td>
<td>++/ -</td>
<td>++/ -</td>
</tr>
<tr>
<td>Obsessive-compulsive behaviour</td>
<td>++</td>
<td>++/ -</td>
<td>++/ -</td>
</tr>
<tr>
<td>Shyness</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interpersonal sensitivity (social anxiety)</td>
<td>++</td>
<td>++/ -</td>
<td>++/ -</td>
</tr>
<tr>
<td>Hostility</td>
<td>++</td>
<td>++/ -</td>
<td>++/ -</td>
</tr>
<tr>
<td>Psychoticism</td>
<td>+</td>
<td>++/ -</td>
<td>++/ -</td>
</tr>
<tr>
<td>Extraversion</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatization</td>
<td>+</td>
<td>++/ -</td>
<td>++/ -</td>
</tr>
<tr>
<td>Hysterical personality</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perfectionism</td>
<td>+</td>
<td></td>
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</tr>
<tr>
<td>Low self-esteem</td>
<td>+</td>
<td></td>
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</tr>
<tr>
<td>Harm avoidance</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erotophobia</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive sexual self-schema</td>
<td>-</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Negative sexual self-schema</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catastrophizing thoughts</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital problems</td>
<td>++</td>
<td>-</td>
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<table>
<thead>
<tr>
<th>Aspects of sexual functioning</th>
<th>Dyspareunia</th>
<th>VVS</th>
<th>Vaginismus</th>
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<tbody>
<tr>
<td>Sexual trauma</td>
<td>-</td>
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<td>+/ -</td>
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<tr>
<td>Less sexual self-stimulation</td>
<td>+</td>
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<tr>
<td>Sexual desire problem</td>
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<tr>
<td>Sexual arousal problems (with partner contact)</td>
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<tr>
<td>Lubrication problems (with partner contact)</td>
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<tr>
<td>Sexual arousal problems (with masturbation)</td>
<td>+</td>
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<tr>
<td>Lubrication problems (with masturbation)</td>
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<tr>
<td>Lack of sexual pleasure</td>
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<td>Negative feelings about sexual interaction</td>
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<tr>
<th>Psychological factors in etiology (results of controlled comparisons/experimental manipulation)</th>
<th>Dyspareunia</th>
<th>VVS</th>
<th>Vaginismus</th>
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<tr>
<td>Lower heat pain threshold</td>
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<tr>
<td>Lower tactile pain threshold</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Anxiety</td>
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<tr>
<td>Marital adjustment</td>
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<tr>
<td>Attentional bias towards pain stimuli</td>
<td>+</td>
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<tr>
<td>Lower genital arousal associated with intercourse</td>
<td>+</td>
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<tr>
<td>Attribution of pain to psychosocial factors</td>
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<tr>
<td>Deficient pelvic muscle control</td>
<td>-</td>
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<tr>
<td>Pelvic muscle contractions in response to threat</td>
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1 clinical diagnosis of anxiety disorder includes agoraphobia without panic disorder, generalized anxiety disorder, simple phobia, obsessive compulsive disorder, social phobia; 2 no higher than healthy controls.

+: significant; ++: more than one study; -: not significantly different from healthy controls; --: more than one study; ++/ -: found in one/some studies, but not in other(s).
On self-report measures (see Tables 29 and 32), conflicting findings were reported. Women with vaginismus are found to have equal and higher scores on neuroticism**, depression**, state anxiety**, phobic anxiety**, social phobia**, obsessive-compulsive behaviour**, paranoid ideation**, psychoticism**, somatization**, and hostility**.

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*.

3. Psychological processes

As to psychological processes causing or maintaining vaginismus (see Tables 30 and 32), 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 threatening and sexual-threatening stimuli*. Erotic stimulation does not increase pelvic floor muscle activity in women with vaginismus. Experienced threat of the stimuli correlates significantly with EMG-measured muscle activity*.

Thus far, no randomized controlled trials of psychological treatment for vaginismus have been published.

4. Prediction of treatment

Prediction of treatment by means of psychological, psychosexual and psychosocial variables has been investigated in vaginismus in three non-controlled studies (see Table 30).

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 pretreatment ratings of the female partner of marital tension*.

Negatively associated with treatment length were: pretreatment 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 of: history of sexual abuse*, presence of additional sexual dysfunction in either partner*. No replications of prediction models have been reported.

5. Conclusions re women with vaginismus

Summarizing, women with vaginismus were found to have significantly increased comorbid anxiety 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 been investigated as yet. Psychological characteristics, measured with self-report instruments do not unequivocally corroborate the presence of anxiety disorders. Personality traits found to be more often present in this group suggest the presence of self-focused attention and negative self-evaluation 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 documented the role of experienced threat in increased pelvic floor muscle tension, but did not discriminate between women with and without vaginismus. The causation and maintenance of vaginismus by psychological factors thus remain unresolved although fear of penetration and associated attentional bias may play a role.

U. Pelvic Floor and Sexual Pain Disorders

Problems with the pelvic floor musculature have been closely linked with the diagnosis and treatment of the “sexual pain disorders”. For example, both the AFUD and DSM nosologies have used the concept
of vaginal muscle spasm to classify vaginismus [56, 142]. The traditional treatment for vaginismus, «vaginal dilatation», was presumed by many to follow from this definition. Poor pelvic muscle strength, and increased tonicity have been suggested as important correlates of dyspareunia resulting from VVS. This idea has resulted in the development of pelvic floor biofeedback and physical therapy as treatment modalities [446, 447].

Clinicians and researchers working with “sexual pain” patients are often faced with a bewildering array of terms to describe and define muscle states that are presumed to be linked to clinical pain problems. Among the terms used are the following: tonicity, contracture, spasm, compliance, stiffness, tetany, dystonia, trigger point etc. Although there are formal definitions for many of these terms [448], these definitions are rarely used consistently in the clinical or research literatures. With respect to the sexual pain disorders of vaginismus and dyspareunia, this has resulted in much confusion. The basic issue to be addressed here is the following: can sexual pain be considered a disorder of the pelvic floor?

1. THE ENTITY OF “VAGINISMUS”

It is remarkable that there has been almost no controversy until very recently, concerning the spasm based definition of vaginismus. This definition can be traced back to the writings of Trotula of Salerno who described the condition as a result “…of tightening of the vulva so that even a woman who has been seduced may appear a virgin” [449]. This idea of vaginal tightening was transformed into vaginal spasm by the 19th century so that Sims (1861) described the condition as “spasmodic contraction of the sphincter vaginae…”. Despite the absence of research confirming this spasm criterion, the 1998 consensus diagnostic formulation is as follows: “recurrent or persistent spasm of the musculature of the outer third of the vagina which interferes with vaginal penetration and causes personal distress” [142]. This consensus definition did not essentially change the current ICD 10 or DSM diagnostic statements except for changing the “interference criterion” from interference with intercourse or penile entry specifically to interference “with vaginal penetration in general”. Further revision of the definition omitting reference to spasm and noting the variable avoidance typical of this syndrome, has just been published [64] see p77.

Issues relating to the role of the pelvic floor in vaginismus can perhaps be usefully divided into four separate questions: 1) can vaginismus be diagnosed reliably? 2) can vaginal spasm be assessed reliably? 3) are there differences in baseline tonicity or voluntary control over the pelvic musculature that distinguish women suffering from vaginismus from controls? 4) are therapies based on self-placement of progressively larger vaginal inserts effective?

2. DIAGNOSIS OF “VAGINISMUS”

Perhaps because there has been so little controversy concerning the diagnosis, there have been very few studies examining the reliability and/or validity of diagnosis. In two consecutive clinical case studies (level 4b), the authors have pointed out that it is often hard to distinguish vaginismus from dyspareunia resulting from VVS [342, 451]. A Dutch group has shown in one retrospective and one prospective study based on structured gynecological examinations, interviews and psychometric testing, level 2b, that it is very difficult to distinguish vaginismus from dyspareunia [340, 341].

Finally, in a formal diagnostic reliability study, level 2b, it was shown that although gynecologists and pelvic floor physical therapists can distinguish women suffering from sexual pain disorders from matched controls, they could not reliably distinguish women diagnosed with vaginismus from those diagnosed with VVS based on vaginal spasm, pelvic hypertonicity or pain. Furthermore inter-gynecologist reliability for the diagnosis of vaginismus was quite poor [452]. Overall, part of this difficulty in differentiating vaginismus from dyspareunia has been the idea held by some diagnosticians, who have understood the concept of “interference with intercourse” to mean “the total preclusion of intercourse”. Therefore, a “not stoic” woman with dyspareunia from what ever cause who does not want to tolerate the pain of penetration would be diagnosed with “vaginismus”. For this reason, the diagnosis of vaginismus should only be made if structural or other physical abnormalities have been ruled out or addressed [64]. Additionally, a woman without evidence of VVS or other variety of dyspareunia, displays signs of fear of vaginal entry with tightening of pelvic and abdominal muscles (and often thigh, jaw, hand muscles, etc), may nevertheless experience full penetration by a persistent partner who does not desist despite lack of erotic quality of the interaction. She has “vaginismus” but can just about tolerate full entry +/- some thrusting.

3. VAGINAL “SPASM” IN VAGINISMUS

Because all previous definitions of vaginismus were based on the concept of vaginal spasm and because
the differential diagnosis of vaginismus from dyspareunia is questionable, there is reason to suspect that the diagnosis of vaginal muscle spasm may also not be reliable. In fact, the general validity of the concept of muscle spasm has been called into question [453]. As far as we are aware, only one study has directly investigated whether muscle spasm specifically characterizes vaginismus [452]. The results of this study strongly suggest that vaginal muscle spasm does not characterize vaginismus and that different professionals diagnose spasm very differently. Interestingly, less than a quarter of the women in the vaginismus group attributed their difficulties with intercourse to vaginal spasm.

4. MUSCLE TONE OR STRENGTH IN VAGINISMUS

Four studies have investigated this issue using a variety of measurement techniques including vaginal and non-vaginal EMG, pelvic floor physical therapist and gynecologist ratings (level 2b) [435, 436, 452, 453]. EMG pelvic floor measurements were taken in response to a) film stimuli displaying erotic, neutral, sexually and non-sexually threatening situations, b) gynecological examinations, and c) instructions to consciously contract and relax vaginal/pelvic muscles. In only one of the studies [452] did EMG measures differentiate vaginismic women from matched controls. Such studies are intrinsic problematic. Women with typical/severe “vaginismus” have never been able to tolerate the insertion of a finger, a tampon, a penis, speculum and before any therapy would not be likely to comply with these protocols. Indeed, in the above study, over half the women suffering from vaginismus refused to insert the EMG sensor for one of the two testing sessions. There was, however, consistent data from this study indicating that a structured protocol of manual measurement of the pelvic floor musculature carried out by physical therapists is reliable and can differentiate women with vaginismus from matched normal controls.

5. THERAPEUTIC RESULTS

Since Masters and Johnson, most therapies for vaginismus have used vaginal “dilatation” as a major treatment intervention: Initially the woman becomes accustomed to self touch to the introitus and insertion of her own finger though the introitus and part way into her vagina. She then places the first of a series of inserts of gradually increasing diameter into her vagina. In reality of course there is no “dilata-

II. DYSPAREUNIA

1. THE QUESTION OF MUSCLE TONE

Almost all the research regarding the contribution of pelvic floor muscle physiology to dyspareunia is linked to the work of Howard Glazer who has focused primarily on the use of vaginal electromyographic biofeedback (“Glazer protocol”) as a treatment modality for VVS/vulvodynia. The discussion will focus on two questions: 1) are there demonstrable pelvic floor muscular differences in women with dyspareunia? 2) are pelvic floor focused therapies for dyspareunia effective?
2. Pelvic floor in women with dyspareunia

In a series of uncontrolled consecutive patient outcome studies using vaginal electromyographic feedback, level 4b, the investigator has reported impressive pain reduction/return to intercourse results for women suffering from VVS and vulvodynia [446, 460-462].

As a result, the author has suggested that changes in resting pelvic muscle tone and contractility may characterize these disorders. Another study, level 2, also examined this issue using a Glazer based vaginal EMG protocol and structured physical therapist palpation [452].

Their EMG data confirm differences in muscle strength but not muscle tone between VVS sufferers and matched controls. However, for physical therapist-based palpation data, the authors found increased pelvic floor tonicity and lowered muscle strength in women with VVS compared with normal matched controls.

Combined with the findings summarized above from vaginismic women, there does appear some indication that pelvic floor muscle tone and strength measures for women suffering from VVS are intermediate between those of women with vaginismus and no pain controls.

3. Therapeutic Results

Bergeron et al., level 2b, have carried out a prospective, randomized controlled treatment outcome study which compared the Glazer treatment protocol to cognitive-behavioral group pain management and vestibulectomy [463].

Glazer type biofeedback resulted in significant clinical improvement as compared with baseline and approximately a 40% reduction in pain. The same authors have also carried out an uncontrolled retrospective, level 4b, consecutive case investigation of whether pelvic floor physical therapy including but not limited to biofeedback was useful in the treatment of VVS [438].

The pelvic floor physical therapy typically lasted 6-8 sessions and included a variety of manual techniques, biofeedback, electrical stimulation and homework exercises designed to stretch, strengthen, relax and heighten awareness of the pelvic floor muscles. Approximately 50% of the patients reported complete to great improvement and another 20% reported moderate gains.

III. Summary

Although psychiatric and psychological texts often attribute sexual pain to the pelvic muscle dysfunction, standard medical texts focusing on the pelvic floor rarely, if ever, mention vaginismus or dyspareunia [464]. Such texts deal with a wide variety of disorders some of which can be described as urogenital pain syndromes e.g. “levator ani syndrome” or “proctalgia fugax”. These syndromes, however, generally refer to perineal or rectal pain rather than vulvovaginal pain. There does appear to be a “minority multidisciplinary movement” among some specialists to consider the pelvic floor as an “integrated functional structure” and to subsume a variety of related “voiding, sexual, genital and defecatory behaviors and problems” under the umbrella of pelvic floor dysfunction. While this idea is an intuitively appealing one, there is currently no empirical support for it.

It is remarkable that there is no empirical evidence to support the 500 year old definition of vaginismus as related to spasm of the muscles of the pelvic floor. The existing evidence directly contradicts it. While there is some indication of differences in resting muscle tone or strength between vaginismus, dyspareunia and no pain controls, these are not well established and could equally well be the result of or the expectation of pain rather than the cause. In fact, there is accumulating basic research to support the idea that the pelvic floor musculature, like other muscle groups is indirectly innervated by the limbic system and therefore highly reactive to emotional stimuli and states [466-468].

There is encouraging preliminary information to suggest that vaginal EMG biofeedback, pelvic floor physical therapy and cognitive behavioral therapy may be useful interventions for VVS [444]. If this is true, it also seems likely that this would be true for vaginismus. Such “limited therapy outcome evidence” however, cannot be used to characterize the nature of the problem. Overall, “sexual pain” cannot be currently characterized simply as a pelvic floor disorder. The problems of vaginismus and dyspareunia, in fact, may not constitute discrete categories at all but may result from the interaction of a variety of factors including genital pain, emotional and behavioral reactions to vaginal penetration/touch, sexual interest and arousability, the presence/absence of infection, structural anomalies, disease and pelvic floor dysfunction.
Sexual pain disorders of genital skin and mucous membranes are common. Most of these painful disorders are transient and are caused by inflammation from acute genital infection. Acute infections that most commonly cause vulvo-vaginal inflammation include acute episodes of candidiasis, trichomoniases, genital herpes, furuncles and infection of the greater vestibular glands. The cause of 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 recent review provides a systematic approach to vulvar disease and offers a comprehensive list of diseases to consider [469]. Treatment often does not totally remove pain. In many cases, treatment is not standard and does little to even substantially reduce pain. Unfortunately, iatrogenic inflammation of the vulvar skin is common from self-treatment or contact with irritants. Nearly all women with chronic vulvar symptoms first use over-the-counter anti-fungal medication. However, candida was found by physicians in only one third of such patients. This self treatment may be associated with increased duration of symptoms, which suggests a detrimental effect from the medication [470]. Some chronic genital pain is constant even without intercourse, but intercourse usually causes an exacerbation of the pain, often to the point where intercourse is avoided or stopped totally.

II. TYPES OF MUCOUS MEMBRANE DISEASE

1. vulvodynia

When signs of VVS or other diagnosis are absent, and biopsies and culture is negative, the term dysesthetic vulvodynia is used. Here all the vulval structures are of normal appearance and the woman describes vulvar burning and pain (vulvodynia) severe enough to cause sexual and psychological distress [410]. The syndrome is difficult to treat. Topical treatment of any kind usually increases the amount of pain. Oral therapy using tri-cyclic antidepressants or anticonvulsants offer a reduction, but not a total resolution [410].

2. 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 [469, 473, 474]. The diagnosis of these conditions can be more easily discerned by experienced clinicians. Lichen simplex chronicus results when chronic scratching produces inflammation of the skin and results in an itch-scratch cycle. The cycle can be interrupted by topical steroid and oral antihistamine therapy [475]. Lichen sclerosis is an indolent chronic condition of unknown etiology where thinning of the epidermis occurs, resulting in a parchment-paper appearance of the skin. Underlying subepithelial inflammation can result in mild to intense itching that is possible to reduce better with topical steroid therapy than with topical testosterone [476]. Lichen planus results in superficial ulcers of the epithelium often resulting in intense pain. 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 therapy is needed of the ulcerated and inflamed areas [477].

Raised vulvar lesions usually do not cause pain but must be accurately diagnosed and treated.

3. Vulvar vestibulitis syndrome

VVS represents one of the most common causes of genital pain and pain with intercourse. Pain usually is noticed with attempted or completed vaginal penetration, although in more severe cases pain will be present with other activity like sitting or running. Besides pain, vulvar burning and itching are common. Together, these symptoms cause physical, sexual and psychological distress [478]. Community studies suggest vulvar pain is common, but the pre-
Valence has varied widely from 3-18% [479, 480]. VVS has been described in up to 15% of gynecologic outpatients [481]. VVS was thought to primarily affect Caucasian women [482, 483]. A recent survey of ethnically diverse women gave similar lifetime prevalences of chronic vulvar burning or pain on contact [484].

Although VVS is easy to diagnose for the experienced clinician, the mean time between the onset of symptoms and diagnosis usually reaches two years or longer. A triad of conditions are necessary to diagnose VVS: 1) pain with penetration or attempted penetration; 2) tenderness of the vestibular area upon even light touch with a cotton applicator; and 3) variable erythema of the vestibular area [417]. The areas of allodynia (sensation of pain from light touch stimulus, are typically between 4 and 8 o'clock on the introitus, just exterior to the hymeneal ring but may involve the skin around the openings of the Skene's ducts. However, the whole introital rim may be involved. The area of tenderness, allodynia and erythema can be difficult to locate because they are usually hidden in folds of the vulva—presumably explaining the typical long time between the onset and diagnosis.

### III. Etiology

#### 1. Inflammation in Vulvar Vestibulitis Syndrome

The etiology of VVS is unknown but VVS may represent a chronic local inflammatory condition with a wide variety of etiologic causes. T-cell lymphocytes make up most of the inflammatory cells present in vulvar biopsies obtained from those with VVS [485, 486]. 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. The vulvar tissue of patients with VVS contains elevated tissue levels of interleukin-1 beta (IL-1) and tumor necrosis factor alpha (TNF-α), but these pro-inflammatory mediators are 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 [487].

#### 2. Genetics of Vulvar Vestibulitis Syndrome

Recent work points to a possible genetic involvement. In fact, as is common for inflammatory conditions, allele 2 of the IL-18 gene was found in significantly more women with VVS (40%) than controls (25%) [488]. Leukocytes in blood from women with VVS also produce less interleukin-1 receptor antagonist, which suggests a failure in down regulation of inflammation [489]. Allele. 3 of the gene encoding the interleukin-1 receptor antagonist was present in the homozygous form in 53% of women with VVS compared to an 8.5% of control women [490].

#### 3. Possible Antigen(s) Involved in Vulvar Vestibulitis Syndrome

The presence of a high T-lymphocyte concentration and increased levels of pro-inflammatory mediators point to a chronic immunologic induced inflammatory response to some antigen [491].

The antigen that induced VVS for an individual could still be present in vulvar tissues in a small concentration or the antigen could have stimulated the inflammation, but be gone by the time patients usually present with VVS. The most likely antigen candidate would be from microbes that commonly affect the vulva. Human papilloma virus (HPV) was first considered, but in multiple studies, HPV was as common in controls as women with VVS [492-494]. Herpes simplex virus (HSV) is also a common vulvar infection, but, to date, HSV does not appear to cause VVS [384, 495]. Candida is an antigen present in the vulva more frequently than HPV or HSV. Up to 80% of women develop symptomatic candidiasis during their lifetime. Patients with VVS have a frequent history of candidiasis, often recurrent [496, 497]. A modest prevalence of recovery of candida occurs from women with VVS [498, 499]. Undoubtedly, other microbial antigens from bacteria, viruses or other microbes or non-microbial antigens are present in the environment or in chemicals that come in contact with vulvar skin could also cause VVS.

Candida is infrequently identified by potassium hydroxide wet mounts, which require about 10⁶ microbes to be positive. Candida frequently is isolated on culture from women with VVS, although extensive comparisons with control groups are lacking [496, 497]. Some patients with chronic recurrent vulvo-vaginitis candidiasis (VVC) are noted to develop VVS when they are prospectively followed. Further, some women relate the onset of VVS to an acute episode of VVC and patients cured of VVS often develop recurrent genital pain when another episode of VVC occurs.
4. IMMUNOLOGIC MODEL OF VULVAR VESTIBULITIS SYNDROME

The immunologic response that results in cutaneous T lymphocyte cell pathology is well described for other examples of disease with chronic T-lymphocyte infiltration [491]. The innate immune system acts to arrange for cutaneous skin immune surveillance by the identification of antigens in the skin and the translation of antigen signal to memory T lymphocytes. Certain memory T cells contain a cell surface adhesion molecule called cutaneous lymphocyte antigen (CLA). T cells with CLA circulate preferentially in the skin as opposed to circulating to internal organs. Antigens in the vulvar skin initially are identified by dendritic cells with macrophage-like characteristics (see Figure 8). As an example, macromolecules from candida antigens are efficiently internalized by dendritic cells, which, in turn, migrate to the regional lymph node.

In the lymph node, dendritic cells meet continuously circulating naive T cells. When a naive T cell encounters and interacts with the candida antigens in a dendritic cell, it becomes activated. Activation of the T cell in the lymph node produces a memory T cell (see Figure 8) and the expression of CLA provides this cell with the keys that, when it migrates out of the lymph node and into blood, allows it to escape the blood and circulate only in skin.

Thus, activated T cells have the molecular keys that allow their exit from the blood through the vascular endothelium in skin (3 in Figure 8). The adhesion molecule property of CLA allows tethering to occur of activated memory CLA-positive T cells traveling in post capillary venules to the endothelium of these venules. The specific venule is identified by the expression of intracellular adhesion molecules and vascular-cell adhesion molecules on the inner endothelial surface. These adhesion molecules tether and slow travel of the T cell in the venule, which allows it to slide between endothelial cells into the local skin tissue [491]. The adhesion molecules are expressed in the endothelial cells by the action of nuclear factor-kB (NF-kB) which is formed in the local skin. The identification of antigens such as candida by dendritic cells and especially by activated T cells produces IL-1 and TNF-α, which, in turn, activate the NF-kB pathway. The persistence of candida or any antigen in the skin further activates memory CLA T cells and produces a further acceleration in the production of IL-1 and TNF-α (4 in Figure 8). The IL-1 and TNF-α signal produces even more NF-kB results in a circle effect of even more local inflammation, more activation of T cells, more adhesion molecule expression (5 in Figure 8) and an increased collection of activated T cells [491].

5. CLINICAL RELEVANCE OF IMMUNOLOGICAL AND NEUROGENIC INFLAMMATORY THEORIES

In this model, it is proposed that repetitive antigen stimulation or the prolonged presence of antigen markedly up-regulates the local inflammation (6 in Figure 9). The presence of a high concentration or a persistence of chronic pro-inflammatory molecules such as IL-1 and TNF-α, but also serotonin, bradykinin and histamine could sensitize local C nerve fibers [500] Inflammation also increases the synthesis of sensory neuropeptides (such as calcitonin gene-related peptide [CGRP] and substance P) from activated C fibers. These substances themselves have a pro-inflammation effect [501]. Prolonged C fiber firing reduces the threshold of pain and results in hyperalgesia (7 in Figure 9). Further, transport of CGRP and substance P to the dorsal horn of the spinal cord sensitizes cord neurons with the end result that touch is perceived as pain (allodynia). A significant increase in the number of intra-epithelial nerve endings occur in women with VVS compared to controls [384, 388]. The nerve endings appear to be nociceptors [502], and it has been suggested that the erythema results from a neurogenic rather than an inflammatory source [503]. This chronic pain may lead to hypertonicity of the pelvic muscles (8 in Figure 9). The reduced pain threshold and pelvic muscle hypertonicity, in turn, causes more pelvic pain than one might expect otherwise.

It is unclear why surgery improves the local pain and decreases pain with intercourse in some subjects with VVS, but it is possible that surgery removes the target tissue of skin containing pro-inflammatory molecules and the local vascular epithelium to which CLA T-cells home.

W. MANAGEMENT OF SEXUAL PAIN DISORDERS

I. GENERAL REMARKS

Sexual pain disorders are heterogeneous, multisystemic and multifactorial disorders that should be trea-
Figure 8. Immunological model of vulvar vestibulitis

Figure 9. Immunological model of vulvar vestibulitis cont.
ted in a multimodal way according to etiological factors, risk profile and context. The following algorithm with three distinctive characteristics meets these requirements.

1. **GENERAL RECOMMENDATIONS**

1. A multidimensional and multidisciplinary approach with specific attention to 6 areas: the mucous membrane, the pelvic floor, the experience of pain, sex & partner therapy, the emotional profile and genital mutilation/sexual abuse (Table 34). There is no “one size fits all” approach and no “or-or” approach but an “and-and” approach.

2. Individualized treatment After careful listening to her story and after she has been well informed about the illness and its natural course and possible treatments or ways of handling it, a treatment plan is made.

3. Patient focused approach: it is up to the woman and her partner to decide which treatment they wish to embark on. If the careful assessment of psychological function has shown some psychopathology, this should be treated first with psychotherapy. By involving the women in the decision process, regarding the specific treatment of the pain, they share the responsibility for treatment choice and this is known to have a positive effect on the treatment outcome [504]. Shifts in preference for a certain approach will depend on the country in question, women's attitudes regarding psychosexual therapy versus surgery, individual health care systems, cost effectiveness of the various modalities, e.g. for VVS - surgery, cognitive behavioral therapy, biofeedback, or combination.

2. **A COUNSELING MODEL**

This approach implies that the health care provider has to be familiar with the counseling model. He or she is advisor and counselor and takes care that the woman is in full command of the situation. This is a treatment that is very time-consuming, requires great patience, great empathy, sensitivity to non-verbal signals and insight into relational interactions. He or she must be able to identify the woman's ambivalent feelings regarding coitus, sex, her partner, her own body, her desire to have children. He or she must be able to bring to light serious relational problems or severe traumatic experiences (sexual violence) and he or she has to realise that being able to have sex does not automatically mean that the coitus is enjoyed. It is highly recommended that the health care provider receives suitable training.

II. THERAPEUTIC OPTIONS

In table 34 the various treatment modalities for VVS are presented by area.

1. **MEDICAL INTERVENTION**

On medical intervention for VVS there are only two published studies that are methodologically correct (level 2): Fluconazole, Cromolyn [505, 506]. Both interventions proved to be no more effective than placebo. One confounding factor is a consistent improvement of 20-30% of patients with VVS when treated with placebo or with no therapy [506]. In spite of this, many clinicians continue to include in their biopsychosocial therapeutic approaches, medical interventions of unknown efficacy. Unless part of a RCT, it is recommended that topical medication be restricted to inert creams. (Possibly repeated touch at sub threshold pain levels provides therapeutic benefit).

Tricyclic anti-depressants, venlafaxine, anticonvulsants - usually carbamazepine or gabapentin offer some pain relief, although total pain resolution with these drugs appears infrequent (level 3b). The starting dose of nortriptyline and other tricyclic antidepressants is low, 10mg, but can be gradually increased to 40-60mg daily as tolerated. Similar doses used to treat essential (dysesthetic) vulvodynia [336] have augmented the treatment of the pain in women with VVS [410].

2. **HYGIENE MEASURES**

Preventive hygienic measures (level 5) include no soap, no vaginal douching, no nylon underwear (“ventilation”), no pantyliner (mini pads), fluids to produce 1500 ml urine daily and toilet hygiene. Hydration with sitz baths may help reduce inflammation and symptoms.

3. **RECOMMENDATIONS RE SEXUAL ACTIVITY**

For protection of the mucous membrane no vulvar penetration with penis, finger or tongue should be advised and no semen in the vulva. Some women feel very guilty and some men feel very frustrated about this. Persistent lack of sexual desire in spite of significant improvement in sexual frequency has been observed [447]. Therefore normalizing, reframing and encouragement of non-penetrative sex is needed since healing usually takes many months. It is recommended the couple aim at pleasurable and
Table 34: Algorithm of management of sexual pain disorders

1. **Sexual Pain Disorders**
   - History + Physical Exam + Multidisciplinary assessment
   - Diagnosis

   - **Area 1: Mucous Membrane**
     - A. B. C. D. E.
   - **Area 2: Pelvic Floor**
     - A. B. C. D. E.
   - **Area 3: Pain**
     - A. B. C. D. E.
   - **Area 4: Sexual Partner Relationship**
     - A. B. C. D. E.
   - **Area 5: Emotional Profile**
     - A. B. C. D. E.
   - **Area 6: Genital Mut/Sexual Abuse**
     - A. B. C. D. E.

2. **Explanation of treatment modalities in each area**
3. **Psychological Profile Assessment**
4. The woman, with guidance chooses from the available options
5. Goals of treatment formulated together, assisted by psychological profile
relaxing sex (with orgasms for both partners as desired) without guilt feelings for the woman and without negative sexual tension for the man.

4. VAGINAL EMG BIOFEEDBACK, PELVIC FLOOR PHYSICAL THERAPY, COGNITIVE BEHAVIORAL THERAPY AND VESTIBULECTOMY

There is preliminary information to suggest that vaginal EMG biofeedback, pelvic floor physical therapy, cognitive behavioral therapy and vestibulec- tomy may all be useful interventions for VVS (level 2b-4b) [444-447]. Treatment results are very similar. This may indicate a non-specific treatment effect in terms of attention, validation of her pain, and the patient's feeling 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 deserves further study.

5. PROGNOSTIC FACTORS AND SURGERY FOR VVS

A detailed recent critique of gynecological/surgical procedures for VVS suggest the following indicate better prognosis [507]:

a. Lack of any characteristics of vaginismus before the surgery
b. Acquired rather than lifelong introital dyspareunia
c. Very small amount of surface area involved with alodynia
d. Lack of involvement of the Skene duct openings
e. Lack of vulvodynia, i.e. only introital dyspareunia
f. Willingness to have sex therapy if offered.

One problem with many of the studies in this review is that the follow-up was short term or unspecified. Clinical experience is that benefit from surgery is often temporary with symptoms returning at about 18-36 months. However, longer follow-up with remaining good outcome is reported by some investigators [508-510].

X. CONCLUSIONS RE SEXUAL PAIN

I. NEUROLOGICAL MECHANISMS

From this database, the following recommendations can be drawn with regard to the role of neurological factors in the etiology (causation and/or maintenance) of distinct sexual pain disorders:

From animal studies and clinical observations there is increasing evidence for the role of neuropathic pain mechanisms (neurogenic inflammation, peripheral sensitization, sensitized nociceptors, primary hyperalgesia, and central sensitization) in the pathophysiology of sexual pain disorders. More basic research in this field is needed. In clinical research the use of a diagnostic tool capable of differentiating among women with different types of genital pain, quantifying the severity of the pain and changes of the pain as a result of treatment is highly recommended.

II. PSYCHOLOGICAL FACTORS

With regard to the role of psychological factors in the possible etiology (causation and/or maintenance) of distinct sexual pain disorders the following recommendations can be drawn:

Empirical literature has demonstrated the comorbid presence of clinical psychopathology in the sexual pain disorders. The pervasiveness of clinical psychopathology warrants careful assessment of clinically relevant depression and anxiety disorders for the purpose of treatment planning.

The role of psychopathology and of attentional and cognitive processes in the etiology of dyspareunia generally and VVS was demonstrated in controlled studies, although these findings await replication. Psychological etiological factors underlying vaginismus are unresolved.

Women with VVS demonstrate attentional bias for pain-related stimuli (thermal and tactile stimulation) as compared with normal controls, and lowered sensitivity to pain than asymptomatic women. This lowered sensitivity is not limited to the genital area,
is stable over time and the level of hypervigilence is largely accounted for by state and trait anxiety levels. These experimental findings need replication. Also impairment of genital responding in women with dyspareunia by specific sexual stimulation (audiovisual representation of penile-vaginal intercourse) during laboratory investigation needs replication.

Psychosocial variables predictive for better outcome in women with VVS were higher socioeconomic status, lower education, and childlessness. Willingness to be psychologically evaluated was highly predictive for positive outcome of limited vestibulectomy, as was cooperation of patient in postoperative counseling, localized disease, acquired vs. lifelong symptoms, absence of vulvodynia and non-involvement of Skene duct openings. Prediction of treatment by means of psychological or psychosocial variables has not been investigated in dyspareunia not stated to be due to vestibulitis. Prediction of treatment by means of psychological or psychosocial variables has been investigated in vaginismus but the three studies were non-controlled. More prospective research with special attention for predictor variables is needed.

III. PELVIC FLOOR FACTORS

With regard to the role of the pelvic floor in the etiology (causation and/or maintenance) of distinct sexual pain disorders: Consistent level 2 studies reveal

1. that differentiation between vaginismus and dyspareunia using clinical tools is difficult, or nearly impossible;
2. that vaginal spasms have not been identified;
3. that only physical therapists can differentiate vaginismic women from matched controls based on muscle tone or strength differences;
4. that despite strong clinical support for the treatment the traditional treatment of vaginismus with vaginal “dilatation” plus psycho-education, desensitization etc., it is not to date supported by scientific study.
5. that there does appear some indication that pelvic floor muscle tone and strength measures for women suffering from VVS are intermediate between those of women with vaginismus and no pain controls.

6. that there is accumulating basic research to support the idea that the pelvic floor musculature, like other muscle groups is indirectly innervated by the limbic system and therefore highly reactive to emotional stimuli and states and
7. that pelvic floor focused therapies for dyspareunia may be effective.

IV. DEFINITIONS RE SEXUAL PAIN

It is recommended that definitions of vaginismus and dyspareunia are revised, as in the recent consensus paper [64] and further modified as knowledge of the underlying pathophysiological mechanisms increases. Also, vaginismus and dyspareunia should not be characterized as simply “disorders of the pelvic floor” or as a “pain problem” or as a “vestibulum problem” or as “psychological problem”. It is obvious that current diagnostic categories may overlap, and need to be reconceptualized. Symptoms may be cause as well as effect of the complaints. For treatment an integrated approach is recommended.

V. TREATMENT

The treatment of vulvar vestibulitis with EMG biofeedback, pelvic floor physical therapy, cognitive behavioral therapy and vestibulectomy has been evaluated to be effective. Significant improvement in experienced pain, and in intercourse frequency and other measures of sexual functioning is reported. Results were found to be maintained over time. Irrespective of the kind of treatment, the results are very similar. This indicates a non-specific treatment effect that could be specified as a “patient centered approach”. In future research this non-specific treatment aspect has to be validated. Controlled studies are needed to test promising interventions.

VI. RECOMMENDATIONS FOR CLINICAL PRACTICE

The examination technique to search for the cause of dyspareunia is more detailed and requires much
more finesse than a routine pelvic examination. If the medical examination is conducted correctly, it can be highly therapeutic. Such an examination can best be referred to as an "educational gynecological sexual examination".

The use of brief personality and psychological questionnaires is advocated because they could be of interest to detect possible comorbidity, for tailoring treatment and to evaluate the effect of the treatment. The degree of pain should be documented and the use of the vulvalgesiometer is recommended.

It is recommended that the whole area of prevention of sexual pain by education re sexuality be addressed.

Y. CONCLUSIONS TO CHAPTER

Much of the research reviewed in this chapter is based on assumptions about women's sexual function which are not supported by clinical and empirical data. The past focus on assessing and treating apparent lack of genital congestion may now change to attempting to understand the disconnection from/inattention to, the genital events, which do occur promptly in response to sexual stimulation in most women complaining of lack of arousal. An emphasis on analysis of the emotions and thoughts engendered by that sexual stimulation is needed, given both are known to strongly influence the woman's subjective experience of arousal. Better understanding of genital vasocongestion and its disruption in the small subgroup of women with genital arousal disorder is expected from delineation of the autonomic innervation of the genitalia and the identification of the neurotransmitters involved in vaginal smooth muscle relaxation.

The focus on assessing and attempting to change a woman's frequency of apparently spontaneous sexual thoughts, fantasies and desire for sex is now strongly challenged by the evidence that many sexually satisfied women in longer term relationships rarely experience these traditional markers of sexual desire. There is evidence of a very broad normative range. Moreover, sexual desire is not the reason usually given for women's agreeing to or instigating sexual activity. Thus, an understanding of why there may be few or no reasons/incentives or interest for a sexual experience, becomes the focus worthy of future study.

That approximately 15% of younger women have chronic dyspareunia that is poorly understood and for which cure is infrequent, makes this an urgent health issue. Unlike complaints of "low desire/low interest", the vast majority of women with chronic dyspareunia see it as hugely problematic and distressing. Despite this distress, and the persistent repeated requests for help from some women, the total lack of request for help by many others also deserves study.

Abusive experiences of many types leave long-term sexual sequelae, the optimal management of which is unclear. Clearly, a focus on prevention is vital.

The contextual nature of women's sexuality and the importance of the subjective over the physical experience strongly supports the need for biopsychosocial assessment of sexual dysfunction and similarly an integrated treatment. Given the comorbidity of women's sexual dysfunctions, despite the inherent complexity, future research would merit focusing on this comorbidity as well as a biopsychosocial approach.

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Chapter 23

2004

Summary of the Recommendations on Women’s Sexual Dysfunctions


“There exists fundamental rights for the individual, including the right to sexual health and a capacity to enjoy and control sexual and reproductive behavior in accordance with a social personal ethic - freedom from fear, shame, guilt, false beliefs and other factors inhibiting sexual response and impairing sexual relationships - freedom from organic disorders, disease and deficiencies that interfere with sexual and reproductive function.”

WHO 1994

The 2nd International Consultation on Sexual Dysfunction in men and women was convened in Paris, France June 28 - July 1, 2003. Its mission was to update the present knowledge in this fast developing area of medicine and develop recommendations for the evaluation and management of Sexual Dysfunction in men and women.

This summary encompasses the recommendations concerning Sexual Dysfunction in women. The recommendations are based on a thorough review of the available literature following the Evidence-based Medicine principles as developed by the Consultation in collaboration with the Oxford and Cochrane institutions.

The focused recommendations of the 9 committees addressing women were discussed in an open session in Paris by a large audience of experts. The final recommendations were refined by the Scientific Committee consisting of the chairpersons of each committee.

These recommendations published in 2004 will be periodically re-evaluated in the light of clinical experience and progress within the field.
A. Recommendations Regarding Assessment of Women’s Sexual Dysfunction

DEFINITION

Women’s sexual dysfunctions include persistent or recurrent disorders of sexual interest/desire, disorders of subjective and genital arousal, orgasm disorders, pain and difficulty with attempted or completed intercourse.

I. GENERAL REMARKS

◆ The framework for assessment of sexual dysfunction is to assess predisposing, precipitating and maintaining factors.
◆ When there is a current sexual relationship, both partners need to be assessed to understand the above factors.
◆ Collaboration between different disciplines is recommended for optimal assessment.
◆ Current contextual/environmental factors are commonly etiologically important.
◆ Past history - developmental and past relationships are commonly etiologically important especially for lifelong dysfunctions.
◆ Comorbidity of women’s sexual dysfunctions is very common.
A COMPREHENSIVE MEDICAL AND PSYCHOSEXUAL HISTORY IS HIGHLY RECOMMENDED FOR ALL SEXUAL DYSFUNCTIONS – SEE TABLE 1

**Table 1: Components of a comprehensive sexual, medical, psychosocial history**

<table>
<thead>
<tr>
<th>BIOLOGICAL</th>
<th>PSYCHOSOCIAL</th>
<th>SEXUAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>general systems inquiry</td>
<td>mood,</td>
</tr>
<tr>
<td>Present context</td>
<td>medications/substance abuse, fatigue, presence</td>
<td>the sexual difficulties in her own words</td>
</tr>
<tr>
<td>(Precipitating/</td>
<td>of non-sexual pain.</td>
<td></td>
</tr>
<tr>
<td>maintaining)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past Context</td>
<td>past medical history</td>
<td>particularly for lifelong problems,</td>
</tr>
<tr>
<td>(Predisposing/</td>
<td></td>
<td>developmental history, including</td>
</tr>
<tr>
<td>precipitating)</td>
<td></td>
<td>relationships with caregivers, siblings,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>traumas, and losses.</td>
</tr>
<tr>
<td>Onset (Precipitating)</td>
<td>past medical, psychiatric</td>
<td>psychosocial circumstances including</td>
</tr>
<tr>
<td></td>
<td>details at time of onset of sexual problems.</td>
<td>relationship at time of onset of sexual</td>
</tr>
<tr>
<td></td>
<td></td>
<td>problems.</td>
</tr>
<tr>
<td>Full picture of her</td>
<td>details re effects of medical condition on</td>
<td>sexual details at onset of dysfunctions</td>
</tr>
<tr>
<td>current sexual</td>
<td>sexual activity, e.g. cardiac compromise.</td>
<td></td>
</tr>
<tr>
<td>role response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role of the partner</td>
<td>partner’s medical health</td>
<td>partner’s mood and mental health,</td>
</tr>
<tr>
<td>(Precipitating/</td>
<td></td>
<td>partner’s reaction to sexual problems</td>
</tr>
<tr>
<td>Maintaining)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distress</td>
<td>re medical issues</td>
<td>re psychosocial issues.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>re sexual dysfunction</td>
</tr>
</tbody>
</table>
III

FURTHER ASSESSMENT OF THE WOMAN WHO DISCLOSES PAST SEXUAL ABUSE IS RECOMMENDED

◆ Assessment of the woman’s recovery from the abuse (with or without past therapy)
  - history of recurrent depression, substance abuse, self-harm, promiscuity, inability to trust, exaggerated need for control or need to please (and inability to say no)
  - Details of the abuse may be necessary, especially if previously unaddressed – see Chapter 16. Assessment of the sexual dysfunction per se may be deferred temporarily.

IV

FURTHER DETAILS RE THE COMPONENTS OF ENQUIRY FOR INDIVIDUAL DYSFUNCTIONS ARE RECOMMENDED

a) Arousal Disorders

It is recommended to clarify which component(s) of arousal is absent/problematic – see Figure 1.

b) Sexual Interest/Desire Disorder, Subjective and Combined Sexual Arousal Disorders

Frequently these dysfunctions are comorbid. For all or any of them the following possible etiological factors should be assessed, see Figure 2.

◆ Usually a number of factors contribute.

Note, occasionally women with emotionally traumatic pasts tell of sexual interest only when emotional closeness with a partner is absent. There is inability to sustain that interest when and if emotional intimacy with the partner develops. (This is a fear of intimacy – not strictly a sexual dysfunction).

Figure 1: Detailed clarification of complaint of low sexual arousal

Figure 2: Assessment of etiological factors in women’s complaints of low sexual interest/desire/low subjective sexual arousal/absent or impaired orgasm.
c) Women’s Orgasmic Disorder

It is recommended to clarify:-

◆ Are orgasms absent and/or very delayed and/or markedly reduced in intensity?
◆ Is there adequate and acceptable stimulation
  – a) with partner
  – b) with masturbation?
◆ Is the degree of trust and safety she feels she needs present?
◆ Is there fear of letting go control?
◆ What does she fear may happen that could be negative?
◆ Is information re women’s sexual response needed for one or both partners?

This information will guide choice of therapy.

---

d) Dyspareunia and Vaginismus

It is recommended to clarify the aspects of her pain, her fear of pain, avoidance responses, as shown in Table 2

V DETAILED MEDICAL ENQUIRY

A detailed medical enquiry with review of systems is highly recommended for all sexual dysfunctions – see 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.

VI PSYCHOSOCIAL HISTORY

Assessment of the psychosocial and psychosexual history is strongly recommended for all sexual dysfunctions – see Table 1.

Table 2. Further details of enquiry for dyspareunia and vaginismus

<table>
<thead>
<tr>
<th>1. Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Where does it hurt? How would you describe the pain?</td>
</tr>
<tr>
<td>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 your partner’s ejaculation, after withdrawal, with subsequent micturition?</td>
</tr>
<tr>
<td>Do you find your body is tensing when you or your partner attempts to insert his penis? What are your thoughts and feelings at this time?</td>
</tr>
<tr>
<td>How long does the pain last? Does touching elsewhere in the genital area cause pain? Does it hurt when you ride your bicycle or when you wear tight clothes? Do other forms of penetration hurt (tampons, fingers)?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Pelvic floor muscle tension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you recognise the feeling of pelvic floor muscle tension during sexual contact?</td>
</tr>
<tr>
<td>Do you recognise the feeling of pelvic floor muscle tension in other (non-sexual) situations?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Arousal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you feel subjectively excited when you attempt intercourse? Does your vagina become sufficiently moist? Do you recognise the feeling of drying-up?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Consequences of the complaint</th>
</tr>
</thead>
<tbody>
<tr>
<td>What do you do when you experience pain during sexual contact? (Continue/stop intercourse/continue to make love without intercourse?)</td>
</tr>
<tr>
<td>Do you currently 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?</td>
</tr>
<tr>
<td>What consequences does the pain have on the rest of your relationship?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Biomedical antecedents</th>
</tr>
</thead>
<tbody>
<tr>
<td>When and how did the pain start? What tests have been done? What treatment have you received?</td>
</tr>
</tbody>
</table>
The genital exam is often highly informative, can be very therapeutic (see chapter 16), but its intimate nature demands there must be a reason for its inclusion.

For women with dyspareunia – for some women, (especially those with lifelong pain and difficulty with penile entry), an educational exam is recommended.

For women diagnosed with vaginismus, 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, of course, be limited because the genitalia are in non-aroused state but estrogen deficiency or more rarely, disease such as connective tissue disorder, can be identified.

For women with combined arousal disorder. 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 vulval 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 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/STD investigation should be taken. Please see chapter 16 for recommended details of procedure of examination of women with sexual dysfunction.

A general physical exam is highly recommended as follows:

- As dictated by the general medical enquiry
- For women with chronic illness
- As part of good medical care e.g. evaluation of blood pressure, breast exam etc.

LABORATORY INVESTIGATIONS

Although frequently none are needed for the assessment of the sexual dysfunction per se, certain situations may require laboratory testing:

- As indicated by the medical assessment e.g. fasting blood glucose, TSH*.
- When an infective etiology for dyspareunia remains possible e.g. vaginal, cervical, vulval discharge microscopy/cultures
- When investigational testosterone therapy is contemplated, accurate assays of free testosterone or accurate assays of total testosterone and SHBG* are required.

The Sodergard equation can be reliably used to calculate free testosterone if total testosterone, albumin and SHBG* are known. This method requires a reliable determination of total testosterone and SHBG; albumin is quantified by routine methodology.

No rapid, simple assay of total testosterone has been shown to produce reliable results in women with low testosterone levels. Liquid chromatography (LC)-MS/MS appears to provide the most reliable measurement of low testosterone concentrations. Measurement of free testosterone by analogue assays are notoriously unreliable, particularly at the lower end of the normal female range and are not recommended for use.

Regardless of which assay method is used, a thorough validation of each method is required. The validation should include assay sensitivity, precision, accuracy and specificity.

* STD = Sexually Transmitted Disease
* TSH = Thyroid Stimulating Hormone
* SHBG = Sex Hormone Binding Globulin
women’s sexual experiences frequently begin for reasons other than sexual desire
desire is consequently experienced after arousal such that continued arousal and a responsive type of
desire coexist and reinforce each other,
are acknowledged.
Such acknowledgment would lead to conceptualization of women’s sexual response in keeping with the
following Figure 3.

Apparently innate or “spontaneous” desire, present before stimulation begins may sometimes also be present as is shown in Figure 4, but its absence does not equate to dysfunction

Figure 3: Alternative model of woman’s sexual response

Figure 4: Blended sex response cycle showing many motivations to be sexual, spontaneous desire and responsive desire accessed en route
The following revised definitions of women’s sexual dysfunction are recommended:

a) Hypoactive sexual desire/interest disorder

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 become sexually aroused are scarce or absent. The lack of interest is considered to be beyond a normative lessening with lifecycle and relationship duration.

b) Arousal disorders

It is recommended that the data confirming women diagnosed with arousal disorder usually show physiologically healthy vasocongestive responses in the genitalia in response to erotic sexual stimulation be acknowledged. Thus it is their lack of subjective arousal that is key to their distress, rather than failure of genital congestion.

It is recommended that the following subtypes of sexual arousal disorder are recognized.

**Subjective Sexual Arousal Disorder**

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.

Given the range of awareness of genital congestion among women, recognition of a “subjective arousal disorder” is advocated.

**Genital Sexual Arousal Disorder**

Complaints of 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 sensations from caressing genitalia. Subjective sexual excitement still occurs from non genital sexual stimuli.

A women diagnosed with the genital subtype of arousal disorder indicates 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.

Of note, it is the woman’s self-report of absent or impaired genital congestion and lubrication that is the basis of the definition. There may or may not be demonstrable physical pathophysiology if such testing were available. Moreover, loss of sexual quality of sensations despite apparently adequate engorgement can occur and is little understood.

**Combined Genital and Subjective Arousal Disorder**

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).

Note, it is the lack of the subjective excitement from any type of sexual stimulation that distinguishes these women from those with genital arousal disorder.

**Persistent Sexual Arousal Disorder**

The following provisional definition of a poorly understood but recently more frequently recognised syndrome, is recommended to facilitate investigation of prevalence and etiology.

Spontaneous, intrusive and unwanted genital arousal (e.g. 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 feelings of arousal persist for hours or days.
The following definition of orgasmic disorder is recommended.

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.

In the past, the criterion of high or “adequate” arousal/excitement was often ignored. It is hoped that by changing the sentence structure misuse of the definition will lessen.

d) Dyspareunia

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.

Persistent or recurrent pain with attempted or complete vaginal entry and/or penile vaginal intercourse.

e) Vaginismus

The following definition of vaginismus is recommended as the presence of a “vaginal spasm” has never been documented despite its inclusion in earlier definitions. Reflexive involuntary contraction of the pelvic muscles as well as thigh adduction, contraction of the abdominal muscles, muscles in the back and limbs, associated with varying degrees of fear of pain, typically but not invariably precludes full entry of a penis, tampon, speculum or finger.

The persistent or recurrent difficulties of 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.

f) Sexual Aversion Disorder

The following definition is recommended but it is acknowledged that many clinicians feel the syndrome of extreme anxiety/panic associated with activation of the autonomic nervous system is a form of phobic reaction.

However, it is felt that the sexual context and sexual repercussions warrant its inclusion as a sexual dysfunction.

Extreme anxiety and/or disgust at the anticipation of/or attempt to have any sexual activity.
The detailed sexual enquiry allows diagnosis of the various sexual dysfunctions to be made – see the following algorithm. It is recommended that the clinician is aware of the usual need to make more than one diagnosis, e.g. sexual interest disorder and combined arousal disorder (Figures 5 Part 1, Part 2).
It is recommended to clarify the dysfunction as lifelong or acquired.

Lifelong dysfunction necessitates more detailed psychosexual enquiry regarding childhood, adolescence and past relationships.

Acquired dysfunction necessitates careful enquiry into the context (psychological and medical) surrounding the onset of the dysfunction.

It is recommended to clarify if the dysfunction is situational or generalized.

Situational problems suggest an absence of organic disruption of the sexual response. Situational problems may be adaptive/logical to the problematic context and this has obvious therapeutic relevance.

It is recommended to clarify the degree of distress: None, mild, moderate, marked.

In the absence of distress, a disruption of sexual response (or lack of interest) still has epidemiological but rather little clinical importance.

It is recommended to clarify contextual factors:

1. PAST negative upbringing/losses/trauma (physical, sexual, emotional, past interpersonal relationship, cultural/religious restrictions).
2. CURRENT interpersonal difficulties, partner sexual dysfunction, inadequate stimulation and unsatisfactory sexual emotional contexts.
3. MEDICAL conditions, psychiatric conditions, medications, substance abuse.

Given that women’s sexuality is contextual, there is some difficulty with the concept of diagnosing a woman as having a sexual dysfunction when the primary problem appears to be the “sexual context” in which the sexual exchange occurs. However, she is reporting that dysfunction is present even though factors other than her own sexuality need to be highlighted. It is therefore strongly recommended to include contextual descriptors within each diagnosis.

Ongoing studies of the usefulness and validity of these recommended revisions of definitions of sexual dysfunction are strongly recommended.
C. Recommendations Regarding Management of Women’s Sexual Dysfunction

I. GENERAL REMARKS

A. In general, interpersonal problems within the relationship should be addressed prior to specific recommendations re sexual dysfunction.

B. A number of investigational pharmacological agents are being used to treat specific sexual disorders – the lack of long term safety data should always be openly discussed.

C. Collaboration between different disciplines is recommended.

D. 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.

II. RECOMMENDATIONS REGARDING MANAGEMENT OF SEXUAL INTEREST/ DESIRE AND COMORBID AROUSAL DISORDERS (COMBINED AND SUBJECTIVE)

a) Psychological Management of Low Sexual Interest and Arousal Disorders (Combined and Subjective)

- Cognitive-behavioural techniques (CBT). Conventional treatment currently involves CBT techniques. Although widely used, there is limited evidence of benefit in terms of controlled trials. Nevertheless, the treatment is benign and there are no safety issues – Grade B-C.
  - There is some empirical support for traditional sex therapy with sensate focus – Grade C.
  - Psychodynamic treatment is currently frequently recommended but again, there are no randomized studies – Grade D.

b) Non-Hormonal Pharmacological Management of Sexual Interest/Desire and Arousal Disorders (Combined and Subjective)

- The use of tibolone for postmenopausal women, though promising, cannot be recommended currently. (There are two RCTs of 3 and 12 months’ duration but the women were not identified as complaining of sexual dysfunction) – Grade C.
  - The use of bupropion hydrochloride is of interest but needs further study before this can be recommended – Grade C.
  - The use of phosphodiesterase inhibitors is not recommended – Grade B.

- Sexual sequelae of low estrogen levels, including poor sleep, dislike of sensual touching, and lack of well being may be treated with low-dose estrogen – Grade C.

- HOWEVER:
  - Clinicians are recommended to prescribe the
lowest dose of systemic estrogen for the shortest duration consistent with treatment goals, benefits, and risks for the individual woman, taking into account quality of life issues – Grade A. Although clinical trials are lacking, all systemic estrogen types and modes of administration may provide relief.

It is highly recommended clinicians are fully aware of recognized risks:-

◆ Because of the increased risk of endometrial hyperplasia and adenocarcinoma with systemic ET, all women with an intact uterus should also be prescribed progestogen to oppose estrogen’s adverse effects – Grade A.

Oral estrogen increases the risk of venothrombotic events (VTE) in the initial years of use Grade A. Parenteral therapy appears to have less risk for VTE – Grade B.

A set regime of oral CEE+MPA is associated with an increase in breast cancer risk beyond 5 years use – Grade A. There is some evidence that oral estrogen alone, other estrogen – progestin regimens (including lower doses, non-oral estrogen +/- progesterone therapy or tibolone) also convey this order of risk – Grade B-C.

There is increasing use of estrogen +/- progestogen therapy after breast cancer. However, there is some evidence that hormone therapy increases recurrence from breast cancer, so this therapy should be limited to moderate to severely symptomatic women, requires informed patient consent, and management of the patient should be in partnership with the physicians monitoring the woman’s cancer. Grade B

Oral CEE+MPA is associated with an increase in cardiovascular events in the first years of use and this risk wanes over 4 years level 1b. The use of other estrogen regimens and modes of administration and other steroids (tibolone) do not necessarily convey the same risk but data is lacking – Grade B.

Thus careful attention to cardiovascular, thrombotic and breast cancer risks and thorough examination should be undertaken before any treatment is prescribed.

No firm recommendation can be given regarding the long-term benefit vs. risks of systemic ET given the lack of RCTs of women who are symptomatic of estrogen deficiency and begin ET during the perimenopause or immediately with menopause. Risks outweigh benefit when ET is commenced some years postmenopause in women who are not identified as being symptomatic from estrogen deficiency – Grade A.

d) Androgen Therapy (AT) for Sexual Interest/Desire Disorder and Arousal Disorders

◆ Long-term data for safety and benefit of testosterone therapy in women is lacking but required before long-term use of testosterone can be recommended.

◆ Safety data for the use of testosterone in non-estrogen replaced postmenopausal women is lacking and no recommendation for its use can be made currently.

◆ There is minimal safety data and any enduring benefit after short-term treatment is unproven. Theoretically supplementing testosterone on a temporary basis only, could have adverse effects on the couple when it is withdrawn if an improvement associated with AT is no longer apparent.

If despite the above, AT is contemplated:-

◆ Careful assessment (see algorithm in chapter 16) must establish absence of ongoing psychological (interpersonal, intrapersonal, contextual, societal) and/or physical factors negatively affecting sexuality.

◆ There are significant potential complications and contraindications to androgen therapy –
see Chapter 12 and Chapter 16. Regular follow up for efficacy and safety is essential, including:

- Inspection of skin and hair for seborrhea, acne, hirsutism and alopecia
- Lab monitoring of free/bioavailable testosterone and SHBG – keeping these values within the normal range for premenopausal women – possibly a target level for older women should be even lower but this remains unclear. Accurate assays must be used – see earlier section on laboratory investigations
- Lipid profile and monitoring of glucose tolerance.

**Based on available data, no specific testosterone therapy or dose can yet be recommended.** In the future, any formulation of testosterone must have pharmacokinetic data indicating that it produces blood levels within the normal premenopausal range. Achieving physiological free testosterone levels by transdermal delivery appears to be the best approach for minimizing the adverse effects of androgens.

**Contraindications** to testosterone therapy include androgenic alopecia, seborrhea or acne, hirsutism as well as a history of polycystic ovary syndrome, estrogen depletion. Oral methyl testosterone therapy is contraindicated in women with hyperlipidemia or liver dysfunction.

**Testosterone administration should be discontinued** in the event of the following:
- Failure of response after up to 6 months of treatment
- Secondary treatment failure
- Appearance of one or more androgen induced skin and hair changes, bearing in mind that these conditions are progressive and unpredictable
- After 12 months unless new data confirms safety of more prolonged treatment.

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### III RECOMMENDATIONS REGARDING MANAGEMENT OF GENITAL AROUSAL DISORDER

#### a) Estrogen

The use of local estrogen therapy is highly recommended for sexual symptoms resulting from vulvovaginal atrophy – **Grade A**. These include not only genital arousal disorder with its lack of pleasure from direct genital stimulation, vaginal dryness and dyspareunia, but also frequent UTIs lowering sexual interest and arousability and increasing the chance of orgasmic disorder.

**The use of long-term systemic ET for the sexual consequences of vulvovaginal atrophy cannot be recommended at this time due to lack of safety vs. benefit data in women who are symptomatic and begin ET at the time of menopause. Risks outweigh benefit when ET is commenced some years postmenopause in women who are not identified as being symptomatic from estrogen deficiency – Grade A.**

#### b) Phosphodiesterase Inhibitors

The **investigational use of phosphodiesterase inhibitors** is cautiously recommended for genital arousal disorder unresponsive to local (or if indicated, systemic) ERT – **Grade B** recommendation. (This is based on two short-term 1b studies which support investigational use of sildenafil). The optimal means of identifying which women with symptoms of genital arousal disorder will benefit is unclear.

#### c) Tibolone

The use of tibolone is **of interest but cannot be recommended currently for postmenopausal women** with genital arousal disorder – **Grade C**. Note: The women in the level 1b and level 4 studies were not identified as having sexual dysfunction.
**RECOMMENDATIONS REGARDING MANAGEMENT OF ORGASMIC DISORDER**

**a) Generalized Orgasmic Disorder**

A directed masturbation program (see chapter 9) is recommended for lifelong generalized orgasmic disorder – Grade B.

**b) Situational Orgasmic Disorder**

For the woman with orgasms with masturbation but not with her partner, the focus of therapy is on the relationship especially the trust and safety necessary for the woman to be sufficiently vulnerable. The partner may need information regarding women’s sexual function and the woman support for the need to guide her partner – Grade D.

**c) Anxiety Reduction**

Anxiety reduction techniques are best suited for anorgasmic women only when sexual anxiety is coexistent – Grade C.

**d) Pharmacological Agents**

No pharmacological agents can be recommended – Grade B.

**RECOMMENDATIONS REGARDING MANAGEMENT OF DYSPAREUNIA ND VAGINISMUS**

**a) General Recommendations**

The following recommendations are Grade D due to paucity of controlled trials in this area.

- The evidence is that the syndromes of vaginismus and VVS overlap, as do the syndromes of vaginismus and dyspareunia not due to VVS.
- Treatment should be individualized for each woman and/or partner, whenever possible with their input.
- Psychological issues (as well as interpersonal issues) should be addressed early on with psychotherapy.

**b) Vulvar Vestibulitis Specific Recommendations**

- Given the lack of understanding of etiology and the progression of this syndrome, the overall safety and overall risks of any intervention must be kept in mind. The following interventions have been used individually and in combination-with reported clinical benefit but without scientific evidence. There are, however, minimal safety concerns.
  - vaginal muscle EMG biofeedback, pelvic floor physical therapy with cognitive behavioural therapy
  - hygiene measures including avoidance of soap, perfumes, pantyliners.
  - medical: topical estrogen, cromolyn, xylocaine to sites of allodynia
  - fluconazole for associated recurrent candidiasis
- medications for chronic pain

On the not yet proven assumption that neuropathic pain is at least in part responsible for the pain of VVS, the use of tricyclic antidepressants, venlafaxine, or anticonvulsants such as gabapentin or carbamazepine or topiramax is cautiously recommended.

- Surgical – Vestibulectomy/vestibuloplasty/perinoplasty. Although controversial, one level 2b study suggests vestibulectomy to be superior to behavioural and physiotherapy modalities although all modalities of therapy were beneficial. Poor surgical prognosis is associated with lifelong as opposed to acquired symptoms, associated features of vaginismus, vulvodynia in addition to the introital dyspareunia, larger areas of allodynia, involvement of the openings of the peri urethral ducts and declining of the offer of sex therapy.
c) Recommendations Specific for Vaginismus

- Conventional treatment involves psycho-education, CBT, sex therapy and the use of vaginal inserts, and is recommended. However, there is a marked lack of scientific outcome evidence to support this use.

- Given the preliminary information suggesting benefit from pelvic floor physiotherapy and EMG biofeedback for VVS, it is possible this will prove true for vaginismus. Again, there is notable lack of outcome data.

- Although many clinicians define vaginal penetration as the goal of therapy, in the future outcome measures should be broader to include sexual pleasure.

The need for treatment for sexual trauma must be considered. If considered necessary, it should predate any treatment for sexual dysfunction.

Therapy should help women understand any possible connections between past and current sexual functioning, particularly re trust and being sexually vulnerable.

Important aspects of therapy include:

- Encouragement that women can be in control of their sexual encounters.
- Their learning to be able to mentally and physically relax prior to 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.

While not all women report sexual problems as a result of female genital excision, it is important to offer such women an opportunity to discuss such feelings and learn skills to increase self-esteem and sexual satisfaction.

Encourage women with previous genital excision to seek out support groups.

Offer, when indicated, vaginal repair for aiding the woman’s enjoyment of/possibility of having intercourse.

Offer, when indicated, other vulval surgery, e.g. to free partially obstructed urine flow associated with recurrent infections.

Encourage decision making within the partnership/within the family in many instances.

Provide information about health consequences of decisions they may make regarding undergoing surgery to again restrict the introital opening to an extremely small diameter.

Clarify the legal and ethical responsibility of the physician who must decline to perform requested restitching after childbirth.

Offer psychotherapy for addressing the emotional traumatic sequelae from previous genital excision.

Provide specific management of sexual dysfunction as needed.
Chapter 3

Committee 2

Psychological and Interpersonal Dimensions of Sexual Function and Dysfunction

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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 promoting sexual health or dysfunction. More significantly, individual vulnerability to sexual disruption stems from personality and constitutional/biological dispositions to psychiatric and medical illness as well as the ability to develop and sustain intimate relationships.

This chapter will review the most significant psychological and interpersonal dimensions contributing to sexual health. We will consider the predisposing, precipitating, maintaining and contextual factors involved in sexual dysfunction as well as the success 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.

It must be noted at the outset that there is a dearth of 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.

There is an inherent tension between evidenced-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 healing. 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 outcome, include such things as the placebo factors that enhance hope and expectancy, extra-therapeutic factors such as client motivation and chance events (e.g., meeting a new partner), relationship comfort between client and therapist and finally, the degree to which the model and structure of therapy conform to the client’s expectations [1].

Laboratory research is important, but does not easily translate into clearly prescribed clinical interventions that enhance sexual life. While we know that distracting thoughts usually interfere with sexual arousal, it is not always obvious how to help clients re-focus on a sexual situation when they experience performance anxiety or negative thoughts. Sex therapy, in actual practice, is usually an idiosyncratic blend of interventions and interpretations, utilizing behavioral, relational, psychoanalytic and cognitive psychology concepts. Evidenced-base medicine cannot fully capture the art of psychotherapy. Nonetheless, it may help delineate the efficacy of specific clinical interventions.

**2. Definition of sexual therapy**

Sex therapy is a specialized form of psychotherapy that draws upon an array of technical interventions known to effectively treat male and female sexual dysfunctions (e.g., in the case of female anorgasmia,
directed masturbation). Treatment may be conducted in an individual, couples or group format depending upon the initial problem and the motivation of both partners.

Psychosexual evaluation goes beyond traditional psychological assessment to examine the patient’s or couple’s sexual history, current sexual practices, relationship quality and history, emotional health and contextual factors currently influencing their lives (e.g., young children, chronic illness, financial concerns, etc.). Usually, a thorough psychosexual and developmental history is taken as well in order to identify past experiences that may be contributing to the presenting sexual or emotional problem (e.g., past sexual trauma; an over-sexualizing parent). It is important to assess all of the relevant medical and biological factors that may also be contributory to the development or maintenance of the current difficulty.

Sexual therapy techniques comprise behavioral/cognitive interventions as well as psychodynamic, systems relationship and educational interventions (e.g., reading, videotapes, illustrations, anatomical models). Effective comprehensive treatment may involve collaboration with other specialists such as urologists, gynecologists, endocrinologists, neurologists, or physical therapists. Individuals trained and qualified as sex therapists may include physicians, psychologists, social workers, nurses, marriage and family therapists.

A. ETIOLOGICAL BACKGROUND OF SEXUAL DYSFUNCTION

Table 1. Etiological Model for Understanding Sexual Function and Dysfunction

<table>
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<th>I. PREDISPOsing FACTORS</th>
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<tr>
<td>A. Constitutional Factors</td>
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<tr>
<td>1. Anatomical Deformities, e.g., intersex conditions</td>
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<tr>
<td>2. Hormonal Irregularities</td>
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<tr>
<td>3. Temperament, e.g., shyness vs. impulsivity; inhibition/excitation</td>
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<tr>
<td>4. Physical Resiliency</td>
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<tr>
<td>5. Personality Traits, e.g., obsessive-compulsive vs. histrionic</td>
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<th>B. Developmental Factors</th>
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<tbody>
<tr>
<td>1. Problematic attachment/experiences with parents or parental surrogates</td>
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<tr>
<td>2. Exposure to physical, sexual coercion, violence</td>
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<tr>
<td>3. Surgical intervention/medical illness</td>
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<tr>
<td>4. Event based or process-based trauma</td>
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<tr>
<td>5. Early sexual experiences, e.g., first intercourse</td>
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<tr>
<td>6. Sexual abuse</td>
</tr>
<tr>
<td>7. Religious/cultural messages, expectations, constraints</td>
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<tr>
<th>II. PRECIPITATING FACTORS (PARTIAL LIST ONLY)</th>
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<tr>
<td>1. Life-stage stressors such as divorce, separation, loss of partner, infidelity, menopausal complaints</td>
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<tr>
<td>2. Infertility or post-partum experiences</td>
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<tr>
<td>3. Humiliating sexual encounters/experiences</td>
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<tr>
<td>4. Depression/anxiety</td>
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<td>5. Relationship Discord</td>
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<td>6. Substance abuse</td>
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<tr>
<th>III. MAINTAINING FACTORS</th>
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<tr>
<td>1. Ongoing interpersonal conflict</td>
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<td>2. Stress, emotional, occupational, personal</td>
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<tr>
<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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<th>IV. CONTEXTUAL FACTORS (PARTIAL LIST ONLY)</th>
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<tr>
<td>1. Environmental constraints- lack of privacy, time</td>
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<tr>
<td>2. Distractions due to work-related demands, children, etc.</td>
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Sexual dysfunction is typically influenced by a variety of predisposing, precipitating and maintaining factors [2] (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.

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.

Finally, maintaining factors such as relationship conflict, performance anxiety, lack of privacy or medications may prolong and exacerbate problems, irrespective of the original predisposing or precipitating conditions. Maintaining factors also include contextual factors that can interfere or interrupt sexual activity, such as environmental constraints or anger/resentment towards a partner. Each of these domains contributes to both the individual's and the couples' ability to sustain an active and satisfying sexual life (Table 1).
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.

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 [3]. 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 [4]. Childhood gender non-conformity predicts adolescent and adult homosexuality with greater accuracy in boys than it does in girls [5]. Erotic fantasy often appears in the 10th year of life in both genders [6]. 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 [7]. Sexually atypical adolescents may become gay or lesbian and in extreme instances may be diagnosed as having a gender identity disorder or a paraphilia (such as voyeurism, exhibitionism, fetishism, sadism, masochism, pedophilia) [8]. Although there is much speculation about the specific developmental factors that organize children's gender identity, orientation, and sexual scripts, research has been unable to clarify these developmental processes precisely [9].

b) Trauma - Event and process based trauma

Two types of developmental factors are thought to increase the likelihood of sexual dysfunction: event-based trauma and process-based trauma (on-going interactions or behaviors) with caregivers [10]. 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 [11] 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, 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 that get shaped by cultural expectations of sexuality [12].

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 gate-keepers [12]. 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 [13]. This may help explain why women tend to have a higher incidence of sexual problems as adults than men [14].

d) Impact and initiation of first intercourse

Udry and Billy [15] 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' education and locus of control.

In a qualitative study of adolescent girls' first intercourse, Thompson [16] 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

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 [17] 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, were identified. The national representative sample consisted of 1,335 Swedish women aged 18-74. The main finding was that 12% 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 childhood sexual abuse, 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 [18]. It was 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 sexual function and dysfunction in men 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 [19, 20], negative consequences have been found in men as well. In a questionnaire study of 301 men in a non-clinical 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 [21]. Methodological factors that may affect outcome in these studies have included the definition of sexual abuse [22], whether or not an age discrepancy between offender and victim is required in defining childhood abuse [23], and whether sexual abuse has occurred as a single incident or as repeated victimization [24].

Sexual abuse is considered a salient risk factor for later adult sexual dysfunction, increased prevalence of high-risk sexual behavior and increased adult psychopathology [25, 26]. For instance, a recent study [27] 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 [26, 28-32]. 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 [33]. 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 [34].

For example, in a study of 409 women with a past history of sexual coercion and physical partner abuse, Goldberg [35] found that 37% of the sample suffered from chronic and troubling dyspareunia and 75% reported various sexual dysfunctions. Notably, only a small number of women had ever discussed these concerns with their physician [36].

### 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.

Faith and Schare [37] 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 coerciveness than a single negative or traumatic episode [38].

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 [39]. 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” [40].

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.

B. 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. The following sections provide a review of the relationships between anxiety, depression and sexual dysfunction. It should be noted that the literature is based on two research methodologies: controlled laboratory investigations involving experimental manipulation and more qualitative clinical samples of individuals who have been diagnosed with anxiety or depression. Both approaches are useful in helping identify the possible mechanisms involved in the development and maintenance of sexual problems.

I. 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 [41] and Helen Kaplan [42]. 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 2. A review by Norton & Jehu [43] reported high levels of anxiety in sexually dysfunctional individuals [44-51], which varied in amount and quality. Some studies found higher levels of sexually related anxiety, but no differences in social or general anxiety [48, 49, 52, 53].

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 & Sullivan [54] 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.

Kaplan [55, 56] 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 [57].

Campillo et al. [58] 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. [59] 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 [53] 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 [60], 41 ED-patients completed the State-Trait-Anxiety-Index (STAI) and the International 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.[61] 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.

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. While some studies highlight the significance of anxiety as a trait or stable personality factor, others have indicated that elevated anxiety levels are confined to the sexual sphere. Correlational evidence exists for the relationship between ED and anxiety. However, this does not imply causality.

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
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>Methodology</th>
<th>Results</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper, AJ (1968 a)[44]</td>
<td>54</td>
<td>“Impotent” 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, AJ (1968 b)[45]</td>
<td>53</td>
<td>diagnoses ‘impotence’ or ejaculatory disorder and investigated 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, AJ (1969)[46]</td>
<td>49</td>
<td>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, L.R., Meyer, JK (1979)[47]</td>
<td>87</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 normals. The most pronounced elevations were found on depression and anxiety.</td>
<td>3</td>
</tr>
<tr>
<td>Kockott, G et al. (1980a)[48]</td>
<td>42</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>2B</td>
</tr>
<tr>
<td>Kockott, G et al. (1980b)[49]</td>
<td>42</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>2B</td>
</tr>
<tr>
<td>Munjack, DJ et al. (1978)[50]</td>
<td>35</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>2B</td>
</tr>
<tr>
<td>Munjack, DJ et al. (1981)[51]</td>
<td>90</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. 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>2B</td>
</tr>
<tr>
<td>Fahrner, EM (1983)[52]</td>
<td>86</td>
<td>41 female and 45 male sexual dysfunction patients levels of social insecurity and self-uncertainty were measured on two standardized psychological inventories</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>
Table 2. 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>Feil, M.G., Ruckert-Appell, H.</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 sexual situations, but did not exhibit higher levels of general insecurity.</td>
<td>3</td>
</tr>
<tr>
<td>Murphy, C., Sullivan, M (1981)</td>
<td>20</td>
<td>Twenty women diagnosed as sexually aversive and 35 controls were compared on the dimensions anxiety, self-concept, and social esteem 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>Kaplan, DSM (1995) [73]</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, 33% 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>Campillo, GI et al. (1999) [61]</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 trauma.</td>
<td>2 B</td>
</tr>
<tr>
<td>Trudel, G., Lundy, L., Lawve, Y.</td>
<td>20</td>
<td>Twenty couples with low desire problems were compared with 29 control couples on several psychological measures including the Beck Depression Inventory and an anxiety scale (IPAT).</td>
<td>The lower desire subsets showed normal levels of depression and moderate levels of anxiety.</td>
<td>2</td>
</tr>
<tr>
<td>Mallis, D., Meyersid, K., Hatzielios, D. (2000) [60]</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>
</tr>
<tr>
<td>Mas, M et al. (2002) [61]</td>
<td>78</td>
<td>The influence of personality characteristics on the erectile response to intracavernosal injection 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>
<td>3</td>
</tr>
<tr>
<td>Beggs, V., Calhoun, KS, Wolfe, S. (1987) [66]</td>
<td>19</td>
<td>In 19 sexually functional women, general 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>
<td>3</td>
</tr>
<tr>
<td>Palasz, EM &amp; Gonzalez, BB (1980) [67]</td>
<td>16</td>
<td>In 16 sexually dysfunctional women and 18 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>
<td>2</td>
</tr>
</tbody>
</table>
Table 2. 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>Palace, FM &amp; Gorzalka, BB</td>
<td>16</td>
<td>In 16 sexually dysfucntional women and 16 controls, physiological and subjective sexual arousal were determined under refined stimulus conditions by employing alternate methods of data collection and subjective assessment</td>
<td>The results provide evidence that sexually functional and dysfunctional women exhibit different patterns of genital and subjective response.</td>
<td>2</td>
</tr>
<tr>
<td>Meston, CM, Gorzalka, BB</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>
<td>3</td>
</tr>
<tr>
<td>Meston, CM, Gorzalka, BB</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>
<td>3</td>
</tr>
<tr>
<td>Meston, CM, Heiman, JR</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>
<td>3</td>
</tr>
<tr>
<td>Van Minnen, A, Kampman, M</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>
</tbody>
</table>
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 for sexually functional and dysfunctional subjects [62]. Contrary to the clinical studies' findings for an inhibition effect of anxiety, the laboratory evidence 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 [63] 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 [64].

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 [65].

a) The laboratory evidence for women

For women, the relationship between anxiety and sexual performance can be summarized as follows:

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) [66-71]. Overall, the evidence for the role of anxiety in sexually dysfunctional women is mixed, with the suggestion that it is more negative than facilitory [72].

The table below summarizes the significant clinical implications of anxiety as it relates to sexual behavior (Table 3).

<table>
<thead>
<tr>
<th>Table 3. Clinical Aspects of Sexual Anxiety</th>
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<tbody>
<tr>
<td>- Sexual anxiety can be either conscious or unconscious (automatic)</td>
</tr>
<tr>
<td>- Sexual anxiety can manifest itself in:</td>
</tr>
<tr>
<td>• Fear of performance failure (performance anxiety)</td>
</tr>
<tr>
<td>• Fear of the threats unconsciously associated with sexual performance</td>
</tr>
<tr>
<td>- Sexual activity can lead to:</td>
</tr>
<tr>
<td>• Functional or dysfunctional defense mechanisms</td>
</tr>
<tr>
<td>• Sudden and acute anxiety attacks (failure of defense)</td>
</tr>
<tr>
<td>• Fear of the fear</td>
</tr>
<tr>
<td>• Lack of sexual desire or impairment of sexual arousal (when the perceived threats are too powerful)</td>
</tr>
<tr>
<td>• Avoidance behavior and/or depressive resignation (when there is no more sense of control of hope of mastering the situation)</td>
</tr>
</tbody>
</table>

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 [57].

II. 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 [74, 75]. 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 [76].

1. DEPRESSION AND HYPOACTIVE SEXUAL DESIRE

The most common sexual pattern associated with
depression is loss or reduction of sexual interest and/or sexual arousal. Beck [77] found low sexual interest in 61% of severe depressives compared with 27% of non-depressed controls. In two landmark studies, Derogatis et al. [78] and Schreiner-Engel and Schiavi [79] 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 SCL-90R to a sample of 325 patients (199 men and 126 women). Men with erectile dysfunction (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 & Schiavi [79] studied the lifetime history of psychopathology in patients presenting with desire disorders. Forty-six subjects (22 men and 24 women) were compared with 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. Schreiner-Engel and Schiavi 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 [80]. These researchers studied 47 college women with low Beck Depression Inventory scores 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 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 and depression in women (Table 4).

2. DEPRESSION AND ERECTILE DYSFUNCTION

More recent studies on the role of depression in sexual disorders have concentrated solely on men with erectile dysfunctions. Data from the Massachusetts Male Aging Study [81] 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 [82]. 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 depressed symptoms compared to those who did not.

Shabsigh et al. [83] 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. [85] stressed that both conditions have a significant negative impact on the quality of life of patients and their partners.

Strand et al [84] 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 [78].

Seidman [86] suggested that ED and the accompanying psychosocial distress may stimulate the development of depressive illness in vulnerable individuals, or that depression might cause ED. He also postulated a third, as yet unknown factor might be responsible for the genesis of the ED and depression.
Table 4. Empirical studies on the relationship between depression and sexual dysfunction

<table>
<thead>
<tr>
<th>Author et al. (Year)</th>
<th>N</th>
<th>Methodology</th>
<th>Results</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck (1987)[77]</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>
<td>3</td>
</tr>
<tr>
<td>Derogatis, Meyer, King (1981)[78]</td>
<td>325</td>
<td>199 male and 126 female patients seeking treatment for sexual dysfunction underwent a psychiatric evaluation and completed a symptom checklist (SCL-90-R).</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-deprecation.</td>
<td>3</td>
</tr>
<tr>
<td>Schaefer-Engel, P., Schulz, RC (1986)[79]</td>
<td>46</td>
<td>The lifetime history of psychopathology in male and female low desire patients was compared to 36 matched controls on various measures.</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 suggested a common etiology of both disorders.</td>
<td>3</td>
</tr>
<tr>
<td>Feldman, HA, Goldstein, I., Hatzichristou, DG et al. (1995)[81]</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>
<td>2 B</td>
</tr>
<tr>
<td>Attia, AB, Dunante, R., Feldman, HA (1998)[82]</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 B</td>
</tr>
<tr>
<td>Shabsigh, R et al. (1998)[83]</td>
<td>120</td>
<td>120 men who presented with either ED only, RPH (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 RPH 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>
<td>3</td>
</tr>
<tr>
<td>Strand, J et al. (2002)[84]</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 dysthymic affects indicating a significant degree of emotional distress.</td>
<td>3</td>
</tr>
</tbody>
</table>
3. COUNTRY-WIDE STUDY OF DEPRESSION AND SEXUAL DYSFUNCTION

Finally, the results of a large-scale study of 4557 depressed patients in France found high rates of sexual dysfunction. 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 Ss 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).

4. 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. The following recommendations are indicated, based on the available data.

a) Recommendations

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 [87].

The role of anti-depressants and anti-anxiety medications as contributory factors to the sexual dysfunction should be evaluated and if implicated, changes in medications may be indicated.

III. OTHER PSYCHOPATHOLOGY AND SEXUAL FUNCTION/DYSFUNCTION

1. OBSESSIVE-COMPULSIVE DISORDERS AND SEXUAL DYSFUNCTION

There are a few reports examining the association between obsessive-compulsive disorder (OCD) and sexual dysfunction. Independent studies [88-91] suggest that approximately 50% of individuals with OCD report sexual problems and that between 60% to 73% are dissatisfied with their sexual lives.

While Van Minnen & Kampman [57] believe that OCD develops as a reaction to severe sexual conflicts within the patients or in their family of origin, Staebler et al [91] 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 & Tsuang [90] reported that 32% had sexual impulses that conflicted with their values. In a comparable study, 36% of the sample patients had sexual obsessions [88].

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 & Hurlbert [92] 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 [93] found that
women with borderline personality disorders showed higher sexual self-esteem and sexual assertiveness when 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 [92].

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 scant to draw conclusions regarding causal relationships between any specific personality disorder and any sexual dysfunction.

Overall, the literature review suggests that sexual dysfunction in general is not associated with severe psychological disorders. On the other hand, 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, 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 available today 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 were 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.

IV. OTHER PRECIPITATING FACTORS FOR SEXUAL FUNCTION AND DYSFUNCTION

In addition to the disorders described above, there are 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.

C. 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 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 [94]. Heiman, et. al. [94] 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.

The preponderance of studies examining the impact of interpersonal issues on sexual function is of the case report variety rather than randomized controls trials, limiting the generalizations that may be drawn.

I. RELATIONSHIP DYNAMICS AND HYPOACTIVE SEXUAL DESIRE

Hypoactive sexual desire disorder 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 [95-97], and 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 [98] object relations perspective; differentiation theories, e.g., Schnarch [99] and cognitive behavioral theories, e.g., Pridal & LoPiccolo [100] 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 [101] relational model and Rosen and Leiblum's [102] sexual scripting paradigm. Zilbergeld and Ellison [103] and others [99] 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 [104].

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 [73, 105]. In fact, 73% of surveyed physicians endorse 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 [106]. Further, there is empirical evidence indicating that sex therapy with the couple is more efficacious than treating the HSDD patient alone [107], that combined marital and sex therapy approaches are more efficacious than sex therapy alone for couples with HSDD [108], and that women with HSDD show modest improvement in desire and other aspects of sexual functioning following brief marital therapy [109].

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 [110]. For example, couples with HSDD have poorer levels of dyadic adjustment than couples without HSDD [111]. Similarly, Trudel, Landry and Larose [59] found that compared to controls, couples in which one partner was diagnosed with HSDD obtained lower adjustment scores on the Marital Happiness Scale.

A recent large scale health and sexuality survey of 2050 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 [112].

McCabe [113] 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., [114] examined discrepancies between partners' levels of sexual desire, and found that for both husbands and wives, individuals who felt that there was discrepancy between their own and their partner's desire reported lower relationship satisfaction.

1. Reduced Sexual Frequency with Relationship Duration

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 [115], 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.

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.

II. Sexual Dysfunction and Relationship Variables

McCabe and Cobain [116] 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. Donahey and Carroll [117] reported similar findings: female clients with HSDD demonstrated lower levels of relationship satisfaction than male clients with HSDD.

### III. RELATIONSHIP DYNAMICS

Roffe and Britt [118] 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.

Wiederman [119] suggests that treatment focused solely on the sexual dysfunction is likely to fail if the underlying relationship dynamics are ignored. He maintains 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 no empirical research to either support or refute this view.

#### 1. THE IMPACT OF RELATIONSHIP THERAPY ON SEXUAL DYSFUNCTION

In a comprehensive review of treatments for sexual dysfunction, Besharat [120] 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.

Stravynski et al. [121] conducted a study to determine if treatment outcome 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 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.

The existing research supports the observation that the quality of the relationship plays an important role in the outcome of sex therapy [122]. Kilmann et al. [123] also found that relationship adjustment was the strongest predictor of a successful treatment outcome among men with erectile dysfunction. Similar findings were obtained among sexually dysfunctional women [124].

In contrast to the above findings, Hawton, Catalan, and Fagg [125] 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 [126]. 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.

In a series of case studies, Leiblum [127] and Althof [128] 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 are 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 [127] and Althof [128] highlighted the importance of obtaining a thorough assessment and treatment of both the interpersonal and sexual relationship as well as included the partner, where possible, in the therapy process (Table 5).
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 vigorous controlled studies need to be conducted to determine the validity of this argument more conclusively.

### IV. IMPLICATIONS AND RECOMMENDATIONS

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 vigorous controlled studies need to be conducted to determine the validity of this argument more conclusively.

### D. LOVE AND INTIMACY

It would be neglectful to discuss psychological and interpersonal contributions to sexual function and dysfunction without including some reference 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 [3]. 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 part-

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### Table 5. Summary of Studies: Related to Interpersonal Dimensions of Sexual function and Dysfunction

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment Method</th>
<th>Summary of Study Findings</th>
<th>Evidence Based Medicine Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heiman, Gladue, Roberts, &amp; Lo Piccolo, 1986 [94]</td>
<td>Survey of non-clinical respondents</td>
<td>Sexual and relationship functioning are independent domains</td>
<td>3</td>
</tr>
<tr>
<td>Laumann et al., 1999 [95]</td>
<td>Survey of prevalence of sexual dysfunction</td>
<td>Hypoactive sexual desire more common among women</td>
<td>4</td>
</tr>
<tr>
<td>Rosen &amp; Leiblum, 1995 [96]</td>
<td>Survey of prevalence of sexual dysfunction</td>
<td>Hypoactive sexual desire more common among women</td>
<td>4</td>
</tr>
<tr>
<td>Segraves &amp; Segraves, 1991 [97]</td>
<td>Survey of prevalence of sexual dysfunction</td>
<td>Hypoactive sexual desire more common among women</td>
<td>4</td>
</tr>
<tr>
<td>Scharff, 1988 [98]</td>
<td>Theoretical paper</td>
<td>Object relations theory explains sexual dysfunction</td>
<td>5</td>
</tr>
<tr>
<td>Schnarch, 2000 [99]</td>
<td>Theoretical paper</td>
<td>Differentiation theory explains sexual dysfunction</td>
<td>5</td>
</tr>
<tr>
<td>Talmadge &amp; Talmadge, 1986 [101]</td>
<td>Theoretical paper</td>
<td>Developed relational model to explain HSDD</td>
<td>5</td>
</tr>
</tbody>
</table>
ner 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, than over time.

E. 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, 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. Often the factors that maintain sexual dysfunction are not the ones that initially predisposed or precipitated the initial sexual failure. However, by the time individuals present for treatment, the maintaining factors may be the most disruptive to therapeutic outcome. A case illustration may illuminate this point:

A 34-year-old woman complains of inability to become both physically and subjectively aroused during sexual intercourse with her boyfriend 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 boyfriend 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 boyfriend leads to performance anxiety and further inhibits her response, creating a downward spiraling negative cycle.

I. PERFORMANCE ANXIETY

Early etiological theories [41] 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 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. OTHER MAINTAINING FACTORS

Space precludes a detailed 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 contextual factors that enhance or impede sexual spontaneity, comfort and satisfaction. Finally, it is clear that a problem in one partner can trigger problems in the other partner and vice versa. It is therefore essential to assess how sexual partners mirror each other in terms of desire, arousal and satisfaction.

F. 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) [128, 129].

Specifically, 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 [130].

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 [128]. 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?

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 homosexual and autosexual men) or the degree of penile rigidity?

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 & Johnson's 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 [131]. 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 sex therapy pose some unique challenges. Spence [132] 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 [133] 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. Finally, 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. Finally, the overlap between different sexual dysfunction diagnosies 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 [97, 134]. This 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 several male and female sexual dysfunctions.

G. PSYCHOLOGICAL TREATMENT OF SEXUAL DYSFUNCTIONS - GENERAL FORMULATIONS

Masters and Johnson's groundbreaking contributions recounted in Human Sexual Inadequacy [41] 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 [135-137]. 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 [135, 138].

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 [132]. 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.

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.

H. WOMEN’S SEXUAL COMPLAINTS AND DYSFUNCTIONS : OVERVIEW

The plethora of female sexual complaints range from a lack of, or diminished sexual desire or interest, to pain during both genital and non-genital sexual activities [134]. In addition to formal sexual diagnoses, many women report sexual dissatisfactions that do not involve actual physical impairment but rather, complaints involving lack of pleasure, enjoyment, satisfaction and passion [139, 140]. While these complaints are fairly ubiquitous and important and while they obviously enhance or impede sexual enthusiasm, they tend not to be identified as legitimate outcome measures in most research studies. Nevertheless, it is often the case that with successful treatment, these important sexual parameters change as well as the formal targets of intervention. Moreover, for many women, it is these behaviors that may well constitute the most salient end-points of treatment. Sexual performance or genital arousal without pleasure is an unsatisfactory compromise for most women.
In this section, treatment outcome will be described for the recognized DSM-IV-TR categories of female sexual disorders, namely, hypoactive sexual desire disorders, sexual arousal disorder, orgasmic disorder and sexual pain disorders. Heiman [141] and Heiman and Meston [133] have published comprehensive reviews of most of the available research studies looking at the prevalence, etiological factors and treatment success for the various female dysfunctions.

1. 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 [139]. There is no shortage of published descriptions of psychological treatments [99, 142], but few have been subjected to rigorous outcome 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 look at sexual frequencies of various sexual behaviors or attempt to assess the degree of internal motivation to engage in sexual activity? Do we count sexual fantasies or frequency of various sexual behaviors as a measure of desire or interest?

Basson [143] and others [144, 145] 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 [143] has 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.

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 [145]. 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 [146] conducted a prospective, non-controlled study of a community sample of couples who underwent a modified Masters & Johnson treatment program. Sexual desire problems seemed to be alleviated largely or completely in 56% of the period following treatment. However 75% of the sample relapsed at 1-6 year follow-up. In a later review of the efficacy of sex therapy for sexual dysfunctions, Hawton [137] noted the variable outcome that is often found across studies. He observed that outcome is poorer when the male partner has low desire than when the female partner is the target of treatment.

Hurlbert [93] 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 [147] found that of the 43% of women complaining of HSDD who underwent 10 sessions of CBT, 54% had the same complaint following treatment. 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. [148] comparing cognitive behavioral interventions specifically formulated to address desire disorders with a control condition, only 26% of the low desire women continued to report this problem at the end of treatment. 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.

At this time, most of the funded research seeking to
enhance female sexual desire have focused on pharmacological treatment, e.g., bupropion [149] or hormonal interventions such as androgen supplementation delivered via gels, creams, patches, pills or injections [150-152]. To date, there are few double-blind, placebo-controlled studies investigating the long-term treatment of hormonal interventions on women's sexual desire and arousal although several are underway. Unfortunately, there are no studies comparing hormonal supplementation with sex therapy or couples' therapy and none looking at the impact of combined treatment. This is an area that warrants well-controlled research with different populations of women, pre and post-menopausal.

2. SEXUAL AROUSAL DISORDERS

To date, there are no published outcome studies 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 [112]. The emphasis has focused on studying women with physiological or genital arousal complaints although there is growing recognition that the largest category of complaints center on the lack of subjective rather than physical arousal. Recently, a group of experts in women's sexuality proposed a new nomenclature for diagnosing women's sexual disorders [153]. Sexual arousal disorders were divided into three sub-types: genital sexual arousal disorder, subjective sexual arousal disorder and combined genital and subjective arousal disorder. This group also acknowledged the existence of a heretofore undiagnosed arousal complaint, namely that of persistent genital arousal characterized by insistent feelings of genital vaso-congestion and throbbing in the absence of conscious desire [154]. Chapter 16 provides a comprehensive discussion of female sexual arousal disorders.

3. 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 [112]. Summarizing several studies, Haavio-Mannila and Kontula [155] 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 [156, 157]. 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 [158]. In general, women with orgasm difficulties tend to experience more sex guilt [159, 160], tend to be less sexually assertive [161, 162], and endorse more negative attitudes towards sexual activity and masturbation [116, 159]. Women with orgasmic difficulties have been found to be less aware of physiological signs of arousal and orgasm [156, 163]. Heiman and Grafton-Becker [158] note 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 [133]. 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 & Meston [133] note that across all studies involving nearly 600 women seen for between 6-14 sessions with directed masturbation, directed masturbation alone was superior to systematic desensitization and directed masturbation with sensate focus was more effective than sensate focus alone [164-175]. Women with acquired and situational female orgasmic disorder tend to be more distressed about and less satisfied with their overall relationship [123, 176, 177]. In addition to many of the factors mentioned above, acquired orgasmic dysfunction may be the result of medication side effects, especially antidepressants. Most treatment packages for acquired female orgasm problems include a combination of sex education, sexual skills training, couple's therapy, masturbation and non-demand touching exercises, as well as interventions to address body image concerns and negative sexual attitudes [130, 133].

The Coital Alignment Technique (CAT) [178-180] was developed specifically to treat female orgasmic disorder. This technique involves a sexual position in which the man lies across the woman, without support of his elbows, and then shifts forward (relative to the standard missionary position) such that the base of his penis makes direct contact with the woman's clitoris. The “CAT’s” sexual position makes vaginal penetration with constant clitoral stimulation
possible. The penile-clitoral connection is maintained by the pressure and counter pressure simultaneously exerted by both partners. One potential pitfall in the use of CAT is that this rather goal oriented treatment may increase performance pressure and anxiety in the woman.

Treatment for coital anorgasmia typically involves directive cognitive-behavioral interventions and sensate focus exercises with both the woman alone and with her partner. For example, Heiman and LoPiccolo [136] reported on outcome with 16 couples where the presenting complaint was lack of orgasm during intercourse. Outcome included significant improvement in various ratings of sexual and marital satisfaction but a non-significant increase from 12% to 30% in orgasmic ability with manual stimulation and a modest increase from 12-30% in orgasm during intercourse.

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 [123, 177, 181]. 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 [147] study cited above, of the 36 women (67% of the initial sample of 54) presenting with anorgasmia and who completed treatment, successful outcome was achieved with 89% of the women.

Heiman [141] notes 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 might be sexual arousal disorder rather than orgasmic dysfunction [153] (Table 6).

4. 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 [95].

The AFUD recommended definition of dyspareunia 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 [188].

Etiologically, a host of psychological factors have been associated with the complaint of dyspareunia but it is difficult to determine which is cause and which are the effects of living with a chronic pain disorder [189]. 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 [190]. 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
<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>N</th>
<th>Treatment Method</th>
<th>Control or Wait List</th>
<th>Post-Treatment Success Rate</th>
<th>Duration of Follow-up</th>
<th>Follow-up Success Rate</th>
<th>Evidence Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blakeney et al., 1976 [182]</td>
<td>38</td>
<td>Two and a half day Masters And Johnson model</td>
<td>No control Group</td>
<td>Primary-70%, Secondary-57%</td>
<td></td>
<td></td>
<td>2c</td>
</tr>
<tr>
<td>Cooper, 1970 [164]</td>
<td>50</td>
<td>In vivo desensitization Sex therapy, psychotherapy</td>
<td>No control Group</td>
<td>50%</td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>DeArminas et al., 1985 [175]</td>
<td>22</td>
<td>Sensate focus, directed Masturbation, Sensual awareness, Communication Training, Modification of sexual behaviors</td>
<td>No control group</td>
<td>64% - 76%</td>
<td>3 years</td>
<td>64% - 76%</td>
<td>2c</td>
</tr>
<tr>
<td>Ersner-Hershfield &amp; Kope, 1979 [171]</td>
<td>22</td>
<td>Directed masturbation spaced: Versus massed sessions and Group couples versus group Individual sessions</td>
<td>No control Group</td>
<td>91% with masturbation 73% with partner No difference Between group/ Couples or group/ Individual Or spaced or Massed sessions</td>
<td>10 weeks</td>
<td>82% orgasmic with partner</td>
<td>2c</td>
</tr>
<tr>
<td>Heiman &amp; LoPiccolo, 1983 [136]</td>
<td>41</td>
<td>Cognitive behavioral therapy, Communication training, Directed Masturbation, sensate focus, systems Conceptualization</td>
<td>Wait list Control</td>
<td>15% - 40%</td>
<td>3 months</td>
<td></td>
<td>2c</td>
</tr>
<tr>
<td>Kiilman et al., 1986 [177]</td>
<td>55</td>
<td>Group couples communication Skills &amp; sex education vs-group Couples sexual skills Systematic desensitization, directed Masturbation &amp; assertiveness Training</td>
<td>Wait list &amp; Attention placebo No control group</td>
<td>25%</td>
<td>6 months</td>
<td>25%</td>
<td>2c</td>
</tr>
<tr>
<td>Kuriansky et al., 1982 [172]</td>
<td>19</td>
<td></td>
<td></td>
<td>95%</td>
<td>2 years</td>
<td>84%</td>
<td>4</td>
</tr>
<tr>
<td>Lazarus, 1963</td>
<td>16</td>
<td>Individual systematic Desensitization</td>
<td>No control Group</td>
<td>56.25%</td>
<td>15 months</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Leiblum &amp; Ersner- Hershfield, 1977 [170]</td>
<td>16</td>
<td>Group directed masturbation</td>
<td>No control Group</td>
<td>80% with masturbation</td>
<td></td>
<td></td>
<td>2c</td>
</tr>
<tr>
<td>LoPiccolo &amp; Lobitz, 1972 [165]</td>
<td>8</td>
<td>Directed masturbation</td>
<td>No control Group</td>
<td>Mast 100%, Coitus 75% Primary-100% Secondary- no change</td>
<td></td>
<td></td>
<td>3b</td>
</tr>
<tr>
<td>McGovern et al., 1975 [168]</td>
<td>12</td>
<td>Sexual and communication Skills, anxiety reduction, Directed masturbation</td>
<td>No control Group</td>
<td>No control group</td>
<td></td>
<td></td>
<td>3b</td>
</tr>
<tr>
<td>McGovern et al., 1976 [176]</td>
<td>4</td>
<td>Group directed masturbation</td>
<td>No control Group</td>
<td>100% with masturbation 75% with coitus</td>
<td></td>
<td></td>
<td>3b</td>
</tr>
<tr>
<td>McMullen &amp; Rosen, 1979 [174]</td>
<td>60</td>
<td>Directed masturbation &amp; Bibliotherapy vs directed Masturbation &amp; videotape</td>
<td>Wait list Control</td>
<td>Bib 66% With Mast, Bib 50% With coitus Videotape 50% with mast Videotape 30% with coitus 0% wait list</td>
<td></td>
<td></td>
<td>2c</td>
</tr>
</tbody>
</table>
## Table 6: Psychotherapy Outcome Studies for the Treatment of Female Orgasmic Dysfunction

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>N</th>
<th>Treatment Method</th>
<th>Control or Wait List</th>
<th>Post-Treatment Success Rate</th>
<th>Duration of Follow-up</th>
<th>Follow-up Success Rate</th>
<th>Evidence Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masters &amp; Johnson, 1970 [41]</td>
<td>34</td>
<td>Sensate focus, couples therapy, Systematic desensitization, sex Education &amp; communication Training</td>
<td>No control group</td>
<td>83% - 77%</td>
<td>5 years</td>
<td>82%</td>
<td>4</td>
</tr>
<tr>
<td>Matthews et al, 1976 [184]</td>
<td>18</td>
<td>Couples systematic desensitization &amp; sex therapy vs. couples sensate focus &amp; sex therapy vs. couples sensate focus &amp; bibliotherapy</td>
<td>No control group</td>
<td>11% No differences Between Groups</td>
<td>4 months</td>
<td>No differences Between groups</td>
<td>2b</td>
</tr>
<tr>
<td>Obler, 1973 [166]</td>
<td>37</td>
<td>Systematic desensitization with Videotape vs. psychoanalytic Treatment with videotape</td>
<td>Wait list Control</td>
<td>Denial, 85% Psychoanalytic 23% Wait list 23%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riley &amp; Riley, 1978 [185]</td>
<td>37</td>
<td>Couples directed masturbation &amp; Sensate focus vs. couples's Sensate focus</td>
<td>No control group</td>
<td>90% with dual treatment 53% with sensate focus</td>
<td>1 year</td>
<td>90% with dual treatment 53% with sensate focus</td>
<td>2b</td>
</tr>
<tr>
<td>Schneider &amp; McGuire, 1976 [169]</td>
<td>20</td>
<td>Masters and Johnson model</td>
<td>No control Group</td>
<td>55% with masturbation 5% with coitus</td>
<td>6 months</td>
<td>70% with masturbation 5% with coitus</td>
<td>2c</td>
</tr>
<tr>
<td>Wallace &amp; Barbach, 1974 [186]</td>
<td>17</td>
<td>Group directed masturbation</td>
<td>No control group</td>
<td>91% with masturbation</td>
<td>8 months</td>
<td>Gains Maintained</td>
<td>3b</td>
</tr>
<tr>
<td>Winoz &amp; Caird, 1976 [187]</td>
<td>21</td>
<td>Imaginal systematic desensitization Vs. video systematic desensitization</td>
<td>Wait list Control</td>
<td>18% No differences Between groups</td>
<td>1 - 3 months</td>
<td>25%</td>
<td>2b</td>
</tr>
</tbody>
</table>
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 has been done by Bergeron, Binik, Khalife, et al. [191], who compared biofeedback, cognitive behavioral therapy and vestibulectomy in with a randomized series of 78 patients. While all three groups reported improvement in symptomatology post-treatment and at 6 month follow-up, the most successful and maintained outcome was achieved with vestibulectomy. 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.

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 [153].

It is usually treated through a combination of relaxation exercises and in vivo graduated self-insertion of dilators of increasing size [192]. Typically, education about the female anatomy as well as Kegel and puboccygeal exercises is 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 [193]. There are no randomized control studies studying outcome.

Chapter 16 provides a comprehensive overview of the etiology and treatment of sexual pain disorders.

5. 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 & Durlak [194] reported 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.

6. Factors associated with positive outcome of sex therapy

Based on clinical observation and experience as well as some empirical research, Hawton [137] and others [96] have identified a variety of factors that appear to be related to more positive outcome with psychological treatment interventions (These are summarized in Table 7). 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.

Summary: Overall, psychological interventions utilizing Masters & Johnson 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, arousal and sexual pain complaints is more variable since these problems tend to co-occur and a variety of contextual factors can interfere with outcome. Treating the contextual and relationship issues that inevitably accompany these problems is crucial, particularly for long-term improvement.

A number of factors have been identified which are associated with positive treatment outcome including the motivation for success of both partners, relationship satisfaction and compliance with homework assignments (Table 7).
This section will review the existing psychological research on male sexual dysfunction. While current research tends to focus on pharmacological interventions, this in 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. PSYCHOLOGICAL TREATMENT OF MALE SEXUAL DYSFUNCTION

This section will review the existing psychological research on male sexual dysfunction. While current research tends to focus on pharmacological interventions, this in 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 hypoactive sexual desire disorders. Some men with HSDD are included in studies of men and women presenting with mixed sexual dysfunctions but the small numbers of these men do not lend itself to a careful outcome analysis.

### II. PSYCHOTHERAPY OF ERECTILE DYSFUNCTION

Men with lifelong and acquired erectile dysfunctions typically achieve significant gains both initially and over the long-term following participation in sex therapy (Table 8) although men with acquired disorders tend to fare better than those with lifelong problems.

Masters and Johnson [41] reported initial failure rates of 41% and 26% for lifelong (primary) and acquired (secondary) erectile dysfunction, respectively. Their two to five year follow-up of this cohort indicated sustained gains.

In a review of the studies of treatment for erectile dysfunction, Mohr and Beutler [198] wrote:

The component parts of these treatments typically include 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 six months to six years.

These studies utilized either a couples or a group format. The duration of couples 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. There are few controlled reports on individual therapy for single men, except for that of Reynolds [199] who highlighted the difficulties of treating men without partners.

Sex therapy treatment of ED consists of a variety of interventions: systematic desensitization, sensate focus, interpersonal therapy, behavioral assignments, sex education, communications and sexual skills training and masturbation exercises. It has not been possible to statistically analyze the precise contribution of any of these single interventions to overall success.

Wylie [197] reports on prospective study of 23 couples where the man presented with ED. Utilizing a combination package of modified sex therapy and behavioral systems couple therapy, 87% of men

---

**Table 7. Factors associated with positive outcome in sex therapy trials.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Factors associated with positive outcome in sex therapy trials</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whitehead &amp; Mathews, 1986 [122]; Hawton, Catalan, &amp; Fagg, 1991 [125]</td>
<td>Couple’s motivation to enter treatment</td>
<td>4</td>
</tr>
<tr>
<td>Hawton, 1995 [137]</td>
<td>Degree of physical attraction between partners</td>
<td>5</td>
</tr>
<tr>
<td>Hawton, 1995 [137]</td>
<td>Absence of major psychiatric disorders</td>
<td>5</td>
</tr>
<tr>
<td>Hawton, 1995 [137]</td>
<td>Evidence of early homework compliance</td>
<td>5</td>
</tr>
<tr>
<td>Besharat, 2001 [120]</td>
<td>Attention to systemic issues in the relationship</td>
<td>2a</td>
</tr>
<tr>
<td>Hawton, Catalan, &amp; Fagg, 1991 [125]; Hirst &amp; Watson, 1997 [126]</td>
<td>Male partner’s motivation to obtain a successful outcome</td>
<td>2c</td>
</tr>
</tbody>
</table>

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Table 8. Psychotherapy Outcome Studies for the Treatment of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Treatment Method</th>
<th>Study Design</th>
<th>Post-Treatment Success Rate</th>
<th>Follow-Up</th>
<th>Success Rate</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldberg, LoPiccolo, DiAmicis et al., 1985 [175]</td>
<td>32</td>
<td>Cognitive/behavioral therapy, sensate focus, sexual skills training, sensual awareness training</td>
<td>No control group</td>
<td>66%</td>
<td>3 years</td>
<td>52%</td>
<td>2b</td>
</tr>
<tr>
<td>Hawton et al., 1986 [146]</td>
<td></td>
<td>Masters and Johnson co-therapy model sex education &amp; psychotherapy</td>
<td>No control group</td>
<td>78%</td>
<td>1 - 6 years</td>
<td>61%</td>
<td>2b</td>
</tr>
<tr>
<td>Hawton, 1995 [137]</td>
<td></td>
<td>Cognitive Behavioral Therapy sensate focus communications training systems conceptualization</td>
<td>No control group</td>
<td>65 - 70%</td>
<td>3 months</td>
<td>65 - 70%</td>
<td>3</td>
</tr>
<tr>
<td>Heiman &amp; LoPiccolo, 1983 [136]</td>
<td>19</td>
<td>Systematic Desensitization</td>
<td>No control group</td>
<td>81%</td>
<td>3 months</td>
<td>81%</td>
<td>3</td>
</tr>
<tr>
<td>Kilman et al., 1987 [124]</td>
<td>16</td>
<td>Sensate focus and conjoint psychotherapy</td>
<td>No control group or wait list</td>
<td>38%</td>
<td>1 year</td>
<td>6%</td>
<td>3</td>
</tr>
<tr>
<td>Levine &amp; Agle, 1981 [195]</td>
<td>16</td>
<td>Quasi-residential, daily Combination of individual &amp; conjoint treatment, sensate focus, sexual Skills and communication training</td>
<td>No control group or wait list</td>
<td>Lifelong ED = 59% Acquired ED = 74%</td>
<td>2 - 5 years</td>
<td>Lifelong ED = 59% Acquired ED = 69%</td>
<td>2a</td>
</tr>
<tr>
<td>Masters &amp; Johnson, 1970 [41]</td>
<td>245</td>
<td>Systematic desensitization and assertiveness training versus psychoanalytic tt.</td>
<td>No control group</td>
<td>80%</td>
<td>18 months</td>
<td>80%</td>
<td>3</td>
</tr>
<tr>
<td>Obler, 1973 [166]</td>
<td>27</td>
<td>Didactic presentations and discussion directed masturbation and bibliotherapy</td>
<td>No control group</td>
<td></td>
<td></td>
<td>64%</td>
<td>2b</td>
</tr>
<tr>
<td>Tackfen &amp; Bremer, 1984 [196]</td>
<td>16</td>
<td>Sensate focus &amp; communication training</td>
<td>No control group</td>
<td>80%</td>
<td>18 months</td>
<td>80%</td>
<td>3</td>
</tr>
<tr>
<td>Wylie, 1997 [197]</td>
<td>23</td>
<td>Modified modern sex therapy Behavioral systems couples therapy</td>
<td>No control group, Prospective study</td>
<td>87%</td>
<td>6 months</td>
<td>87%</td>
<td>2b</td>
</tr>
</tbody>
</table>
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. All studies with long-term follow-up find a tendency for men to relapse. Hawton [146] 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 (Table 8).

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 [200] 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 RAPID EJACULATION

Since the early 1970's, an array of individual, conjoint, and group therapy approaches employing behavioral strategies such as stop-start [41] or squeeze techniques [201] have been used to treat rapid ejaculation [10, 42, 200, 202, 203]. Table 9 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 reported failure rates of 2.2% immediately after treatment and 2.7% at the five year follow-up. Other researchers have been unable to replicate Masters & Johnson’s success rates. For instance, only 64% of men in Hawton’s [146] study were characterized as successful in overcoming rapid ejaculation.

The majority of studies that included long-term follow-up have documented reduced success rates post-therapy. No one has been able to replicate the 60% to 95% success rate reported by Masters & Johnson [41]. Three years after treatment, success rates often dwindle to 25% [175, 205, 206].

Cognitive behavioral therapy [207] as well as multimodal psychodynamic and behavioral treatments [10, 208] 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 [209]. This finding may not hold for more complex situations that involve relationship and communication difficulties (Table 9).

J. THE SUCCESS OF INTEGRATED TREATMENT FOR THE RESOLUTION OF SEXUAL DYSFUNCTION: RESEARCH EVIDENCE

This section begins by examining the reasons why medical treatments alone are often insufficient in helping couples resume a satisfying sexual life. Next, the articles that report on combination therapy are reviewed. Finally, this section concludes by recommending an as yet unproven three-tiered integrated model for treating sexual dysfunction.

The term integrated is used to denote concurrent or step-wise combinations of psychological and medical interventions. Too often, medical treatments are directed narrowly at a specific sexual dysfunction and fail to address the larger biopsychosocial issues (see Table 10). While medical therapies, especially for ED, are generally efficacious (50%-90%), approximately 50% of individuals fail to continue treatment. This is partly due to the clinician’s failure to address the relevant psychological and interpersonal issues [128]. Examples of relevant biopsychosocial factors include: 1) Patient variables such as performance anxiety and depression; 2) Partner variables such as health status and partner disinterest; 3) Interpersonal non-sexual variables such as quality of the overall relationship; 4) Interpersonal sexual variables such as the interval of abstinence and sexual scripts and; Contextual variables such as current life stresses, finances, children.
<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Treatment Method</th>
<th>Study Design Control/Wait List</th>
<th>Post-Treatment Success Rate</th>
<th>Long-Term Follow-Up</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeAmicis et al, 1985 [175]</td>
<td>20</td>
<td>Sensual awareness communication training modification of sexual interactions</td>
<td>no control/wait list</td>
<td>75%</td>
<td>3 years</td>
<td>2b</td>
</tr>
<tr>
<td>Hawton et al, 1986 [146] Hawton, 1995 [137]</td>
<td>14</td>
<td>Modification of Masters &amp; Johnson sex education psychotherapy</td>
<td>no control/wait list</td>
<td>75%</td>
<td>1 - 6 years</td>
<td>2b</td>
</tr>
<tr>
<td>Heiman &amp; LoPiccolo, 1983 [136]</td>
<td>21</td>
<td>Cognitive behavioral therapy communication training systems conceptualization pause &amp; squeeze sensate focus</td>
<td>wait list</td>
<td></td>
<td>3 months</td>
<td>2</td>
</tr>
<tr>
<td>Lobitz &amp; LoPiccolo, 1982 [204]</td>
<td>6</td>
<td>Modification of pause and squeeze technique</td>
<td>No control/wait list</td>
<td>100%</td>
<td>6 months</td>
<td>4</td>
</tr>
<tr>
<td>Masters &amp; Johnson, 1970 [41]</td>
<td>186</td>
<td>Quasi-residential daily combination of individual &amp; conjoint trt, sensate focus, squeeze technique, sexual skills &amp; communication training</td>
<td>no control/wait list</td>
<td>97.80%</td>
<td>2 - 5 years</td>
<td>2b</td>
</tr>
<tr>
<td>Obler, 1973 [166]</td>
<td>9</td>
<td>Systematic desensitization and assertiveness training versus psychoanalytic trt</td>
<td>No control/wait list</td>
<td>80%</td>
<td>18 months</td>
<td>3</td>
</tr>
</tbody>
</table>
There is an emerging literature that demonstrates a synergistic benefit from the use of both psychological interventions and pharmacological treatments for a number of psychiatric conditions including depression, post-traumatic stress disorder and [230] and to a lesser degree, schizophrenia [230, 231]. It is regrettable that there are so few well-designed randomized control studies focusing on integrated approaches to the treatment of sexual dysfunction. The few studies that exist focus on treatment for erectile dysfunction; there are only a few reports of combined therapies for female dysfunction. These studies are summarized in Table 10.

I. INTEGRATED TREATMENTS: ED

There have been several articles recommending the combination of medical and psychological approaches to the treatment of erectile dysfunction [206, 229, 232, 233]. This section summarizes the studies that report on psychological interventions combined with either intercavernosal injection (ICI) or vacuum tumescence therapy.

Kaplan [219] presented five cases where patients did not benefit from ICI therapy because of hidden emotional and marital relationship difficulties. She argued that brief psychodynamic techniques to manage the resistances to ICI could help some of the couples adjust to and enjoy the pharmacological restoration of potency. Similarly, Turner et al, [228] found that a single successful pharmacologically induced erection administered in the doctor's office was not effective in improving psychogenic erectile dysfunction when it was not accompanied by psychological counselling.

Hartmann and Langer [217] described an integrated treatment program involving injection therapy and sex counseling. They concluded that a combined approach was beneficial but when the etiology of the ED was primarily psychogenic, improvement could occur only in the absence of partner problems or premature ejaculation.

Colson [215] described the results of an 8-year study where 1001 participated in a three-phase combined therapy protocol. In the first phase patients were given training in ICI technique and participated in cognitive behavioral type therapy including sensate focus. The second phase consisted of men using the ICI in the privacy of their homes. In the third phase, men attempted to reduce the dose of ICI or decrease the frequency of injections. Full recovery, meaning recovery of satisfactory sexual intercourse with complete discontinuation of injection therapy was observed globally in 51% of patients. Injection therapy alone without cognitive behavioral therapy, resulted in improvement in 24% of cases. The investigators noted that injection therapies that facilitate erections such as moxisylyte, are better suited for combination with CBT than other products such as prostaglandin E1 or Papaverine which induced erections.

Lottman et al, [221], described short-term therapy with intracavernosal injections and counseling. In the ICI and counseling group it was found that providing information about factors that contribute to erectile function and enabling couples to communicate about sexual problems were the most important factors contributing to the efficacy of ICI treatment.

There have been numerous case reports attesting to the gains realized when behavioral or cognitive therapy are combined with medical treatments for ED [222, 224, 226]. Leiblum [127] has noted that couples frequently need preparation and counseling in order to resume a mutually satisfying sexual life after an extended period of sexual avoidance due to ED.

Wylie et al [229] reported on 45 patients with primarily psychogenic ED who were randomized into two groups. The first group participated only in couple therapy while the second was instructed in the use of a vacuum device while simultaneously receiving couple therapy. Improvement was reported by eighty-four percent of the combined group in contrast to 60% of the therapy only group. Interestingly, the authors report that 75% of those who failed to improve in the combined therapy group never used the vacuum device!

The authors suggested that early combination treatment of couple therapy and a physical treatment such as a vacuum device may lead to greater beneficial response in men with ED than psychotherapy alone. They also highlighted the importance of demonstrating potential benefits from a physical intervention early in therapy and believe that delaying the demonstration may have a negative impact on treatment outcome (Table 10).
Table 10. Summary of Combined Therapy Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Summary of study findings</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Althof SE, Turner L.A., et al, 1987 [210]</td>
<td>82</td>
<td>82 consecutive patients admitted to the ICI program and followed for 1 year. ICI associated with increases in quality of erection, intercourse frequency and sexual satisfaction. Men also reported decreases in general psychiatric symptomatology. Partners demonstrated increased sexual satisfaction.</td>
<td>4</td>
</tr>
<tr>
<td>Bähr W., Scherf et al, 1989 [211]</td>
<td>156</td>
<td>Fourteen couples (9%) reported that ICI treatments saved their marriage whilst the relationship was improved in another 98 (65%) of couples.</td>
<td>2b</td>
</tr>
<tr>
<td>Banner L, 2001 [212]</td>
<td>57</td>
<td>Couples were randomly assigned to sildenafil or placebo. After four weeks all couples received the combined treatment. Two couples (11%) from the integrated group and one couple (4%) from the sildenafil group met criterion scores for success after four weeks. At the end of eight weeks 66% of men and 63% of women met criterion scores on IIEF 5.</td>
<td>3b</td>
</tr>
<tr>
<td>Bergeron S, Binik, Y.M., 2001 [191]</td>
<td>28</td>
<td>The values of biofeedback, group cognitive behavior therapy or vestibulocentomy were compared in women with vulvar vestibulitis. All showed positive sexual function and psychological adjustment outcomes.</td>
<td>1b</td>
</tr>
<tr>
<td>Chen J., 2002 [214]</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>
<td>3b</td>
</tr>
<tr>
<td>Colson, 1996 [215]</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 intercourse with complete discontinuation of injection therapy in 50% of patients compared to 24.5% of cases where injection therapy was given alone. Injection therapies that facilitate erections such as moxisylyte were better suited for combination with CBT than prostaglandin or Pupavine.</td>
<td>2c</td>
</tr>
<tr>
<td>Di Bisceglie C, Tagliaube M et al, 2002 [216]</td>
<td>111</td>
<td>Men with a stable sexual relationship but affected by erectile dysfunction. Of 87% whose partners were post-menopausal only 3% were on HRT. 38% of the women turned up for endogynaecological consultation and most were found to have a low sex drive. The women exhibited an interest in HRT only to improve their general quality of life and prevention of further diseases. The patients whose partners chose to start HRT exhibited a better compliance to medical treatment at the 6th month of treatment.</td>
<td>3b</td>
</tr>
<tr>
<td>Gutierrez P et al, 2002 [218]</td>
<td>25</td>
<td>Clinically relevant improvement in 15 (60%) patients, the IIEF score changing from severe to mild range. Useful for salvaging non-responding patients.</td>
<td>1c</td>
</tr>
<tr>
<td>Hawton, 1998 [206]</td>
<td>0</td>
<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 specialised in sexual medicine.</td>
<td>5</td>
</tr>
<tr>
<td>Hartmann and Langer, 1993 [217]</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 psychogenic impotence, employment of auto-injection therapy, adequate sexual stimulation by partner.</td>
<td>2a</td>
</tr>
<tr>
<td>Kaplan H.S., 1990 [219]</td>
<td>1000</td>
<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>
<td>4</td>
</tr>
<tr>
<td>Kingsberg S., 1998 [220]</td>
<td>4</td>
<td>Sexual 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>
<td>4</td>
</tr>
<tr>
<td>Leiblum S. R., 2002 [127]</td>
<td>4</td>
<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 characterised by sexual apathy and or/relationship conflict.</td>
<td>5</td>
</tr>
<tr>
<td>Lottman P.E., Hendrix et al, 1998 [221]</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+ 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>
<td>3a</td>
</tr>
</tbody>
</table>
II. SUMMARY

While medical interventions are quite successful in facilitating the achievement and maintenance of erections, they do not motivate the sexually reluctant patient to try treatment, nor do they help overcome the biopsychosocial obstacles that have prevented success in the past. Without adequate desire, motivation and realistic expectations, treatment outcome is often disappointing and discontinuation rates are high. It is only when medical interventions are combined with counseling that treatment obstacles can be overcome and therapeutic outcome enhanced.

III. OTHER DYSFUNCTIONS

It is surprising that there are no reports of combined therapy for rapid ejaculation, inhibited sexual desire or any of the female sexual dysfunctions. These areas have a critical need for controlled trials to address the integration of biological and psychological treatments.

Presently, there are no FDA approved pharmacological interventions for female dysfunctions. There are several herbal or neutraceutical compounds that claim efficacy but none of these agents have undergone large scale, rigorous, randomized, double-blind, placebo-controlled trials using validated and reliable outcome measures. Over the next few years it is likely that efficacious pharmacological compounds will receive approval by the established regulatory agencies. Prior to their availability it would be worth considering how such pharmacological treatments might be integrated with various forms of psychological intervention.

IV. A PROPOSED INTEGRATED MODEL FOR TREATING ERECTILE DYSFUNCTION

The purpose of this section is to offer a paradigm and rationale for combined treatments of erectile dysfunction. The model is presented to stretch the boundaries of the current treatment algorithms [232]. Splitting psychological and medical treatments is outdated and reduces the long-term effectiveness and satisfaction from either treatment.

The individual or couple level of psychosocial complexity constitutes the cornerstone of this approach. Psychosocial complexity refers to the contextual features characteristic of the individual or couple. It includes such factors as the: length of time the couple has been sexually abstinent, the quality of the interpersonal relationship, the motivation of each partner to resume lovemaking, the presence of serious psychiatric psychopathology, etc. The clinician categorizes the couple as having:

1. No or insignificant barriers preventing use of the medical intervention;
2. Mild to moderate barriers; or
3. Profound psychological/interpersonal difficulties that will render any medical intervention relatively ineffective.

Individuals or couple’s who are classified as having no or insignificant barriers to utilizing treatment suggestions generally have a good to excellent relationship. Although the male has ED, they continue to be affectionate and maintain non-coital sexual play. One or both partners have realistic expectations for treatment. They value their return to a satisfying sexual life. In such ideal circumstances and if the ED is mild to moderate in severity, pharmacotherapy, most likely will ameliorate the sexual symptoms. Such couples require nothing more than a medical prescription and practical suggestions as to how to maximize the treatment’s effect.

However, the most frequently encountered clinical situation is the second scenario in which individuals/couples are judged as having “mild to moderate psychosocial barriers”. These patients have been sexually abstinent for an extended period of time. Expressions of affection have dwindled. At least one person is mildly depressed and uncertain of how to re-initiate lovemaking. Brief, directed coaching is often helpful in improving this couple’s sexual life. Coaching refers to offering the patients guidance, suggestions and techniques for overcoming their resistance or inhibitions.

Suggestions for increasing emotional intimacy or planning a romantic evening prior to initiating sexual behavior can “break the ice”. Addressing one or both partners’ depression, attending to performance anxiety, or inquiring about any physical obstacles-such as vaginal dryness -that might diminish the quality of their sexual experiences will likely prove helpful.

It is relatively easy to recognize those individuals/couples with profound psychological or interperso-
nal difficulties (or both). Medication alone is likely to be ineffective with these patients. Common patient obstacles include: poorly managed or unresolved anger, power and control issues, abandonment concerns, broken attachments, substance abuse, serious depression, contempt, and disappointment. These psychological states, complicated by prolonged sexual abstinence, must be addressed prior to, or during, the pharmacological treatment intervention, in order for the couple to benefit from medical interventions and to achieve emotional satisfaction from sex. Red flags are raised when the couple voices unrealistic expectations, saying or implying, “With a restored erection, lovemaking will definitely be more frequent”, or “I will feel more lovable/successful in life”, or “This will cure my marital woes”. Such over-optimistic expectations are likely to be thwarted since they do not reflect an understanding of the complexity of sexual and emotional life.

Although these suggestions may appear time consuming to the busy physician, taking the time to assess the couple’s psychosocial “health” and treatment expectations will result in greater patient satisfaction and long-term improvement in the man’s erectile functioning and the couple’s overall sexual satisfaction.

K. 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 2a) 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 PDE-5 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 motivations 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. Assessment of male, female and couples’ sexual dysfunction should include inquiry about:
  A. Predisposing Factors
  B. Precipitating Factors
  C. Maintaining Factors
  D. Contextual Factors
- 4. Treatment of life-long and/or chronic dysfunction will be different from acquired/recent dysfunction.
- 5. Research is needed to identify efficacious combined and/or integrated treatments for sexual dysfunction.
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Committee 3

Ethical, Socio-cultural and Educational Aspects of Sexual Medicine

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### REFERENCES
The past 60 years have seen tumultuous changes in many aspects of human sexuality, primarily due to our development of a wide range of sophisticated technologies.

These developments have, in various ways, affected our sexual behaviour and, as a consequence, they have also affected the traditional gender roles. Antibiotics, the contraceptive pill and oral Erectile Dysfunction (ED) therapies are examples of influential biomedical developments, but other technological changes have also had dramatic effects. At the beginning of the last century, mobility and communication were still quite limited and often the preserve of the wealthy. Television, satellite communication and the Internet have led to an explosion in global communication and access to knowledge, and are increasingly becoming available to a much wider public, including those in isolated, rural communities all over the world. The development of the air-travel industry allows unprecedented global mobility for millions of people who might previously have never travelled further than the next city, let alone outside their own country.

Medical practitioners nowadays not only have to cope with familiar, local problems, and work within familiar customs and practices, but they must now also be aware of, and respect the sometimes very different perceptions of people who, although they live in their community, come from many different cultures from all around the world.

This committee has tried to address some of the challenges but, unlike most others, cannot provide a wholly evidence-based report. Our work on education and socio-cultural issues must, by its very nature, be primarily descriptive. Ethics may be approached in a systematic manner but it is, and will remain, a subjective discipline, influenced by widely varying socio-cultural and religious factors.

In our work, we have tried to embrace, and to celebrate, the wonderful diversity of human beings from all around the globe. We have found that, from an ethical viewpoint, there is so much more that unites us than divides us. We hope that we have identified some common ground that all health professionals working in the new discipline of sexual medicine can share. Respect, understanding and tolerance must form the foundation of all our work.

1. INTRODUCTION

Ethics is a term used to describe the ways in which we understand the moral life. Morality comprises the norms for human conduct, what is right and what is wrong. As well as standards of conduct, it includes obligations, recommendations, rights and virtues. Some are widely held throughout humanity, such as prohibitions against killing, causing harm to others, stealing and falsehood. Others are specific to the community to which we belong and may not only differ between communities, but what is permitted or even virtuous in one may be forbidden or sinful in another.

In an increasingly complex world, developments in healthcare technology and international communications compel us to look very carefully at our assumptions as to what is ethical thought and action, the essence of “doing right” and “not doing wrong”. In a liberal, Western, Judaean-Christian ethical tradition, it is all too easy to universalise that worldview and to
make moral and ethical judgements about the beliefs and actions of others with a differing moral and ethical system, even though that system is just as soundly based in their worldview. The world's major religious and socio-cultural traditions have far more in common than they have to divide them, but there is no “universal” system of morality and ethics. Health professionals, as citizens of the world, would do well to reflect on that fact and respect (even if they must disagree) with the sincerely-held views of others. For medical doctors it is a must to live up to their Hippocratic oath.

Many of the moral and ethical concepts surrounding life, death, organ donation, abortion and many other issues have been widely debated. Sexuality and sexual behaviour have been less well explored, particularly in a wider public arena, because of their particular sensitivity, and their connection to a range of widely differing socio-cultural and religious mores.

In this chapter, there is no attempt to achieve a “universal” framework of ethics for sexual medicine. Indeed, this is probably an impossible task. However, it will try to identify areas where those from different traditions can agree, and increase our understanding of why, in other areas, we cannot agree.

2. MORALITY AND COMMUNITY

The “Universal Morality” comprises a set of norms upheld by all morally serious people. A little reflection demonstrates how difficult it is to agree on any universal norm binding on all people at all times. A prohibition against killing another person seems like a good candidate, but judicial killing is considered morally acceptable by some and immoral in all circumstances by others. Abortion, whether for social or therapeutic reasons, presents similar dilemmas. Morality is usually community-specific and reflects norms derived from institutional, cultural and religious sources. Norms may also operate in a hierarchy, the structure of which may vary between communities, where some norms take precedence over others.

Attitudes towards extra-marital sexual behaviour vary greatly around the world. In some communities and particularly in the West, such behaviour is accepted, or at least tolerated. In others, it may, in some circumstances, result in the judicial killing of the perpetrators. Attitudes towards homosexuality vary in a similar manner. On the other hand, polygamy is most often criminalised in the West but is accepted in the Muslim world, and even recommended if its practice is thought to prevent adultery or other immoral (as perceived in that community) behaviour.

Many of these norms arise from Holy Scripture. Whether revealed in the Torah, New Testament, Holy Koran or any other Scripture, such norms are considered by each community to be commanded by God and unchangeable by man. Some Muslims find it unacceptable that they might be criminalised in Western countries for practising what is permitted by their faith. Some Westerners find the penalties permitted by Sharia law for homosexuality and adultery equally unacceptable. It is unlikely that common ground, a universal norm, will ever be found, unless all communities accept some new Revelation or interpretation of Divine Will in the future. In the meantime, the best hope that we have is to try to understand and be tolerant of each others’ viewpoint, and to try not to insult or demonise each other. Understanding, tolerance and the concept of mercy can be found in most legal codes, including both Sharia and the secular legal codes of the West.

A small survey was made at the Pan Arab Conference on Sexual Dysfunction (Cairo, 2003).

Participants were: The Egyptian Orthodox church, the Advisory Committee for Islamic Legalities, and 372 attending medical doctors. The following subjects were discussed:
- Pornography, polygamy, prostitution.
- Masturbation, Female Sexual Mutilation.
- Homosexuality and Sexual Education.

a) Pornography

Both The Egyptian Orthodox Church and The Advisory Committee for Islamic Legalities refused pornography as an art form and considered it a sin. They also both refused the use of pornographic material as a sexual aid for a couple's private use even if they are married. They also refused its use in the context of the diagnosis of Sexual Dysfunction.

However, the Physician Survey showed that:
- 40% agreed to use pornographic material as a sexual aid for couples while 60% refused.
- 62% agreed to its use during diagnosis of Sexual Dysfunction while 38% refused.

b) Polygamy

The Egyptian Orthodox Church considered this a subject for the Muslim community.
The Advisory Committee for Islamic Legalities considered polygamy a better solution than prostitution and unmarried sexual activity. Polygamy is regarded as a better “sexual door” than both of the above, and the committee asked for world-wide recognition of this Muslim religious right, which is criminalized in certain parts of the world and considered as a form of discrimination against Muslims.

c) Prostitution Legalization
Both the Egyptian Orthodox Church and The Advisory Committee for Islamic Legalities refused the allowing of legalized prostitution in their society, and they refused any claimed benefits for the society.

The Physician Survey showed that: 6% agreed that increased sexual freedom (including allowing legalized prostitution) will decrease the incidence of rape, while 94% did not agree.

d) Masturbation
The Egyptian Orthodox Church refuses it under all conditions. The Advisory Committee for Islamic Legalities did not encourage it but can allow it under certain compelling conditions like fear of sin or rape, but encourage early marriage if possible.

The Physician Survey showed that:
74% agreed to the use of masturbation to protect oneself from adultery, while 26% refused.
Also, the use of masturbation for the non-married as prevention for ED was supported by only 35% and refused by 65%.

e) Female Genital mutilation All parties rejected the act and encourage more social and educational efforts to eliminate this illegal act.

f) Homosexuality
All parties refused to accept any rights or requirements in this context.

g) Sexual Education
Advisory Committee for Islamic Legalities: all recognized that sex education is lacking and its absence causes social problems. Sex education should be through schools after adjusting the content to each age.

The Orthodox Church: sex education should be conducted through the church in small groups or private meetings.

The Physician Survey showed that:
58% are in favor of sexual education in schools, while 42% are against it. 72% also agreed to sexual education in mosques and churches and 28% were against it.

Regarding sexual education through/provided by the media newspapers and magazines only 36% were in favor and 64% had refused.
The use of the Internet or cinema as methods of education was supported by 28% while 72% refused.

h) Conclusion
The topics of sexual concept, orientation, education and rights in the Arab/Muslim World, as well as the Orthodox Church, are sensitive subjects. The freedom to discuss these areas is limited within medical and religious communities and largely restricted in the media. The committee recognizes that this survey is small, but describes an actual situation.

3. A FRAMEWORK OF MORAL PRINCIPLES FOR SEXUAL MEDICINE

In their book, Principles of Biomedical Ethics, Beauchamp and Childress [1] describe a framework of moral principles that is useful when considering ethical issues in sexual medicine. They consider morality to include of a set of widely (although not necessarily universally) accepted principles that are central to the study of biomedical ethics.

Respect for autonomy: the principle of acceptance of the right of a patient to make informed choices about their life and actions, including choices about healthcare and sexual activity, without interference from others. Respect for autonomy relies, therefore, on a patient
- giving consent to participate in a given course of action (such as a surgical procedure, taking medication or engaging in psychotherapy) with or at the recommendation of the health professional
- being competent to give consent (having the cognitive capacity to make autonomous choices, without significant impairment as a consequence of mental health problems or intoxication)
- having the knowledge and understanding to give that consent in an informed manner, to include an understanding of the nature and purpose of the action, its benefits and risks, available alternative options for action or inaction, and the likely consequences of each
- being able to make choices about self-governance without undue influence from other individuals or society; individuals may, by the same principles,
consent to surrender some degree of autonomy as a requirement for membership in a social or religious community.

When considering issues of autonomy and consent, health professionals should carefully consider whether a patient is being unduly influenced by their partner, family or social group. A patient consenting to surrender some degree of their autonomy as a requirement for membership in a community is ethically acceptable, but the consent must be freely given by a competent individual who is not acting under any form of duress. Patients will sometimes seek treatment for a sexual problem that they are experiencing for reasons other than for their own physical or emotional benefit. They may indicate that the treatment is for the benefit of their partner or to facilitate the maintenance of their relationship. The patient may perceive that the treatment might bestow benefits not foreseen by the professional. Again, provided that consent is freely given by a competent individual who is not acting under any form of duress, this should be ethically acceptable.

In sexual medicine, health professionals have an obligation to respect the autonomy of any individual that they treat, regardless of that individual’s religious or socio-cultural tradition, race, gender or sexual orientation. They may not share the ethical worldview presented to them but they are obliged to respect the individual’s autonomy, right to self-governance and choice. If there is an insurmountable conflict between the ethical worldview of patient and professional, the professional should respectfully explain this and suggest other sources where the patient might obtain healthcare advice. Neither patient nor professional should be obliged to betray their moral code but, equally, neither should impose their moral code on others to their detriment. Difficulties will undoubtedly remain where the legality of actions is involved, such as with abortion, homos*xuality and extra marital sex.

“Nonmaleficence” : the principle of refraining from causing harm, or undue risk, to a patient by direct action or neglect. Clearly, this involves not causing injury, pain or offence, but it also prohibits negligence. In order to determine whether negligence has occurred, we also need to determine the standard of care that should be expected of a health professional in a particular circumstance. This might involve diligently exercising proper skill in performing a procedure and also refraining from attempting procedures that the professional is inadequately trained to perform. Generally, the health professional will not deliberately recommend or provide a treatment that causes harm to their patient. However, almost all treatments bear some risk and informing the patient of the nature and extent of the risk is a part of the above-mentioned principle of respect for autonomy. Surgical procedures often convey a risk of morbidity and mortality. Psychotherapy may result in unforeseen or unwanted effects on interpersonal relationships, leading to some form of loss. Drug therapy frequently has unwanted side-effects, from relatively benign symptoms like dyspepsia and flushing (PDE5 inhibitors), though priapism and penile fibrosis (intracavernosal alprostadil), to exacerbating cancer, thrombo-embolic disorders and sudden death (sex steroids, such as testosterone and oestrogen). Provided that the risks and benefits have been considered, and that both the professional and the patient have had the opportunity to be involved in agreeing to that balance, the risk might be ethically acceptable.

It is ethically unacceptable for a health professional to recommend or provide a treatment that has been demonstrated as ineffective. In most circumstances, procedures for penile augmentation (attempts to increase penile length or girth) would fall into this category. Female genital mutilation will always fall into this category. Some would argue that male circumcision, other than for a clear medical indication, might also fall into this category. However, this is a highly complex matter that cannot be dealt with simplistically.

Beneficence : the principle of not only taking action to benefit a patient, but also, where possible and in most circumstances, to remove or prevent harm. It also includes defending the rights of the patient. This principle should be applied impartially, so that the professional acts with equal beneficence towards all patients, regardless of their religious or socio-cultural tradition, race, gender or sexual orientation. Nonmaleficence is, in most circumstances, obligatory. Beneficence is often recommended and only rarely obligatory. The strength of any recommendation to act with beneficence will vary, depending upon the duty of care the professional has towards their patient and the degree of burden (economic or personal) or risk that the act will impose upon them. Into this category fall several sorts of preventive or prophylactic measures.

Paternalism is a maladaptation of beneficence, where the professionals take what they presume to be a beneficent action without due respect to the autonomy of the patient. A gross example would be for
the professional to take therapeutic action without the patient’s consent. An example of a less severe but still paternalistic action would be where the professional presents the patient only with treatment options that they thought suitable for them, even though other reasonable options exist. True beneficence is to be encouraged and paternalism avoided.

**Justice**: the principle of providing healthcare in a fair, equitable and appropriate manner; in essence, equals should be treated equally. Men and women should have equal access to and quality of care, regardless of their religious or socio-cultural tradition, race or sexual orientation.

Disputes over equity of access to healthcare are increasingly common, particularly as resources are usually limited or scarce. There are stark differences around the world. In some countries, there are barely adequate resources available to feed the people and to provide protection against harm from preventable infectious diseases. Sexual medicine is most unlikely to be a priority in their healthcare systems. In others, sexual medicine services are available but may be rationed in some manner, according to the principles of distributive justice. However, there is no universal system of distributive justice. Utilitarian, libertarian (predominant in the USA), communitarian (predominant in the EU) and egalitarian theories all have their proponents and all have their strengths and weaknesses.

**Dignity**: Respect for “Dignity”: The principle of respect for human dignity is stated in Article 1 of the Universal Declaration of human rights.

“All human beings are born free and equal in dignity and rights. They are endowed with reason and conscience and should act towards one another in a spirit of brotherhood”.

The respect of human dignity is applied in various codes of medical ethics and in the Principles of European Medical Ethics: CIOMS 1995: art. 1

“The vocation of the physician is to protect the physical and mental health of Man and to relieve his suffering in the respect of life and dignity of the human person, without any discrimination of age, race, religion, nationality, social condition, and political ideology, or any other reason, in time of peace and in time of war”.

The principle of dignity is related to the principle of freedom and should not be considered as a legal constraint or an “evidenced fact” by the physician but, rather, as a value to be recognized. It is not a measurable principle.

Respect for human dignity is just as important as our right to personal freedom. It is not a relative principle that can be measured or quantified, but an absolute value that is the birthright of every human being. It is not conditional upon conformity or other social factors but is an innate value possessed in equal measure by us all.

The everyday working lives of every health professional are filled with ethical dilemmas. Those who are working in sexual medicine are no exception, and they also face the additional challenge of working with issues that are charged with a diversity of social, cultural and religious requirements and restrictions, particularly in multi-cultural societies. There are few, if any, universally right answers to ethical questions but all health professionals have a duty to consider each question in a morally serious manner. They may use the five principals described above, respect for autonomy, nonmaleficence, beneficence, dignity and justice, to describe the ethical dimensions of the problem, considering it within the worldview of the patient, society and themselves. In cases of doubt or difficulty, they would be well-advised to share the dilemma with respected colleagues, whilst preserving the right to privacy and confidentiality of their patient, and, where relevant, to document the reasoning. On some occasions, they may also need to seek legal guidance.

Here is one example. A man with a 13cm flaccid, stretched penis requests that a surgeon perform penile augmentation surgery, as he is dissatisfied with the length of his erect penis. The principal of respect for autonomy seems to require the surgeon to allow the patient to choose a particular course of action, provided that they can be shown to be competent, informed and are not acting under duress. The principal of beneficence recommends that the surgeon take action to ease the patient’s psychological distress, which might include surgery. Justice requires the surgeon to act in a similar manner for this patient as for any other, regardless of financial, social, cultural, religious, racial or other factors. The principal of nonmaleficence requires that the surgeon does not recommend or provide a treatment that has been demonstrated as ineffective. There is no surgical procedure that has been demonstrated as effective in increasing the length of the erect penis. The morally serious surgeon would have to give precedence to the principle of nonmaleficence over their respect for the patient’s autonomy. To perform an augmentation could not be considered beneficent and in this case, justice would require that all patients making a simi-
lar request should be managed in the same way, irrespective of whether the treatment was to be funded privately or through a state-funded healthcare system. Documenting this decision-making process may be helpful in defending the decision if the patient were later to make a complaint against the surgeon.

4. DIVERSITY

Diversity and freedom of expression are highly valued in most societies but only within limits. Those limits vary from community to community and no universal agreement on what is acceptable with respect to sexual behaviours, sexual orientation and gender identity is currently possible. Health professionals working in a specific community have an obligation to uphold the law within that community and, usually, will have the autonomy to leave that community if they cannot accept some of its norms. Their patients will have similar responsibilities and rights, but conflicts will almost inevitably arise.

As sexual function problems are unlikely to be life-threatening, the health professional has the option of being able to refuse to act in a way that condones any behaviour in serious conflict with their moral code. Their duty to respect the confidentiality of any information revealed to them by their patients should remain binding upon them unless non-disclosure is likely to result in serious harm occurring to others. For example, if the professional is aware that their patient has, or is about to commit a serious sexual assault, their duty of beneficence towards others usually would outweigh their duty of confidentiality towards the individual.

The concept of sexual rights has appeared in literature in the course of the last two decades. Its link to medical action is not clear for many physicians, a difficulty very understandable as this concept derives from disciplines not close to medicine. Sexual rights are human rights. They are not new rights created within a specific political environment, but they are statements that intend to relate the language of human rights to sexuality [2].

The World Health Organization has held a Consultation to develop working definitions of sex, sexuality and sexual health in January 2002. During this consultation, it was agreed that sexual rights are a necessary condition for sexual health. The working definitions arrived at by the WHO consultation are:

a) Sex

Sex refers to the biological characteristics which define humans as female or male.

These sets of biological characteristics are not mutually exclusive as there are individuals who possess both, but these characteristics tend to differentiate humans as males and females. In general use in many languages, the term sex is often used to mean “sexual activity”, but for technical purposes in the context of sexuality and sexual health discussions, the above definition is preferred.

b) Sexuality

Sexuality is a central aspect of being human throughout life and encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy and reproduction.

Sexuality is experienced and expressed in thoughts, fantasies, desires, beliefs, attitudes, values, behaviours, practices, roles and relationships. While sexuality can include all of these dimensions, not all of them are always experienced or expressed. Sexuality is influenced by the interaction of biological, psychological, social, economic, political, cultural, ethical, legal, historical and religious and spiritual factors.

c) Sexual health

Sexual health is a state of physical, emotional, mental and social well-being related to sexuality; it is not merely the absence of disease, dysfunction or infirmity [3]. 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. For sexual health to be attained and maintained, the sexual rights of all persons must be respected, protected and fulfilled.

d) Sexual rights

Sexual rights embrace human rights that are already recognized in national laws, international human rights documents and other consensus documents. These include the right of all persons, free of coercion, discrimination and violence, to:

- The highest attainable standard of health in relation to sexuality, including access to sexual and reproductive health care services;
- Seek, receive and impart information in relation to sexuality;
- Sexuality education;
- Respect for bodily integrity;
- Choice of partner;
- Decide to be sexually active or not;
- Consensual sexual relations;
- Consensual marriage;
- Decide whether or not, and when to have children; and
- Pursue a satisfying, safe and pleasurable sexual life.

The responsible exercise of human rights requires that all persons respect the rights of others.

Whether sexual rights can be demonstrated empirically is a question still awaiting a definitive answer. What is clear, at least in the above mentioned review, is that the definition of sexual rights permits the identification of a certain minimum to be achieved, below which the presence of human sexual problems (pathology) can be identified and above which the pursuit of sexual health can be articulated.

5. WORLD ASSOCIATION OF SEXOLOGY (WAS) DECLARATION OF SEXUAL RIGHTS

At the 14th World Congress of Sexology in Hong Kong, the World Association of Sexology adopted the following Declaration of Sexual Rights on August 26, 1999.

“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 recognises, respects and exercises these sexual rights.

a) 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 situation in life.

b) 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.

c) The right to sexual privacy

This involves the right for individual decisions and behaviours about intimacy as long as they do not intrude on the sexual rights of others.

d) 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.

e) The right to sexual pleasure

Sexual pleasure, including autoeroticism, is a source of physical, psychological, intellectual and spiritual well being.

f) 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.

g) 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.

h) 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.

i) 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.

j) The right to comprehensive sexuality education

This is a lifelong process from birth throughout the
life cycle and should involve all social institutions.

**k) 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”**

Aside from specific prohibitions towards male masturbation and certain forms of contraception in some codes, this declaration appears to be compatible with the major religious and socio-cultural traditions, and should be, as far as is morally acceptable within those **traditions, adopted and promoted**.

Most traditions have affirmed, admittedly in very different terms, some of these rights for millennia but others may be more problematic. The behaviours seen to comprise the “right to sexually associate freely” will be very different from a liberal, secular viewpoint than from a conservative, religious viewpoint, be it Judaic-Christian, Muslim or Hindu. The right “to divorce” or “to establish other types of responsible sexual associations” may be particularly troublesome for observant members of some communities.

Attitudes towards the morality of enjoyment of sexual pleasure vary considerably. In much of the **Christian West**, “continence”, abstention from sexual behaviour was traditionally recommended. In Jewish tradition and in the East, particularly in **India**, sex was celebrated as a gift from God that might offer mystical insights. In the **Muslim world**, sex is clearly reserved to married couples but the Holy Koran is curiously modern in the instruction it gives to the faithful in these matters. Women are to be respected and their needs fulfilled. Foreplay is important and men are commanded, “Let-not the one of you fall upon his wife like a beast (camel) falls. It is more appropriate to set a messenger afore the act”. Equally interesting is the instruction, “Women have rights even as they have obligations in an equitable way”.

**II. SOCIO-CULTURAL ISSUES**

**1. FEMALE SOCIAL CULTURAL ISSUES (AFRICA)**

Cultural issues and social mores play an important role in the acceptance and achievement of normal sexual function for both men and women. **Tradition, law, education, and the status of women are important indicators of the reproductive function of and freedom of women** [4-6]. Cultural mores dictate a woman’s freedom during her entire life span. This includes marriage, pregnancy, menses and postpartum. It also includes specific tribal customs. The acceptance and availability of prostitutes in a particular country will also be important determinants. **Sexually transmitted infections** (STIs) often change the dynamics of cultural practices in a particular region.

A specific issue impacting on the sexual health of women is the tradition of **Female Genital Cutting** (FGC or FGM) [4, 7-19]. The origin of the practice of FGC cannot be traced. It has been attributed to religion, tradition and culture. The term Female Genital Cutting, which is gaining acceptance, is a culturally neutral term unlike female genital mutilation [9, 20-23]. The use of the term Female Genital Cutting is to be encouraged. Other terms used have been Female Genital Mutilation (FGM) and Female Circumcision (FC). The term **mutilation** is offensive to the involved population. The term female circumcision is clearly inaccurate and refers to the removal of part of the prepuce, if this were possible.

FGC is primarily a prepubertal custom or a rite of passage. It is a physical marking of a woman's marriage ability, the ensurance of virginity, and the formation of a chastity belt of her own tissue. This rite symbolizes the differences between the sexes and clearly establishes female identity. In some cultures, protecting the female child as a virgin clearly is very important. Her value increases; her lineage is clearly identified and she is saleable as a commodity. The perpetuation of this custom is difficult to understand since the risks to the health of women are so great. However, harm is not the intention. It is done to ensure that the daughters fit into the community and are marriageable. With time these traditional practices will be replaced [23, 24].

The term FGC represents **surgical excisions** from removal of the clitoral prepuce to complete removal of the clitoris and parts of the labia minora, and occasionally the majora, sutting the remaining tissue to occlude the external genitalia.

Women are fertile although sexual intercourse is impeded. Several providers have noted that pregnancy occurs despite the absence of a vaginal opening sufficient for penetration of the penis. This would suggest that sperm have somehow managed to access
the appropriate pathway from outside the vagina. One report states that intercourse may take place in some through a false vagina or through the anus [25-26]. Childbirth also requires appropriate care, including anesthesia and a mid-longitudinal cut, to avoid extensive tearing and obstetrical delay. In many areas infibulated women would have been prepared with deinfibulation in the second trimester [26].

Does FGC allow women to have a normal and fulfilling sexual relationship? The ability to “engage in a mutually fulfilling sexual relationship is an important element in reproductive health” [27]. It is not clear whether FGC allows women to have a mutually fulfilling sexual partnership. The role of FGC in the normal cycle of sexuality in women is unclear. It is also difficult to look with western eyes to sexuality in another culture. It is a known fact, however that in the South East of Nigeria, one of the reasons given by cutters and believers of FGC is that it will reduce the woman's libido. This occurs in a culture where the woman is not allowed to initiate sex or openly show she enjoys sex [28]. Although FGC is supposed to control sexuality before marriage these same women are expected to be sexually responsive to their spouses in marriage. It is reported, anecdotally, that men believe uncircumcised women are difficult to satisfy sexually. Dyspareunia may be universal. Coital difficulty or inability to have vaginal intercourse at all because of stenosis of the vagina may affect up to 35% of Pharaonically circumcised women. Some women interviewed in Sudan who had undergone FGC had no idea of the existence of an orgasm. It is probable that sexual pain disorders may play a role and have an indirect effect on desire, arousal and orgasmic sexual responses. Sexual dysfunction is highly associated with negative experiences in sexual relationships and overall well-being. Sexual complications include the pain and fear that may accompany sexual intercourse and can lead to marital problems [7].

Major sexual complications of FGC have not been researched; however, anecdotal reports confirm these problems.

More research in this area needs to be done to evaluate the contradictory and conflicting reports and evaluate differences between 'climax' and both clitoral and vaginal orgasms [14, 17].

Most immigrant women do not feel comfortable discussing intimate problems with health care workers they view as strangers. Toubia (1999) [19] cautions health workers to first assume that satisfactory sexual and emotional relationships exist in couples regardless of the degree of the woman's genital cutting.

a) Other traditional practices

Unlike the Western world, the perception of a lubricated vagina does not appear to be the ideal state in many African countries.

'Dry sex' refers to the preference for a dry, tight vagina during sexual intercourse [30]. Women in selected sub-Saharan African countries, e.g. Southern and Central Africa have been found to use a variety of drying agents to achieve these effects as well as vaginal incisions [29, 31-33-38]. These reports include the following Subsaharan countries: Malawi, Zaire, Zambia, Zimbabwe. That is, agents are thought to dry and tighten a woman's vagina, and also to serve as 'love potions' to attract sexual partners and ensure their faithfulness. Participants reported that drying agents had physical and psychological consequences.

Dry sex has been regarded as a necessary part of successful marital relations in some countries [34]. The practice appears to be widespread in Zambia irrespective of educational level. The major reason given by women for the practice is that it increases men's sexual satisfaction, it ensures marital fidelity, and it maintains the woman in a 'virginal' state - a state that is prized by men [34, 39].

The most common purpose of the herbs and other agents was to make the vagina tight for sexual enjoyment and to create friction during intercourse. These agents provided the necessary grip and rough surface needed for a pleasurable sexual experience for the man. It is presumed that these agents make the vagina small by drawing the moisture out of it, which also makes it dry [34].

Substances used include powdery herbs or agents directly on the vagina, insertion of the herb or agent for a particular length of time and wrapped in cotton wool, a clean cloth or a stocking before inserted, and at times a vaginal slit made to place the agents.

These agents were available from traditional healers (N'angas), sold at major bus terminals. Results suggested that the majority of the respondents in that study by Pitts et al [34] were against the practice. Women believed that the practice was a reflection of female oppression. In one Malawian study the use of these traditional practices of intravaginal herbs ranged between 35% of married women and 42% of prostitutes questioned [33].
The most common mode of HIV transmission is heterosexual intercourse. Implications of the ‘dry sex’ practice for AIDS prevention programs and development of new HIV prevention technologies are discussed. “Dry sex preferences clearly have implications for HIV risk. There was agreement among participants that condoms frequently broke when used in conjunction with drying agents. Participants primarily attributed condom breakage to excessive vaginal tightness. Lubricants were not routinely used during sex or with condoms. However, participants preferred the use of lubricated condoms when they used condoms. Although vaginal dryness was not found to deter the use of condoms, some women were reluctant to use condoms for fear of blocking the ‘magic’ of drying agents” [33].

b) What are these products?
These substances include herbs, chemicals, e.g. copper sulphate and fertilizers, and common household items [29]. They are frequently used, especially after childbirth, to make the vagina tight. One concept is that they make the body warm, dry and tighten the vagina and improve sexual drive [37]. A wet vagina can make embarrassing sounds during intercourse.

Drying agents include: non-traditional household or pharmaceutical agents, e.g., Vicks, love drops, tissue newspaper, cold water, dental antiseptic, tiger balm, alub powder, sugar and salt, ice cubes, Colgate toothpaste/Colgate and salt [29-30].

Although this practise appears harmful, especially when associated with other traditional practises, it should be remembered that there is a very high prevalence of bacterial vaginosis with associated secretions in these areas.

c) Summary
Changes in reproductive rights and information must change the culture of silence that has been associated with sex education and contraceptive understanding. Young girls must be informed about what FGC actually entails, and appropriate reproductive education to prevent infections. There are many challenges in understanding issues of sexuality for women in different countries. Traditional practices may have encouraged women to recognize, participate, and initiate sexual pleasure as a married woman. Although the traditional polygamous unions were life long and recognized under current statutes in many African Countries, the search for employment in Africa has moved millions of women and men. Many men have travelled to urban areas leaving behind families and creating new families in the cities for what may be temporary urbanized arrangements.

2. MALE PENILE CIRCUMCISION
About one-fifth of the world’s men have been circumcised, mostly for religious and cultural reasons [40-43]. The first evidence of circumcision comes from early Egyptian wall paintings that are more than 5000 years old. Its true origins and purpose are lost in the very earliest mists of time and it has persisted as a central feature of many cultures all over the world [44].

Circumcision is commonly performed for religious and cultural reasons shortly after birth or around puberty. Although adult circumcision is occasionally performed as an act of religious dedication, adulthood is the most common time that the operation is performed for medical reasons.

Non-religious circumcision is widely practised in the USA. At present, up to 80% of US males have been circumcised [41]. The incidence of neonatal circumcision in the US has fallen from 90% in the 1950s to around 60% today. In Korea, more than 90% of men have been circumcised, mostly without medical justification, usually in their teens and twenties (www.circumstitions.com last accessed September 18, 2003).

In the UK in 1948, around 20% of boys were circumcised shortly after birth. It was more prevalent in the south of England and was associated with higher socio-economic status. By 1975, the prevalence had fallen to 6%.

Reasons for circumcision fall into three broad groups
• Circumcision as an act of religious dedication
• Circumcision to prevent future disease
• Circumcision for an immediate medical indication

a) Circumcision as an act of religious dedication
The circumcision of male children is a common feature of both Judaism and Islam. It is also important in many African and New World cultures.

In Judaism, circumcision is a commandment and, for most Jews, there is no room for debate on the matter. In the book of Genesis (17:10-14), circumcision represents the covenant made between God and Abraham, and his descendants. It is repeated in the book of Leviticus (12:4), “On the eighth day the flesh of his foreskin shall be circumcised”. It would
usually be performed on the eighth day after birth, unless there were a danger to the child's health, in which case it should be delayed until that danger had passed. A father who delays or fails to circumcise his son might be considered to have betrayed the Covenant between the Jews and God. Traditional religious circumcision would be performed by a mohel (pronounced mo-hell in Hebrew or moyle in Yiddish). In the UK, mohelim undergo a period of training and will attend 40 to 50 circumcisions and have to pass practical and theoretical examinations before performing one alone, in other countries the Rabbi or a Jewish doctor performs the ritual depending on the legal situation.

Circumcision is not mentioned in the Holy Koran, but has the status of Sunnah (Prophet’s tradition). The divine law, or Sharia, defines every aspect of Muslim life. It is based upon the Koran, the Hadith (the sayings of the Prophet Mohammed) and the Sunnah. All Muslims agree that these are the three sources of Islamic law, but different groups interpret their application in different ways. Only the Shafiite school of law regards circumcision as obligatory (wajib), whilst the Hanafite, Jafarite, Malikite, Hanbalite and Zaidite regard it as only recommended, as it is Sunnah. Even those who consider circumcision an obligatory duty upon themselves do not see it as a legally essential requirement for others in becoming a Muslim. However, it is very widely practised and is certainly seen as an important external symbol of submission to God’s will.

An increasing number of committed Jews and Muslims reject circumcision on ethical grounds, although they are certainly in a minority at present. Attitudes to circumcision may provoke fierce hostility within families and amongst communities.

In Africa, two varieties of circumcision are commonly practised. Amongst the South East Bantu, in Central and Western Africa, the entire foreskin is removed at one stroke. Amongst the Masai in Eastern Africa, the foreskin is incised from the coronal sulcus to the preputial margin. Circumcision is seen as a central part of a ritual symbolising the transition from childhood to adulthood. During this period of transition, the peri-pubertal young man will often live apart from the family unit and village. Completion of the ritual is seen as necessary for them to become full members of their society and to marry.

b) Circumcision to prevent future disease
Prevention of disease is the next most commonly cited indication, although the evidence that it has any beneficial effect on future health is poor [45-46]. It is, more likely, rooted in cultural traditions, although the western medical communities may find this an uncomfortable conclusion.

Penile Cancer: Penile cancer is a rare disease and, in the early part of this century, was almost unheard of in circumcised men. However, the benefit may be related to the timing of circumcision and adult surgery may not offer any protection. Personal hygiene, smoking and exposure to human papilloma virus are at least as important as risk factors. As circumcised men are more at risk from penile warts, their risk of developing penile cancer is now approaching that of uncircumcised men. Routine circumcision cannot be recommended as a preventive measure against penile cancer.

Sexually Transmitted Diseases (STDs): There are far more effective and reliable methods of reducing the risk of contracting STDs than circumcision, such as the use of condoms and adoption of safer sexual practices, and it cannot be recommended as a preventive measure.

Human Immunodeficiency Virus infection (HIV): There are conflicting views on the role of circumcision in the prevention of HIV infection. A review in the British Journal of Urology concluded that there is no link between the foreskin and HIV infection whilst another in the British Medical Journal takes exactly the opposite view [47]. Circumcision may be appropriate as a routine preventive measure in countries where there is a high prevalence of infection, such as sub-Saharan Africa. There is inadequate evidence to recommend it as a preventive measure in other parts of the world.

c) Sexual Function and Penile Circumcision
Two recent studies had conflicting conclusions, one (prospective) with 15 adult men with foreskin problems (phimosis, balanitis) [48], and the second retrospective with 43 adult men (responding out of 123 men), who also for medical reasons had circumcisions performed [49]. Both studies included questionnaires related to erectile and ejaculatory function, and sexual interest. The prospective study concluded that circumcision does not have adverse effects on male sexual function, while the retrospective study concluded that worsened erectile function and decreased penile sensitivity occur after the surgical procedure. The committee has not been able to identify any properly conducted studies regarding physiological function of the penis in adult men who have been circumcised as infants, compared to uncircumcised men.
d) Conclusions

Circumcision will remain a controversial procedure, as it has already been for thousands of years. Male circumcision is perceived as vitally important in some religious and cultural groups. Hopefully, the use of general anaesthesia in infant circumcision will increase and medical and religious authorities should work together to promote this change.

There are very few absolute medical indications for circumcision, and none for routine circumcision outside of areas with a high prevalence of HIV infection. Far too many circumcisions are performed without good reason in Europe and the USA and this practice should be deprecated. The best advice is “if it isn’t absolutely necessary, don’t circumcise”.

3. THE ETHICS OF PENILE ENLARGEMENT SURGERY

The 1st International Consultation on Erectile Dysfunction (Paris, 1999) only recommended surgery in patients with stretched or erect penile length of < 7.5 cms or in men with a flaccid length of < 4 cms. The committee noted a significant and growing number of men with normal penile dimensions demanding penile enhancement surgery and sadly this trend has continued.

Many men do not consult their GP’s regarding concerns about penile size but often respond directly to advertisements placed in newspapers and male magazines by private clinics. Dissatisfaction with the results of surgery is high, as is the complication rate. Problems are mainly associated with inappropriate case selection and by the severe limitations of the surgical procedures offered.

Some men who seek so-called penile enhancement surgery suffer from a body dysmorphic disorder or from social phobia and social anxiety disorder. These men require assessment by a psychiatrist or other appropriate specialist with a particular interest and expertise in sexual problems, who works independently from the surgeon who might perform the procedure.

The independent specialist should, when it is appropriate, provide the surgeon with a letter of recommendation for surgery, giving a comprehensive account of the patient's mental and physical health, together with any relevant information on social and relationship issues. We consider that it is unethical to operate on men with a penile size within the normal range for financial gain.

III. EDUCATIONAL ASPECTS

1. UNDERGRADUATE TEACHING AT MEDICAL SCHOOLS

In a recent study on sexual health training in medical schools in the USA and Canada, the 141 medical schools in the U.S. and Canada were surveyed and 101 valid responses were returned. A total of 84 respondents (83%) used a lecture format. A single discipline was responsible for this teaching in 32
(31%) schools, but a multidisciplinary team was responsible in 64 (63%) schools (five schools failed to respond to the question). The majority (54%) of the schools provided 3-10 h of education. Causes of sexual dysfunction (94%), its treatment (85%) altered sexual identification (79%) and issues of sexuality in illness or disability (69%) were included in the curriculum of 96 respondents. Only 43 (42%) of schools offered clinical programs, which included a focus 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 conclusion, expansion of human sexuality education in medical schools may be necessary to meet public demand for an informed health provider [69].

In a survey of 25 UK medical schools’ teaching on ED to undergraduates, only 9 indicated that the subject was covered within their curriculum and only 5 provide significant exposure within an integrated programme of teaching on sexuality. The others stated that ED is covered by a 30 - 60 minute lecture, either during urology or gynecology attachments.

In a global survey undertaken in collaboration between ISSIR (Int. Soc. for Sexual and Impotence Research), WHO, and World Federation of Medical Education (WFME), it can be tentatively concluded that approximatively 30% of medical schools have no educational programme in human sexuality or Sexual Medicine. Fifty per cent have less than 10 hours teaching and it seems mostly related to reproduction.

The disciplines mostly involved in teaching are Gynecology, Psychiatry and Urology: 15% have more than 20 hours of teaching with multidisciplinary faculties.

Thus, the need for intensifying undergraduate teaching, including an actual curriculum, is clearly demonstrated in these surveys.

An initiative taken by ISSIR’s educational committee (www.issir.org) has the purpose of creating a globally applicable curriculum (www.medsexedu.net)

This committee recommends an intensified global strategy in the future teaching of medical doctors in Sexual Medicine.

Training of Health Professionals in Sexual Health, as suggested by PAHO (the America’s regional WHO), 2000.

Basic sexual health education should form an obligatory part of the learning requirements for all health professionals.

The committee suggested that a minimum requirement for basic education in Sexual Medicine for health professionals should be developed for those training in each disciplines (medical, nursing, health promoters, etc.) This educational programme should involve activities that will lead to the acquisition of an appropriate level of knowledge and skills, together with the opportunity to develop appropriate professional values and attitudes towards sexual and sexual health.

A number of suitable learning programmes have already been developed by several institutions around the world. The implementation of a particular programme in any country must take into account the specific needs of that country or region.

In any case, it 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 and, if necessary, referring to the appropriate professional, problems of sexual health.

It was also agreed that there is a need for the establishment and support of continuing education for established health professionals. This is particularly important because of the relative “newness” of sexual medicine and our rapidly changing understanding of sexuality, sexual function and its problems.

This committee believes that there should be a requirement for health professionals specializing in sexology and sexual medicine to undertake a specified training programme appropriate to their discipline. Its content might include:

Knowledge

- Basic sciences
- Psychology
- The biological basis of human sexuality
- Sexual development
- Sexual identity and orientation
- Gender identity
- Sexual behaviour
- Sexual dysfunction
- Therapeutic interventions for sexual dysfunction

Basic sexual health education should form an obli-
Sexual medicine
Sexual surgery
Sexual counseling
Sexual psychotherapy
Sex and society
Sex and reproductive health
Sex and ageing
Sex and the effect of medical problems and their treatments
Medico-legal aspects of sexuality and sexual behaviour
Ethical aspects of sexual medicine
Sexual research

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

Such programmes, whether at a basic level or for the specialist, should be properly validated and supervised by an appropriate academic authority.

2. Problems of both education and information

For the last few years, several epidemiological studies of erectile dysfunction (ED) in many nations around the world have given a clear indication of the following facts. 1) Its prevalence increases with age and various chronic morbidities, explaining its important place among the general population. 2) It is a symptom and is relevant to the individual’s overall state of health (not only sexual, but also psychological and physical). It also influences the general sense of well-being and quality of life of both men and their partners. 3) Despite its increasing prevalence and increasing demand from patients, ED remains under-diagnosed and under-treated by doctors. The reasons for this paradoxical situation are related to lack of knowledge about ED and sexuality amongst those affected, difficulty with communication about sexual matters between men, their partners and health professionals, lack of understanding of the importance of sexuality by society in general, and lack of appropriate training on sexuality and its problems amongst medical and other health professionals.

a) Lack of information in the general population. France as an example

Despite the definition of sexual health by the World Health Organisation as early as 1974 and the recognition of the need for educating the general population, the reality is that sexual education at school has shown little, if any, development in most countries, primarily for socio-cultural reasons. Such education often focuses on reproductive health, and the prevention of sexually transmitted disease and pregnancy. It rarely, if ever, deals with the taboo issues of “sexual desire and sexual pleasure”. If sex education causes anxiety, it’s because it makes people face the “matter-of-fact”, practical reality of their sexuality, rather than conceal it within strong social rituals and taboos. It remains hidden and is often not spoken of, between partners, between parents and children, between patients and their doctors. The consequences of this failure to acknowledge sexuality as just another facet of normal human experience is well-illustrated by two global events. 1) The global spread of HIV infection and AIDS since the 1980s has been exacerbated by an unwillingness to talk openly about sexual behaviour in general, and the promotion of safer sexual behaviours in particular. 2) The availability of an effective oral therapy for ED in 1998 revealed major learning needs for health professionals, health policy makers and the pharmaceutical industry. Apart from a small circle of specialists, these groups were largely ignorant of ED and its relationship to a wide range of other health problems, such as diabetes and cardiovascular disease. This initially led to a focus on genital function, rather than the broader implications of sexual dysfunction for health, the family and society at large.

Deficiencies in sexual education are not only responsible for misunderstandings amongst adults about sexuality and its problems but also amongst young people. There are numerous, unhelpful myths about sex that are too often perpetuated by the media. Sex education in France provides a good example of these difficulties. In France, the provision of education about sex in school began in 1947, with the provision of information on reproductive health and STDs from 1975. Initially, the advent of AIDS revolutionised French society’s attitude towards sexuality, and was one of the most important factors behind the conduct of a national inquiry into the sexual behaviour of French people. However, the information about sex offered was very quickly limited to that required for the prevention of AIDS and STDs.
In fact, an evaluation of sex education activities in schools between 1988 and 1993 showed that teenagers wanted to know about far more than sexual biology and contraception, and that the information given was not sufficient to change their sexual behaviour [53]. In 1996, sex education in school was made compulsory for young people aged 14-15 years. Schools were required to teach a minimum number of hours on sex education and to distribute specific educational materials to students. The Ministry of National Education defined the aims of this education programme as: for students to develop personal responsibility in their sexual behaviour and in relationships with others; for students to understand the principle of sexual equality between men and women, based on humanist criteria of tolerance and liberty, self-respect and respect for the dignity of others. Education in school was intended to be complementary with sex education at home, giving teenagers the opportunity of obtaining knowledge and understanding of the different dimensions of their sexuality, their personal sexual morality, and their right to intimacy [53]. Nowadays, nearly half the secondary schools in France have implemented this programme, involving 600,000 French teenagers every year.

b) Inadequacy of initial and post-graduate medical and paramedical education

ED is increasingly becoming, at least in developed countries, a major public health problem. This might be for the following reasons:

Medical: ED may be the first symptom of many chronic health problems and its onset can be a major motivating factor for men to seek medical advice, providing the opportunity for both primary and secondary prevention.

Social: In an aging society, people expect to enjoy good health and quality of life into old age. They are less likely to accept disability and ill-health than earlier generations.

Economic: The high and increasing prevalence of ED inevitably increases the cost of healthcare, whether it is funded by the individual, the state or an insurer. The increasing medicalisation of sexual problems and the focus on genital function contributes to this trend.

There is increasing demand for both information about sexuality and its problems, and for medical care for those problems. However, many doctors and most healthcare systems are ill-equipped to deal with sexual problems, and, in most countries there are few specialist clinics and health professionals have inadequate training to meet the needs of their patients. In reality, until 1998, undergraduate and postgraduate education about sexual health was mainly concerned with the prevention of STDs, with contraception, reproduction and sexual offenders. The arrival of sildenafil in 1998 revealed large gaps in the knowledge of many health professionals about sexual problems and quickly revealed the need for education: a) to augment the knowledge and skills of specialists already involved in ED care (urologists, andrologists and sexologists), b) to inform and promote the interest of generalist and specialist doctors with no previous knowledge of ED, many of whom knew little about the association of ED with other health problems or its effect on quality of life c) to educate and inform both the media and patients. The pharmaceutical industry played an important, responsible and useful part in facilitating basic science, clinical and epidemiologic research, as well as in the development of educational initiatives. However, there were concerns that these matters should not be left solely to the pharmaceutical industry and that education and research should properly be led by independent academic bodies and health professionals.

These concerns led many professional societies, and national and international institutions (WHO, ICED, ISSIR, WAS), to develop evidence-based guidelines for ED care. It was considered important to make such information as widely available as possible, to better inform those providing care for the first time in such a sensitive clinical area. This was related to the following issues:

a) Individuals' sexuality and sexual behaviour are quite diverse, influenced by social, cultural and religious factors, which should always be carefully considered and respected. For example, the development and discussion of sexual problems may have a different significance in northern and southern Europe (Anglo-Saxon, Protestant and Latin, Catholic worldviews) for cultural reasons, and in Eastern and Western Europe for economic reasons.

b) Sexual behaviour is not entirely innate and is, to some degree, learned.

c) Patients may perceive non-sexual health problems as being more important and worthy of professional help than sexual problems. Sexual problems may remain hidden by many men and women because of the difficulty and discomfort they experience when
asking a stranger for advice about something so intimate and personal. Many men will wait several years before asking a doctor for help with ED.

d) The function of a doctor in dealing with a sexual problem goes beyond treating the physical problem alone. They also help by listening to their patients' concerns, by dispelling myth and misunderstanding, by removing fear and by promoting a positive attitude towards sexuality and intimacy.

The undergraduate and postgraduate teaching of sexuality and its problems to doctors in France is a good example of the deficiencies and difficulties encountered, but it also suggests some possible solutions. In 1998, in response to the intense media interest in sildenafil, two official reports were requested by the Ministry of Health: (1) a review of the “treatments of impotence and its taking over” [54], and (2) a remarkable notice from the National Consultative Ethic Committee for the Sciences of Life and Health (CCNE). These reports clearly established the necessity for information about ED and the education of doctors [54], as the number of hours devoted to sexuality in undergraduate medical training was small. Postgraduate education, consisting of one to three years inter-university or university diploma courses in sexology and andrology was accessible to only a limited number of generalists and specialists. This led to the development of innovative educational programmes by French scientific societies involved in the field of ED, in partnership with the pharmaceutical industry. Objectif Dysfonction Erectile (ODE) was developed in partnership with Pfizer. This programme was led by three national scientific societies (urologists, andrologists and sexologists), and gathered together specialists in ED from different disciplines, with the production of a consensus statement on ED care and a range of educational materials. ODE was, as far as we know, one of the first national educational programmes with a multidisciplinary consensus approach. At least one thousand specialists and ten thousand generalists participated in eight hundred meetings all over France during 1998. Nevertheless, ODE was more a program to quickly provide information about ED than broader education about sexuality for doctors. The second step, in 2000, was to carry out more specific educational opportunities. These included a) practicing consultation and sexual history-taking skills through role play (Dialogue et Sexualité program, in partnership with Pfizer) ; b) interactive seminars using e-learning (Uroform program, in partnership with Pfizer) ; c) individual learning, using CD-ROMs, for both generalist and specialist doctors (road-map, in partnership with Sanofi Synthelabo); DEF1 program (in partnership with GSK-Bayer).

The third step is a national project to provide information and education to a larger audience. This project (EFITEA) is currently in development and involves several scientific societies and national institutions, working in collaboration with patient associations and the pharmaceutical industry. Its objective is to give an easily accessible, consensus-based reference work on ED, to meet the specific requirements of French-speaking people.

c) Conclusions

There is a pressing need to inform and to educate not only health professionals but the public, too. Unfortunately, the lack of adequate sex education both at school and in universities leads to frequent misunderstandings about sexuality and its problems. Sex education must meet the needs of modern teenagers, so that they can understand and enjoy their own sexuality, respect the sexuality of others, and practice responsible sexual behaviours. The huge amount of information now available, and the rapid scientific progress in our understanding of the causes, treatment and complexity of sexual problems require that we develop evidence-based information and educational activities that are both appropriate to and respectful of cultural specificities. For all these reasons, both information and formation are no longer the privilege of a small group of people, they are now the responsibility of everyone. We must urgently promote the cooperation of all the major players in the world of health and communication. We should try to develop a network of specialists and generalists, involving scientific societies, basic scientists and, perhaps, pharmaceutical laboratories, too. [50-54]

3. HEALTH (SEXUALITY) INFORMATION ON THE WEB

At present there are more than 10,000 health sites on the Internet. We have no easy way of finding our way through them, nor can we be sure about the accuracy or reliability of the information [55-60]. Millions of people do not have access to accurate, clear and current information about sexuality. These same people take enormous risks with their sexual health. As consumers increasingly rely on the web for answers to health questions, the medical community is increasingly concerned about the value of the e-health information [61-62]. Many have reported considerable variability in the accuracy and completeness of health information on the internet [63-
Public sex education is perhaps the most important health-related web information available. The question is, how can one grade the quality of this information?

Regulatory action by many governments is limited to oversight of product-related health claims. In the United States the Federal Trade Commission, the Food and Drug Administration, and the Department of Justice provide US consumers with limited oversight of product-related health claims made on the Internet.

Other countries, such as France and Germany, have tried to address the problem of how to grade available health-related web information (AFGIS, 2003). In a wider-reaching effort, the Information Society Directorate-General organized a workshop for the European Commission of the European Union (ECISDQ, 2003).

There have been other attempts to set criteria which include:

http://europa.eu.int/information_society/eeurope/ehealth/quality/draft_guidelines/index_en.htm

The following are examples of good sexuality information on the web:

http://www.ippf.org/ - the sexwise project.
http://www.who.int/search/en/
http://www.who.int/reproductive-health/index.htm
http://www.healthfinder.gov/justforyou/

All around the world millions of people, especially young people, do not have access to accurate, clear and up-to-date information about sex. They are unable to make choices, and they take enormous risks with their lives and sexual and reproductive health. Thousands die as a result each day. (For example, 2.6 million people died of HIV/AIDS in 1999 and, every year, 600,000 women die from complications of pregnancy and childbirth).

Using the effective communication medium of radio, the Sexwise programmes and accompanying books provide listeners with unbiased and accurate information, presented in an accessible style and in local languages.

The issues covered in the BBC Sexwise radio programmes and books have been discussed with IPPF's staff and its network of national Family Planning Associations (FPAs) around the world (www.bbc.co.uk/worldservice/sexwise)

The BBC producers have consulted and worked closely with FPAs on the ground who have assisted with information and relevant people to interview. It is the FPAs, too, who will ensure follow-up support to listeners, including hotlines, counselling and services, as well as distribution of books on request.

The BBC has created a Sexwise website: www.bbc.co.uk/worldservice/sexwise/ which also provides links, information and advice to thousands of online users.

Started as a pilot project in 1996, Sexwise programmes in 8 languages reached millions of listeners to the BBC in South Asia and generated an enormous amount of feedback: 75,000 listeners wrote in to seek further information and to request copies of the accompanying Sexwise books.

The IPPF/BBC Sexwise project is funded by the David and Lucile Packard Foundation (USA), the UK Department for International Development (DFID) and the European Commission. London, June 2000.

The Internet can be a valuable resource for users seeking health information. The quality of this information is critically important as it could potentially affect health outcomes for millions. Yet the quality of health information on the Internet is extremely variable and difficult to assess. Thus the choice of appropriate evaluation criteria for the information is both crucial and challenging. This problem is generally recognized. There is no consensus, however, on how to resolve the problem, and there remain no uniform guidelines for quality assessment of Web-based health information for consumers. A number of websites display rating schemes, and there are “stamps of approval”, but there is little explanation of how those schemes were developed or how the ratings have been applied.

To address this problem, the Health Information Technology Institute of Mitretek Systems convened a Health Summit Working Group.

a) Methods and Process

The Health Information Technology Institute convened a one-day Health Summit Meeting in 1996. To ensure objectivity in the development of the criteria, 18 individuals with diverse backgrounds, including leaders of medical schools, libraries, pharmaceutical associations, government agencies, professional medical associations, and consumer groups, were invited to attend. The meeting consisted of a series of presentations, open discussions, and breakout groups, and resulted in the initial identification of
potential criteria and their strengths and weaknesses, as well as a list of items for future action. Additionally, participants in the meeting developed the preliminary draft of this policy paper that was presented for comment as described above (http://hitiweb.mitretek.org/docs/criteria.htm) [68].

The next step in the process was to rank these initial criteria in order of importance. Members of the Health Summit Working Group and other individuals and organizations were invited to provide their suggested rankings. The criteria were categorized as either “Essential”, “Important”, or “Desirable”, and these ratings served as a starting point for further refinement of the criteria at the second Health Summit Meeting.

The second Health Summit Meeting was convened in 1997. Participants included those who attended the first meeting, as well as many newly recruited individuals. The purpose of this meeting was to develop an implementable set of criteria (based on the policy paper) for use by the general public. The participants first reviewed and identified those criteria capable of being implemented, and then further refined these criteria into a usable question-answer rating format to be incorporated into a tool developed by the Health Information Technology Institute. In breakout sessions, participants worked on an implementation strategy and identified next steps, which included testing of the tool by volunteers from each of four working groups comprising consumers, librarians, health-care providers, and website developers.

The criteria set by a Health Summit Working Group convened by the Health Information Technology Institute of Mitretek Systems are:

**Credibility**: includes the source, currency, relevance/utility, and editorial review process for the information.

**Content**: must be accurate and complete, and an appropriate disclaimer provided.

**Disclosure**: includes informing the user of the purpose of the site, as well as any profiling or collection of information associated with using the site.

**Links**: evaluated according to selection, architecture, content, and back linkages.

**Design**: encompasses accessibility, logical organization (navigability), and internal search capability.

**Interactivity**: includes feedback mechanisms and means for exchange of information among users.

**Caution**: clarification of whether site function is to market products and services or is a primary information content provider.

b) Summary of the Health Summit Meeting

The Internet presents a powerful mechanism for helping users improve their health-care decision making by providing easy and rapid access, exchange, and dissemination for enormous amounts of health information. Yet users must be aware of the potential for misinformation and recognize the critical need to assess the quality of the information provided. Content providers must be encouraged to develop and post high-quality information, and policymakers and health-care professionals must be educated on this important health issue. The Health Summit Working Group has developed this set of criteria to address this critical need. These criteria are intended as a resource for users seeking health-related information on the Internet, and should aid in evaluating information to determine whether it is usable and credible.

The complete white paper can be found at the Mitretek web site: http://hitiweb.mitretek.org/

The European Sexual Dysfunction Alliance (ESDA) is an umbrella organisation with the aim of developing patient groups or publicly accessible Knowledge Centres across Europe.

The aim is to raise awareness of the incidence of sexual dysfunction in men and women and to educate sufferers and their partners, health professionals and the media on the treatments available. Each patient organisation or Knowledge Centre is run independently and gives advice and information via a telephone help line.

Patient organisations are currently available in Denmark, France, Germany, Greece, Ireland, Israel, Italy, Portugal, Spain, Sweden, Turkey and the UK. http://www.esda.eu.com

Draft Guidelines on Quality Criteria for Health Related Websites can be found at:


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Committee 4

Economical Aspects of Sexual Dysfunctions

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Economical Aspects of Sexual Dysfunctions

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INTRODUCTION

The limited data available suggests that the economic impact of ED and other sexual dysfunctions has increased significantly during the past several years. The reasons for this increase are: an increase in the number of people at risk; introduction of new drug therapies; introduction of more palatable therapies (oral therapy); increased interest in aging-related quality of life, and increased awareness and education. This increasing economic impact is expected to accelerate with the further growth and aging of the population of the world. There are still many unknown important issues in the economical aspects of ED and other sexual dysfunctions. A great deal of further research is needed to gather data on the economics of ED and other sexual dysfunctions. Moreover, more information is needed to determine ethnic and cultural variations in the economics of these disorders as well as the impact of their treatments on groups and society. Thus, studies should not only be cross-sectional but also longitudinal because of the accumulative impact of ED and sexual dysfunctions and the unknown long-term issues such as patient behavior. Cost-effectiveness considerations may help in refining ED and other sexual dysfunctions management algorithms. Drug combination and drug comparative studies might shed light not only on the efficacy and safety of therapy, but also might help in avoiding unnecessarily expensive and ineffective combinations.

The mission of the Committee on Economical Aspects (the Committee) is to identify, research, summarize and report on all medico-economic issues related to erectile dysfunction (ED) and other male and female sexual dysfunctions. 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 subjects is fundamental in the description of the economic consequences.

2. Analytic economics. This involves the search for the 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. The chapter focuses mainly on erectile dysfunction as registered therapies have been available for over a decade. There are very few therapies specifically registered for FSD. Tracking the drug prescribing practices specific for FSD is by consequence approximate at best and, in many cases must be estimated based upon prevalence data for the types of FSD being studied.

I. EPIDEMIOLOGY OF SEXUAL DYSFUNCTIONS

Sexual dysfunction (SD) is a worldwide problem whose prevalence will probably continue to rise due to population growth, the aging population and an increased awareness of SD. Modern medicine and public health has increased life spans, affording couples a more sexually active life but at the same time increasing the number of people at risk for sexual dysfunction. SD is a broad term that includes many male and female sexual disorders. Male SD
involves such problems as erectile dysfunction (ED), Peyronie's disease, early (premature, rapid) ejaculation, desire disorder, hypogonadism and priapism. Female sexual dysfunction (FSD) includes problems such as lack of desire, arousal and orgasmic difficulties, and dyspareunia. Therefore, for a better understanding of SD epidemiology, it is important to divide the subject into two groups, male and female SD.

1. MALE SEXUAL DYSFUNCTION

The Massachusetts Male Aging Study (MMAS) suggests the number of men in the USA with ED to be 10-20 million [1]. This estimate may reach 30 million by including patients with partial ED. It is estimated that 617,715 new ED cases will be reported annually in the United States (white males only) [2]. Considering the reality of availability of data, the main focus of this review will be on erectile dysfunction (ED). The world prevalence of ED is projected to double through the 30 year period that runs from 1995 to 2025 [3]. On the other hand, it has been estimated that 70% of all ED is undiagnosed [4] and that, historically, only 5% of men with ED had received medical attention [5].

In a global study of sexual attitudes and behaviors, 83% of males responded that sex was moderately to very important in their overall life [6]. Through the last 12 months prior to the study, 57% of male respondents declared having sex 1-6 times per week. A high proportion of older men somewhat to strongly disagreed with the statement that they no longer have (65%) or want to have (64%) sex [6]. More than twenty studies have been published in the last five years reviewing the prevalence of ED in the general population, in both national and international surveys. Some studies obtained the requested information through a self-administered questionnaire while others used a direct interview. The percentage of ED patients reported by the different studies is more or less uniform for each age group, although there are significant differences in the prevalence of ED presented by each study regarding a specific age group. The reason for these differences may be a non-uniform definition of ED and variations in the design of the ED questionnaire. Although most authors use the consensus definition of ED [7], other refer to ED as “impotence”, “erectic difficulty”, “erectic disabili- ty” or “erection problems” [8]. Another reason for the different data of ED prevalence reported by different authors may be the different of measuring scales for male sexual function or dysfunction, as presented in Table 1.

The prevalence of ED is not the same in different countries or continents and among different ethnic groups. The prevalence rates for mild and severe ED has been reported as 35% in the United States, 26% in Finland, 21% in Italy, 12% in France and 11% in Spain [6, 10]. In Malaysia, Low et al reported a difference in the concept of ED and its prevention and treatment among males from three different ethnic groups living in the country, Malay, Chinese and Indian, without reporting the percentages of each group [12]. Among men consulting for ED in Israel, a multi-ethnic country, 13% were Israel- born, 33% immigrants from North African (Morocco, Libya, Yemen) or other Middle East countries (Iraq, Iran)

Table 1. Some of the different measuring scales for male sexual function or dysfunction.

<table>
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<th>Scale Description</th>
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<tr>
<td>MMAS (Massachusetts Male Aging Study)</td>
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<td>IIEF (International Index for Erectile Function)</td>
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<td>LSC (Life Satisfaction Checklist)</td>
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<td>Erection Distress Scale</td>
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<td>Psychological General Well-Being Index</td>
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<tr>
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and 54% came from North and South America and Europe, respectively [13]. The Cologne study shows an important difference between an overall ED prevalence of 19.2% among 71.3-96% men being involved in regular sexual activity, and 31.5-44% of responders who were dissatisfied with their current sex life [9]. The prevalence of ED may be different depending on the system used to perform the evaluation. ED prevalence has been reported as 12-25% on the basis of self-evaluation as compared to 19-31.6% according to IIEF criteria [11, 14].

Although there is much data on the prevalence of ED, there is little information regarding the incidence of drop out from treatment programs or discontinuation of follow-up visits. Among 4489 responders in the Cologne study, 46.2% were willing to contribute financially towards the cost of a regular treatment for ED [9]. On the other hand, 9 to 25% of sildenafil responders discontinued successful treatment because of medication cost [15-16].

In order to obtain accurate data of ED prevalence, it is important to build uniform reports with uniform nomenclature. There should be consensus in the nomenclature of the severity of ED. The prevalence of ED should be always calculated among groups of the same age range.

In the first US population-based survey of men, aged ≥ 40 y.o, 19% of 1320 men without ED reported “always” or “usually” ejaculating prematurely. Regardless of ethnicity, 50% of participants reported sometimes ejaculating too soon, and 9% reported ejaculating before vaginal penetration. Surprisingly, a small percentage of men considered this a major problem for themselves or their partners. Only 1% of men had received treatment for premature ejaculation (PE) ; however, 1/3 would consider therapy. No drug is approved by the FDA for the treatment of PE. SSRIs and drugs with SSRI-like side effects are safe and effective used to treat PE. Desensitizing creams containing local anesthetic agents are also used as OTC. The exact economic size of the PE market is not known [17, 18].

The prevalence of early (premature, rapid) ejaculation varies widely between different countries and with different methods of assessment. The Keele (UK) study reported a prevalence of 18%, with less than 50% of sufferers wishing treatment. Prevalence in the Middle East and Japan have been reported as high as 45-50%. Inhibited sexual enjoyment was reported by 15% of subjects in the Keele Study with little or no published data on the prevalence of delayed or other ejaculatory disorders.

2. FEMALE SEXUAL DYSFUNCTION (FSD)

FSD is an important health concern which may affect the quality of life significantly. Its etiology includes medical and psychological factors and it is often untreated. Similar to ED, FSD may be age related, having a prevalence of 20-50% [17]. Based on Masters and Johnson's studies [18] female sexual response includes the following 4 phases: sexual desire, sexual excitement, orgasm and resolution. The 'Diagnostic and Statistical Manual of Mental Disorders' (DSM-IV), in its fourth edition, defines FSD as ‘disturbances in sexual desire and in the psychophysiological changes that characterize the sexual response cycle and cause marked distress and interpersonal difficulty' [19].

Sexual desire disorders include low desire, with a prevalence of 33.4% of women between the ages of 18 and 59 [20] and sexual aversion disorder, of which the prevalence is currently unknown. Sexual arousal disorders, characterized mainly by vaginal dryness, have been reported in 20% of women between the ages of 18-59 [10]. Orgasmic disorder may be primary (anorgasmia) or secondary [18]. Anorgasmia has been reported in 24-37% among sex therapy samples [20]. Sexual pain disorders include dyspareunia and vaginismus. Dyspareunia has been experienced by 14.4% of women during sexual activity [10]. Vaginismus appears in 15-17% of women presenting for treatment [21].

As with male SD it is vital to establish more accurate definitions and standardization of female sexual disorders in order to make epidemiologic comparisons in cross-cultural studies. Moreover, further research concerning the risk factors, impact on quality of life and development of effective treatment solutions are needed before the economic impact of these disorders will be fully appreciated.

II. AGING AND SEXUAL DYSFUNCTION

“A man is as old as his arteries” - Sir William Osler. Since the penis is a vascular organ, it is true that a man is as old as his penis. The classical work by Kinsey [22] revealed that aging is a key risk factor for the development of male erectile dysfunction. In his pioneering work the prevalence of erectile dysfunction increased with age from 0.1% at 20 years of age to 75% at 80 years of age. A half century later, the
Massachusetts Male Aging Study (MMAS) [1] showed the same trend. Namely, the prevalence of erectile dysfunction increased from 39% in men in their 40’s to 67% for men in their 70’s. Using the same questionnaire as used in the MMAS study, the cross-national epidemiological study was conducted in four different countries with varying cultures; Brazil, Italy, Japan and Malaysia [23]. The results confirmed the findings of the MMAS with an age-dependent increase in the prevalence of erectile dysfunction in these different countries.

The world is getting older and older, especially in developed countries. Japan is the most aged and still aging country in the world. You can see the future of the rest of the world by studying what is happening in Japan. The ministry of the Health and Welfare of Japan has projected that the percentage of the population over age 65 years will represent as much as 20% by the year of 2010. The French, German and Swedish people will have a similar distribution based upon age by the year 2020. The British and American populations are lagging and thus will not reach that mark, 20% of the population over 65 years old, until the year 2030. Since age has been shown to be a significant risk factor for all types of sexual dysfunction, we anticipate with the growing population over 65, an enormous number of patients with either ED or sexual dysfunction (Figure 1).

Another key factor is treatment-seeking behavior. A striking example for how aging affects treatment-seeking behavior is the marketing of sildenafil in Japan. Despite the fact that Japan has a significant aged population, the sales of sildenafil have been disappointing on a per capita basis. Only 800,000, or 8 % out of the estimated 10,000,000 patients, received prescriptions for sildenafil [23]. This is especially surprising since neither Caverject nor MUSE is available in Japan. Shabsigh and colleagues reported the treatment-seeking behavior in 6 different countries (USA, France, Germany, Italy, Spain and UK) (Figure 2) [24]. They showed the treatment-seeking rate has a peak during middle age except in the USA. The most common reason for the older age group to not seek treatment is their impression that “ED is a natural part of aging”. 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 each culture. However, if we manage to eliminate this kind of stigma by educating the medical professionals and the lay public especially among the older people, the cost will be much higher.

According to the United Nations (UN), there will be over 356 million men worldwide aged over 65 years by 2025, an increase of 197 million from the current number. In 1995, the global proportion of men aged over 65 years was 4.2%, this is set to rise to 9.5% by 2025. Given the correlation between ED and age, global ageing will bring an increase in the number of men with ED in the future. ED is commonly associated with ageing and age related health problems; vascular, hormonal, neural, psychogenic factors, side effects of therapeutic drugs. Current data on ED among the healthy population, in particular for physiological and psychosocial variables, is extremely lacking, despite the prevalence and implications of ED on quality of life.

1. ERECTILE DYSFUNCTION

Erectile dysfunction is common in men with cardiovascular disease and is probably brought about by

![Figure 1: Projections of populations ≥ 65 years old.](image1)

![Figure 2: Prevalence of treatment seeking among ED sufferers.](image2)
shared factors that impair the hemodynamic mechanisms. The majority of ED patients have at least one significant cardiovascular risk factor, for example hypertension, diabetes mellitus, smoking or hyperlipidemia. Therefore, vasculogenic erectile dysfunction may be the harbinger of a systemic vasculopathic state. MMAS results showed the age-adjusted probability of the onset of moderate ED increased from 6.7 to 25% as high-density lipoprotein cholesterol decreased from 90 to 30 mg/dl in younger men (40-55 yrs), and from 0 to 16% in older men (56 to 70 yrs) [1]. In the study, heart disease and associated risk factors, hypertension and low serum high-density lipoprotein were significantly correlated with ED [25]. In a study by Oaks and Moyer, it was reported that 8-10% of all untreated hypertensive patients were impotent at time of diagnosis of hypertension. Furthermore, Wabrek and Burchell reported that in a group of 131 men with acute myocardial infarction aged between 31 and 86, 64% were impotent and in a study of patients who underwent coronary artery surgery 57% were mostly impotent. Several studies on impotent men reported that the number of abnormal penile vascular findings significantly increased when history included vascular risk factors.

Diabetes is another major illness associated with ED. In the MMAS sample the age-related probability of complete ED was three times greater in patients with diabetes than in those without. Other studies using diabetic populations, have consistently found a high prevalence of diabetes related ED, with estimates ranging from 35 to 50% and up to 75%. The prevalence of ED in diabetes has been reported to increase from 15% in men aged 30 to 35 yrs and to 55% at age 60 yrs. ED occurs at an earlier age in people with diabetes than in the general population and often follows, or leads to, the diagnosis of either insulin-dependent or non-insulin dependent diabetes.

The exact link between ED and depression is not well defined, as its significance is two fold; depression can be both a cause and an effect of ED [26]. Depression has a number of ED correlated symptoms; changes in sleep patterns, decreased interest in and response to pleasurable activities, and anticipation of a negative outcome. However, depression brought on by episodes of ED may perpetuate erectile failure, cause deeper depression, and may result in the avoidance of sexual opportunity even with an effective treatment. In the MMAS study, patients with depression had a 1.82 higher chance of developing ED than patients who did not suffer from depression.

The link between cigarette smoking and erectile dysfunction is not clearly understood [27, 28]. The MMAS sample did not show a significant difference in cases of erectile dysfunction between current smokers and non-smokers. However, the association of ED with certain risk factors was greatly amplified in current smokers. According to MMAS data analysis, the age-adjusted probability of complete ED in subjects treated for heart disease was 56% for current smokers, compared with 21% for non-smokers. Furthermore, The Vietnam Experience Study (VES) found that the prevalence of ED was 1.5 fold greater in current smokers than in non-smokers. A cross-sectional study conducted in Italy comparing non-smokers and current smokers on a total of 2010 men aged over 18, presented an odds ratio (OR) of ED of 1.7 and ex-smokers of 1.6. The study also showed that the risk of developing ED is influenced by smoking and that the duration of the habit increases this risk.

Cigarette smoking is certainly one of the most common modifiable risk factors related to the onset of erectile dysfunction. However, other important factors include heavy alcohol consumption, obesity and physical activity. Chronic, heavy alcohol consumption may have an irreversible effect on erectile function due to neurological damage, in particular changes in drinking habits may not influence erectile function. Chronic drug-abuse, especially combined with alcohol consumption, can lead to erectile disorders, in particular due to behavioural changes [29].

Overweight men have an increased risk of developing erectile dysfunction regardless of whether they lose weight and obviously very important concomitant factors are represented by physical activity intensity and stress. The link between erectile dysfunction and the use of certain medication is underestimated. Meinhart et al. presented a list of 332 drugs potentially associated with erectile dysfunction. The main classes of drugs involved were hypoglycaemic agents, antihypertensives, vasodilators, cardiac drugs and psychotropic agents. A close link between erectile dysfunction and pelvic surgery exists with rates ranging up to 80%. Radical prostatectomy, cystectomy, and radical pelvic surgery are strongly associated with ED while It is unclear whether TURP plays role [30].

The rise in the prevalence of ED worldwide, coupled with the new, high profile medical treatments is raising policy issues all over the world [30]. National health systems which are already under-funded, are facing unexpected requests for resources and challenges to current government funding priorities.
wide range of treatment options available since the arrival of new oral drugs effective in the treatment of ED, has above all, re-opened the debate over rationing and funding priorities. Secondly, due to the worldwide prevalence of ED and the consequent popularity of sildenafil, pharmaceutical companies can justify the cost of the drug. This can be seen to challenge the government’s ability to control drug costs. Other implications are that such situations may exacerbate health inequalities.

2. EARLY (PREMATURE, RAPID) EJACULATION

Early (premature, rapid) ejaculation is associated with higher anxiety and depression scores and perceived relationship issues. The Keele study found no significant associations with vascular diseases and LUTS but a clear association with co-existing ED.

3. FEMALE SEXUAL DYSFUNCTIONS

According to the US population census 9.7 million women aged 50-74 self report diminished lubrication, pain and discomfort with intercourse, decreased arousal or difficulty achieving orgasm (Berman 2001). In contrast with males, female sexual problems decrease with age, the exception being those reporting lubrication difficulties. Other demographic factors include, marital status, educational achievement, race and ethnicity are predictive of an increased risk of sexual difficulties. Black women are more likely to experience sexual desire problems and lack of pleasure, whereas white women report pain more frequently. Hispanic women report a consistently low incidence of sexual problems (Laumann 1999). In the Keele (UK) study, the major risk factors for both female sexual desire, and arousal disorder were perceived relationship issues, depression, anxiety and previous hysterectomy. Weak associations were found with diabetes and hypertension. Dyspareunia was associated with perceived marital problems and depression and was negatively associated with age.

IV. IMPACT OF SEXUAL DYSFUNCTION

ED is highly prevalent, the incidence is strongly age related, it is progressive and it is under treated [31]. The world population is rapidly ageing. In 2000 13% of the world population was 65 years or older and it is estimated that by 2020 this population will increase to 20%. The projections made in 1998, that a four-fold increase in the ED industry would occur in the next 4 years to 2002, from about $0.9 billion to $5 billion, have been proven [31, 32]. The impact of a condition with such escalating proportions seems obvious.

The economical impact of a medical condition or disease is not limited by the cost of diagnosis and treatment but, it includes the impact on the patient and society in a variety of ways, such as loss of time at work, decreased productivity for the patient and the effect on the partner, the family and coworkers. The impact is further confounded by the correlates of ED, which have a high economical impact, such as atherosclerosis, myocardial infarction, hypertension, diabetes mellitus, depression and conditions of the prostate such as BPH and cancer of the prostate.

1. ECONOMICAL

An attempt was made to estimate the economical impact of ED in the United Kingdom (UK). In this study, conducted from 1997 to 1998, on the cost of erectile dysfunction in the NHS, it was estimated that £53 million was spent to manage 113,600 patients with erectile dysfunction [33]. The main cost driver was outpatient visits, which accounted for 65% of the cost. Drugs accounted for 25% and genito-urinary consultations and prostheses only accounted for 4% of the cost. It was estimated that the NHS managed 35% of the population with ED. Assuming this was representative, the total population of individuals in the UK was estimated to be approximately 325,600. It was further estimated that these men incur £7.0 million in cost directly attributable to ED, 19.63 days a year to lost work, costing the society another £2.2 million in lost GDP. It was concluded that ED imposes a relatively small economical burden on UK Society (£53 million) of which 83% is borne by the NHS, 13% by patients and 4% as indirect costs to society due to lost productivity. The authors stated that the future burden would depend largely on patient’s eligibility to receive treatment under the NHS.

In an attempt to curb expenditure, the National Health Service (NHS) imposed prescribing restrictions for ED under schedule 11. The effects of these restrictions were assessed in a study by Wilson et al [34]. During the period of the study, from 1997 to 2000, a 30% increase in the number of patients (79,800 to 257,984) and a 40% increase in cost (£29.4 million to £73.8 million) were observed. The actual expenditure per patient decreased by 22% from £368 to £286 and the main expenditures were ascribed to specialist consultations (30%) and drug
prescriptions (25%). The increased cost was mainly
due to a 3 fold increased in the number of patients
presenting to general practitioners, who then referred
patients to specialists, under Schedule 11 restric-
tions. This led to an increased use of all resources,
including sildenafil. The investigators concluded that
the cost effectiveness of transferring prescribing res-
ponsibility in cases of severe distress from specialists
to general practitioners in primary care remained to
be determined.

In a study on the containment of costs by the imple-
mentation of the Department of Health’s (DoH) gui-
delines, following the introduction of sildenafil in
Portsmouth and South East Hampshire, it was obser-
ved that specialist-care and associated costs fell by
70% in the first year following the introduction of
the DoH guidelines, while primary-care prescribing
costs doubled. Overall costs for providing services in
1999-2000 were £232,169 in comparison to
£225,108 (uplifted to 1999-2000 values) incurred in
1998-1999 [35].

These studies indicate that costs can be contained
despite the escalation in the number of patients.
Potential benefits of the impact of introducing oral
treatment for erectile dysfunction have been reported
[36, 37]. Health-care systems have generally rejected
treatment of erectile dysfunction despite not kno-
wing what the effect of non-treatment is [38, 39].

2. QUALITY OF LIFE

General and disease specific quality of life in men
with diseases such as cancer of the prostate and end
stage renal disease, have been evaluated and reported
[40-46].

In a multicenter European study in men with organic
erectile dysfunction, self administration of intra-ure-
thal prostaglandin E1 (MUSE), resulted in a 70%
 improvement in the quality of erections, a 34%
 improvement in relationship with partners and statis-
tically significant improvements in personal well-
ness, contentment and self esteem, which translates
indirectly to an improvement in quality of life [47].
Intracavernosal injection of prostaglandin E1 also
resulted in significant improvement as measured by
the Life Satisfaction Checklist (LSC) [48]. Accor-
ding to the LSC it was possible to differentiate be-
tween patients with organic, psychogenic and no
erectile dysfunction. The study indicated that sexual
satisfaction was a major indicator for life satisfaction
in general. In 2 further studies on intra-cavernous
injection for erectile dysfunction, a large percentage
of patients indicated that treatment improved the
quality of their life [49, 50].

Most reports from studies on various aspects of qua-
lity of life, in patients with erectile dysfunction, such
as the International Index of Erectile Function (Question 13, overall satisfaction with sex life, and
question 14, sexual relationship with partner), Erect-
ion Distress Scale, Psychological General Well-Being
Index, showed improvement in quality of life.
However, it was unclear why some instruments such
as the Rosenberg Self-Esteem Scale, Medical Out-
come Study, as measures of self-control and anxiety
did not detect improvement in quality of life [51-54].
Most studies have limited and diverse quality of life
measurements, but they all support the notion that
ED therapy improves quality of life.

3. RELATIONSHIP

Improvement in patients' quality of life affects their
partners. In studies where partners were assessed
about their responses, they responded equally as well
to treatment and reported a significant increases in
intercourse frequency, sexual arousal, orgasm and
overall sexual satisfaction [55]. The mental and
social domains, as measured by the Duke health Pro-
file, improved significantly after intracavernosal
injection of prostaglandin E1 as treatment of erectile
dysfunction [56]. A 34% improvement in “relation-
ship with partner” domain was reported in a the mul-
ticentric European study of 249 men with organic
ED treated with self administered transurethral
alprostadil [57].

4. CO-MORBID CONDITIONS

Co-morbid conditions affect erectile function and
quality of life negatively and treatments of these
conditions usually improve erectile function and
quality of life. An interesting observation was, that
symptomatic treatment of ED with sildenafil, resul-
ted in an improvement of depression as measured by
depressive scales [57].

V. TREATMENT SEEKING BEHAVIOR

Behavioral factors significantly influence the beha-
vior of ED patients and their partners. This influence
ranges from attitudes toward diagnosis, treatment
seeking and ultimately to treatment compliance and
dropout.

In a study by Althof, he stated that the high rate of
discontinuation for men receiving treatment for ED (50-60%) could not be explained by inefficacy. Dr. Althof explored psychological reasons for dropout and proposed 7 factors that may explain why men, women, and couples resist continued treatment [5]. In another study 30 of 47 patients successfully treated with intercavernous vasoactive agents responded to a self-questionnaire asking their reasons for dropping out of the program. The authors concluded that discontinuation was not due to treatment-related problems [59]. Another 2 studies showed a factor that might affect dropout or noncompliance. It was the tendency to attribute one’s problems to external factors (i.e., the partner) and therefore, the alleviation of the problem might not be properly attributed to medical intervention [60, 61]. A Japanese study specifically addressed patient attitudes toward ED treatment through a national mail survey sent to married couples 30 to 79 years of age. Of the 2034 males and 1820 females who responded to questions about the male’s sexuality, 29.9% of males felt they had ED and 30.1% of females felt their husbands had ED. Low percentage of seeking treatment was observed; only 4.8% of male sufferers had consulted a physician. Reasons cited might be, in part, cultural (“shyness”, “should be covered by insurance”, or “not bothered by ED”) [62]. In a study using questionnaires sent to 108 patients, 100 (93%) responded. Researchers looked at hospital records and data from the survey. Only 32% continued self-injection treatment, about half of those (56%) discontinued within the first year, and patients who stopped therapy were significantly older and had poor initial impressions of therapy. As with other studies, the authors concluded that dropout had little to do with side effects or etiology [63]. In a study of 195 men comparing treatment compliance and treatment choice with marital satisfaction using the Maudsley Marital Questionnaire (MMQ), no differences were found between the 4 groups tested: 1) patients on ICI treatment, 2) dropouts during the trial-dose phase, 3) patients on other treatment, and 4) patients renouncing treatment after first counseling. However, in the ICI treatment group, efficacy was increased by offering information and enabling couple communication [64]. Finally, a survey of depressive symptoms in patients presenting with ED suggested that ED patients with high depressive scores were more likely to discontinue treatments for ED [57].

A study was performed in the USA and 5 European countries (Germany, United Kingdom, France, Italy, and Spain) [24]. The aim of this study was to be the motivators and barriers influencing treatment-seeking behavior in men with ED. Screening included 32,644 men. Follow-up questionnaires were completed by 2,831 men, who suffered from ED. Men were recruited while they were in waiting rooms in general practice offices. Treatment seeking among ED sufferers was highest among Spanish men (48%) and lowest for German and Italian men (27% and 28%, respectively). Rate of current ED medication use among ED sufferers was quite low across all countries, ranging from only 8% in France and Italy to 14% in the US. The top two barriers to seeking ED treatment were the beliefs that ED was a normal part of aging and that the condition would resolve on its own. Older men were more likely to view ED as a normal condition, and younger men were more likely to hope that their ED would resolve on its own. Once they perceived they have an erection problem, men waited many months before seeking treatment, ranging from just over a year in Italy to almost 3 years in the UK.

Several barriers continue to influence treatment-seeking behavior in men with ED resulting in low rates of utilization and high rates of dropout of therapies for ED. Further research in this field is urgently necessary.

VI. DIAGNOSTIC EVALUATION

There are multiple goals of a diagnostic evaluation for a patient with Sexual Dysfunction. The first goal is to ascertain that the sexual dysfunction is not a symptom of an underlying medical disorder that requires treatment regardless of the status of sexual function. For example, endocrine disorders, such as hyperprolactinemia, may present with sexual dysfunction in both men and women and it is important to recognize because of its destructive effect in the brain. Likewise, diabetes mellitus may present as sexual dysfunction. The second goal of a diagnostic evaluation is to identify any correctable cause of sexual dysfunction. An example of this might be hypogonadism in the male or reduced libido in the female due to low testosterone levels that could be easily corrected with testosterone replacement therapy. Finally, a diagnostic evaluation provides an explanation for the sexual dysfunction. At this point in time there has been little standardization of the diagnostic evaluation for female sexual dysfunction while the male erectile dysfunction evaluation has
been well described. The evaluation for early (pre-mature, rapid) ejaculation is minimal consisting primarily of a medical and sexual history. The remainder of this section will deal with evaluation of erectile dysfunction (ED)

Other factors have to be considered in developing guidelines for the diagnostic evaluation of sexual dysfunction, particularly erectile dysfunction. Is it necessary to perform a complete evaluation in all patients? The answer is likely “no” and that a simple screening with a full medical and psychosexual history is satisfactory the vast majority of patients. There is a tremendous cost to applying a full diagnostic evaluation for all patients with sexual dysfunction since laboratory tests, such as a serum testosterone level, that are taken for granted in the economically advanced countries may be prohibitively expensive in other parts of the world. This, as well as other epidemiologic observations, have made it necessary to develop guidelines for the diagnosis of Erectile Dysfunction in order to adopt a correct, rapid, advantageous (in terms of health and cost) approach to ED and to the pathology that often causes it.

The diagnostic flow-chart is comprised of three levels ranging in invasiveness and expense. This includes 1) Non-invasive, 2) semi-invasive and 3) invasive tests. The first level consists of history, physical examination and limited laboratory tests. A complete medical history as well as a psychosexual history is needed. Validated instruments such as the International Index of Erectile Dysfunction and Beck’s questionnaire for the deflection of mood tone have been utilized. Physical examination of the genitalia, vascular system, neurological system and assessment of endocrine status are required. Routine laboratory tests employed include blood sugar, lipid profile, urine dipstick and hormonal assessment.

The importance of this initial evaluation has been emphasized by the findings of Carbone and colleagues who showed that 15% of the men being evaluated for sexual dysfunction had previously undiagnosed urological tumors [66]. The accuracy of this simple evaluation is much higher than one might expect. Davis-Joseph and co-workers determined the accuracy of establishing the differential diagnosis between organic and psychological erectile dysfunction using medical history and a physical examination alone, compared to that obtained from more advanced diagnostic testing [67]. They concluded that medical history and a physical examination had a sensitivity of 95% but specificity of only 50%, which is quite reasonable considering the simplicity and low costs of this evaluation.

Semi-invasive studies include evaluation of nocturnal erections (NPT), assessment of penile blood flow with non-invasive Doppler ultrasound and psychological assessment. Evaluation of nocturnal erectile activity is typically performed while differentiating between physical causes of ED and psychogenic causes. There are many ways of performing this test from a simple and inexpensive snap gauge test to formal nocturnal sleep monitoring. The most commonly utilized method in the United States is the Rigiscan-NPTR. The sensitivity of the Rigiscan is 90.6% and the specificity is 88.1%. This test does not permit discrimination of subjects with arterial insufficiency and veno-occlusive dysfunction nor is the documentation of a physical cause necessary in the vast majority of patients being treated. This evaluation costs approximately US $600 due to the high cost of equipment and materials as reported in various DRG (Diagnosis Related Group) and insurance reimbursement policy.

Penile Doppler ultrasonography assesses the arterial inflow to the penis. The most up to date equipment utilizes color enhancement along with Power Doppler to most accurately measure low flow systems. Penile blood flow measurement does not directly assess either the pelvic arterial vasculature or diagnose veno-occlusive dysfunction directly but only by inference. This study is often performed in conjunction with pharmacological stimulation of an erection by the intracorporal injection of a vasoactive agent. The cost for the test and necessary drug (Prostaglandin E1) is approximately US $150 as reported in various DRG (Diagnosis Related Group) and insurance reimbursement policy.

More invasive studies include cavernosometry/cavernosography and arteriography. Cavernosometry and cavernosography are gold-standard in the diagnosis of veno-occlusive dysfunction. A major drawback to this diagnostic study is the high rate of false positive results due to a variety of issues but primarily related to subject anxiety. There is a very poor correlation with other objective studies including NPT and there is considerable overlap in results amongst men with ED and normal subjects. Audiovisual Sexual Stimulation together with repetitive administration of vasoactive agent are the methods utilized to overcome the psychological inhibition of the patient. The cost ranges from US $180 to 200 as reported in various DRG (Diagnosis Related Group) and insurance reimbursement policy. Selective arte-
riography of the pelvic arteries has been utilized for the assessment of patients who are potential candidates for vascular surgery. It has a very limited role in the current management of sexual dysfunction.

The semi-invasive and invasive studies have a limited role today. Patients with primary ED can be quite challenging. The majority have a psychological basis and thus it is important to rule out psychogenic ED before proceeding with more invasive testing and therapies. Younger, healthy patients with a history of either pelvic or perineal trauma might benefit from further vascular testing and arterial reconstructive surgery. This sub-population represents significantly less than 1% of the overall ED population. Finally, a more extensive evaluation may be performed in patients that have a specific desire to know their etiology or medical-legal issues.

From the point of view of health administration, establishing a diagnosis with 95% sensitivity without carrying out any examinations is preferred compared to the expense of an extensive evaluation of ED. However, from the patient’s point of view, a simple empirical therapeutic approach, although effective in restoring erection, may leave too many questions unanswered [66-72].

VI. RESEARCH AND DEVELOPMENT

Research-based pharmaceutical companies invested $32 billion in research and development in 2002. The majority of this money was focused on diseases related to endocrinology, oncology, infection and the central nervous system. Approximately 3% of this total was for the development of products involving the genitourinary system. With the expected introduction of two new oral medications to treat ED in 2003, the amount of dollars devoted to discovery in this area is unlikely to materially increase in the near term.

Longer term, the combination of advances in molecular biology and a greater understanding of the physiology of erection and the pathophysiology of erectile dysfunction could allow for the success of gene therapy strategies. In analyzing the overall market for ED, it is necessary to consider non-pharmacologic therapies, such as penile implants and vacuum erection devices. While this data is more difficult to ascertain, it appears that the annual dollars allocated to R&D for penile implants has remained at roughly the $7 million level for the past four years.

VII. COST OF THERAPIES

1. SALES

Worldwide pharmaceutical sales were estimated at $370 billion in 2002, with about 44% occurring in the United States. In the U.S., whereas total healthcare spending is increasing at a 7% rate, pharmaceutical sales are forecast to grow by 12% annually, and now comprise 10% of national healthcare expenditures. The total market for drugs to treat ED represents a very small portion of this total. Sildenafil sales in 2002 were $1.74 billion, an increase of 14% over 2001. In the United States, where Viagra accounts for 98% of ED prescriptions, sales were $1.02 billion, which represented an 11% increase over 2001, probably due to the rising numbers of oral drugs non-responders. Since its introduction, 120 million prescriptions have been written for sildenafil, and more than 20 million men have been treated (Table 2).

Worldwide sales of penile implants approximated $92.60 million in 2002, an increase of 11% over 2001. The continued preference for oral therapies should limit the overall market share achievable by implants.

2. COST-EFFECTIVENESS

The introduction of sildenafil in the United States in 1998 not only revolutionized treatment for an under-diagnosed disease but also forced health plans to reexamine their strategy of prescription drug coverage. The decade of the 1990’s was characterized by the increasing availability of prescription benefit plans, which initially had minimal co-pays and deductibles. The first issue confronting the insurers was that of medical necessity. Once coverage was allowed, the pill quantity of a prescription needed to be ascertained. This was especially relevant in light of the $10 per pill cost of sildenafil, as most patented oral medications were priced at about $1.50 per day.

A cost-effectiveness analysis performed by Smith and Roberts compared Sildenafil with no drug therapy. [39] They concluded that Sildenafil treatment costs approximately $9000 per quality-adjusted life-year. This compares favorably with other interventions for medical conditions, including renal dialysis,
cholesterol-lowering medication and coronary artery bypass grafting. Furthermore, it was well below the $50,000 threshold often used as a benchmark in such analyses [4].

Further support for the cost effectiveness of Sildenafil was provided by an analysis performed in the Netherlands that compared Sildenafil with papaverine-phentolamine injections [5]. It was concluded that Sildenafil created more benefits and more costs, as a greater number of patients were willing to be treated. The mean incremental cost utility ratio of Sildenafil compared with papaverine-phentolamine was 3639 British pounds per quality-adjusted life year in the first year, and improved in subsequent years. This ratio was considered favorable, as acceptable thresholds of cost utility were found to vary between 8,000-25,000 British pounds. Also, it was noted that many interventions with less favorable cost utility ratios were being funded, including breast cancer screening and kidney transplantation [6].

The ED field is still in continuous evolution. It is not clear currently what model it will follow in comparison to prior more established fields. There are similarities between ED and a number of other fields, such as benign prostatic hyperplasia (BPH), arthritis, and depression. All are chronic and potentially progressive. BPH and arthritis have medical and surgical treatments. Medical treatments of all 3 conditions do not provide a cure, rather a control and improvement of symptoms. We have already seen that with the introduction of oral therapy, the treatment of simple cases of ED is mostly with oral medications in the primary care setting. Complex and severe cases are referred to specialists (mostly urologists) for the treatment with injection therapy or in case of failure with prosthesis surgery. This evolution follows very closely the models of BPH and arthritis treatment.

**VIII. ECONOMIC MODELS**

The ED field is still in continuous evolution. It is not clear currently what model it will follow in comparison to prior more established fields. There are similarities between ED and a number of other fields, such as benign prostatic hyperplasia (BPH), arthritis, and depression. All are chronic and potentially progressive. BPH and arthritis have medical and surgical treatments. Medical treatments of all 3 conditions do not provide a cure, rather a control and improvement of symptoms. We have already seen that with the introduction of oral therapy, the treatment of simple cases of ED is mostly with oral medications in the primary care setting. Complex and severe cases are referred to specialists (mostly urologists) for the treatment with injection therapy or in case of failure with prosthesis surgery. This evolution follows very closely the models of BPH and arthritis treatment.

**IX. ECONOMIC IMPACT**

1. **THE DESCRIPTIVE ECONOMICS OF ERECTILE DYSFUNCTION (ED)**

Economic planners and health care providers were obviously concerned by results from the MMAS for the prevalence of ED, both in terms of current status and predictions for the future decade. MMAS estimated 30 million US men to suffer from some degree of ED, expected to increase by 20% by 2010 with 921,000 cases predicted annually. Studies from the UK suggest that the prevalence of ED in primary care is 30%, suggesting over 4 million sufferers. The study also found that only half the sufferers wished treatment and subsequent research has suggested that of these only about half continue on treatment long term. This would tend to suggest that currently only about 7% of all men wish to remain on treatment and that, in the case of oral treatment, frequency of use is around once to twice per week [34].
Response to such predictions and the license of the first oral therapy in 1998, lead to an immediate intervention by the UK government to restrict access the therapy to a few defined medical conditions in an effort to control national health expenditure. A recent analysis of the effects of these measures is discussed later. No other health care system has totally embraced the concept of treating erectile dysfunction as part of state expenditure and, with a few exceptions, data from other countries describes a system where the patient is paying the full private cost of their treatment. This may be a significant influence in restraining ED expenditure but may also have introduced a need for patients to “prioritize” their medications. In such cases the immediate benefits of treating ED may be seen as more advantageous that potential long term benefits of other therapies, such as lipid lowering or anti-hypertensive therapy. The economic Impact of a disease may not be limited to the diagnosis and treatment of that disease. Much is now known of the important associations of ED with ischemic heart disease, hypertension, hyperlipidemia, diabetes, depression and impaired quality of life. The implications of treating ED and the benefits in these associated conditions are discussed in other chapters. These factors are becoming increasingly important when evaluating the cost effectiveness of therapy for ED, and in the future for FSD [73, 31].

2. UTILISATION OF HEALTH CARE SERVICES IN ED

Different health care systems have responded in different ways to the predicted increased demand for effective oral therapy, since 1998. 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 assumption that, because of inconvenience, that frequency of use would be less. Under the UK National Health service, all drugs have been treated equally and therapy has been restricted to patients with certain defined conditions, including severe distress, since 1999. The UK model allows for detailed analysis as all patients are registered with a general practitioner, who is responsible for keeping detailed prescribing and consultation data. A large scale study was published in 2002, which provides the most detailed information yet on the primary and secondary consultation patterns from 1997 to 2000 (Figures 3, 4, 5, and 6). Results show a more than doubling of GP consultations in the 24 months following the release of Sildenafil, from 151,000 to 331,000 with an increase to 490,000 in the following 12 months. The study also showed a considerable increase in secondary care consultations from 9,500 in 1998, to 15,700 in 1999, to 23,600 in 2000. It is not clear whether this trend will continue. As the number of Specialist treatments, such as prostheses, fell in this period, the authors concluded that the need for specialist interpretation of the complex regulations was the major influence driving the increase in hospital costs. Despite this, the direct cost of managing each patient fell from $540 to $420 between 1997 and 2000 [34].

Restricted access to ED therapy has led to a massive market for mail order and internet sales. In many countries, particularly the US, this practice is widespread and a natural consequence of patients exercising their rights in a free market. In the UK, internet selling is illegal for prescription only medication and concerns have been expressed that the requirement to pay for oral medication may lead to patients with important associated conditions, such as ischemic heart disease seeking internet medication rather than seeking a full assessment from their physician. This may have important health economic implications caused by failure to diagnose important treatable disease.

3. MANAGEMENT COSTS WORLDWIDE

Prior to the launch of Sildenafil in 1998, the ED market in the US had been increasing slowly from $100M in 1995 to $200M in 1997 with injection therapy being responsible for 75% (Figures 7 and 8). The release of Sildenafil in 1998 increased the number of men presenting from 6% in 1998 to over 16% in 2002 with the total market of ED drugs increasing over 5 fold to $4.8 billion in 2002, closely in line with the predictions of the 1st International Consultation on ED meeting in Paris in 1999. Sildenafil accounted for 92% of the total licensed ED drug market in 2002 at $4.46 billion. In 2002, intracavernosal accounted for only 3% of the total world market with MUSE at 1% and other at 5%. This mainly reflects the license of Apomorphine (Uprima and Ixense) in 2001. After launch 267,000 prescriptions were written in Europe, Japan and Latin America in the first 12 months, but early 2003, figures suggest a fall of over 30%. Similar changes were seen in the reduction in the prescribing of MUSE, which fell by 33% to 32,000 prescriptions between 2000 and 2001. Between 2000 and 2002, there was a significant increase in the US and European prescribing of Alprostadil (Caverject), presumable related to non-response to Sildenafil, although this effect was not seen in and Latin America, where a fall of around 7% per year continued.
Figure 3: Increase in the number of men presenting to the general practitioners with ED in the UK 1997 through 2000 (Wilson EC, McKeen ES, Scuffham PA, Wylie K, Hackett G. The cost to the United Kingdom National Health Service of managing erectile dysfunction: impact of sildenafil and prescribing restrictions. Pharmacoeconomics 20(13): 879-889, 2002).

Figure 4: Total direct cost of management of ED in the National Health System in the UK 1997 through 2000 (Wilson EC, McKeen ES, Scuffham PA, Wylie K, Hackett G. The cost to the United Kingdom National Health Service of managing erectile dysfunction: impact of sildenafil and prescribing restrictions. Pharmacoeconomics 20(13): 879-889, 2002).

Figure 5: While total cost of the management of ED is increasing, the utilization of intracavernosal therapy, intravesical therapy, and penile prosthesis is decreasing in the UK 1997 through 2000 (Wilson EC, McKeen ES, Scuffham PA, Wylie K, Hackett G. The cost to the United Kingdom National Health Service of managing erectile dysfunction: impact of sildenafil and prescribing restrictions. Pharmacoeconomics 20(13): 879-889, 2002).

Figure 6: Cost of ED therapy in the National Health System in the UK in 2002.

Figure 7: Sildenafil prescription tracking in USA from launch in 1998 through 2002.

Figure 8: Sildenafil monthly prescription tracking in USA from May 2002 through May 2003.
Data from the UK study showed that Sildenafil costs rose from $13M in 1999 to $27M in 2000. The injection and MUSE markets fell by 30% and 10% respectively over the same period. Psychosexual therapy consultations remained constant at around 90,000 sessions per year but the number of prostheses inserted fell from 679 in 1999, prior to Sildenafil to only 245 in 2000. During the period from 1997 to 2000, the Vacuum device market rose from 16,000 per annum in 1997 to 28,000 in 2000, possibly influenced by their inclusion as an NHS item in 1999 [68]. Although the utilization of sildenafil continues to grow, the rate of growth has slowed down suggesting a possible deceleration of the growth of the ED pharmaceutical market (Figures 9 and 10). Another possible explanation may be the saturation of a single medication market.

In 2001, Apomorphine was launched in Europe as Uprima or Ixense, with worldwide releases (excluding the US and Japan) throughout 2002. In February and March 2003, 2 new oral PDE5 inhibitors, Tadalafil (Cialis) and Vardenafil (Levitra) have been released in Europe (not in the US) but at the time of writing this report, only preliminary data are available. Early suggestions are that, particularly with the potential benefits of a longer duration of action, Tadalafil has lead to an overall increase in patients presenting for treatment, but sales of Sildenafil have continued to be the market leader over this period (Figures 11, 12 and 13).

It is worth noting that the majority of prescriptions for PDE-5 inhibitors are currently written by primary care physicians. Urologists represent the highest prescription rate relative to their numbers (Figure 14).

Of special interest is the growth of the testosterone market in the USA (Figure 15). It is clear that the introduction of the efficacious and safe transcutaneous delivery system of Androgel accounted for this increase. The use of testosterone therapy is expected to increase with the introduction of newer buccal delivery systems. The approved indication is the treatment of hypogonadism. Although ED is one of the symptoms of hypogonadism, it is not known, how many patients receiving testosterone therapy present with a chief complaint of ED.

The exact cost of the treatment of female sexual dysfunction is not known currently. This field is in its early stages of development and pharmacologic treatments are mostly in research & development (Table 3). The utilization of hormone replacement therapy over the past several years yields very interesting observations. The negative publicity about the safety of hormone replacement therapy results in substantial decrease in its utilization (Figures 16, 17 and 18). However, the market of FSD therapy is expected to grow significantly due to the high prevalence of FSD, the increasing awareness of it and the development of new therapies.

4. Future predictions for the sexual dysfunction market

The world prevalence of ED is projected to double through the 30 year period that runs from 1995 to 2025 [3]. On the other hand, it has been estimated that 70% of all ED is undiagnosed [4] and that, historically, only 5% of men with ED had received medical attention [5]. The combined effect of population growth combined with increased life expectancy will result in around 1 million new cases presenting annually in the US, particularly as patients are presented with more choice. Studies such as the MMAS
Figure 11: PDE-5 inhibitors total prescriptions in Germany May 2001 through April 2003.

Figure 12: PDE-5 inhibitors total prescriptions in the UK May 2001 through April 2003.

Figure 13: PDE-5 inhibitors total prescriptions in France May 2001 through April 2003.
Figure 14: Sildenafil total prescriptions in the USA by provider.

Figure 15: Testosterone products prescription tracking in USA June 2000 through May 2003.

Figure 16: Oral hormone replacement therapy in women prescription tracking in USA 1999 through 2002.

Figure 17: Premarin and Prempro total prescription tracking in USA June 2002 - May 2003.
and Keele (UK) have consistently shown that 50% of men do not wish therapy and around 37% discontinue for various reasons, such as lack of efficacy, side-effects, cost and partner reluctance. This pattern is likely to be only slightly influenced by the newer PDE5 inhibitors and it is likely to be at least 5 years before any new classes of oral therapy are available [73-77].

Population studies have suggested that Female Sexual Dysfunction (FSD) is as common as erectile dysfunction but that only around one third of women would wish help. Currently there are few licensed preparations proven to be beneficial in FSD and a recent BMJ editorial questioned the validity of a number of the studies. Drugs are currently being assessed in Hypoactive Sexual Desire disorder in women and sildenafil appears to show some promise in Female Arousal Disorder. The need for women to take regular oral therapy for FSD may prove a major drawback and it is difficult to predict with accuracy the potential size of the market. HRT has been shown to be beneficial in some women with FSD but little is known about how many women currently use HRT for this reason. There is still much research to be done in the diagnosis and assessment of women with FSD before accurate assessments of a predicted market can be made (Figure 2, Table 2 and 3).

X. SUMMARY

Review of the economic aspects of sexual dysfunctions reveals the following observations:

1) ED remains under treated despite its high prevalence.
2) Treatment seeking behavior influences utilization of therapy with motivators, barriers and patient attitudes having a significant impact.
3) Majority of patients with ED are managed by PCP’s. However, urologists remain the leading specialty.
4) Utilization of oral therapy for ED continues to grow 5 years after the introduction of sildenafil.
5) Oral therapy for ED retains a very large market share.
6) Introduction of new PDE5i expands the ED patient base.
7) Widespread utilization of herbal and OTC products is suspected with no definitive data.
8) Growth of ED market may be decelerating. Penile injection therapy remains the leading second line therapy with a small market share compared to oral therapy.
9) Penile prostheses utilization shows a small recent recovery and growth after a period of decline with the introduction of pharmacologic therapy.
10) Very little data is available on the economics of: early (premature, rapid) ejaculation, hypoactive sexual desire disorder, retarded ejaculation, Peyronie’s disease.
11) Testosterone therapy has experienced substantial growth recently after the introduction of transcutaneous delivery.
12) Little is known about the economics of FSD. However, many new pharmacologic therapies are in various stages of development.
13) Hormone replacement therapy in women declined recently after publications raising concerns about its safety.
14) R&D for pharmacologic treatments of male and female sexual dysfunctions are expanding globally.

XI. RECOMMENDATIONS

Based on the current status of the economical aspects of sexual dysfunctions, the following recommendations are presented:

1) Research should be intensified on the impact of sexual dysfunctions on society and economy to appreciate the importance of these dysfunctions.
2) Treatment utilization data should be disseminated among academicians and clinicians to help understand the economical aspects of sexual dysfunctions.
3) Education of patients (consumers in economic terms) with sexual dysfunctions is highly important to enhance their informed choices.

Figure 18 : Growth of hormone replacement therapy in USA 2000 through 200203
<table>
<thead>
<tr>
<th>Drug/Product</th>
<th>Manufacturer</th>
<th>Key Ingredient</th>
<th>Use/Potential Use</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androsorb (cream)</td>
<td>Novavax</td>
<td>Testosterone</td>
<td>Hypoactive sexual desire disorder and possibly other FSD’s</td>
<td>Phase II clinical trials</td>
</tr>
<tr>
<td>Alista</td>
<td>Vivus</td>
<td>Prostaglandin E1</td>
<td>Vasodilator. Increased blood flow to genitalia</td>
<td>Phase II clinical trials</td>
</tr>
<tr>
<td>EROS-CTD (clitoral therapy device)</td>
<td>Urometrics</td>
<td>Clitoral therapy device</td>
<td>Increases sensation and blood flow to clitoris by suction</td>
<td>Available with doctor’s order</td>
</tr>
<tr>
<td>Estrace cream</td>
<td>Warner Chilcott</td>
<td>Estrogen</td>
<td>Hormone Replacement therapy (HRT) Vaginal dryness and discomfort</td>
<td>Available with doctor’s order</td>
</tr>
<tr>
<td>Estratest (pill)</td>
<td>Solvay Pharmaceuticals</td>
<td>Estrogen-testosterone combination</td>
<td>Hormone replacement therapy (HRT) to treat hot flashes. Increases desire in some women</td>
<td>Available with doctor’s order</td>
</tr>
<tr>
<td>Evista</td>
<td>Eli Lilly</td>
<td>Selective estrogen receptor modulator (SERM)</td>
<td>Osteoporosis HRT, may thicken vaginal walls</td>
<td>Available with doctor’s order</td>
</tr>
<tr>
<td>Femprox (cream)</td>
<td>NexMed, Inc.</td>
<td>Prostaglandine E1</td>
<td>Vasodilator. Improves blood flow to genitals</td>
<td>Phase II clinical trials</td>
</tr>
<tr>
<td>Intrinsa (patch)</td>
<td>Proctor &amp; Gamble Watson Laboratories</td>
<td>Testosterone</td>
<td>Hypoactive sexual desire and possibly other FSD’s</td>
<td>Phase II clinical trials</td>
</tr>
<tr>
<td>Livial (pill)</td>
<td>Organon</td>
<td>Selective estrogen receptor modulator (SERM)</td>
<td>Osteoporosis, desire and arousal, treatment and prevention of osteoporosis</td>
<td>Phase III clinical trials</td>
</tr>
<tr>
<td>NM1-870 (pill)</td>
<td>NitroMed</td>
<td>African tree bark fortified with nitric oxide</td>
<td>Increases vaginal blood flow in postmenopausal women</td>
<td>Phase II clinical trials</td>
</tr>
<tr>
<td>Premarin (pill, cream or injection)</td>
<td>Wyeth</td>
<td>Estrogen</td>
<td>Osteoporosis, menopause symptoms. Vaginal dryness and discomfort associated with menopause.</td>
<td>Available with doctor’s order</td>
</tr>
<tr>
<td>Prempro (pill)</td>
<td>Wyeth</td>
<td>Estrogen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premphase (pill)</td>
<td>Wyeth</td>
<td>Estrogen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steryl-Norleucine VIP (cream)</td>
<td>Senetek PLC</td>
<td>Synthetic version of verve chemical</td>
<td>Vaginal dryness and discomfort associated with menopause</td>
<td>In clinical trials</td>
</tr>
<tr>
<td>Testosterone creams</td>
<td>Off-label prescriptions from compounding pharmacies</td>
<td>Testosterone</td>
<td>Male hormone replacement therapy</td>
<td>Not FDA approved for use in women</td>
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<tr>
<td>Tostrelle (gel)</td>
<td>Cellegy</td>
<td>Testosterone</td>
<td>Controlled delivery system for testosterone</td>
<td>Advanced Phase II/III clinical trials</td>
</tr>
<tr>
<td>Vasofem (tablet)</td>
<td>Zonagen</td>
<td>Blood vessel dilator</td>
<td>Increases blood flow to clitoris</td>
<td>Phase II clinical trials</td>
</tr>
<tr>
<td>Viagra</td>
<td>Pfizer</td>
<td>Sildenafil</td>
<td>Vasodilator. Male erectile dysfunction</td>
<td>Increases blood flow to genitals Off-label prescription available.</td>
</tr>
</tbody>
</table>
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CHAPTER 6

Committee 17

Qualitative Health Research and Sexual Dysfunction

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Members
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S. SANDERS (USA)
1. **Qualitative research is NOT:**

2. **Qualitative research IS:**

### II. SPECIAL RELEVANCE OF QUALITATIVE METHODS IN SEXUAL DYSFUNCTION RESEARCH

1. **Development of new assessment tools for measurement of sexual function in men and women.**

2. **Attitudes and practices of health care professionals in managing sexual problems.**

3. **Partner responses to sexual problems, treatment-seeking and treatment satisfaction.**

4. **Sexual problem clarification**

### III. UTILITY OF QUALITATIVE HEALTH RESEARCH TO ADDRESS THESE PROBLEMS

### IV. QUALITATIVE AND QUANTITATIVE HEALTH RESEARCH: A COMPLEMENTARY RELATIONSHIP

### V. SPECIFIC EXAMPLES IN SEXUAL MEDICINE RESEARCH

### VI. QUALITATIVE RESEARCH TRADITIONS, METHODS AND PERSPECTIVES

1. **The nature of qualitative evidence**

### VII. SPECIFIC AREAS OF APPLICATION TO SEXUAL PROBLEMS AND DYSFUNCTION

1. **Better understanding of individuals’ experiences of sexual problems**

2. **Design of assessment and treatment studies**

3. **Additional areas for application of QR research in sexual medicine:**

### VIII. SUMMARY AND RECOMMENDATIONS

### REFERENCES
Qualitative Health Research and Sexual Dysfunction

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A. Giambi, J. Popay, C. Graham, S. Sanders

INTRODUCTION

“When the central objectives of an inquiry are to explore and explain behavior rather than describe it, when the subject matter is unfamiliar and insufficiently researched, or when a suitable vocabulary with which to communicate with respondents is not available, researchers are well advised to address their research questions through the use of qualitative methods. Investigation into most aspects of sexual and reproductive health fall into one or the other of these categories.” (Ulin, Robinson, Tolley & McNeill, 2002, p. v) [1].

Human sexuality is highly complex and multi-faceted, involving subjective, physical and cultural components, which vary from one individual to another and profoundly affect the nature of the sexual experience. Some of these components are neglected in traditional quantitative or experimental research which focuses on quantifiable aspects and measures of behavior. Qualitative research (QR) can precede, complement or extend quantitative approaches, by adding insights about the subjective, contextual, or interpersonal aspects of the experience. Often, qualitative research serves to generate hypotheses rather than to test hypotheses. Overall, qualitative health research occupies a complementary and uniquely valuable place in the broader framework of evidence-based medicine, as described by Summerskill [2].

“Qualitative research explains social interactions, and provides insights to questions of “how” and “why”. In contrast to quantitative research, which sets out to challenge an existing hypothesis, qualitative research is hypothesis-generating. Just as quantitative research employs different trial designs to answer different questions, qualitative research also uses a variety of approaches. Qualitative studies have a special role in evidence-based medicine. Understanding patient and practitioner attitudes and behavior allows evidence to be applied in the most effective manner” Summerskill (2001; p. 47) [2].

Lack of familiarity or training in qualitative health research presents a significant barrier to its acceptance and use in sexual health research. Few physicians, health professionals or medical researchers receive formal training in qualitative health research techniques. Neither are they familiar with qualitative research traditions and approaches that have been developed and extensively used in nursing and social science, and they may even dismiss the qualitative perspective as inappropriate or unnecessary for the study of sexual dysfunction or, indeed, any health area. This resistance to the use of qualitative methods results from a lack of awareness or understanding of the goals and methods of QR. For example, a common misconception is that qualitative research is purely descriptive, and lacks a defined strategy for data collection or data analysis. On the contrary, QR can be evaluated based on research design, sampling approach or method of recruiting subjects, analysis and reporting of data, and finally, how results are presented in the final publication. Since it provides a unique “lens” through which key issues and problems in medicine can be studied, qualitative health research should be viewed as an integral component of the basic and applied study of sexuality and sexual problems. Level of evidence or fidelity in qualitative research is addressed using traditional and non-traditional criteria of evaluation.

Qualitative methods are proliferating and finding advocates and adherents within various specialties. For example, the second edition of a qualitative heal-
th research text by primary care physician-researchers Dr. Benjamin Crabtree and Dr. William Miller is a primer of various data collection strategies and methods of analysis [3]. Over a dozen journals specialize in empirical qualitative research, and many sexuality journals (especially multidisciplinary journals that include social science as well as biomedical studies) include qualitative research projects.

The overall purpose of this chapter is to introduce this area of research along with some of its leading texts and primary methods, and to provide examples to readers of how it may be used to address specific problems in sexual dysfunction research. Rather than offering a comprehensive overview of all areas of qualitative health research, this chapter will provide a basic summary of the methods, along with case examples of the application of qualitative methods. Our major goal in this chapter is to introduce readers to the core concepts and ideas, and to encourage more attention to this approach in future years. Hopefully, interested readers will pursue further study in the area and will consider the use of qualitative health research methods to address key problems in the field of sexual dysfunctions, such as problem identification, communication between patient and provider, diversity of experiences with treatment, and help-seeking behavior. Qualitative methods may also provide an outstanding avenue for conducting initial research on partner responses to sexual dysfunction and treatment.

I. APPRAISING QUALITY IN QUALITATIVE RESEARCH (QR)

The prima facie criteria used to assess “quality” are common to all research. These include:

- Sufficient explanation of background
- Method appropriate to question
- Succinct statement of objectives and research questions
- Full description of methods
- Clear presentation of findings

Beyond these fundamental criteria, evaluation of the quality or “trustworthiness” of QR requires criteria tailored to its particular research “paradigms.” A detailed presentation of these criteria are beyond the scope of this chapter, but will be discussed briefly below.

1. QUALITATIVE RESEARCH IS NOT:

   - Just a list of tools or methods (such as in-depth interviews and focus groups)
   - Always conducted on a small scale
   - The opposite of quantitative research
   - Only concerned with subjective personal experience.

2. QUALITATIVE RESEARCH IS:

   - A different but legitimate approach to scientific enquiry
   - Dependent on conceptual rather than numerical analysis
   - Concerned with the negotiation and construction of meaning within a social context
   - Focused on elucidating the relationships among subjective experience, lay knowledge, social structures (e.g. the material world) and action (i.e. behavior)

II. SPECIAL RELEVANCE OF QUALITATIVE METHODS IN SEXUAL DYSFUNCTION RESEARCH

With the rapid growth of sexual dysfunction research and practice, limitations or critical gaps have appeared in a number of areas. For example, we know that clinical trial data in numerous studies of men with ED have proven overall safety and efficacy of new pharmacological treatments (See: Vol. 1; Chapter 13). However, recent data have also shown that many men either do not seek treatment for their problem, or discontinue treatment prematurely [4]. In this multinational survey of more than 20,000 men in 8 countries, less than 20% of those identified with ED were active in treatment at the time of the study, although more than half of those with ED had spoken with a health professional at some time about the problem. Recent large-scale surveys in women have shown that women with sexual problems vary greatly in the amount of subjective or interpersonal distress they experience [5]. Traditional clinical trial or survey-type research provides little information about these phenomena and hypotheses are needed to guide future explanatory research. Thus, qualitative studies are being conducted in these areas to investigate subjective and interpersonal processes that influence sexual distress, and to better understand...
the motivations associated with treatment-seeking for sexual problems in both men and women.

**Other Key Areas of Application of QR to Sexual Dysfunction Research Include:**

1. **Development of New Assessment Tools for Measurement of Sexual Function in Men and Women.**

In conjunction with this Consultation, a brief, new screening questionnaire for male sexual dysfunction has been developed (See Vol 1; Chapter 5). In the early stages of development, qualitative focus groups and one-to-one interviews provided valuable insights into issues of relevance, definitions and terminology to be used and subjective responses of men to this new instrument. *Qualitative approaches have similarly been used in the development of new scales and questionnaires for assessing women’s sexual dysfunction [6,7]* It is important to acknowledge, however, that brief questionnaires are often criticized by qualitative researchers as superficial and misleading. Greater communication between quantitative and qualitative researchers will illuminate these tensions and likely lead to better research by both groups.

2. **Attitudes and Practices of Health Care Professionals in Managing Sexual Problems.**

Large-scale survey studies have revealed that most patients do not feel comfortable in discussing sexual problems with their physician or health-care provider, and few have confidence that their physician will be able to help them with their problem [8]. Physician discomfort and lack of familiarity with sexual dysfunction is a major obstacle to effective communication in this area. *Qualitative research studies are being conducted to investigate these issues more fully, and to gain insight into the subjective and interpersonal processes that limit patient-physician communication about sexuality.*

3. **Partner Responses to Sexual Problems, Treatment-Seeking and Treatment Satisfaction.**

Little is known about the consequences or impact for the partner of sexual problems in men or women, or the role of the partner in treatment-seeking or outcomes associated with treatment. This is a potentially critical area for future development of the field, and an ideal topic to be addressed from the perspective of qualitative health research.

4. **Sexual Problem Clarification**

Qualitative research methods can begin to address criticisms of the traditional definitions of sexual dysfunctions that they are overly mechanical or decontextualized. Patient-centered research on sexual distress can clarify appropriate definitions and categories.

*QR approaches are typically focused on generating explanatory constructs or theory, rather than testing specific hypotheses.* They are best used in a field where there are fewer answers than questions. “Many quantitatively trained researchers first started working qualitatively because they recognized that the statistical analyses of particular survey responses did not seem to fit what those in situations of interest said or what people wrote in their open-ended answers”. [9] In contemporary clinical sexology, the use of surveys exceeds our understanding of the experiences underlying survey responses. *Qualitative health research offers a specific approach to examine contradictions, inconsistencies, and connections among elements touched on by surveys.*

### III. Utility of Qualitative Health Research to Address These Problems

Qualitative health research is well suited to investigate topics and issues in sexual dysfunction research for several reasons:

- Qualitative health research encompasses a wide choice of methods to suit particular questions;
- Qualitative health research includes methods designed to examine the subjective and interpersonal domains, which are typically neglected areas in clinical trials or large-scale survey research.
- Qualitative health research emphasizes the context of behavior, and thus is well suited to examine cultural, gender, and age variations in the quality of sexual experience.

As noted above, qualitative research is particularly valuable in generating hypotheses or constructs to explain conflicting or problematic outcomes. For example, *qualitative interviews with patients, partners or health-care providers may provide insights*
regarding incentives or obstacles for treatment-seeking or maintenance of treatment for sexual dysfunction.

These insights can be used to guide more sophisticated clinical care and can also be used in further quantitative research.

IV. QUALITATIVE AND QUANTITATIVE HEALTH RESEARCH: A COMPLEMENTARY RELATIONSHIP

In the past, qualitative and quantitative methods have been viewed as competing or rival approaches, and it was not uncommon for quantitative researchers to demean, demote or even dismiss evidence obtained from qualitative observations or interviews. More recently, however, it has been observed that: “the classic qualitative-quantitative debate has been largely resolved with recognition that a variety of methodological approaches are needed and credible, that mixed methods can be especially valuable, and that the challenge is to appropriately match methods to questions rather than adhering to some narrow methodological orthodoxy”. [10] As in other areas of health research, a combined and integrated approach is optimally effective. [2] Common reasons for considering qualitative approaches, described in Read Me First for a User’s Guide to Qualitative Methods, [9] include:

- A gap exists in the literature because a topic has been overlooked
- Another way of looking at a topic is needed because research is contradictory or confused
- People ask “What is going on here” about some subject because they need more detail and theoretical substance
- Researchers want to begin studying a subject (although they plan to end up with quantitative inquiry)
- People employed in a particular setting with patients and coworkers are thinking about beginning a program of research.

V. SPECIFIC EXAMPLES IN SEXUAL MEDICINE RESEARCH

Clinical examples are valuable to illuminate the approach and style of qualitative health research. The following recent studies illustrate some of the methods used, in addition to the ways in which goals, questions, conclusions and motives play an essential role in qualitative research.

Two New York City family physicians (assisted by four medical students) conducted a qualitative interview study with 44 women recently diagnosed with vaginitis [11]. The researchers were concerned about outcomes associated with clinical management of vaginal complaints in women because of: poor correlation between microorganism identification and patients’ report of symptoms, “fifty per cent of women with symptoms remain undiagnosed even after extensive diagnostic workup,” [11] and symptoms associated with vaginitis such as discharge, odor and itching are common in the normal population and do not necessarily indicate the presence of disease. The researchers decided to use qualitative methods to explore the patients’ subjective perspectives of these symptoms to help illuminate and resolve these management problems.

They conducted semi-structured 30-45 minute individual interviews of their primarily Caribbean patients “to investigate how women interpret vaginal sensations as symptoms and construct these symptoms as a problem requiring medical care” “Given the symbolic significance of the vagina, we thought it likely that women’s experiences with vaginal symptoms might be suffused with meanings related to sexuality, morality, and women’s gender roles” [11].

The results were presented largely as quotes from the interviews along with brief commentary, showing that women ranged widely in their conceptions of a normal vagina and the possible causes of vaginal symptoms. Most women in the study had not discussed their most serious worries or concerns with their providers, nor had they mentioned alternative treatments they had used. Many of the subjects interviewed expressed strong disgust and shame about their vaginal symptoms, and a number of the women were extremely anxious about the fertility and sexuality implications of their vaginal symptoms.

The authors interpreted their findings as evidence that physicians do not typically understand patients’ experience of vaginal symptoms, and that many times patients and doctors are “talking past each other” [11]. Physicians often ignore the psychosocial aspects of the situation, fail to address fears and false information, and are surprised when medical recommendations are not followed and complaints become
chronic. They conclude that “the conventional disease model of vaginitis is an inadequate conceptual framework, both for understanding and for managing this common disorder...[and recommend] open dialogue about symptoms, about their meaning and implications, and about the normal variation among individuals in vaginal wetness, odor and itching” [11].

This study illustrates the valuable role of qualitative research in elucidating the subjective reactions of women to common symptoms of vaginitis. Just as the researchers in this study gained significant insights into the responses of their subjects to vaginitis, similar methods can and should be used to assess subjective responses to sexual dysfunction. There are enough similarities between the problems giving rise to this study and its conclusions and the clinical situation surrounding sexual dysfunction to suggest a valuable role for qualitative inquiry. Many sexual medicine clinicians will recognize elements of their own practice in this picture of patients who give their symptoms diverse, shame-infused meanings, who have vague and extreme fears, who withhold information, and who return time and again with their condition unimproved.

Another example may illuminate how sexual complexities in women’s lives that remain hidden in quantitative survey research can be revealed by qualitative research. Psychologists Sherry Hamby and Mary Koss recently conducted five ethnically and geographically diverse focus groups to discuss sexual victimization [12]. They recruited African-American women and conservative Christian women from church settings, Apache Native American women from office settings, men employed as corrections officers and college student men. Each group reflected on survey questions popularly used to inquire about unwanted, nonvoluntary, forced, and coerced sex among women, and all groups felt these terms had very different meanings and would produce very different statistics. The groups discussed their discomfort with sexually explicit language, and yet “most seemed to feel that it was preferable to be explicit and get good data than to use potentially ambiguous terms like unwanted or nonvoluntary and then not be sure about exactly what you have” [12]. The authors provide many excerpts from the group discussions of these complex issues, and conclude that “qualitative research and theory development have key roles to play in furthering our understanding of the varieties of negative sexual experience...Reducing confusion over terminology is key to continuing to improve our assessment of sexual victimization.” [12]. As with the study of vaginitis, there are direct parallels to our understanding of sexual dysfunction to be found in this research.

VI. QUALITATIVE RESEARCH TRADITIONS, METHODS AND PERSPECTIVES

1. THE NATURE OF QUALITATIVE EVIDENCE

The evidence-based medicine (EBM) movement rightly promotes “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” [13] (p. 71, emphasis added). The EBM movement embraces the role of clinical skills and experience in the diagnostic process, but not in determining the choice of therapy [14]. This determination should be based on quantitative research that is rank-ordered according to certain methodological qualifications. The highest level of evidence is obtained from systematic reviews of randomized controlled trials (RCTs) (e.g. Cochrane’s reviews) and the fifth and lowest level of evidence “represents the opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees” [15]. It is noteworthy that qualitative methods have recently been adopted as a component of evidence-based medicine [2] and that a Cochrane’s Review Committee for Qualitative Health Research has recently been established.

The choice of study design in qualitative health research is usually based on the nature of the question being addressed and population to be studied. General approaches include the following [2]

Phenomenological or subjective experience. As illustrated in the above examples, qualitative studies are often designed to obtain as much information as possible about the personal and subjective experience of individual subjects in relation to the topic of interest (e.g. vaginitis, sexual coercion). In-depth, one-to-one interviews or small discussion groups led by experienced researchers are typically used for obtaining this information. Formal techniques are used for distinguishing between the verbatim narrative of the subjects and the thematic interpretation of researchers based on the narratives provided.

Grounded theory. Based on responses from individuals or groups of individuals, the researcher typically develops a conceptual framework or “grounded
theory” to explain the issue or problem under consideration. This theory is then evaluated in further qualitative studies with other groups of subjects, and modified accordingly. Theoretical constructs are developed and refined inductively, based always on the qualitative responses of involved subjects.

**Action research.** Participatory or action research is based on the essential idea of collaboration or positive participation between researchers and subjects. “Action to promote change” is a core construct of qualitative health research. *Ideally, subjects and researchers share a common commitment to this principle, and participate actively together in defining the research agenda and identifying suitable topics to be explored.*

**VII. SPECIFIC AREAS OF APPLICATION TO SEXUAL PROBLEMS AND DYSFUNCTION**

1. **Better understanding of individuals’ experiences of sexual problems**

Qualitative sexual research (QR) can explore the concern that current models of sexual response and dysfunction may be too genitally focused and make distinctions between sexual arousal and sexual interest that are arbitrary and that do not reflect an individual’s experiences. QR can provide a balance in research perspectives. QR explores the myriad of psychological and interpersonal factors that can affect desire and arousal.

Current diagnostic approaches for sexual problems in women are often felt to be unsatisfactory, and recent attempts to modify the DSM-IV diagnostic categories have been criticized (for detailed discussion see *Journal of Sex and Marital Therapy*, Vol 27 No 2, 2001). Rather than having researchers/clinicians try to reach “consensus” on the classification of sexual problems (particularly for women), QR allows and encourages women research participants to describe their experiences in ways that may allow us to arrive at a broader and more inclusive diagnostic system more attuned to the range of women’s and men’s sexual complaints.

Researchers should strive to understand the nature of sexual desire and arousal in non-clinical as well as clinical samples. We need a clearer understanding of how individuals experience sexual problems, in their own terms. To do this requires QR into basic questions e.g., “How do women and men experience, and conceptualize, sexual desire and arousal? “How does sexual desire relate to sexual response, and behavior in the context of relationships?” [16] How do the experiences of sexual response and problems, and the factors related to them, vary in different cultural contexts? QR addressing these questions could improve our understanding of how men and women conceptualize, prioritize, report and recall their sexual experiences and sexual difficulties and generate hypotheses for further research.

2. **Design of assessment and treatment studies**

QR has been recommended as a means to construct questionnaires for more than a decade [17] but has seldom been used in the area of sexuality research. Similarly, clinical “end-points” in sexual dysfunction studies often focus on quantifiable elements such as frequency of intercourse, genital response, and orgasm. There is a widespread assumption, not supported by much social science research, that orgasm is a necessary requirement for a “successful and satisfactory sexual event” [18]. In a recent US survey, for example, physical aspects of sexual response in women including arousal, lubrication, and orgasm were not good predictors of distress about sex, whereas general well-being and relationship with partner were [5]. Qualitative research could inform more meaningful assessment instruments and clinical end-points for treatment studies.

Qualitative research is of crucial importance for developing research instruments to use in varied cultural (and sub-cultural) settings. For example, in a World Health Organization study [19] evaluating changes in sexuality in women in Scotland and the Philippines after starting oral contraceptives, there were marked pre-treatment differences in sexuality-related variables between these two cultural settings. The researchers discussed the possibility that the methods of assessment may have been less appropriate for the Philippine women. The key question is “How can we define sexual functioning in culturally sensitive ways?” QR offers several different methods to address this question.

Many sexual dysfunction treatments focus on improving genital response, but the success and consequences of treatment may be affected as much by relational and cultural factors as by physical and psychological changes [20]. *Little systematic research is being undertaken into the nature of relational*
and cultural factors and QR has the potential of elucidating the many factors that can affect sexual functioning. Also, we do not have a clear idea of the range of answers and advice patients are looking for when they seek treatment. Again, QR can shed light on this issue.

In a recent focus group study designed to help inform the development of a questionnaire to assess sexual excitement and inhibition in women, a broad range of factors were cited as influencing sexual arousal [21]. Women reported that they recognize sexual arousal using a wide range of cues, including physical (genital and non-genital), as well as emotional, behavioral, and cognitive changes. Lubrication was one of many cues for arousal, but neither a necessary nor sufficient one. Participants also did not clearly differentiate between desire and arousal, nor did desire always precede arousal, as the triphasic model of sexual response [22] underlying current diagnostic categories would imply.

3. ADDITIONAL AREAS FOR APPLICATION OF QR RESEARCH IN SEXUAL MEDICINE:

1) evaluating couples and individual’s experiences of therapies (both sex therapy and drug therapies); 2) better understanding of patients’ experiences in placebo controlled trials; 3) identification of prognostic factors in treatment outcome; and 4) exploring gender differences and dynamics in diagnosis, treatment and evaluation of outcomes. QR potentially gives voice to patients’ views on the actual experience of sexual problems and treatment that can help inform future research and clinical work.

VIII. SUMMARY AND RECOMMENDATIONS

This chapter provides a broad overview of the conceptual basis and rationale for applying QR methods in the study of sexual dysfunction problems in men and women. QR is a rapidly developing field of study, with broad application in both the biomedical and psychosocial sciences. A major point of emphasis in this chapter is that QR should be viewed as a complementary approach, and is not inherently antithetical or contradictory to traditional quantitative methods in sexual medicine. Ten- sions exist, but they are not irresolvable, and more and more researchers are combining these approaches as appropriate to different phases and aspects of study. Qualitative methods are particu- larly well-suited to investigate the psychological or interpersonal reactions of individuals to their sexual problems, as well as the responses of partners or other affected individuals. QR also focuses attention on the social context of sexual dysfunction, and may be used to generate hypotheses for including these factors in more formal quantitative studies.

Specific examples are provided in this chapter of QR applications to current problem areas in sexual dysfunction research. In particular, qualitative studies are being used increasingly in the early stages of questionnaire development for identifying relevant domains and topic areas to be addressed. Subjects are invited to participate actively in focus groups or individual interview settings to collaborate with investigators in developing relevant and psychologically meaningful questionnaires. However, casual group discussion is not the same as professionally conducted and analyzed qualitative focus groups. Informal interviews and group discussion have a place in the preliminary information-gathering stages of all research, but this should be distinguished from well-prepared, conducted and analyzed QR. Qualitative methods are also being used to investigate treatment-seeking motivation and barriers to care in men and women with sexual problems. Finally, communication between physicians and patients regarding sexual health issues are being investigated in QR studies. Overall, qualitative health research provides a complementary or alternative approach for addressing important issues or topics not addressed in traditional quantitative research. It is strongly recommended that this approach be used more frequently and systematically in future research on sexual dysfunction in men and women.

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A. Morales (Canada), J. Buvat (France), L.J. Groen (Netherlands), A.T. Guay (USA), J.M. Kaufman (Belgium), Young C. Kim (Korea), H.M. Tan (Malaysia), L.O. Torres (Brazil)

CHAPTER 12 Committee 8 Priapism, Peyronie’s Disease, Penile Reconstructive Surgery
J. Pryor (U.K), E. Akkus (Turkey), G. Alter (USA), G. Jordan (USA), T. Lebret (France), L. Levine (USA), J. Mulhall (USA), S. Perovic (Serbia), D. Ralph (U.K), W. Stackl (Austria)

CHAPTER 13 Committee 9 A Disorders of Orgasm and Ejaculation in Men
C. G McMahon (Australia), C. Abdo (Brazil), E. Hull (USA), L. Incrocci (Netherlands), R. Levin (U.K), M. Perelman (USA), D. Rowland (USA), M. Sipski (USA), B. Stuckey (Australia), M. Waldinger (The Netherlands) Z. Cheng Xin (China)

CHAPTER 14 Committee 13 Implants, Mechanical Devices and Vascular Surgery for Erectile Dysfunction
John J. Mulcahy (USA), E. Austoni (Italy), J. H. Barada (USA), H. Ki Choi (Korea), W. J.G. Hellstrom (USA), S. Krishnamurthi (India), I. Moncada (Spain), D. Shulteiss (Germany), M. Sohn (Germany), H. Wessells (USA)

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H. Padma-Nathan (USA), G. Christ (USA), G. Adakian (Singapore), E. Becher (Argentina), G. Brock (Canada), S. Carrier (Canada), C. Carson (USA), J. Corbin (USA), S. Francis (USA), R. DeBusk (USA), I. Eardley (U.K), H. Hedlund (Norway), A. Hutter (USA), G. Jackson (U.K), R. Kloner (USA), C. Lin (USA), K. McVary (USA), A. McCullough (USA), A. Nehra (USA), H. Porst (Germany), C. Schulman (Belgium), A. Seftel (USA), I. Shalrip (USA), C. Stief (Germany), C. Teloken (Brazil)

CHAPTER 16 Committee 15 Future Treatment Targets
K-E Andersson (Sweden), A. Argiolas (Italy), A. Burnett (USA), K.K Chen (China), T.M Mills (USA), W. D Steers (USA)

CHAPTER 17 SUMMARY OF THE RECOMMENDATION FOR MEN
Committee 5

Clinical Evaluation and Symptom Scales: Sexual Dysfunction Assessment in Men

Chairmen

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2. RECOMMENDED QUESTIONNAIRES FOR MEN AND WOMEN

3. SUMMARY AND CONCLUSIONS

REFERENCES
Sexual problems are highly prevalent and bothersome, yet frequently neglected in clinical practice. Even among clinicians who acknowledge the relevance of addressing sexual concerns in their patients, there is a general lack of understanding of the optimal approach for sexual problem identification and evaluation. In this chapter, we provide basic guidelines and describe the broad approach for assessing sexual problems in primary care or general medical practice. Guidelines are presented for specialized assessment of erectile dysfunction (ED), which is the most common presenting problem in men. Specialized diagnostic approaches for evaluating other sexual problems in men are described in Chapter 7 (Priapism and Peyronie’s Disease) Chapter 8 (Orgasm Disorders), and Chapter 11 (Endocrine Disorders). Specialized approaches in women are described in Volume II; Chapter 7 (Orgasm Disorders in Women), Chapter 9 (Endocrine Disorders in Women) and Chapter 10 (Women’s Sexual Dysfunctions). Readers are referred to these chapters for detailed guidelines on diagnostic evaluation of these problem areas.

Three basic principles or approaches underly the management of sexual problems in both men and women. These concepts are: (i) adoption of a patient-centered framework for evaluation and treatment; (ii) application of the principles of evidence-based medicine in diagnostic and treatment planning; and (iii) use of a unified management approach in evaluating and treating 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 dysfunction.

Traditionally, the dominant model in medicine has been the “disease-centered” approach, which assumes that disease is “fully accounted for by deviations from the norm of measurable biological variables”[1]. The “disease-centered” model focuses on medical consultation and establishment of an essentially patriarchal doctor-patient relationship, in which the patient fulfills a passive role and the doctor embodies medical expertise. It aims to measure outcomes in an objective and quantifiable way, while often neglecting that “people do not come in for diagnosis and treatment; they come to be made well, made whole, to recover the sense of health, of being well, fully alive, in-the-world” [2]. This applies particularly in the case of sexual medicine. Patient-centered care, on the contrary, is “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” [3].

Balint [4], in describing the term “patient-centered medicine”, has emphasized the significance of “understanding the patient as a unique human being”. One recent definition describes it as the health care approach that establishes a partnership among practitioners, patients and their families (when appropriate) to ensure that medical decisions respect patients’ wants, needs and preferences, and solicit patients’ input on the education and support needed to make key decisions and participate in their own care.

Patient-centered medicine assumes a holistic approach that takes into account not only the biological dimension of disease, but also its psycholo-
gical and social implications, in accordance with the definition of health of the World Health Organization [5].

The term “goal-directed approach”[6], is similarly focused on the need to consider the patient’s goals and motivation in making diagnostic or treatment decisions. The goal-directed approach was developed as an alternative to costly and invasive diagnostic testing for ED, and emphasizes the role of patient education and dialogue. This approach views the medical and psychosocial history as the cornerstone of effective diagnosis [7].

1. PATIENT-CENTERED CRITERIA FOR DEFINING SEXUAL DYSFUNCTION

In defining a sexual dysfunction, the following patient-centered criteria should be considered:

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 problem. Sexual dysfunctions are essentially self-reported conditions; as such, 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.

Current WHO definitions [5] view sexual health as “a state of physical, emotional, mental and social well-being related to sexuality; it is not merely the absence of disease, dysfunction or infirmity”. According to this definition, 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.

Outcomes assessment should focus not only on resolution of symptoms, but also on overall patient satisfaction. Scant data are available on outcomes evaluation with patient-centered approaches in sexual medicine. However, published data on patient-centered management of other medical conditions have shown that this approach is associated with increased efficiency of care (fewer diagnostic tests and referrals) [8], increased patient [9,10] and physician satisfaction [11], higher compliance [12] and fewer malpractice complaints [13].

2. THE PATIENT-PHYSICIAN DIALOGUE: FORMING A HEALING RELATIONSHIP

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.

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. As McCormick and others have observed: “it is as important to know the patient who has the disease, as it is to know the disease which the patient has” [13].

This patient-centered framework is essential to understanding the context of the sexual problem, and at times to answer the question “why now?”. Ideally, each of these elements should take place within a healing doctor-patient relationship, characterized by empathy, genuineness, respect, caring, mutual trust, and readiness to accept difference. Patient-centred medicine is “two-person medicine”, in contrast to the traditional doctor-centered approach, which can be characterized as “one person medicine” [14]. The patient-centered approach provides an important complement to the principle of evidence-based medicine, as described below.

3. EVIDENCE-BASED ASSESSMENT OF SEXUAL DYSFUNCTION

Clinical decision-making is guided increasingly by the results of randomized, clinical trials (RCT’s), 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 and systematic reviews can inform the decision-making process in multiple ways. In selecting among available diagnostic and treatment options, both clinicians and patients should evaluate the potential risks and
benefits as determined by the weight of clinical evidence. As noted by McGovern: “Evidence-based medicine (EBM) has become an established component of the way we look after our patients. It has blossomed into a multidimensional concept that is evolving to respond better to the needs of patients and to the health professionals looking after them”[15] Evidence-based evaluation implies that patients, as well as physicians, should be guided in their decision-making by the findings from controlled research. EBM should be applied to patient, as well as physician decision-making. Specifically, each patient has the right to be fully informed concerning his or her 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 [16].

Strong consideration should be given to the evidence basis for diagnostic evaluation in each case. 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 treatment 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. As noted above, EBM and patient-centered medicine are viewed as highly complementary and equally applicable in the clinical management of sexual dysfunction.

Although not usually applied to diagnostic testing, a recent evidence-based analysis of laboratory hormone evaluations in ED showed that among 3,500 men with ED in the U.S. Veterans Administration (VA) Health Care System, 18.7% had low testosterone, 14.6% had abnormal LH levels, and 4.6% had increased prolactin levels [17]. The authors argue that these data strongly support the need for laboratory hormone analysis as part of the EBM-based evaluation of men with ED.

4. A COMMON MANAGEMENT APPROACH IN MEN AND WOMEN

The evaluation of sexual dysfunction problems in men and women includes patient-physician dialogue, history taking (sexual, medical and psychosocial), focused physical examination, and specific laboratory tests (in most cases). Specialist referral may be considered at any time that the patient or treating physician feels is appropriate. Following the initial evaluation, all patients should be provided with a detailed review of findings and explanation of the nature and likely causes of their problem. If the initial findings do not preclude direct treatment for the sexual problem, patients should be informed as to the available treatment options and the likely benefits and disadvantages or risks of each option. Patients should always be encouraged to participate actively in the decision-making process.

Available treatment options should be described based on evidence-based review of the literature and a shared decision-making process should guide the development of an individualized management plan. In cases where initial findings indicate a need for further evaluation, referral to a specialist or specialized testing should be considered. Careful attention should always be paid to the presence of significant comorbidities or underlying etiologies (e.g., cardiovascular disease, diabetes, depression). These are described in greater detail below.

The overall approach for sexual problem management in men and women is illustrated diagrammatically in the following schematic. A detailed description of each stage in the process will follow (Table 1).

II. CLINICAL ASSESSMENT AND DIAGNOSIS

1. DEVELOPMENT OF A BASIC MANAGEMENT STRATEGY: “ALLOW”

Initial assessment of a sexual problem should always include a detailed sexual, medical and psychosocial history. 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 brief checklists or questionnaires may be of value in the recognition and initial evaluation of a sexual problem (see below), 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.

Primary care clinicians who identify sexual issues or complaints during the initial evaluation, but who feel uncomfortable in exploring the topic further, should refer such individuals – either to a specialist, if one is available, or to a colleague with aptitude or interest in managing sexual problems. This flexibility of response to the patient’s sexual concern or problem is illustrated by the acronym, “ALLOW” (See Table 1. Basic Algorithm for Sexual Dysfunction (SD) Evaluation in Men and Women)

2) The “ALLOW” acronym draws attention to the need for all clinicians to inquire about sexual activity, while recognizing the limitations and varied needs and interests of clinicians in specifically 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 and typical examples are provided in Table 3. 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. Based on this self-evaluation by the clinician, the next step is taken and the clinician has done it “ALL” for the patient. Step 4 involves “Opening up
the discussion” and the potential referral to a colleague or sub-specialist to further investigate and manage the patient’s problem. The final stage in the process involves dialogue with the patient to identify an appropriate goal and mutually acceptable management plan (Figure 2).

Table 2. “ALLOW” Algorithm for Managing Sexual Dysfunction: A Sample Management Plan

2. Identifying a Sexual Problem: The Brief Sexual Symptom Checklist (BSSC)

Sexual problem identification should be regarded as a routine and necessary aspect of medical care. 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. A single question (e.g., “Do you have questions or concerns about your sexual functioning?”) may be sufficient in some circumstances, whereas a more detailed sexual history is indicated in others. Sexual inquiry is most often conducted by face-to-face interview with the patient, although paper-and-pencil questionnaires, or computer-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.

Symptom scales 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. The most commonly used questionnaires are reviewed in Part IV of this chapter. To facilitate initial identification of a sexual problem, a brief screening checklist has been developed specifically by this committee. This brief checklist consists of 4 simple questions (see below). The brief symptom checklist is suitable for use in primary care settings and addresses the patient’s level of satisfaction with sexual function (the major outcome measure in sexual health). 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 men (Table 3).

Table 3. Brief Sexual Symptom Checklist for Men
Please answer the following questions about your overall sexual function in the past 3 months or more.
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. 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. Basic principles for sexual history-taking are summarized below (Table 4).

**Table 4. Basic Principles for Sexual History-Taking**

- Allow the patient to feel in control
- Provide explanations for answers
- Help the patient feel less abnormal (destigmatize)
- Provide encouragement and positive support
- Initiate the discussion of sensitive topics
- Defer sensitive questions
- Be aware of patient’s cultural background
- Ensure confidentiality
- Avoid judgmentalism

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. **The medical and sexual history are 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 5 below. These questions apply specifically to the evaluation of male arousal, desire and orgasm/ejaculation difficulties. In principle, these questions may addressed to all men presenting with sexual difficulties.

**Table 5. Sample Topics for Sexual History Taking in Men**

**AROUSAL / PERFORMANCE**

**CHRONOLOGY**
When was the last time you had a satisfactory erection?
Was the onset of your problem gradual or sudden?
When was your last normal erection?

**QUANTIFY**
Do you have morning or night time erections?
On a scale of 1 to 10 rate your rigidity during sex?
With sexual stimulation can you initiate an erection?
With sexual stimulation can you maintain an erection?

**QUALIFY**
Is your erectile dysfunction partner or situational specific?
Do you lose erection before penetration, or before climax?
Do you have to concentrate to maintain an erection?
Is there a significant bend in your penis?
Do you have pain with erection?
Are there any sexual positions that are difficult for you?

**LIBIDO / INTEREST**

Do you still look forward to sex?
Do you still enjoy sexual activity?
Do you fantasize about sex?
Do you have sexual dreams?
How easily sexually aroused (turned on) are you?
How strong is your sex drive?

**EJACULATION / ORGASM / SATISFACTION**

Are you able to ejaculate when you have sex?
Are you able to ejaculate when you masturbate?

If you have a problem with ejaculating, is it:
- You ejaculate before you want to?
- You ejaculate before your partner wants you to?
- You take too long to ejaculate?
- You feel like nothing comes out?

Do you have pain with ejaculation?
Do you see blood in your ejaculation?
Do you have difficulty reaching orgasm?
Is your orgasm satisfying?
What percentage of sexual attempts are satisfactory to your partner?
3. MEDICAL AND PSYCHOSOCIAL ASSESSMENT

A detailed medical and psychosocial history 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. Table 6 below provides a sample checklist of medical conditions to be assessed in male patients with sexual dysfunction (ii) To differentiate between potential organic and psychogenic causes in the etiology of a patient’s sexual problem. Table 6 illustrates this aspect of the evaluation. (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 (e.g. nitrates, alpha-blockers) may be important contraindications for the use of specific treatments (e.g. PDE-5 inhibitors) (Tables 6, 7).

a) Differentiating Organic and Psychogenic Etiologies

The etiology or causal factors for sexual dysfunction may or may not be apparent from the patient’s history alone. Further investigation by means of a physical examination and selected laboratory testing may be of value in confirming or disconfirming specific etiologies or comorbidities. Potential etiologies for sexual dysfunction include a wide range of organic/medical factors (e.g. cardiovascular disease, hyperlipidemia, diabetes, hypogonadism) and/or multiple psychological or interpersonal factors (e.g. anxiety, depression, relationship distress). Psychosocial factors are described in greater detail in Chapter 4. It is important to note that, in many cases, organic and psychogenic factors may coexist, particularly in individuals or couples with long-standing or chronic sexual dysfunction. In such cases, clinicians should assess the independent and interactive role of both organic and psychogenic factors, and these should be reviewed with the patient during the final stages of assessment.

Key aspects of the history may be used to identify the potential role of specific organic and psychogenic causes or etiologies. Although not always definitive, a detailed medical and psychosexual history may provide suggestive evidence for or against the role of specific organic or psychogenic factors. The following table provides an overview of specific aspects of the patient’s history that may be useful in differentiating organic from psychogenic erectile dysfunction (ED). It should be emphasized however that psychogenic and organic etiologies co-exist in a large number of cases (Table 8).

b) Psychosocial History

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. Sample topics for psychosocial assessment are illustrated in Table 9 below.

c) Physical Examination

The physical examination is an essential component of sexual dysfunction evaluation in every case. In most cases, the physical examination will not identify the specific etiology or cause of sexual dysfunction, however a focused examination should be performed on every patient with sexual problems. 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 genitalia and secondary sex characteristics (See Table 10). 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) (Table 10).
Table 6. Medical History Checklist

Has a doctor ever diagnosed any of the following illnesses? [check for yes]

- High blood pressure
- Heart disease (heart attack, chest pain with exercise or sex)
- Diabetes (high blood sugars)
- Hyperlipidemia (elevated cholesterol or triglycerides)
- Vascular diseases (stroke, mini-stroke, blockage of arteries, aneurysms)
- Emotional problems (depression, anxiety or other psychiatric conditions)
- Hormone problems (Testosterone, Thyroid, Steroids)
- Kidney disease
- Neurological problems (Parkinson’s, Multiple Sclerosis, spine injury)
- Trauma or injury to: penis, pelvis, perineum, testes, or rectum
- Prostate problems (enlargement, BPH, elevated PSA, infection)
- Urinary problems (urgency, frequency, hesitancy, weak stream, infection)
- Sleep apnea (severe snoring, daytime sleepiness)
- Chronic fatigue or weakness
- Cancer of the bladder, prostate or rectum
- Radiation of the bladder, prostate or rectum
- Unexplained weight loss
- Joint pains (severe or chronic problems moving or changing positions)
- Sexually transmitted diseases

Table 7. Medication Checklist

Are you taking or have you used any of the following medications, nutritional supplements or drugs in the last three months? (check for yes)

**Prescription Medications** [check for yes]

- High blood pressure pills,
- Heart pills
- You keep nitroglycerin tablets in your pocket or home
- Blood thinning pills (Aspirin, Coumadin, Heparin)
- Diabetes pills or Insulin
- Cholesterol lowering pills
- Prostate pills
- Hormone pills or injections (Testosterone, Thyroid, Steroids)
- Breathing pills or inhalors
- Antidepressant pills
- Ulcer treatment or prevention pills
- Other

**Over the Counter** [check for yes]

- Herbs or nutritional supplements for dieting,
- Herbs or nutritional supplements for depression, headache or memory enhancement
- Herbs or nutritional supplements for prostate health
- Other

**Recreational Drugs** [check for yes]

- Smoke cigarettes or cigars
- Alcohol
- Marijuana
- Ecstasy
- Heroin
- Cocaine
- Other

Table 8. Distinguishing Psychogenic from Organic Erectile Dysfunction

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Organic</th>
<th>Psychogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>older</td>
<td>younger</td>
</tr>
<tr>
<td>Onset</td>
<td>gradual (except trauma or surgery)</td>
<td>acute</td>
</tr>
<tr>
<td>Circumstances</td>
<td>global</td>
<td>situational</td>
</tr>
<tr>
<td>Symptom Course</td>
<td>consistent or progressive</td>
<td>intermittent</td>
</tr>
<tr>
<td>Morning Erection</td>
<td>poor</td>
<td>rigid</td>
</tr>
<tr>
<td>Desire</td>
<td>normal</td>
<td>decreased</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 and fear</td>
<td>secondary</td>
<td>primary</td>
</tr>
</tbody>
</table>

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 are presented in greater detail in Chapter 16.

In some instances, a physical examination may be desirable, although not strictly essential. Possible examples include:

1) situational problems;
2) generalized dissatisfaction with sexual activity in the absence of specific sexual dysfunction;
3) mood disturbances; or
4) 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.

d) Laboratory Testing

Recommended laboratory tests for men and women with sexual problems typically include fasting glucose, cholesterol, lipids and hormonal profile (See Table 11). 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 Chapter 11. Additional laboratory tests (e.g., thyroid function) may be performed at the discretion of the physician, based on the medical history and clinician’s judgement.

Table 11 below summarizes the required, recommended and optional aspects of the initial evaluation of male sexual dysfunction. As is shown, all male patients presenting with sexual dysfunction should receive a detailed sexual, medical and psychosocial history. A focused physical examination and laboratory testing (fasting glucose, lipid profile and testosterone assessment) should be performed in every case. Specialized and optional aspects of the evaluation are presented in the following sections (Table 11).

4. REVIEW OF FINDINGS AND PATIENT-PARTNER DIALOGUE

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 psychiatric 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.

5. SPECIALIST CONSULTATION AND REFERRAL

With the advent of effective oral treatment for ED, primary care practitioners currently manage the majority of cases of male sexual dysfunction. This is

<table>
<thead>
<tr>
<th>Required Evaluation</th>
<th>Recommended Tests</th>
<th>Optional Diagnostics</th>
<th>Specialized Evaluations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief Sexual, Medical and Psycho-Social History:</td>
<td>Fasting glucose</td>
<td>Prolactin</td>
<td>Cavernous Injection/Stimulation (CIS)</td>
</tr>
<tr>
<td>a) Patient/Physician Dialogue</td>
<td>HgbA1C</td>
<td>LH</td>
<td>CIS and Color Duplex Doppler</td>
</tr>
<tr>
<td>b) Checklists</td>
<td>Lipid profile</td>
<td>TSH</td>
<td>Dynamic Infusion</td>
</tr>
<tr>
<td>c) Questionnaires</td>
<td>Testosterone (AM)</td>
<td>CBC</td>
<td>Cavernosometry and Cavernosography</td>
</tr>
<tr>
<td>d) Scales</td>
<td></td>
<td>PSA</td>
<td>(DHCC/CASOP)</td>
</tr>
</tbody>
</table>

| Comprehensive History: Libido vs. ED vs. EJD | | | |
| a) Dialogue | | | Penile Angiography |
| b) Checklists | | | Nighttime Penile Tumescence and Rigidity (NPTR) |
| c) Questionnaires | | | Neurophysiology testing |
| d) Scales | | | Cardiovascular testing |
| e) Event Diaries | | | Endocrine testing |

Table 11. Key Elements in the Diagnostic Evaluation of Male Sexual Dysfunction
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. Major reasons for selecting this option are summarized in the following table. 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. 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 (Table 12).

### Table 12. Indications for Specialized Referral and/or Diagnostic Evaluation

- Patient request
- Treatment failure
- Primary ED (poorly sustained erections, life-long)
- Anatomic penile deformities
  - Peyronie’s Disease
  - Congenital: hypospadius, chordee
  - Trauma
  - Phimosis
  - Short penis, buried penis
- Pelvic/ perineal trauma
- Endocrinopathy
- Psychiatric or Psychosexual disorder
- Relationship problems
- Complex vascular problems
- Complex neurologic problems

A broad array of specialized diagnostic tests and procedures are available, particularly for assessing ED. 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, couple’s conflict). Further details regarding the vascular and neurologic assessment of ED are provided below.

### 6. Shared Decision-Making and Treatment Planning

Following completion of the initial diagnostic evaluation, patients (and partners where possible), should be given a detailed description of the available treatment options. These should include both medical and non-medical options, whenever indicated. Although certain options (e.g. PDE5 inhibitors) may be preferred by the majority of men with ED, all patients should be informed about the availability of other treatment options, such as vacuum erection devices, intra-urethral suppositories or intracorporal injections, and 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. 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.
7. Developing a Follow-Up Strategy: “FAST”

A key issue in the management of sexual dysfunction is the need to address psychosocial components and the specific relationship and cultural aspects of the problem. A partner’s reluctance to provide support or unrealistic expectations may negatively influence the response to treatment. Any treatment is associated with a certain level of expectation of success; it is, therefore, essential to educate both patients and partners on optimizing treatment success with a specific type of treatment before seeking alternative management options. Regardless of the treatment option chosen, follow-up is essential 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 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 are important considerations in the follow up visit, especially in difficult-to-treat populations, such as post radical prostatectomy ED.

In patients who do not respond to so-called first line treatments (e.g. oral therapy), second-line and third-line treatment options should always be considered, since most of these treatments have demonstrated reasonable response and satisfaction rates in controlled studies (See Chapters 13, 14). Diagnosis and treatment of sexual dysfunction however, should not be delayed or postponed if patients desire immediate treatment. A variety of first-line treatment options are currently available for most forms of sexual dysfunction. Treatment should be efficient and comprehensive whenever possible. Follow-up is the last essential element in ensuring adequate management of common sexual problems.

The following “FAST” acronym is a useful reminder of the key aspects of follow-up for sexual dysfunction generally (Table 13).

Table 13. The “FAST” Guideline for Follow-Up

- **Follow-up of Patients.**
  Sexual dysfunction should be managed in a similar way to other chronic medical or psychological conditions. Follow-up visits are essential to improve physician-patient communication, 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 Dosage.**
  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 partners on suitable methods of stimulation.

- **Titrating to the Maximum Tolerated Dose.**
  Titrating to the maximum tolerated dose is essential to achieving optimal efficacy and maximizing response rates to pharmacotherapy.

(Source: DG Hatzichristou: [19])

III. Specialized Evaluation of Male 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 presented in Chapter 8. Evaluation of hypoactive sexual desire disorder (HSDD) is provided in Chapter 2 (Psychological aspects) and Chapter 11 (Endocrine aspects). Guidelines for evaluation of Priapism and La Peyronie’s disease are presented in Chapter 7. Finally, the summary chapter (Chapter 15) offers an overview and specific algorithms for diagnosis and clinical evaluation of each aspect of male sexual dysfunction. Overall, it should be noted that psychological and physiological processes interact in complex ways in many disease states. Erectile dysfunction is no exception to this general principle, rather it is a primary example of this phenomenon.

The goal of specialized evaluation is to define the cause of ED. Generally in medicine a specific diagnosis is needed to formulate a treatment plan; in most cases of sexual dysfunction in men this can be
done without extensive testing. On the other hand in the absence of diagnostic testing, efficacy and satisfaction with treatment become a matter of chance. Generally accepted indications for specialized vascular evaluation are: failure of initial treatment, Peyronie’s disease, primary ED, history of pelvic/perineal trauma, cases requiring vascular or neurosurgical intervention, complicated endocrinopathy, complicated psychiatric disorder, complex relationship problems and medico-legal concerns. Furthermore, penile testing may be important for clinical science especially in groups of patients with chronic disease states. [20] The following table summarizes the most frequently employed, evidence-based procedures for diagnostic evaluation of ED (Table 14).

1. VASCULAR EVALUATION

Recent studies strongly support the role of vascular pathophysiology in the majority of cases of ED (See Chapter 10). Specialized vascular testing is thus aimed at identifying and quantifying arterial and veno-occlusive erectile function. In practice, vascular ED is sub-classified as: arterial, veno-occlusive, or mixed vascular insufficiency. The primary etiologies of arteriogenic ED are atherosclerotic vascular disease and traumatic, arterial occlusion (following pelvic or perineal trauma) (Table 15).

The quality of penile inflow has been directly related to common vascular comorbidities, including age, diabetes mellitus, hypertension, atherosclerotic coronary / peripheral vascular disease, hyperlipidemia and cigarette smoking. Veno-occlusion is similarly a hydraulic phenomenon regulating intrapenile pressure changes by penile outflow. The quality of veno-occlusion depends on the tone of cavernous smooth muscle. Clinically, imaging and quantifying veno-occlusion is more difficult than documenting penile arterial inflow. Regulation of cavernous smooth muscle tone is similarly complex. Specific clinical risk factors for veno-occlusive ED have not yet been identified. The forces at play include: neuropharmacologically mediated adrenergic tone, smooth muscle versus extracellular matrix composition, molecular mediators of contraction, and quality of cell to cell communication. These mechanisms are described in detail in Chapter 10.

Vascular evaluation is aimed at diagnosis of two specific aspects: arterial and veno-occlusive dysfunction. At least a decade of experience is available with several tests: ICI pharmacotesting, PBFS, DICC, selective penile angiography.[21] Recently, Burnett

### Table 14. Summary of Evidence-based Tests for Organic ED

<table>
<thead>
<tr>
<th>TEST</th>
<th>LEVEL OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td></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>• Penile Blood Flow Study (PBFS)</td>
<td>2B</td>
</tr>
<tr>
<td>• 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>AVSS: 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>Neurologic</td>
<td></td>
</tr>
<tr>
<td>• NPTR (nocturnal penile tumescence and rigidity)</td>
<td>2B</td>
</tr>
<tr>
<td>• Erectiometer/ Rigidometer</td>
<td>4D</td>
</tr>
<tr>
<td>• Biothesiometry (vibratory thresholds)</td>
<td>3C</td>
</tr>
<tr>
<td>• Dorsal Nerve Conduction Velocity</td>
<td>3C</td>
</tr>
<tr>
<td>• Bulbocavernousus Reflex Latency</td>
<td>2B</td>
</tr>
<tr>
<td>• Plethysmography/ Electrobioimpedence</td>
<td>4D</td>
</tr>
<tr>
<td>• CC-EMG (corpus cavernosum electromyography)</td>
<td>3C</td>
</tr>
<tr>
<td>• MRI or PET scanning of brain (during AVSS)</td>
<td>5D</td>
</tr>
</tbody>
</table>

### Table 15. Indications For Specialized Vascular Testing

- To select patients for penile vascular surgery
- To establish the proper dose of drug for intra- cavernous injection therapy
- To allow the patient to experience the degree of rigidity he may achieve after a maximal pharmacological stimulus
- For scientific and clinical reasons to define the cause of ED in groups of patients with a chronic disease, such as diabetes mellitus or renal failure
- For medicolegal reasons.
et al described the use of a specialized near infrared spectrophotometry instrument for continuous monitoring of the hemodynamics of erection. Near infrared spectrophotometry is a safe, biomedical optics technique that provides quantitative measurements of the vascular physiology of penile erection. [22]

An intracavernous injection pharmacotest (ICI) is easily performed. This is the most commonly used in-office diagnostic. In most cases it is performed without monitoring equipment. Comparison to other hemodynamic tests suggests a normal ICI pharmacotest is associated with normal veno-occlusion (flow to maintain rigidity values of 0.5-3mL/min). Pharmacotesting may be normal (false negative) in as many as 20% of patients with borderline arterial inflow (when nl is defined as > 35 cm/sec peak systolic flow on Doppler and borderline defined as 25-35 cm/sec). False positives occur most commonly because of patient anxiety and or inadequate pharmacologic stimulation. [23] Many vasoactive agents have been described for pharmacotesting, most commonly used is PGE1 at a dosage from 10-20 mcg for initial injection. Aversa et al concluded that a pharmacotest alone is a misleading diagnostic test to exclude vascular ED and that pharmacotesting with color duplex Doppler ultrasound (PBFS) should be offered to patients investigated for male ED. [24] In many cases the response to pharmacotesting is suboptimal, leaving the physician questioning: ‘Does my patient have venous leakage, arterial insufficiency, high anxiety or was the pharmacological challenge insufficient? Should visual erotic and / or vibratory challenge be added?’ (Table 16)

When diagnostic vascular evaluation is indicated, the penile blood flow study, which typically employs intracavernous injection and assessment by color duplex Doppler ultrasound, is the most informative and least invasive means of evaluating vasculogenic ED. This testing may be all that is needed to define and determine severity. Pharmacotesting with duplex Doppler (PBFS) should be performed before more invasive testing is considered. PBFS provides an objective, minimally invasive evaluation of penile hemodynamics [25]. PBFS is the least invasive technology for evaluating vascular ED, distinguishing high-flow from low-flow priapism and identifying Peyronie’s plaques. Recently, the combination of oral sildenafil citrate in association with visual erotic stimulation with virtual glasses has been shown to be an effective non-invasive pharmacological induction method for the purpose of PBFS evaluation. [26, 27, 28]

Table 16. Penile Pharmacotesting Evaluation

<table>
<thead>
<tr>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracavernous penile injection of a vasoactive agent</td>
</tr>
<tr>
<td>Visual rating of erection</td>
</tr>
<tr>
<td>- Compared to best home erection</td>
</tr>
<tr>
<td>- Inadequate, Adequate, Unbending rigidity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
</tr>
<tr>
<td>Minimally Invasive</td>
</tr>
<tr>
<td>Office Test</td>
</tr>
<tr>
<td>A positive response in a neurologically intact patient implies psychogenic impotence.</td>
</tr>
<tr>
<td>A normal injection test indicates normal veno-occlusion.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Despite pharmacologic erection, there may be borderline arterial function.</td>
</tr>
<tr>
<td>Anxiety in testing situations may prevent duplicating best home erection.</td>
</tr>
<tr>
<td>Pharmacologic re-dosing or Doppler ultrasonography may be needed.</td>
</tr>
<tr>
<td>Prolonged erections</td>
</tr>
</tbody>
</table>

The parameters used to infer the integrity of the penile inflow tract are: cavernous arterial diameters, peak systolic arterial velocity (PSV is the maximum of the systolic waveform), end diastolic arterial velocity (EDV), systolic rise time (measured in ms from the start of systole to maximum value), cavernous artery acceleration time (AT is PSV divided by systolic rise time), and index of vascular resistance (RI is PSV minus EDV divided by PSV). PSV < 25 cm/sec following ICI and sexual stimulation has a 100% sensitivity and 95% specificity in selecting patients with abnormal penile arteriography. PSV < 25 cm/sec reflects severe cavernous arterial insufficiency. Whereas, a PSV > 35 cm/sec consistently is associated with normal arteriography and defines normal cavernous arterial inflow. There is a negative relationship between age and PSV [29] Recently Speel et al [30] showed that AT has more power than PSV to diagnose atherosclerotic ED. PBFS is accurate in the assessment of venogenic erectile dysfunction. It should be performed before cavernosometry and a cavernosogram (Table 17).

Cavernosometry and cavernosography should only be performed in cases when PBFS suggests venous impotence, and when surgery is contemplated [31]
Doppler parameters to assess veno-occlusive function are: EDV and RI. After being used at one time as a routine test in almost every patient with ED, DICC is now reserved for the rare patient who might have a site-specific venous leak, history of penile fracture, perineal / pelvic trauma history (Table 18).

Dynamic Infusion Cavernosometry and Cavernosography (DICC) is an invasive evaluation of erection hemodynamics, requiring a needle in each corporal body – one infusing – one recording. DICC is reserved for young men who might be candidates for penile vascular operations, specifically those with a history of pelvic trauma or life-long ED (primary ED). Testing protocols require complete smooth muscle relaxation; higher intracavernous dosing and often re-dosing compared to penile Doppler (PBFS). Recently, Kayigil et al postulated that the percent decrease in the amplitudes of the electrical activity of corpus cavernosum as assessed with ccEMG may be utilized as a measure of the degree of relaxation of the cavernous smooth muscle. [32] Mulhall et al described a simple mathematical model to determine the area of leak during erection. [33]

Selective internal pudendal angiography is primarily reserved for imaging and subsequent embolization of arterio-cavernous fistula causing high-flow priapism. [34, 35] Additionally, penile angiography is indicated in those few cases of young men with ED who have a history of pelvic / perineal trauma and who may be candidates for operative revascularization. [36] (Table 19)

Penile magnetic resonance imaging (MRI) is a new diagnostic technique with significant opportunities for application in the field of penile pathologies. It allows a better definition of anatomical details and penile micro-circulation. [37] The signal intensity depends on the rate of blood flow within the cavernous spaces. MR imaging is expensive and time consuming; it may be used to detect and stage arteriogenic ED, identify penile fractures, evaluates

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**Table 17. Penile Doppler Flow Studies**

<table>
<thead>
<tr>
<th>ADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Minimally invasive</td>
</tr>
<tr>
<td>• Pairs two methods: intracavernous pharmacotesting (ICI) and Doppler sonography.</td>
</tr>
<tr>
<td>• Power Doppler visualizes small vessel anatomy</td>
</tr>
<tr>
<td>• If results are normal, further vascular investigations are not needed</td>
</tr>
</tbody>
</table>

**PRIMARY INDICATION TO QUALIFY AND QUANTIFY SEVERITY OF ED**

- Organic vs. Psychogenic
  - Arterial insufficiency
  - Venous insufficiency
  - Mixed vascular disease

**ADDITIONAL INDICATIONS**

- Trauma
- High flow Priapism
- Drug therapy fialures
- Peyronie’s Disease

**INDUCING ERECTIONS**

- Intracavernous pharmacotesting
- PDE-5 Inhibitor testing
- Visual Sexual Stimulation (VSS) testing

**PLANNING SURGERY**

- Peyronie’s
- Microvascular arterial bypass
- Venous ligations
- Arterial embolization

---

**Table 18. Indications For Dynamic Infusion Cavernosometry and Cavernosography (DICC)**

Test is indicated for patients who are suspected to have a site-specific vasculogenic leak and for whom vascular surgery is considered a treatment option:

- Congenital
- Peyronie’s disease with poor rigidity
- History of penile fracture Perineal / pelvic trauma history

---

**Table 19. Penile Doppler Ultrasound Assessment**

- Parameters: Peak Systolic blood flow Velocity (PSV) and Acceleration Time.
- PSV < 25cm/s and/or an acceleration time > 122ms are indicative for severe penile arterial insufficiency.
- PSV > 25 cm/sec byt < 30 cm/s suggests mild arterial insufficiency
- To assess the penile inflow tract, the blood flow velocities should be measured between 1 and 10 minutes following pharmacostimulation
- Cavernous blood flow velocities decrease with age. A functional venoocclusive mechanism may compensate for decreased inflow across a wide range of velocities
penile protheses, and identify plaques of Peyronie disease (calcification is indistinguishable from thickening). [38]

Functional magnetic resonance imaging (MRI and PET scanning) may be used to assess brain centers involved in different phases of the sexual response cycle; simultaneous audio-visual sexual stimulation (AVSS) is required. [39] Radioisotopic penography assesses the rate of washout of a radioisotope from the penis following pharmacotesting or visual erotic stimulation. This test remains experimental. [40]

2. PSYCHOPHYSIOLOGICAL EVALUATION

NPT or sleep-related erection is a recurring cycle of erections associated with rapid eye movement (REM) during sleep. Spinal regulation is critical for nocturnal erectile activity, and the isolated thoracic cord is less effective than the isolated cervical cord in maintaining NPT. The main advantage of NPT testing is that it is relatively free from psychologically mediated effects. Traditionally NPT has been useful in distinguishing psychological from organic cases. NPT quality appears to correlate well with corporeal smooth muscle content. [41,42,43] 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. Disadvantages of NPT evaluation are that it is age-dependent and costly, as it is ideally done in a specially equipped sleep center using a Rigiscan® (NPTR). Circumferential changes measured by the Rigiscan® correlate well to penile rigidity measured by Erectiometer®. [44,45]

At present, NPT evaluation is rarely used; it has reported utility in cases of pelvic surgery, to quantify the erectogenic effect of oral agents, transdermal DHT and the antierectogenic effect of environmental agents [46,47,48,49,50,51,52,53,54,55,56] A full erectile response to audio-visual sexual stimulation (AVSS) without vasoactive drugs makes a psychogenic cause of ED likely. [57] Unlike NPTR, responses to AVSS, are susceptible to psychological factors, and inhibitions. AVSS may be normal in states of endocrine abnormality. Moreover, the response to AVSS is negatively correlated with age, limiting its value in older man. To date, the most important application of AVSS is to investigate the erectogenic or antierectogenic effect of pharmacological agents in clinical pharmacology studies.

3. NEUROLOGICAL EVALUATION

Neurological testing is only recommended in specific research protocols or medico-legal investigations, including cases of trauma or surgical complications. [59,60] Based on the available evidence, these tests lack adequate sensitivity and reliability for routine clinical diagnosis.

Penile erection is elicited by two different neurophysiologic mechanisms and mediated by somatic and autonomic pathways. Psychogenic erections are initiated in supraspinal centres in response to auditory, visual, olfactory, and imaginative stimuli. Reflexogenic erections, are elicited by tactile stimulation at the genital level; they are mediated by a spinal reflex arc consisting of afferent somatic and efferent parasympathetic nerve fibres [61] The ideal neurophysiological assessment would objectively and quantitatively evaluate all parts of this neurological network; no one test alone achieves this [62]

In the last two decades, a series of tests have been developed, each of which evaluates a specific component of the neural network. As with all ED diagnostics the medical history and physical examination provide the basis for these tests. [63,64] Tests can be classified as those detecting somatic efferent (motor) pathways, afferent (sensory) pathways, reflexes and autonomic responses. The somatic nerves are evaluated by testing nerve conduction velocities and evoked potentials. These tests have well-known reproducibility and validity. 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, hypo- and hypervolemia, mood state, 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 fibres and target organs, which may not be equally affected by neuropathy. Toxic metabolic events especially cause length-dependent neuropathy, because long fibres are more prone to metabolic damage than short fibres. Finally, current autonomic tests are not well standardised, and lack reproducibility, validity and comparability. Thus, autonomic testing is difficult and must be tailored to the specific small fibres or target organ to be tested, with elimination or standardisation of confounding factors. If these conditions are fulfilled, a normal test result will rule out neuropathy (Table 20).
A well known and widely-used test is the bulbocavernous EMG, which is used to identify damage to the sacral motor roots and the pudendal efferents. It samples large myelinated fibres. It is relevant in ED associated with lesions to the low back, with nerve root damage. Clinical indications are lumbar disc disorders, pelvic anatomical lesions, pelvic surgery. [65] Dorsal nerve conduction velocity is a test for the large myelinated dorsal penile sensory fibres, 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. [66,67]

Latencies of SEPs are a measure for the conduction velocity along the sensory pathways from the genital region to the sensory cerebral cortex. [68] 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 fibres. The rationale for performing this test is that evidence of impaired thermal sensation might suggest similar impairment of the autonomic motoric innervation of the cavernous body. Thermal thresholds assess small nerve fiber damage, which can indirectly reflect autonomic disturbances, particularly in the context of a diffuse neuropathy such as diabetic polyneuropathy. Penile thermal sensory testing is correlated strongly with the clinical evaluation of erectile function and is a new and promising tool for the diagnosis of neurogenic impotence. [69, 70] 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 handgrip, 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 hypervolemia, and dysfunction of baroreceptors or target organs. [71]

CeEMG is a relatively new technique, in which needle or surface electrodes record the electrical activity of the CC. [72] 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 [73,74] Sympathetic skin response measures a sudomotor-related potential, which is evoked in response to sympathetic activation. The potential can be recorded from the penis, assessing the sympathetic innervation of this organ. However, basic questions regarding the technique are still unresolved, and its clinical usefulness is limited. [75]

4. HORMONAL EVALUATION

Sex hormones and their specific role in male sexual dysfunction are described in detail in Chapter 11. Historically, hypogonadism was thought to be a rare cause of ED. However, recent data support a significant prevalence of hypogonadism as men age and further define the role for hypogonadism as a comorbidity in male sexual dysfunction. There is now recognition of the interrelationship between hypogonadism, depression and ED, underscoring the importance of the endocrine evaluation as an important component in evaluating male sexual dysfunction. The majority of endocrinopathy in male sexual dysfunction centers around testosterone (T).

The decrease or absence of hormonal secretion from the gonads in males, is traditionally and correctly referred to as hypogonadism. More contemporary designations attempt to acknowledge ageing as the primary etiology of declining androgens:
androgen deficiency of the ageing male (ADAM), partial androgen deficiency of the ageing male (PADAM), hypo-androgenism, and andropause.

Testosterone (T) plays an essential role in normal male development as well as in the maintenance of many male characteristics, including muscle mass and strength, bone density, libido, potency, and spermatogenesis. Androgen deficiency (hypoandrogenism, hypogonadism) results from testicular disorders that directly reduce T production from the testis or from hypothalamic-pituitary disorders that reduce pituitary luteinizing hormone (LH) secretion, which is the primary signal for T production by the interstitial (Leydig) cells of the testes.

Testosterone is converted within target cells by 5-alpha reductase to dihydrotestosterone (DHT). DHT binds to androgen nuclear receptors and is primarily responsible for androgen effects on the prostate, seminal vesicles, external genitalia and scalp (male pattern baldness). The adrenal cortex is the secondary source of steroid hormones in males. Dihydropiandrostenedione (DHEA) and DHEAS are secreted by the zona reticularis. DHEA/DHEAS are weak steroid hormones but are converted to testosterone, androstenedione and estradiol in target tissues.

a) Normal Testosterone Metabolism

Testosterone secretion by Leydig cells of the testes is regulated by a negative feedback loop involving gonadotropin-releasing hormone (GnRH) and LH. Testosterone is normally produced in men at a rate of about 4 – 8 mg/day (~0.24 mol/day), occurring in a pulsatile manner. [76,77,78,79] The diurnal pattern has a peak level in the early morning and a nadir in the evening. Testosterone can be converted to dihydrotestosterone (DHT) within androgen target cells (skin, liver, prostate, and other organs) that contain the enzyme 5-alpha-reductase. [80] Testosterone is also metabolized to estradiol (E2) by the aromatase enzyme complex in brain, fat, liver, and the testes. [80] In typical healthy males, the ratios of the resulting serum levels of DHT and E2 to the total T level are approximately 1:10 and 1:200, respectively.

In normal males, 2% of T is unbound (free T) and 30% is bound to sex-hormone-binding globulin (SHBG). [2, 4, 6, 7] The remainder is bound with lower affinity to albumin and other serum proteins. Free T and albumin-bound portions make up the bioavailable T fraction. The relative concentrations of these carrier proteins (SHBG and albumin) modulate androgen function. The synthesis of SHBG by the liver is down-regulated by androgens and up-regulated by estrogens. Sex-hormone-binding globulin has a higher affinity for T than for E2, and changes in SHBG concentration change or amplify the hormonal milieu. Elevated estrogens, thyroid hormone, and ageing each variably increase serum SHBG levels and decrease to some extent bioavailable T. On the other hand, exogenous androgens, growth hormone, and obesity depress SHBG levels and increase the free T levels.

b) Mechanisms of Androgen Action

Androgens and estrogens, like other steroid hormones, initiate their effect at the cellular level by interacting with high-affinity receptor proteins located within target cells. Androgen receptors are present in the highest concentration in androgen target tissues such as the accessory organs of male reproduction [83] Testosterone acts in cells directly through androgen receptor mediated interactions and indirectly through the metabolism of T to either E2 or DHT. Dihydrotestosterone acts principally through the androgen receptor and primarily on the prostate; E2 acts directly on the estrogen receptor. The role of other T metabolites is not well defined.

c) Types of Hypogonadism

Hypogonadism may occur if the hypothalamic-pituitary-gonadal (HPG) axis is interrupted at any level. Hypergonadotropic hypogonadism (primary hypogonadism) results if the gonad does not produce the amount of testosterone sufficient to suppress secretion of LH and follicle-stimulating hormone (FSH) at normal levels. Hypogonadotropic hypogonadism (secondary hypogonadism) may result from failure of the hypothalamic LH releasing hormone (LHRH) pulse generator or from inability of the pituitary to respond with secretion of LH and FSH. Most commonly, hypogonadotropic hypogonadism is observed as one aspect of multiple pituitary hormone deficiencies resulting from malformations (e.g., septo-optic dysplasia or other midline defects) or lesions of the pituitary that are acquired post-natal.

d) Age-Related Declines in Serum Testosterone

Although wide inter-individual variations exist, mean total and free T levels decline with age, whereas DHT and E2 levels tend to remain relatively constant. At 75 years, mean total T level in the morning is about two thirds of the mean level at age 20 – 30 years, whereas the mean free T and bioactive T (free T plus albumin bound T) levels are only 40% of the mean levels in younger males. [84] Furthermore, the circadian rhythm of serum T levels is generally lost or blunted in elderly men. [85]
Numerous cross-sectional and longitudinal studies have confirmed the age-related decrease in serum T concentration. [86-94] The Baltimore Longitudinal Study on Ageing, [92] which found that there were invariant, longitudinal effects of age on both T and the free T index is noteworthy. Based on measurements of total T, incidence of hypogonadal T levels increase to about 20% in men over 60, 30% in men over 70, and 50% in men over 80 years of age. In these men and certainly in any patient who presents with a complaint of decreased libido whether young or old, the specialist should be aware of drugs which can adversely alter androgen levels and, or bioavailability (Table 21).

Table 21. Drugs which Inhibit Testosterone or Androgen Precursors

- Spironolactone
- Common chemotherapies: methotrexate, alkylating agents
- Ketoconazole
- Metronidazole
- Flutamide
- Bicaludamide
- Cimetidine
- Cyproterone

DRUGS WHICH INHIBIT GnRH RELEASE/PRODUCTION
- Progesterone
- Estrogen
- GnRH agonists (leuprolide, goserelin)
- Elevated Prolactin levels
- Estrogen
- Phenothiazines
- Tricyclic antidepressants
- Reserpine
- Opioid analgesics
- Cocaine

e) Effects of Testosterone Deficiency on Male Sexual Function

Sexual interest and activity and erectile rigidity and duration decline in men as they age. Erectile dysfunction (ED) is seen with an age-stratified incidence of 1.9% at 40 years and 25% or greater by age 65. [95] The reported incidence of endocrinopathy as the etiology of erectile dysfunction is 1% to 35%. [96] Interestingly, the prevalence of abnormally low serum T levels, even among men with ED, has historically been reported to be low (<10%). The majority of studies show that ED has a clear association with ageing, but no consistent correlation of total T with erectile function has been identified. [97-101] The role T plays in penile erection is unclear, and so far appears to be different from the effects in animal models. The physiology of erection depends on the integrity of corporal smooth muscle. In a variety of experimental conditions, orchiectomy has been associated with decreased smooth muscle content and increased interstitial/collagen in the penis. At the cellular level, the absence of T reduces nitric oxide synthase production. Recent clinical recommendations have been made regarding assessment of T levels in patients who fail PDE-5 inhibitor therapy. Though no direct link has been made to muscular atrophy or penile neurologic control in men, it may be that T not only effects sex behavior, but also subtly changes a number of physiologic parameters directly regulating erection. [102]

Recent studies with topical gel replacement T therapy have suggested that T has a role in sexual desire, frequency of nocturnal erections, frequency of intercourse, erection fullness and erection satisfaction [103,104]. The Steidle study, a placebo-controlled study of 406 men demonstrated a clear benefit with T replacement therapy (Testim topical gel) in hypogonadal men, at both 30 and 90 days, in the domains of sexual desire and nocturnal erections, with a subtler benefit on frequency of sexual intercourse. The Wang data set, also using a topical gel for T replacement, evaluated 227 hypogonadal men over 180 days. This non-placebo controlled study demonstrated a benefit in the domains of sexual motivation and sexual desire, with a tendency toward improvement in the frequency of sexual intercourse, satisfaction with an erection along with erection fullness. Thus, at present, the role of T in male sexual function is clearly associated with an increase sexual desire as well nocturnal erections, with a less clear benefit on frequency of sexual intercourse and erectile function. More recent evidence suggests that there may be a threshold T level that is required for sexual desire and nocturnal erections. Seftel et al [105] noted that the clinically significant benefit in sexual desire and frequency of nocturnal erections was seen at an average 24 hour T concentration (C_{ave}) of 506 ng./dl. The hypogonadal men in this study complained of sexual dysfunction, and 10 mg. Testim improved these 2 domains using a validated questionnaire.
and a telephone phone in system. Sexual desire increased 1.2 on a Likert-type scale of 0-7. The frequency of self-reported nocturnal erections increased significantly over the course of a 7 day period as well.

f) Diagnostic criteria

Other than for hypogonadism, no consensus criteria have been established to identify the appropriate candidates for androgen therapy. Few would argue T treatment for men with both sexual dysfunction and low T levels caused by testicular failure or hypothalamic-pituitary dysfunction. The controversy surrounds men with sexual dysfunction and low normal T levels. Generally a diagnosis of hypogonadism in an elderly male should be based on libido complaint and/or evaluation with a symptom-based instrument, followed by a laboratory work-up of serum T. [101,107] In a large clinical series of men with ED screened for hypogonadism, low serum T was correlated with age over 50, low libido and small testes. [118]

Although there is general understanding of what constitutes normal T levels in healthy younger individuals, there is no consensus on the serum T levels that can be used to define androgen deficiency in ageing. Furthermore, no clinically useful biological marker for androgen action is available. Bioavailable T levels below 60 ng/dL [108] or total T levels below 300 ng/dL [79, 109-111] warrant androgen replacement therapies, especially if associated with other symptoms suggestive of androgen deficiency (Table 22).

Table 22. Secondary Causes For Male Hyperprolactinemia

- Hypothyroidism
- Stress
- Chronic renal failure
- Exercise
- Liver disease
- Sleep
- Drugs (22) (e.g., protirelin, fenfluramine, thyrotropin-releasing hormone, estrogens, antipsychotic agents, methyldopa, opiates, opioids, metoclopramide, reserpine and amoxapine)

h) Andropause

«Andropause» is gaining recognition as a clinical problem in the ageing male. Admittedly, andropause is a normal physiologic phase of ageing, but for some men, it is accompanied by distressing declines in sexuality, mood, and energy. Not all physicians agree that these symptoms need treatment with T. Indeed, lifestyle changes and other interventions may improve many of the symptoms associated with andropause. Nevertheless, in the face of emerging clinical data, long held negative views on the need for and effects of ART in the ageing are being challenged. A growing number of clinicians now agree that for select patients, T supplementation provides significant benefit.

The clinical findings in secondary hypogonadism (testicular failure) were first described half a century ago by Werner. [112] The symptom complex is composed of at least one of the following components. Suspicion of age-related hypogonadism does not require that all of the signs be present:

- Decreased sexual desire and erectile quality, particularly nocturnal erections
- Changes in mood with concomitant decreases in intellectual activity and spatial orientation ability, and increases in fatigue, depression, and anger
- Decrease in lean body mass with associated diminution in muscle volume and strength
- Decrease in body hair and skin alterations
- Decrease in bone mineral density, resulting in osteoporosis
- Increase in visceral fat.

i) Serum Endocrine Evaluations: Choice of Assay

Three validated questionnaires have been developed to aid in the identification of males with androgen deficiencies. These instruments provide reasonable screening questions. Each has been validated by comparing questionnaire results with other aspects of andropause, including laboratory T levels.

The specific instruments are:

- A New Ageing Male’s Symptoms (AMS) Rating Scale[113]
- Androgen Deficiency in Ageing Males (ADAM) [114]
- Eight-Item Screener for the Massachusetts Male Ageing Study (MMAS) [115]
Measurement of T bioavailability should be the unbound or free fraction, but commercial assays for free T are inconsistent and have been considered invalid by some investigators. Methods used to measure serum T vary substantially, and even standardized methods such as radioimmunoassay (RIA) are variable depending on whether serum is extracted and/or undergoes chromatography before RIA. Measurement of free T by equilibrium dialysis methods are demanding technically and measure that moiety of T not bound to either SHBG or albumin, but are not available in most settings. Some investigators prefer to use the free T index, a calculated value, usually the ratio of T to SHBG. For the most part, health providers rely on the measurement of total serum T. [116,117]

j) Serum Testosterone Range

The problem of identifying the normal cutoff level for T beyond which therapy should be initiated remains unresolved. Wide individual variability in the threshold of serum T below which impairment of androgen-dependent processes becomes evident makes both diagnosis and treatment difficult. Although the range of normal values for serum T varies among laboratories, morning T values below 300 ng/dL suggest hypogonadism and should be confirmed by a second determination. It is generally accepted that two standard deviations below normal values for young men is conclusively abnormal. This range of values still adheres to the concept of a societal mean that may not be relevant for older men. Beyond hypogonadal levels, the level of serum T that defines deficiency specifically in an older man has yet to be established. Circadian rhythm of T levels should be considered in measuring serum T; blood should be drawn between 6:00 am and 9:00 am. One or more of the following serum laboratory measures may be required to diagnose hormone deficiencies:

- Total/free/bioavailable testosterone
- Sex-hormone-binding globulin
- LH
- Follicle stimulating hormone

5. SUMMARY AND RECOMMENDATIONS

The large majority of patients with ED do not require specialized evaluation. A physical examination, medical and sexual history and basic laboratory tests are sufficient for diagnosis of ED in the majority of cases. Specialized consultation and evaluation may be indicated, however, for patients with specific organic etiologies, based on the patient’s preferences, or in medico-legal circumstances. Typical indications for specialized vascular, neurologic or endocrine evaluation are failure of initial treatment, Peyronie’s disease, primary ED, history of pelvic/perineal trauma, cases requiring vascular or neurosurgical intervention, complicated endocrinopathy, complicated neurologic or psychiatric disorders, and medico-legal concerns. Commonly used vascular evaluation procedures include intracavernous injection pharmacotesting (ICI), color duplex doppler ultrasound, and dynamic infusion cavernosometry and cavernosography (DICC). Less commonly used procedures include arteriography, CT angiography, penile MRI studies, infrared spectrophotometry, visual sexual stimulation (VSS) testing, and radioisotope penography. These latter techniques should be regarded as experimental and lacking evidence-based assessment.

Specialized neurologic procedures include nocturnal penile tumescence and rigidity testing (NPTR), biothesiometry, dorsal nerve conduction studies, bulbocavernous reflex latency, and corpus cavernosum electromyography (CC-EMG). These procedures may be of value in evaluating specific neurologic deficits in individual cases, but are not widely used or generally recommended at this time. Additional experimental procedures include MRI and PET scanning of the brain during visual sexual stimulation. These procedures are only recommended for research purposes.

Patients with complicated endocrinological or psychiatric disorders should be referred for specialized consultation and evaluation when possible. Detailed evaluation of these disorders are described in Chapter 2 (Psychological and Interpersonal Dimensions) and Chapter 11 (Endocrine Disorders). In accordance with the patient-based approach to sexual medicine recommended by this committee, results of specialized testing and evaluation should be clearly communicated to the patient and taken into consideration in the mutual decision-making process.

IV. SYMPTOM SCALES AND QUESTIONNAIRES

1. INTRODUCTION

The ability to measure sexual function in men and women is key to the establishment of current functional level (e.g. ability to respond, level of interest)
in relation to the diagnosis of presence and/or severity of sexual symptoms and to determine whether any form of intervention may have altered an individual's ability to function sexually. The primary format for evaluation of sexual function or sexual symptoms is the self-administered questionnaire. In common with other psychometric instruments the two most fundamental and desirable psychometric requirements for such tools are reliability and validity. Reliability refers to the consistency or replicability of data, with reliability «coefficients» serving as formal indicators of measurement consistency.

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 [119] 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, and sensitivity to therapeutically induced change. The former refers to an instrument's capacity to discriminate sexually dysfunctional individuals from those persons free of any sexual disorders (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.

The following review, along with the detailed information contained in Tables 23 and 24, characterizes 13 contemporary instruments (6 for males and 7 for females) 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 several years. Although not all of these measures were designed specifically for use in clinical trials, most have been designed as outcomes measures that could be easily applied 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 seven instruments described in Table 24 meet minimal criteria; the six instruments described in Table 23 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 (Tables 23, 24).

2. RECOMMENDED QUESTIONNAIRES FOR MEN AND WOMEN

a.) Changes in Sexual Functioning Questionnaire (CSFQ)

• DESCRIPTION
The CSFQ has both a men’s and women’s version [120]. 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. SSRI's). 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.

• ADMINISTRATION TIME
The CSFQ interview requires approximately 15 minutes. The 14-item self report scale can be completed in about 5 minutes.

• TARGET POPULATION
The CSFQ is designed to be appropriate for heterosexual and homosexual respondents.

• 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
### Table 23. Psychometric Properties of Highly Recommended 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>Published Norms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in Sexual Functioning Questionnaire</td>
<td>CI and SR</td>
<td>35/14</td>
<td>&lt;20min/5min</td>
<td>Desire/frequency, desire/interest, pleasure, arousal, orgasm, total</td>
<td>.64-.80</td>
<td>.66-.86</td>
<td>YES</td>
</tr>
<tr>
<td>Derogatis Interview for Sexual Functioning (DISF-SR)</td>
<td>CI and SR</td>
<td>25</td>
<td>&lt;1.5min</td>
<td>Cognition, arousal, behavior, orgasm, drive/relationship, total score</td>
<td>.74-.80</td>
<td>.80-.90</td>
<td>.84-.92</td>
</tr>
<tr>
<td>Female Sexual Function Index (FSFI)</td>
<td>SR Female only</td>
<td>19</td>
<td>15 min</td>
<td>Desire, arousal, lubrication, orgasm, satisfaction, pain</td>
<td>.82</td>
<td>.79-.86</td>
<td>n/a</td>
</tr>
<tr>
<td>Golombok-Rust Inventory of Sexual Satisfaction (GRISS)</td>
<td>SR Male and Female</td>
<td>28</td>
<td>&lt;15min</td>
<td>5 male domains, 2 male and female domains, total score</td>
<td>η-.70</td>
<td>η-.82</td>
<td>n/a</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>.73-.95</td>
<td>.64-.84</td>
<td>n/a</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>.79-.91</td>
<td>.42-.78</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**SR = Self Report, CI = Clinical Interview**
Table 24. Psychometric Properties of Additional Recommended 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>Arizona Sexual Experience Scale (ASEX)³</td>
<td>SR Men and Woman</td>
<td>5</td>
<td>&lt;10 min.</td>
<td>Drive, arousal, penile erection/vaginal lubrication, orgasm, satisfaction</td>
<td>.91</td>
<td>YES</td>
<td>.82/.90</td>
<td>NO</td>
</tr>
<tr>
<td>Brief Male Sexual Functioning Inventory (BMSF)³</td>
<td>SR Men only</td>
<td>11</td>
<td>&lt;10 min.</td>
<td>Drive, erection, ejaculation, satisfaction</td>
<td>.92</td>
<td>YES</td>
<td></td>
<td>NO</td>
</tr>
<tr>
<td>Brief Index of Sexual Functioning for Women (BISE-W)³</td>
<td>SR Women only</td>
<td>22</td>
<td>15 min.</td>
<td>Desire, sexual activity, satisfaction</td>
<td>.39-0.83</td>
<td>YES</td>
<td></td>
<td>NO</td>
</tr>
<tr>
<td>Center for Marital and Sexual Health Sexual Functioning Questionnaire (CMASH-SFQ)³</td>
<td>SR Men and Partner</td>
<td>21</td>
<td>&lt;15 min.</td>
<td>Sexual frequency, sexual satisfaction, orgasm, erectile function</td>
<td>Y</td>
<td>YES</td>
<td></td>
<td>NO</td>
</tr>
<tr>
<td>Derogatis Sexual Functioning Inventory⁸</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>.71-.97</td>
<td>YES</td>
<td></td>
<td>YES</td>
</tr>
<tr>
<td>Profile of Female Sexual Function (PFSF)⁹,¹⁰</td>
<td>SR Women only</td>
<td>37</td>
<td>&lt;20 min.</td>
<td>Desire, arousal, orgasm, pleasure, concerns, responsiveness, self-image</td>
<td>.87-.96</td>
<td>YES</td>
<td>.86/.93</td>
<td>NO</td>
</tr>
<tr>
<td>Short Scale to Measure Female Sexual Functioning (SPEQ)³</td>
<td>SR Women only</td>
<td>9</td>
<td>&lt;5 min.</td>
<td>Feelings for partner, sexual responsiveness, sexual frequency, libido, dyspareunia, partner problems</td>
<td>.74-.80</td>
<td>YES</td>
<td>.79/.79</td>
<td>YES</td>
</tr>
</tbody>
</table>

*SR = Self Report,
comparisons with analogous measures from the Derogatis Interview for Sexual Functioning (DISF), with r’s ranging from .66 to .86 [121]. Discriminative validity of a specific type was demonstrated by its ability to discriminate between a clinical sample (depressed patients) and a non-clinical sample [122]. The instrument was also able to demonstrate differential rates of sexual dysfunction associated with specific antidepressant medications [123].

• **NORMS**

Norms are available for the CSFQ based on the medical student/resident sample, and medical outpatients.

• **LANGUAGES**

Validated in English and Spanish, with linguistic validation in 7 other languages (French, German, Dutch, Italian, Swedish, Finnish, and French Canadian).[124]

• **RATING ON AVAILABLE EVIDENCE**

Grade B and Level 2 or 3

**b.) Derogatis Interview for Sexual Functioning (DISF/DISF-SR)**

• **DESCRIPTION**

The DISF/DISF-SR represents a coordinated set of brief matched instruments designed to provide an estimate of the quality of an individual’s current sexual functioning [125,126]. 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 domains of sexual functioning: sexual cognition/fantasy, sexual arousal, sexual behavior/ experience, orgasm, and sexual drive/relationship. An aggregate DISF Total Score summarizes quality of sexual functioning across the five primary DISF domains.

• **ADMINISTRATION TIME**

Both the DISF and the DISF-SR take approximately 12 to 15 minutes to administer.

• **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.

• **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.

• **NORMS**

Gender-keyed actuarial norms (in terms of area T-scores) are available for all versions of the test.

• **LANGUAGES**

The DISF/DISF-SR are currently available in 10 languages.

• **RATING ON AVAILABLE EVIDENCE**

Grade B and Level 3 evidence

**c.) Female Sexual Function Index (FSFI)**

• **DESCRIPTION**

An expert panel was formed to design the FSFI to assess Female Sexual Arousal Disorder (FSAD). The FSFI is a 19-item self-report instrument [127]. Respondents were asked to base their responses on 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 score and each of the subscales indicate better sexual function.

• **ADMINISTRATION TIME**

10 to 15 minutes

• **TARGET POPULATION**

Clinical trial and community populations. This instrument was designed for use among heterosexual and homosexual respondents.

• **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 [128]. 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 [129], 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.

- **NORMS**
  Norms available

- **LANGUAGES**
  The FSFI is available in 7 languages. Only the English version has received independent validation.

- **RATING ON AVAILABLE EVIDENCE**
  Grade B and Level 3 evidence.

**d) Golombok Rust Inventory of Sexual Satisfaction (GRISS)**

- **DESCRIPTION**
  The GRISS is a 56-item (28 items for women and 28 items for men) self-report instrument designed to assess the existence and severity of sexual problems among 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) [130]

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 [131] A transformation key allows couples to see their scores plotted on a profile provided for the couple as part of therapy.

- **ADMINISTRATION TIME**
  Approximately 15 minutes

- **TARGET POPULATION**
  The GRISS was designed for use with heterosexual sex therapy clients

- **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 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.

- **NORMS**
  Norms are available from the development sample of therapy clients as well as for a comparison nonclinical sample of 59 general practitioner patients.

- **LANGUAGES**
  Dutch and English language versions are available

- **RATING ON AVAILABLE EVIDENCE**
  Grade C and Level 4 evidence.
e) International Index of Erectile Function (IIEF)

• **DESCRIPTION**
The IIEF is a 15-item self-report inventory developed by Rosen and his colleagues [132] to provide a brief measure of erectile function and capacity. It has been frequently recommended as a primary endpoint in clinical trials of erectile dysfunction (ED). 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 [133]. 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.

• **ADMINISTRATION TIME**
The IIEF takes approximately 10 to 15 minutes to complete.

• **TARGET POPULATION**
Men from the community and medical populations

• **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 [134]. 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 [133].

• **NORMS**
Numerous normative cut-off scores have been published for the IIEF.

• **LANGUAGES**
The IIEF has been linguistically validated in 32 languages.

f) Sexual Function Questionnaire

• **DESCRIPTION**
The initial version of the Sexual Function Questionnaire (SFQ-V1) was developed to be a patient-centered multidimensional measure of sexual function in women [135]. A series of 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).

• **ADMINISTRATION TIME**
10 to 15 minutes

• **TARGET POPULATION**
Women in a sexual relationship or having taken part in sexual activity within the previous month.

• **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-SR, the Life Satisfaction Checklist and the Hospital Anxiety and Depression Scale.

• NORMS
Normative data are available for all SFQ domains.

• LANGUAGES
The SFQ is available in sixteen language versions including Hispanic and French Canadian.

• RATING ON AVAILABLE EVIDENCE
Grade B and Level 2 or 3 evidence.

g.) Female Sexual Distress Scale (FSDS)
• DESCRIPTION
The FSDS is a brief 12-item self-report inventory designed to measure sexually related personal distress 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 [135]. The FSDS is a 12-item self-report scale that is unidimensional and serves as a valid and effective quantitative definition of personal distress.

• ADMINISTRATION TIME
The FSDS can be completed in 5 minutes.

• TARGET POPULATION
Women presenting for an evaluation concerning sexual dysfunction.

• RELIABILITY AND VALIDITY
Reliability estimates for the FSDS are available from 3 distinct trials. Coefficients α 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.

• NORMS
Provisional cut-off score of 15 for distress level is currently recommended.

• LANGUAGES
The FSDS is currently available in 14 languages.

• RATING ON AVAILABLE EVIDENCE
Grade C and Level 4 evidence.

3. SUMMARY AND CONCLUSIONS
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 several questionnaires and symptom scales are currently available and recommended for use in practice settings and clinical trials. 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. 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. 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. 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 com-
prehension when indicated. 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.

REFERENCES


204
Please answer the following questions as honestly and clearly as possible. 

*In answering these questions the following definitions apply:*

- Sexual activity included intercourse, caressing, foreplay and masturbation.
- Sexual intercourse is defined as vaginal penetration of the partner (you entered your partner).
- Sexual stimulation includes situations like foreplay with a partner, looking at erotic pictures, etc.
- Ejaculation is defined as the ejection of semen from the penis (or the feeling of this).

*Please answer the following questions for the past -------weeks by checking one box per question.*

<table>
<thead>
<tr>
<th>1. How often were you able to get an erection during sexual activity?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No sexual activity</td>
</tr>
<tr>
<td>• Almost never/never</td>
</tr>
<tr>
<td>• A few times (much less than half the time)</td>
</tr>
<tr>
<td>• Sometimes (about half the time)</td>
</tr>
<tr>
<td>• Most times (much more than half the time)</td>
</tr>
<tr>
<td>• Almost always/always</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No sexual activity</td>
</tr>
<tr>
<td>• Almost never/never</td>
</tr>
<tr>
<td>• A few times (much less than half the time)</td>
</tr>
<tr>
<td>• Sometimes (about half the time)</td>
</tr>
<tr>
<td>• Most times (much more than half the time)</td>
</tr>
<tr>
<td>• Almost always/always</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Did not attempt intercourse</td>
</tr>
<tr>
<td>• Almost never/never</td>
</tr>
<tr>
<td>• A few times (much less than half the time)</td>
</tr>
<tr>
<td>• Sometimes (about half the time)</td>
</tr>
<tr>
<td>• Most times (much more than half the time)</td>
</tr>
<tr>
<td>• Almost always/always</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Did not attempt intercourse</td>
</tr>
<tr>
<td>• Almost never/never</td>
</tr>
<tr>
<td>• A few times (much less than half the time)</td>
</tr>
<tr>
<td>• Sometimes (about half the time)</td>
</tr>
<tr>
<td>• Most times (much more than half the time)</td>
</tr>
<tr>
<td>• Almost always/always</td>
</tr>
</tbody>
</table>
5. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

- Did not attempt intercourse
- Extremely difficult
- Very difficult
- Difficult
- Slightly difficult
- Not difficult

6. How many times have you attempted sexual intercourse?

- No attempts
- One to two attempts
- Three to four attempts
- Five to six attempts
- Seven to ten attempts
- Eleven + attempts

7. When you attempted sexual intercourse, how often was it satisfactory for you?

- Did not attempt intercourse
- Almost never/never
- A few times (much less than half the time)
- Sometimes (about half the time)
- Most times (much more than half the time)
- Almost always/always

8. How much have you enjoyed sexual intercourse?

- No intercourse
- No enjoyment
- Not very enjoyable
- Fairly enjoyable
- Highly enjoyable
- Very highly enjoyable

9. When you had stimulation or intercourse, how often did you ejaculate?

- No sexual stimulation/intercourse
- Almost never/never
- A few times (much less than half the time)
- Sometimes (about half the time)
- Most times (much more than half the time)
- Almost always/always
10. When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?

- No sexual stimulation/intercourse
- Almost never/never
- A few times (much less than half the time)
- Sometimes (about half the time)
- Most times (much more than half the time)
- Almost always/always

The next two questions ask about sexual desire. Let’s define sexual desire as a feeling that may include wanting to have a sexual experience (for example, masturbation or intercourse), thinking about having sex, or feeling frustrated due to lack of sex.

11. How often have you felt sexual desire?

- Almost never/never
- A few times (much less than half the time)
- Sometimes (about half the time)
- Most times (much more than half the time)
- Almost always/always

12. How would you rate your level of sexual desire?

- Very low/none at all
- Low
- Moderate
- High
- Very high

13. How satisfied are you with your overall sex life?

- Dissatisfied
- About equally satisfied and dissatisfied
- Very dissatisfied
- Moderately satisfied
- Very satisfied

14. How satisfied have you been with your sexual relationship with your partner?

- Dissatisfied
- About equally satisfied and dissatisfied
- Very dissatisfied
- Moderately satisfied
- Very satisfied

15. How do you rate your confidence that you could get and keep an erection?

- Very low
- Low
- Moderate
- High
- Very high

REPRODUCED WITH PERMISSION OF THE AUTHOR.
ANNEX II.
THE C-MASH

1. Have you had any difficulties obtaining a firm hard, long-lasting erection?
   YES              NO

2. Are you currently having any difficulties obtaining a firm, hard, long-lasting erection?
   YES            NO

2A. How long ago did this current erectile problem begin? ______________________

3. The following questions ask you to think about your sexual drive during the past 30 days.

3A. How many times in the past 30 days did you feel sexual desire (horney, the desire to have sex)? __________________

3B. How many times in the past 30 days did you engage or attempt to engage in intercourse? __________________

3C. How many times did you and your partner engage in other sexual activity in the past 30 days? __________________

3D. How many times did you masturbate in the past 30 days? ______________________

4. These next questions ask you to judge the quality of your erections under different circumstances during the past 30 days.
   • Each rating scale goes from 0 to 8 (no erection to full erection)
   • Please circle the number (0 to 8) on each scale that best reflects the quality of your erection under each of the following circumstances.
   • If you have not engaged in that particular activity, circle NA (not applicable)

Please rate the quality of your erections during the past 30 days.

4a. Quality of erection during the night or upon awakening

<table>
<thead>
<tr>
<th>NO ERECTION</th>
<th>SEMI-FIRM</th>
<th>FULL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

4b. Quality of erections spontaneously or when reading about, looking at, or thinking about something sexy

<table>
<thead>
<tr>
<th>NO ERECTION</th>
<th>SEMI-FIRM</th>
<th>FULL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

4c. If you have engaged in masturbation during the past 30 days, rate quality of erection during masturbation.

<table>
<thead>
<tr>
<th>NO ERECTION</th>
<th>SEMI-FIRM</th>
<th>FULL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

4d. If you have engaged in foreplay in the past 30 days, rate quality of erection during foreplay.

<table>
<thead>
<tr>
<th>NO ERECTION</th>
<th>SEMI-FIRM</th>
<th>FULL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

4e. If you have engaged in intercourse during the past 30 days, rate quality of erection during intercourse

<table>
<thead>
<tr>
<th>NO ERECTION</th>
<th>SEMI-FIRM</th>
<th>FULL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
5. Now think back over the past 3 months.
The following questions concern your experience with orgasm (ejaculation or “coming”) during this time period.

- Please circle the number (0-8) on each scale that best reflects how often you have reached orgasm under each of the following circumstances.
- If you have not engaged in a particular activity during the past 3 months, circle NA (not applicable for that activity).

5a. How often in the past 3 months have you had an orgasm during intercourse?

<table>
<thead>
<tr>
<th>ALMOST NEVER</th>
<th>SOMETIMES</th>
<th>ABOUT HALF OF THE TIME</th>
<th>MOST OF THE TIME</th>
<th>ALWAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

5b. How often have you had an orgasm during masturbation in the past 3 months?

<table>
<thead>
<tr>
<th>ALMOST NEVER</th>
<th>SOMETIMES</th>
<th>ABOUT HALF OF THE TIME</th>
<th>MOST OF THE TIME</th>
<th>ALWAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

5c. How often did you ejaculate (come) more quickly than you would like during intercourse in the past 3 months?

<table>
<thead>
<tr>
<th>ALMOST NEVER</th>
<th>SOMETIMES</th>
<th>ABOUT HALF OF THE TIME</th>
<th>MOST OF THE TIME</th>
<th>ALWAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

5d. How often did it take you longer than you’d like to reach orgasm during intercourse in the past 3 months?

<table>
<thead>
<tr>
<th>ALMOST NEVER</th>
<th>SOMETIMES</th>
<th>ABOUT HALF OF THE TIME</th>
<th>MOST OF THE TIME</th>
<th>ALWAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

6. The final two questions concern your overall satisfaction with your sexual life during the past 3 months.

- Please circle the number (0-5) on each scale which best reflects your degree of satisfaction.
- If you have not engaged in any type of sexual activity in the past 3 months, circle NA.

6a. How satisfied have you felt after a typical sexual encounter in the past 3 months?

<table>
<thead>
<tr>
<th>EXTREMELY UNSATISFIED</th>
<th>MODERATELY UNSATISFIED</th>
<th>MILDELY UNSATISFIED</th>
<th>MILDELY SATISFIED</th>
<th>MODERATELY SATISFIED</th>
<th>EXTREMELY SATISFIED</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

6b. How satisfied do you think your partner has felt after a typical sexual interaction during this time period?

<table>
<thead>
<tr>
<th>EXTREMELY UNSATISFIED</th>
<th>MODERATELY UNSATISFIED</th>
<th>MILDELY UNSATISFIED</th>
<th>MILDELY SATISFIED</th>
<th>MODERATELY SATISFIED</th>
<th>EXTREMELY SATISFIED</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
ANNEX III.
ARIZONA SEXUAL EXPERIENCES SCALE (ASEX) - MALE

For each item, please indicate your overall level during the past week including today.

1. How strong is your sex drive?

| 1 extremely strong | 2 very strong | 3 somewhat strong | 4 somewhat weak | 5 very weak | 6 no sex drive |

2. How easily are you sexually aroused (turned on)?

| 1 extremely easily | 2 very easily | 3 somewhat easily | 4 somewhat difficult | 5 very difficult | 6 never aroused |

3. Can you easily get and keep an erection?

| 1 extremely easily | 2 very easily | 3 somewhat easily | 4 somewhat difficult | 5 very difficult | 6 never |

4. How easily can you reach an orgasm?

| 1 extremely easily | 2 very easily | 3 somewhat easily | 4 somewhat difficult | 5 very difficult | 6 never reach orgasm |

5. Are your orgasms satisfying?

| 1 extremely satisfying | 2 very satisfying | 3 somewhat satisfying | 4 somewhat unsatisfying | 5 very unsatisfying | 6 can’t reach orgasm |
ANNEX IV.
MARITAL-ADJUSTMENT TEST

1. Check the dot on the scale line below which best describes the degree of happiness, everything considered, of your present marriage. The middle point, "happy", represents the degree of happiness which most people get from marriage, and the scale gradually ranges on one side to those few who are very unhappy in marriage, and on the other, to those few who experience extreme joy or felicity in marriage.

<table>
<thead>
<tr>
<th>Very Unhappy</th>
<th>Happy</th>
<th>Perfectly Happy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

State the approximate extent of agreement or disagreement between you and your mate on the following items. Please check each column.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Almost Always Agree</td>
<td>Almost Always Agree</td>
<td>Occasionally Disagree</td>
<td>Frequently Disagree</td>
<td>Almost Always Disagree</td>
<td>Always Disagree</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For the questions below please check the most appropriate answer.

10. **When disagreements arise, they usually result in:**

Husband giving in (   )  Wife giving in (   ) Agreement by mutual give and take (   )

11. **Do you and your mate engage in outside interests together?**

All of them (   )  Some of them (   ) Very few of them (   ) None of them (   )

12. **In leisure time do you generally prefer:**

To be "on the go" (   )  To stay at home (   )

**Does your mate generally prefer:**

To be "on the go" (   )  To stay at home (   )

13. **Do you ever wish you had not married?**

Frequently (   )  Occasionally (   ) Rarely (   ) Never (   )

14. **If you ever had your life to live over, do you think you would:**

Marry the same person (   )  Marry a different person (   ) Not marry at all (   )

15. **Do you confide in your mate:**

Almost never (   )  Rarely (   ) In most things (   ) In everything (   )
ANNEX V.
CHANGES IN SEXUAL FUNCTIONING QUESTIONNAIRE (CSFQ-M-C)

Patient Name ____________________________

NOTE: This is a questionnaire about sexual activity and sexual function. By sexual activity, we mean sexual intercourse, masturbation, sexual fantasies and other activity.

1. Compared with the most enjoyable it has ever been, how enjoyable or pleasurable is your sexual life right now?
   p 1-No enjoyment or pleasure
   p 2-Little enjoyment or pleasure
   p 3-Some enjoyment or pleasure
   p 4-Much enjoyment or pleasure
   p 5-Great enjoyment or pleasure

2. How frequently do you engage in sexual activity (sexual intercourse, masturbation, etc.) now?
   p 1-Never
   p 2-Rarely (once a month or less)
   p 3-Sometimes (more than once a month, up to twice a week)
   p 4-Often (more than twice a week)
   p 5-Every day

3. How often do you desire to engage in sexual activity?
   p 1-Never
   p 2-Rarely (once a month or less)
   p 3-Sometimes (more than once a month, up to twice a week)
   p 4-Often (more than twice a week)
   p 5-Every day

4. How frequently do you engage in sexual thoughts (thinking about sex, sexual fantasies) now?
   p 1-Never
   p 2-Rarely (once a month or less)
   p 3-Sometimes (more than once a month, up to twice a week)
   p 4-Often (more than twice a week)
   p 5-Every day

5. Do you enjoy books, movies, music or artwork with sexual content?
   p 1-Never
   p 2-Rarely (once a month or less)
   p 3-Sometimes (more than once a month, up to twice a week)
   p 4-Often (more than twice a week)
   p 5-Every day

6. How much pleasure or enjoyment do you get from thinking about and fantasizing about sex?
   p 1-No enjoyment or pleasure
   p 2-Little enjoyment or pleasure
   p 3-Some enjoyment or pleasure
   p 4-Much enjoyment or pleasure
   p 5-Great enjoyment or pleasure

7. How often do you have an erection related or unrelated to sexual activity?
   p 1-Never
   p 2-Rarely (once a month or less)
   p 3-Sometimes (more than once a month, up to twice a week)

Today’s Date ____________________________

8. Do you get an erection easily?
   p 1-Never
   p 2-Rarely (much less than half the time)
   p 3-Sometimes (about half the time)
   p 4-Often (much more than half the time)
   p 5-Always

9. Are you able to maintain an erection?
   p 1-Never
   p 2-Rarely (much less than half the time)
   p 3-Sometimes (about half the time)
   p 4-Often (much more than half the time)
   p 5-Always

10. How often do you experience painful, prolonged erections?
    p 1-Never
    p 2-Rarely (once a month or less)
    p 3-Sometimes (more than once a month, up to twice a week)
    p 2-Often (more than twice a week)
    p 1-Every day

11. How often do you have an ejaculation?
    p 1-Never
    p 2-Rarely (once a month or less)
    p 3-Sometimes (more than once a month, up to twice a week)
    p 4-Often (more than twice a week)
    p 5-Every day

12. Are you able to ejaculate when you want to?
    p 1-Never
    p 2-Rarely (much less than half the time)
    p 3-Sometimes (about half the time)
    p 4-Often (much more than half the time)
    p 5-Always

13. How much pleasure or enjoyment do you get from your orgasms?
    p 1-No enjoyment or pleasure
    p 2-Little enjoyment or pleasure
    p 3-Some enjoyment or pleasure
    p 4-Much enjoyment or pleasure
    p 5-Great enjoyment or pleasure

14. How often do you have painful orgasm?
    p 1-Every day
    p 2-Rarely (once a month or less)
    p 3-Sometimes (more than once a month, up to twice a week)
    p 2-Often (more than twice a week)
    p 1-Every day

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INSTRUCTIONS FOR COMPLETING AND SCORING THE CSFQ

Ask the patient to complete all 14 items on the clinical version of the CSFQ. The patient should place a check (2) in the box corresponding to the response for that particular item. The patient should choose only one response per item.

To score items on the CSFQ, take the numerical value or weight indicated for a particular response. For example, in Item 1, a response of “some enjoyment or pleasure” has a numerical value of 3, whereas a response of “much enjoyment or pleasure” has a numerical value of 4. Some items have responses that are reverse-scored: for example, on Item 14 in the CSFQ-F-C version, a response of “never” has a numerical value of 5, whereas a response of “every day” has a value of 1.

To calculate the Total CSFQ score, add up the values of the responses for all 14 items. To calculate subscale scores, add up the values for only the items that correspond to a particular subscale (see shaded box on front side). To determine if sexual dysfunction is present, refer to the gender-specific scoring protocols below.

Scoring for CSFQ-M-C: (Male Clinical Version)

If the male patient obtains a score at or below the following cut-off points* on any of these scales, it is indicative of sexual dysfunction:

- Total CSFQ score: 47.0 (range: 14 to 70)
- Sexual Desire/Frequency score: 8.0 (range: 2 to 10)
- Sexual Desire/Interest: 11.0 (range: 3 to 15)
- Sexual Pleasure: 4.0 (range: 1 to 5)
- Sexual Arousal/Excitement: 13.0 (range: 3 to 15)
- Sexual Orgasm/Completion: 13.0 (range: 3 to 15)

REFERENCES:


* Based on comparisons of non-depressed participants and clinically depressed patients.
ANNEX VI.
DISF - SR (M)

INSTRUCTIONS

Below you will find a brief set of questions about your sexual activities. The questions are divided into different sections that ask about different aspects of your sexual experiences. One section asks about sexual fantasies or daydreams, while another inquires about the kinds of sexual experiences that you have. You are also asked about the nature of your sexual arousal and the quality of your orgasm. There are also a few other questions about different areas of your sexual relationship.

On some questions you are asked to respond in terms of a frequency scale, that is “how often” do you perform the sexual activities asked about in that section. Some frequency scales go from “0 = not at all” to “8 = four or more times a day”. Other frequency scales range from “0 = never” to “4 = always”. With other questions, you will be asked to respond in terms of a satisfaction scale. This type of scale tells how much you enjoyed, or were satisfied by the sexual activity being asked about. Some satisfaction scales range from “0 = could not be worse” to “8 = could not be better”. Other satisfaction scales go from “0 = not at all satisfied”, to “4 = extremely satisfied”.

In every section of the inventory the scales required for that section are printed just above the questions so it will be easy to follow. Although it is brief, take your time with the inventory. For each item, please circle the scale number that best describes your personal experience. If you have any questions, please ask the person who gave you the inventory for help.

SECTION I - SEXUAL COGNITION/ FANTASY

During the past 30 days, or since the last time you filled out this inventory, how often have you had thoughts, dreams or fantasies about:

| 8 = 4 or more per day |
| 7 = 2 or 3 per day   |
| 6 = 1 per day        |
| 5 = 4 to 6 per week  |
| 4 = 2 or 3 per week  |
| 3 = 1 per week       |
| 2 = 1 or 2 per month |
| 1 = Less than 1 per month |
| 0 = Not at all       |

1.1 A sexually attractive person
1.2 Erotic parts of a woman’s body (e.g., face, genitals, legs)
1.3 Erotic or romantic situations
1.4 Caressing, touching, undressing, or foreplay
1.5 Sexual intercourse, oral sex, touching to orgasm

[ ]

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SECTION II - SEXUAL AROUSAL

During the past 30 days, or since the last time you filled out this inventory, how often did you have the following experiences?

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 A full erection upon awakening</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.2 A full erection during a sexual fantasy or daydream</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.3 A full erection while looking at a sexually arousing person, movie or picture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.4 A full erection during masturbation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5 A full erection throughout the phases of a normal sexual response cycle, that is from undressing and foreplay, through intercourse and orgasm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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SECTION III - SEXUAL BEHAVIOR/ EXPERIENCES

During the past 30 days, or since the last time you filled out this inventory, how often did you engage in the following sexual activities?

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Reading or viewing romantic or erotic books or stories</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>3.2 Masturbation</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>3.3 Casual kissing and petting</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>3.4 Sexual foreplay</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>3.5 Sexual intercourse, oral sex, etc.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

SECTION IV - ORGASM

During the past 30 days, or since the last time you filled out this inventory, how satisfied have you been with the following?

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1 Your ability to have an orgasm</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4.2 The intensity of your orgasm</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4.3 The length or duration of your orgasm</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4.4 The amount of seminal fluid that you ejaculate</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4.5 Your sense of control (timing) of your orgasm</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4.6 Feeling a sense of relaxation and well-being after orgasm</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

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SECTION V - DRIVE / RELATIONSHIP

5.1 With the partner of your choice, what would be your ideal frequency of sexual intercourse?

0 1 2 3 4 5 6 7 8

8 = 4 or more per day
7 = 2 or 3 per day
6 = 1 per day
5 = 4 to 6 per week
4 = 2 or 3 per week
3 = 1 per week
2 = 1 or 2 per month
1 = Less than 1 per month
0 = Not at all

5.2 During this period, how interested have you been in sex?

0 1 2 3 4

4 = Extremely
3 = Highly
2 = Moderately
1 = Slightly
0 = Not at all

5.3 During this period, how satisfied have you been with your personal relationship with your sexual partner?

0 1 2 3 4

4 = Extremely
3 = Highly
2 = Moderately
1 = Slightly
0 = Not at all

5.4 In general, what would represent the best description of the quality of your current sexual functioning?

0 1 2 3 4 5 6 7 8

8 = Could not be better
7 = Very Good
6 = Good
5 = Above average
4 = Adequate
3 = Somewhat inadequate
2 = Poor
1 = Very poor
0 = Could not be worse

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# A Brief Sexual Function Inventory

**Sexual Drive**

Let's define sexual drive as a feeling that may include wanting to have a sexual experience (masturbation or intercourse), thinking about having sex or feeling frustrated due to lack of sex.

<table>
<thead>
<tr>
<th>Question</th>
<th>0 days</th>
<th>Only a few days</th>
<th>Some days</th>
<th>Most days</th>
<th>Almost every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. During the past 30 days, on how many days have you felt sexual drive?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. During the past 30 days, how would you rate your level of sexual drive?</td>
<td>None at all</td>
<td>Low</td>
<td>Medium</td>
<td>Medium High</td>
<td>High</td>
</tr>
<tr>
<td>3. Over the past 30 days, how often have you had partial or full sexual erections when you were sexually stimulated in any way?</td>
<td>Not at all</td>
<td>A few times</td>
<td>Fairly Often</td>
<td>Usually</td>
<td>Always</td>
</tr>
<tr>
<td>4. Over the past 30 days, how often have you had erections, how often were they firm enough to have sexual intercourse?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. How much difficulty did you have getting an erection during the last 30 days?</td>
<td>Did not get erections at all</td>
<td>A lot of difficulty</td>
<td>Some difficulty</td>
<td>Little difficulty</td>
<td>No difficulty</td>
</tr>
<tr>
<td>6. In the past 30 days, how difficult have you had ejaculating when you have been sexually stimulated?</td>
<td>Have had no sexual stimulation in past month</td>
<td>A lot of difficulty</td>
<td>Some difficulty</td>
<td>Little difficulty</td>
<td>No difficulty</td>
</tr>
<tr>
<td>7. In the past 30 days, how much did you consider the amount of semen you ejaculate?</td>
<td>Did not climax</td>
<td>Big problem</td>
<td>Medium problem</td>
<td>Small problem</td>
<td>No problem</td>
</tr>
<tr>
<td><strong>Problem Assessment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. In the past 30 days, to what extent have you considered a lack of sex drive to be a problem?</td>
<td>Big problem</td>
<td>Medium problem</td>
<td>Small problem</td>
<td>Very Small problem</td>
<td>No problem</td>
</tr>
<tr>
<td>9. In the past 30 days, to what extent have you considered your ability to get and keep erections to be a problem?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. In the past 30 days, to what extent have you considered your ejaculatory to be a problem?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>Overall Satisfaction</strong></td>
<td>Very dissatisfied</td>
<td>Mostly dissatisfied</td>
<td>Neutral or mixed</td>
<td>Mostly satisfied</td>
<td>Very satisfied</td>
</tr>
<tr>
<td>11. Overall, during the past 30 days, how satisfied have you been with your sex life?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Committee 6 A

Standards for Clinical Trials in Male Sexual Dysfunction: Erectile Dysfunction and Rapid Ejaculation

Chairman
M. HIRSCH (USA)

Members
C. DONATUCCI (USA),
S. GLINA (BRAZIL),
D. MONTAGUE (USA),
F. MONTORSI (ITALY),
M. WYLLIE (U.K)

Disclaimer: The opinions in this manuscript do not reflect the official position of the United States Food and Drug Administration.
I. INTRODUCTION

II. RATIONALE AND DESIGN OF CLINICAL TRIALS

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1. General principles of patient selection
2. Defining the disease state and the patient population: Proposed inclusion and exclusion criteria in clinical trials for ED and for RE

IV. OUTCOME ASSESSMENTS
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V. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS
1. Fundamental trial design considerations for Phase 3 studies
2. Sample size considerations for Phase 3 trials
3. Statistical analysis issues for Phase 3 studies

VI. OVERALL SUMMARY POINTS: STANDARDS FOR CLINICAL TRIALS

REFERENCES
I. INTRODUCTION

The role of the health care profession is to alleviate the pain and suffering, both physical and emotional, that may accompany sexual dysfunction, whenever possible. In doing so, the disease-specific and overall quality of life of our patients may be enhanced. This mission is accomplished through the delivery of safe and effective therapy, which is the product of clinical trials performed under the highest ethical and scientific standards that can be applied. This chapter will review the parameters of clinical protocol design, study procedures, data collection and analysis, which have led to the introduction of the current therapies employed in the treatment of male erectile dysfunction and which will enhance our current armamentarium with newer safe and effective therapies for ED in the future.

The first International Consultation on Erectile Dysfunction (ED) posed comprehensive recommendations for the standards used in clinical research protocols in the evaluation and treatment of men with ED and touched upon the evolving status of sexual dysfunction in women. As a natural consequence of efforts to expand the benefits of properly performed clinical trials to a broader range of male sexual dysfunction, this document will extend those previous ED recommendations to include a preliminary discussion of trials for male ejaculatory dysfunction; specifically, rapid ejaculation. The authors also hope to extend upon the global success in ED by providing some additional recommendations for clinical trials in ED.

In the area of erectile dysfunction, clinical trial design and conduct has been substantially developed. It is now widely recognized that drug development in sexual dysfunction requires a rational phased approach. It is appreciated that initial Phase 1 studies of novel therapeutics will explore safety, tolerability and pharmacokinetics. Phase 2 studies will assess preliminary evidence of clinical safety and efficacy and will explore a range of doses. Phase 3 pivotal trials will confirm clinical efficacy of a particular dose or dose range. Phase 4 studies can further investigate clinical safety and efficacy in sub-populations, can identify signals of previously unrecognized toxicity, and can identify new benefits of a marketed product.

From the ED experience, we also recognize that results of clinical studies are only interpretable and generalizable when sensitive, reliable, validated outcome assessment instruments are used consistently as primary efficacy endpoints in adequate and well-controlled Phase 3 clinical trials and when these trials are conducted in clearly and consistently defined populations. For ED trials, this chapter will reiterate those elements of Phase 3 trial design that have been used with success. For Phase 3 trial design, the most critical elements include randomization, a placebo control group, patient and investigator blinding, a baseline assessment period followed by a double-blind treatment period, and assessments of safety and efficacy at screening, at baseline and at regular intervals during the treatment period. For study efficacy endpoints, instruments that are validated, reliable and clinically interpretable must be selected. The inclusion and exclusion criteria must be clear and must define a broad range of patients with ED. Finally, safety must be carefully assessed through the use of controlled, uncontrolled, and “focused” clinical safety trials.

Therefore, this chapter will review the current best
practices in ED clinical trial design and procedures, will “fine-tune” those recommendations in ED, and will pose new recommendations for the condition of rapid ejaculation (RE) in men. While the majority of development of novel therapeutics for ED has been in orally administered drugs, it is also appropriate to apply sound basic principles of drug development to other modalities including non-oral formulations and surgical prosthesis.

Studies of novel therapeutics in men with ejaculatory disturbances (such as RE) clearly present new challenges. There is a current lack of consensus in regard to appropriate efficacy endpoints and patient entry criteria for RE. Nevertheless, if the ED experience is used as a template and if we abide by the fundamentals of good clinical trial design and conduct, the authors believe that there is sufficient available information to allow for proposal of at least some preliminary recommendations in the area of RE.

Summary points:

• From the ED experience, we recognize that results of clinical studies are only interpretable and generalizable when sensitive, reliable, validated outcome assessment instruments are consistently used as primary efficacy endpoints in adequate and well-controlled Phase 3 clinical trials and when these trials are conducted in clearly and consistently defined patient populations.

• This chapter will review the parameters of clinical protocol design, study procedures, data collection and analysis, which have led to the successful introduction of therapies for the treatment of male erectile dysfunction.

• As a natural consequence of efforts to expand the benefits of properly performed clinical trials to a broader range of male sexual dysfunction, this document will extend those recommendations to a preliminary discussion of male ejaculatory dysfunction; specifically, rapid ejaculation.

II. RATIONALE AND DESIGN OF CLINICAL TRIALS

It is now generally recognized that drug develop-
ly in-hospital or in a clinical research center 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 elucidate (or to safely “prompt”) these toxicities. Safety assessments are monitored at frequent and regular intervals and these may include clinical adverse events, vitals signs, EKGs, clinical serum and urine laboratories, and other special safety assessments (e.g., injection site monitoring, visual effects monitoring, pain assessments, sedation scores, etc.)

Phase 1 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 ($C_{\text{max}}$), time to maximum concentration ($T_{\text{max}}$), the average concentration ($C_{\text{avg}}$), area-under-the-concentration-time curve (AUC), and elimination half-life ($T_{1/2}$). These parameters are determined 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). 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 ED.

In Phase 1, 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 studies: to assess safety, tolerability and pK. Therefore, 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. One should avoid the tendency to try to answer too many questions in one Phase 1 or Phase 2 study. In other research areas, such as the study of medications for benign prostatic hyperplasia (BPH), a simple urine flowmetry examination may not confound safety assessment.

**Phase 2**

In Phase 2 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 further evaluate its safety. The critical objective of the Phase 2 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 3 trials, the maximally tolerated dose and the toxic dose(s). Again, this is critical in ED, where the tolerance for safety risk is fairly low. For development of drugs for the treatment of ED, Phase 2 has proven to be an important phase, in part because the Phase 3 programs are usually very large and costly and dose-ranging in Phase 3 is unwieldy. Also, toxicities and preliminary efficacy that are identified in Phase 2 tend to predict those that will be seen in Phase 3. Therefore, the Phase 2 estimates can be used to predict Phase 3 outcomes, to plan Phase 3 trial designs, and to focus attention on the most important clinical safety and clinical pharmacology concerns.

In Phase 2, actual patients with the clinical condition (as opposed to healthy volunteers or “subjects”) generally serve as the study population. One would especially like to observe for efficacy and safety in selected high-risk or treatment-resistant groups in Phase 2. Early evidence of efficacy and safety in these “more difficult to treat” groups often bodes well for efficacy and safety in the broader Phase 3 population and may expedite a decision to move the program forward.

In Phase 2, 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 2 efficacy trials are usually similar to those in Phase 3 but may include such “pharmacodynamic” parameters as Rigiscan-monitored percent rigidity, or duration of time for maintaining a certain degree of rigidity. Also, shortened versions of classical endpoints (modified sexual history diaries, patient-reported outcomes measures, 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 2 trial and the overall Phase 2 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.

Trial design in Phase 2 is not unlike Phase 3, except perhaps for the use of shorter treatment intervals and
greater use of crossover designs. It is possible to conduct smaller Phase 2 trials (Phase 2a) or much larger Phase 2 trials (Phase 2b) which resemble Phase 3 trials in their scope. Phase 2 studies are usually designed according to the two-stage designs of Simon [1, 2]. These are based upon deciding between “acceptable” and “unacceptable” response proportions. If the response proportion is high, e.g. “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 2 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 [3]. 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 2 trials taking into account both toxicity and treatment response; for example, using the methodology of Bryant and Day [4]. When using this methodology, the sample sizes 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 too great or treatment response be less than adequate.

**Phase 3**

*Phase 3 trials provide the bulk of the “substantial evidence” towards regulatory approval of a compound.* In ED, at least two such trials are usually conducted. These must be adequate and well-controlled. All Phase 3 trials in ED are randomized, double-blinded and placebo-controlled. 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.

The Phase 3 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. There must be some form of a baseline period to allow for screening and baseline (pre-randomization) 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 purposes of collecting longer-term safety data.

The population in Phase 3 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 3. It may not be possible to conduct distinct subgroup analyses for each of these patient types, but that should not prevent this “open enrollment” 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 a life-threatening arrhythmia. One might exclude patients with very reduced drug clearance such as those with significant renal or hepatic diseases.

Of the greatest importance in Phase 3 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. The later two questions refer to the per-attempt, diary-document 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.

Additional comments relevant to Phase 3 may be
found in the Patient Population and Outcomes Assessments sections below.

• **Phase 4**

*Phase 4 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 4 study.* Some of these reasons include the following:

- To better assess safety and efficacy in a specific subgroup,
- To better assess 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 better interpret the impact on overall quality-of-life,
- To assess longer-term safety in controlled trials,
- To assess patient or physician understanding of product labeling, or compliance with labeled instructions.

Other factors that might prompt a Phase 4 study include health-related economic issues, such as drug costs, overall drug benefit for overall cost, or comparative costs.

In ED, conduct of Phase 4 studies is not unusual. However, because the tolerance of drug risk is fairly low, some regulatory agencies may request that specific potential drug safety issues (for example, selected relevant drug interactions) be studied prior to marketed approval. Phase 4 studies intended for marketing claims must be designed as carefully and must be analyzed as rigorously as Phase 3 studies.

• **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 be investigated. We are now fully aware that the ED 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 ED are 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 ED investigational 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 isoenzyme that is critical to the metabolism of the particular ED drug (e.g. the inhibitory effect of ketoconazole on the 3A4 isoenzyme may affect the metabolism of the PDE5 inhibitors). Or, if the investigational drug itself effects the CYP450 isoenzymes 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 vasodilator for ED and selected anti-hypertensive medications, alpha-adrenergic-receptor 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 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 populations studies may also be appropriate and careful consideration is required in each particular circumstance.
Summary points:

- Drug development requires a carefully phased approach. Trials at each phase have a different purpose and each phase helps investigators answer a different set of questions.
- The earliest studies of a new molecular entity are usually single and multiple-dose safety, tolerability and pharmacokinetic investigations.
- The critical objective of the Phase 2 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 3 trials, the maximally tolerated dose and the toxic dose(s).
- Phase 3 trials provide the bulk of the “substantial evidence” towards regulatory approval of a compound.
- Phase 4 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 4 study.
- 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 ED. 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 ED will require at least some of these types of investigations.

III. STUDY POPULATIONS

1. GENERAL PRINCIPLES OF PATIENT SELECTION

All clinical trials require a precise definition of which patients are eligible for inclusion and which patients are not eligible.

The most important underlying principle guiding this definition is that the study population should represent the overall patient population for whom the treatment under investigation is intended. If the study population is truly representative of the intended treatment population, then the results of a well-designed controlled trial are likely to predict the “real-world” effect. On the contrary, if the study population is too narrowly defined, then the trial results may not generalize to the broader population. Therefore, when conducting pivotal Phase 3 trials, it is important for the investigator to define a group of patients that will be as representative as possible of the intended population at large. The investigator accomplishes this by taking into account such factors as patient age, overall health status, concomitant medications, previous use of medications for the treatment of the same medical condition, and the severity and duration of the disorder. All of these considerations apply in the selection of patients for clinical trials of ED.

A second underlying principle in defining the study population is that the disease state under investigation must be well characterized and well defined. In order for the results of controlled clinical trials to be easily interpreted by practitioners, it is critical that the entrance criteria clearly define a patient population with well-recognized disease manifestations. Although practitioners of clinical medicine are not limited by the boundaries of a particular disease category when they treat patients in the real world, the clinical trial investigator must control these boundaries relatively strictly using eligibility criteria. This is achieved by meticulous definition of the particular disease, using particular signs and symptoms, and considering symptom severity and duration. Careful patient selection using unambiguous inclusion and exclusion criteria should be sufficient to delineate a study population that is easily recognized by all those who assess the study results.

A third principle is that a logical and reasonable balance must be struck between the safety of the enrolled patients and the “openness” of the entrance criteria. Specifically, the trial population should be sufficiently broad to represent the larger group of patients who may eventually benefit from treatment, although it should not be so broad so as to include patients who are at direct high risk of injury from the study treatment or procedures. Such balance requires skillful selection of entry criteria which comes only with a sound understanding of the disease process, experience in the management of such patients, and knowledge of the conduct of clinical trials. A corollary of this principle is that exclusion criteria should be sufficiently strict so as to adequa-
tely define the study population and to safeguard the enrolled population, but should not be so strict as to significantly impair the ability of the investigator to recruit the necessary numbers of patients.

a) Specific study population issues in ED include the following:

1. REPRESENTATIVE PATIENT POPULATION: The Phase 3 study population should include patients with erectile dysfunction of varying aetiologies and severities. Such patients will include those with diabetes, atherosclerosis, hypertension, hyperlipidemia, neurologic disorders, genitourinary disorders, appropriately treated endocrinopathies and depression, tobacco use, and various psychological aetiologies. The practice of attempting to divide the population into “organic” and “psychogenic” aetiologies appears to create artificial and unrealistic subgroups. Such a division may reduce the overall applicability of results. Alternatively, it may be argued that “too much” heterogeneity of disease can increase inter-patient variability and may mask or obscure an underlying treatment effect that would have been observed in a more homogeneous population.

2. REGARDING DISEASE SEVERITY: The Phase 3 study population should provide a representative mixture of the various degrees of severity of erectile dysfunction, as assessed by well-validated and sensitive instruments. It may be argued that the inclusion of milder forms of disease could make the demonstration of a treatment effect more difficult. In addition, it is also possible that patients with more severe forms of disease may be more resistant to treatment. Nevertheless, the principle of generalizability seems to carry sufficient weight that it currently appears most reasonable to recommend including the broadest possible range of aetiologies and severities in the pivotal studies. Currently, the EF domain of the IIEF is used to categorize disease severity.

3. REGARDING SUBGROUPS: Currently, it appears reasonable to recommend the study of certain subgroups of patients in smaller, “special population” trials. These trials may include patients with more severe dysfunctional states, patients who have undergone radical prostatectomy, and patients with spinal-cord injury. It may even be reasonable to perform separate studies in diabetics or depressed patients. Proponents of special population studies argue that patient-related variability is reduced and that the likelihood of obtaining a significant treatment effect is increased. In addition, individual study reports may be easier to interpret. Regardless, such studies are capable of providing important support for the pivotal trials. With regards to the use of PDE5 inhibitors, since the advent of sildenafil in clinical use, Phase 3 trials investigating newer agents in the same class generally exclude patients who either had previously failed to respond to sildenafil treatment or who have discontinued treatment with sildenafil due to poor tolerability. This so-called “sildenafil failures” group might also be considered a “special” ED subgroup, appropriate for a specifically dedicated trial. Until such time as a specific “sildenafil-failure” trial is conducted, it is not possible to predict outcomes in this special population. And, if these trials are not direct head-to-head comparisons using an appropriate array of doses (including a repeated assessment of the efficacy of the “failed” treatment), then the results should also not be used for comparative purposes.

b) Specific study population issues in rapid ejaculation (RE) include the following:

Until very recently, the published literature for controlled clinical trials in the field of oral drug therapy for rapid ejaculation has contained fairly few studies and even those have included small numbers of patients. Nevertheless, as more attention is being focused on this area, study population criteria are evolving.

First, one must assure that the prospective trial participant does indeed have rapid ejaculation and no other co-morbid sexual dysfunction, such as ED. It is also generally recognized that participants in RE trials should have RE that causes “marked personal distress or marked interpersonal difficulties”. However, quantification of this “personal distress” and these “interpersonal difficulties” has not yet been accomplished. RE can be lifelong or acquired. Regardless, for inclusion in Phase 3 trials, the condition should be both chronic in duration (at least 6 months) and recurrent in nature (occurring in the majority of attempts over a 6-month period) for a given patient. There is considerable difficulty in posing the exact definition of RE in terms of duration of intravaginal ejaculatory latency time (IELT) or in severity of ejaculatory control problems. This is related to three factors:

1. There is a spectrum of severity of PE. Some men ejaculate before penetration and others at a short time after penetration.

2. There is no precise definition for what is the “normal” mean time for the ejaculation latency after penetration.
3. No single cut-point for intravaginal ejaculatory latency time has been accepted as the standard definition of “rapid ejaculation”.

4. Patients may complain of RE because their partners do not reach vaginal orgasm, yet these patients may still have a fair amount of ejaculatory control. Therefore, the decision as what degree of “ejaculatory control” dysfunction or what exact intra-vaginal latency time should be used as an inclusion criterion in RE clinical trials remains to be decided. This decision is particularly complicated by the lack of a validated patient-reported outcome instrument for the study of RE. Therefore, until such time as a validated instrument for this purpose is available and found to be generally acceptable, specific entry criteria for IELT and/or ejaculatory latency times cannot be formally recommended.

In terms of aetiology, often no specific pathology for RE is found. If a reversible pathology is found (e.g. genitourinary infection), then such patients should be excluded. However, if no reversible pathology is found, these patients should not be excluded.

2. Defining the Disease State and the Patient Population: Proposed Inclusion and Exclusion Criteria in Clinical Trials for ED and for RE

In this section, some inclusion and exclusion criteria are proposed for both ED and RE. The reader should be aware that these are proposed criteria and these continue to evolve:

a) For ED:

- **Inclusion Criteria**

  Phase 3 studies in erectile dysfunction are typically conducted in adult males, 18 years of age and older. There are usually no upper age limitations. In most circumstances, males are heterosexual and have a stable, monogamous relationship with a willing partner. The partner must agree to participate in the trial. The patient must complain specifically of “erectile dysfunction”; that is a consistent difficulty in achieving and/or maintaining an erection sufficient for sexual intercourse. In general, the dysfunctional state must negatively impact on the enjoyment or satisfaction with the overall sexual experience. The duration of dysfunction is variable in different trials, but in general, the problem should be described as a “consistent” one rather than a “transient” one. Currently, it appears that a duration of at least 3 months is a generally accepted, minimum period of disease, although it may be argued that both shorter and longer duration of dysfunction also constitute ED. Enrolled patients must be willing to provide informed consent and must be willing and able to participate in all necessary and pre-specified study procedures. In some trials, inclusion is limited to patients with “mild to moderate erectile dysfunction”, as assessed by standardized instruments such as the EF domain of the IIEF. In the design of some trials, patients who succeed too often during a pre-specified baseline run-in period (e.g. >75% successful attempts) are excluded from additional study participation.

- **Exclusion Criteria**

  In general, exclusion criteria are used to strictly define the study population and to provide safeguards against enrolling patients who are at inherent high risk from study participation. In studies of agents for the treatment of ED, it has been customary to exclude certain patient groups. These are shown in Table 1.

  In some trials, exclusion criteria have been employed which prevent a particularly susceptible group of patients from being exposed to a particular physiologic response associated with treatment. Such exclusion criteria are often dependent on the proposed mechanism of action of the drug. For example, in trials of potent vasodilator agents, patients with baseline orthostatic hypotension may be excluded. In trials of phosphodiesterase Type 5 inhibitors, patients using nitrate therapy are excluded due to the drug’s enhancement of the systemic vasodilating effect of nitrates. As previously mentioned, with the advent in clinical practice of newer PDE5 inhibitors, some clinical trials excluded patients who had previously failed to respond to sildenafil. This should be considered when extrapolating the results of a given trial to real-world use.

b) For RE:

Proposing eligibility criteria for RE clinical trials is especially difficult, as a validated patient reported outcome measure for this condition is not yet available. Still, some considerations follow:

- **Inclusion Criteria**

  Rapid ejaculation is usually defined as the onset of ejaculation with minimal sexual stimulation before, on or shortly after penetration and before the person...
wishes it. The use of intravaginal ejaculatory latency time (IELT) has been suggested by several authors as the best method to categorize the severity of RE. Some have postulated that an IELT of less than 1 minute [5] or less than 2 minutes [6] could serve as a cut-points for inclusion in a clinical trial. At this time, no single IELT cut-point can be recom-
mended as a formal standard by this committee. Rapid ejaculation, as defined above, should be consistent, i.e. occurring in the majority of attempts over the last 6 months and in the majority of eval-
uable events in a baseline run-in period (for example, 75%).

Patients should be involved in a stable, monogom-
mous, heterosexual relationship. Patients and part-
ners must agree to make at least a certain number of
attempts at sexual intercourse during the baseline
period and during the treatment period. Patients and
partners must provide written informed consent and
must understand they are free to withdraw at any
time.

Concomitant erectile function should be assessed
through the use of validated questionnaires and a
clear distinction should be made between patients
with RE who are potent versus patients with RE who
also have ED. Patients with ED should either be
excluded or should be accounted for using stratifica-
tion or pre-defined subgroup analysis.

• Exclusion criteria

Patients with potentially reversible etiologies of
rapid ejaculation should be excluded. Such exclu-
sion criteria might include: genital infection such as
urethro-prostatovesiculitis, major psychiatric disor-
der such as major depression or schizophrenia, or a
history of drug or alcohol abuse in the recent past.

Patients with other forms of sexual dysfunction, such
as decreased interest in sexual intercourse (dimin-
ished libido) or erectile dysfunction (ED) should pro-
bably be excluded. Patients with anatomical penile
abnormalities, such as a phimosis or a short frenu-
lum, should probably also be excluded. Finally, one
might also consider excluding those with known cli-
nically significant neurological disorders associated
with RE, such as spinal cord injury or spinal cord
surgery, major pelvic injury or pelvic surgery, cere-
brovascular accident, Parkinson’s disease or severe
diabetic neuropathy. These neurological conditions
might be particularly resistant to treatment.

If the study medication is a selective serotonin reup-
take inhibitor (SSRI), then labeled contraindications
to the use of SSRIs (such as concomitant monoami-
ne oxidase [MAO] inhibitors) should also serve as an
exclusion criterion in these trials. Other concomitant
drugs that might significantly alter the pharmacoki-
netics of the particular SSRI under investigation
should also be excluded in Phase 3 trials of that par-
ticular agent, pending a better understanding of its
specific metabolic profile. Such drugs might inclu-

Table 1. Patients Typically Excluded from Clinical Trials of ED

1. Patients with untreated hypogonadism.
2. Patients with penile deformities such as Peyronie’s plaques; patients with penile implants; and patients with predispositions to priapism, such as those with sickle cell disease, blood dyscrasias and multiple myeloma.
3. Patients with significant baseline liver dysfunction, such as those with baseline SGOT or SGPT > 3 times the upper limit of normal.
4. Patients with significant baseline renal dysfunction, such as those with serum creatinine values greater than 2.5 mg/dL, those on dialysis, and those who are status post renal transplant.
5. Patients with a history of HIV infection.
6. Patients with drug, alcohol or substance abuse within 6 months of study initiation.
7. Patients who have participated in another study for the treatment of ED within 30 days of study initiation.
8. Patients who have partners who are nursing, or who wish to become pregnant during the course of the study.
9. Patients who are unable to provide informed consent.
10. Patients with uncontrolled psychiatric disorders, such as psychosis, manic depressive disorders or chronic des-
pression.
11. Patients with uncontrolled diabetes mellitus, as evidenced by elevated hemoglobin A1c levels.

In addition, patients in whom sexual activity itself may be a
risk for cardiovascular events have been excluded from
these trials. The specific exclusion criteria that have been
employed to remove such patients from the study population have included:

1. Patients with unstable angina.
2. Patients with a history of myocardial infarction within 6 months of study initiation.
3. Patients with a history of life-threatening cardiac arryth-
mia within 6 months of study initiation.
4. Patients who have suffered a stroke within 6 months of
study initiation.
5. Patients with uncontrolled hypertension, for example, those with systolic blood pressures above 170 mm Hg or diastolic blood pressure >100 mm Hg.
de: cimetidine, phenobarbital, phenytoin, and St. John’s Wort. The particular SSRI under investigation may itself inhibit the metabolism of other drugs and these also might be considered for exclusion (e.g. astemizole, cisapride, terfenadine). Finally, other potentially confounding drugs that might be excluded include: other SSRIs, other anti-depressants, and anti-psychotics.

Other broad exclusion criteria might include: concurrent use of other forms of RE treatment (e.g. topical anesthetics or behavioral therapy), use of other investigational agents, hypersensitivity to SSRIs or the investigational product itself, and patients or partners who may not be capable of completing the study procedures.

Finally, some partner considerations might serve as exclusion criteria and to this end, one might consider excluding the following: patients with partners who exhibit a decreased interest in sexual intercourse, or have painful intercourse, or have other disturbances that significantly impact the sexual relationship with the trial participant. For example, one consideration is whether to exclude a patient in whom the partner has a clinically meaningful disorder of orgasm regardless of the partner’s ejaculatory control.

Summary Points:

- In general, the study population in clinical trials for ED should be broadly representative of the overall ED patient population. Inclusion criteria should define the patient’s ED as clearly as possible, and should provide minimal duration and severity criteria. Exclusion criteria should be sufficiently strict so as to adequately define the study population and to safeguard the study patients, but not so strict as to limit broad generalizability of study results.

- Special population studies may also be of value in assessing the safety or efficacy of new treatments in selected ED sub-populations. These studies could provide valuable complementary data to the main pivotal trials.

- Patient entry criteria for RE should at least contain the following elements: a consistent problem (for example, at least a certain percentage of attempts fail in the baseline period), a sustained problem (for example, a majority of attempts fail in the last 6 months), a problem causing marked personal or interpersonal distress, and finally, ejaculation prior to, on, or shortly after intromission.

- Appropriate inclusion and exclusion criteria for RE trial participants continue to evolve. No formal recommendation can be given for a particular “cut-point” for intra-vaginal ejaculatory latency time. A validated patient reported outcome assessment instrument would be helpful in further defining RE severity and developing Phase 3 entry criteria.

### IV. Outcome Assessments

The outcomes of controlled clinical trials must be assessed using sensitive, reliable and validated instruments. Proper selection of efficacy endpoints, especially the primary efficacy endpoint, is critical to the success of a clinical trial. Even known efficacious therapy will not be shown to be effective if inappropriate efficacy assessment methodology is used. Not only must the choice of efficacy endpoints be appropriate, but also the timing of measurement during the trial must be carefully considered. It is now generally appreciated that the primary endpoints must be measured at screening, at baseline (following a run-in period), during the course of the treatment period, and at the end of the treatment period.

For ED, these issues of trial design and procedures and outcome assessment selection and timing have now become fairly standardized. On the other hand, for rapid ejaculation (RE), we are still at a relatively early stage of developing and selecting all outcome measures. Nevertheless, there does appear to be sufficient current evidence that certain outcomes in RE have utility and may be used towards drug development. Other potential endpoints require additional research. Herein, the current understanding of outcome assessments in ED and RE are delineated.

### 1. Outcome Assessments in ED

The response variables for ED, or endpoints measured in a clinical trial, include both physiological measures of penile rigidity (e.g. Rigiscan) and patient-based responses to questionnaires (e.g. IIEF or SEP). Other endpoints include global questions in regard to overall patient improvement while on treatment, patient satisfaction with treatment, and concurrent assessments of the partner. The current Phase 3 endpoints of preference are patient-reported
outcomes derived from self-administered questionnaires and from per-event patient diaries. However, each measure has advantages, disadvantages and some place in ED clinical trials.

a) Physiological Measures

Current programs of drug development for ED continue to use physiological measures, such as the Rigiscan, in early Phase 1 and Phase 2 studies. These continue to play a role as a pharmacodynamic response variable in proof-of-concept studies. The Rigiscan (Timm Medical Systems) is the most commonly used device in this regard. It was originally developed for the at-home non-invasive monitoring of nocturnal penile tumescence [7]. In brief, the device is attached to the patient’s thigh and includes two loops which go around the penis at the base and tip of the shaft. Measures of radial rigidity are obtained by application of a pre-determined force to these loops at intervals of 3 minutes, unless there is a nominal increase in the base rigidity, which results in more frequent intervals. Penile tumescence is expressed as a function of displacement when the loop is tightened and penile rigidity is defined in terms of percent stiffness as compared to a hard plastic rod. As noted, the Rigiscan has been used in proof-of-concept drug trials when accompanied by visual sexual stimulation (VSS). This novel test has been used in trials of intracavernosal alprostadil [8], sildenafil [9] and sublingual apomorphine [10].

There are some obvious limitations to the Rigiscan VSS. One of these is the artificial and intrusive environment required for the test. In addition, the Rigiscan measures radial and not axial rigidity. Some argue that axial rigidity is of greater relevance for intromission. Others have argued that axial and radial rigidity are functionally related and both correlate moderately with intracavernous pressure. [11]. Another difficulty is in defining clinically meaningful rigidity and clinically meaningful duration (time) of erection in the Rigiscan-VSS test. The most common definition used for clinically meaningful rigidity has been a base rigidity of 55% [12]. One investigator postulated that 5 minutes could serve as a clinically meaningful duration of erection [13]. Finally, there is still little overall or age-specific normative Rigiscan data. Overall, despite its limitations, the Rigiscan VSS still has a role to play in clinical trials for ED.

Other physiological measures used in drug development programs for ED trials have included volumetric plethysmography and mercury-in-rubber strain gauge plethysmography [14, 15], and ultrasound assessments of blood flow in the cavernous arteries. While these measures provide some information in regard to changes in tumescence, in penile circumference and in penile arterial inflow, they all suffer from a lack of rigidity measurement. Overall, these measures may serve to support or supplement other more clinically relevant variables directly related to the patient experience. It is of interest to note the evolution in clinical trials of ED where so-called “objective” or “physiological” response variables have been firmly supplanted by “subjective” or “patient-reported” outcome measures.

b) Patient-Report Measures

Currently, the primary endpoints in most ED trials are patient reported measures of sexual function. In this category, the most commonly used instruments have been self-administered questionnaires (such as the IIEF) and patient diaries (such as the SEP). These are clearly the most notable patient-reported outcomes in ED [16]. Other patient-reported response variables include the structured interview [17], a Global Question of symptom improvement, various broad and specific quality-of-life (QOL) instruments, and measures of satisfaction with treatment.

The current gold standard questionnaire in ED clinical trials is the International Index of Erectile Function (IIEF). It is a well-known, widely accepted, and extensively validated measure of efficacy for ED and has served successfully as the primary endpoint in several large development programs for drugs intended for the treatment of ED [16]. The instrument consists of 15 items and assesses sexual function in five domains (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction). Average scores are calculated for each domain. In the regulatory setting, the 30-point erectile function (EF) domain score has been of paramount importance. In addition, the 5-point questions #3 and # 4 of the EF domain have also served as stand-alone primary endpoints in Phase 3 clinical trials for ED. Scores on the EF domain have been used to describe erectile dysfunction severity and changes in the clinical status of the condition [18].

The major benefits of the IIEF are its high degree of reliability, as demonstrated in extensive psychometric testing; its responsiveness to treatment (sensitivity and specificity); its brevity, its ease of use, its translation and validation in multiple languages and...
its strong psychometric profile. It may be used to stratify baseline disease severity and to demonstrate improvement or deterioration in disease status within these strata. One drawback may be a potential difficulty in interpreting clinical relevance of very small changes from baseline in individual domain scores. Also, the questionnaire is limited to a four-week retrospective timeframe. Nevertheless, the IIEF is currently widely accepted as the international standard for patient-reported assessments in ED.

Other questionnaires that have been used as response variables for ED include the Brief Sexual Function Inventory, and the Center for Marital and Sexual Health Questionnaire (CMSH-SFQ). In brief, each of these have their own advantages and disadvantages. The BSFI is an 11-item questionnaire which addresses several components of male sexual function. It has a relative high degree of internal consistency and test-retest reliability, adequate discriminant validity for three of the domains (erectile function, problems, overall satisfaction), and is fairly easy to use. However, the limited evaluation of erectile and orgasmic function and lack of evidence for treatment responsiveness are disadvantages. It has had limited utility in large-scale clinical ED trials. The CMSH-SFQ is an 18-item self-report questionnaire. It has had minimal use in ED trials to date. Again, information regarding treatment responsiveness is lacking. Finally, the Derogatis Inventory is a 245 item comprehensive index assessing sexual function in ten different domains. It has been psychometrically validated. Unfortunately, the time required to complete the questionnaire limits its usefulness in large-scale Phase 3 trials for new ED treatments.

Daily diaries or per-event questionnaires are patient-reported outcome measures commonly used in ED trials to complement and assist in the interpretation of retrospective questionnaires. These measures, including the Sexual Encounter Profile, have been extensively used in Phase 3 trials for ED. The SEP is a 6-item event log. Of greatest interest have been questions #2 and #3 of the SEP, which refer to the patient’s ability to insert the penis successfully into the vagina, and to whether the erection was sustained to completion of successful intercourse, respectively. The instrument has undergone some validation testing with a high degree of correlation observed between erection and intercourse satisfaction ratings on the SEP and the IIEF measures in ED patients [20]. Other than the self-report questionnaire and the daily diary, quality of life instruments have been used as response variables in many ED trials. While these have routinely been tested as secondary endpoints, they have not provided evidence that has substantial impact on drug approval decisions. First, most of the broader QOL instruments seek to assess changes in domains not entirely relevant to the broader healthy ED population. These include such issues as cognition and physical limitations, more relevant to a more medically infirmed group. Other disease-specific QOL instruments have been devised, including the 8-item Fugl-Meyer Life Satisfaction Checklist, the Erectile Dysfunction Inventory of Treatment Satisfaction, and the 19-item QOL-MED. These continue to be examined as secondary endpoints and despite little current impact, these may eventually provide support for the long-term risk/benefit analysis for the treatment of ED.

Finally, safety variables are of major import in ED trials. The need to carefully monitor and record these variables is well known to sponsors of new drugs, investigators, practicing clinicians and regulators. Periodic assessment of clinical adverse events is routine in all ED trials. In general, specific questions that attempt to prompt reporting of specific adverse events are not used in Phase 3. Rather, brief open-ended questions have been used. Controlled trial durations of 1 and 2 years, and long-term follow-up in the post-marketing period tend to allow for a good assessment of overall clinical adverse events. Of note, some serious or medically significant adverse events that occur at low frequency may require quite large sample sizes for their capture. One way of managing this problem is to conduct “focused” safety trials intended to address specific safety questions. These might include safety trials aimed at understanding a drug’s effect on vital signs, on vision, on cognition, and in combination with other drugs.

2. OUTCOME ASSESSMENTS IN RE

The spectrum of ejaculatory dysfunction includes premature (or rapid) ejaculation, retarded ejaculation, retrograde ejaculation and inability to ejaculate (anejaculation). We limit our discussion here to rapid ejaculation (RE), as there are very limited data on viable treatment approaches for the other ejaculatory disorders.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) defines premature ejaculation as persistent or recurrent ejaculation with minimal
sexual stimulation, before or shortly after penetration and before the person wishes it, which is associated with marked distress or interpersonal difficulty. There are many published clinical trials in the literature but these lack consistency in regard to study populations and outcome assessments. The previous section in this chapter (Section III) discussed issues specifically related to study populations. This section will focus on outcome assessments.

There is an overall lack of standardized and validated instruments to assess the outcomes of clinical trials in RE. Nevertheless, it is still possible to recommend that controlled clinical trials for treatment of RE should assess efficacy using three basic types of efficacy outcome measures: ejaculatory latency time, ejaculatory control and sexual satisfaction.

a) Ejaculatory latency time (ELT):
The ejaculatory latency time has been defined as the time between the beginning of sexual stimulation or vaginal penetration and ejaculation [21, 22]. ELT has been measured during masturbation [22, 23], during intercourse [21, 24, 25, 26, 27, 28] and during visual sexual stimulation associated with or without vibrotactile stimulation [22, 23]. Intravaginal ELT (IELT) has been estimated by the patient [22, 25, 26, 23, 29] and/or by the partner [26] using a per-event diary or retrospectively during periodic study visits. In addition, IELT has also been measured by the partner [28] or by the patient [24, 27] using a stopwatch or a regular clock.

The direct measurement of intravaginal ELT has been criticized by some because it diverts attention toward the chronometer or clock. Such attention to the clock could add bias to the study design, the results may be difficult to interpret [29], and finally, small increases in IELT may not lead to improved sexual satisfaction [30]. Nevertheless, objective recording is precise and does not require estimation by the patient or partner, which itself may add bias. In fact, IELT measured by stopwatch is usually shorter than estimated ELT [28].

In terms of the procedures for measuring ELT, measurement during intercourse, would appear to be a very reasonable approach. It has been reported that most patients complaining of RE state that their ELT on masturbation is “normal”. It has further been reported that there was no difference in masturbation ELT between patients and controls [22]. Therefore, it would seem that measuring ELT during masturbation is not a reliable tool to be used in clinical trials, except possibly as an exploratory endpoint in Phase 2 trials. For Phase 2, it is possible that visual sexual stimulation testing coupled with vibrotactile stimulation [22] and measurement of ELT could be useful in screening new drugs intended to treat RE. Phase 2 studies might also include measure of IELT in a monitored setting.

Currently, test re-test correlation for this methodology has not been studied extensively. However, it is known that screening, baseline and on-treatment IELT may differ, partly as a consequence of the stopwatch serving as a distraction, as a negative influence, or as a disease severity “magnifier”.

Nevertheless, the objective assessment of intravaginal ELT using the stopwatch methodology still appears useful for conducting clinical trials in PE. It is acknowledged that this method does divert the couple’s attention to the clock. The fundamental elements of good clinical trial design; that is double-blinding, placebo control and randomization, should adequately manage this bias.

There is still clearly a need to evaluate the patient’s subjective perception of satisfaction with sexual intercourse and control over ejaculation in clinical trials of RE. These two specific items are considered fundamental to the primary assessment of drug effectiveness for this condition. Data to support these outcomes should be derived from validated, patient-reported outcome instruments that meet the key requirements of responsiveness, reliability and validity.

b) Ejaculatory control:
It has been reported that in men with RE, the patient’s perceived control over the timing of ejaculation is poor or absent. The patient’s own perception of ejaculatory control is considered to be an important outcome to be assessed in a clinical trial in RE. However, we know of no validated instruments to assess this subjective perception. In one study, Rowland et al [22] used a ten-point scale ranging from 1 (none ejaculatory control at all) to 10 (complete ejaculatory control). A simple scale, using a single question such as reported by Rowland, might be a reasonable approach to measuring ejaculatory control. Of course, validation research must be conducted for such an instrument despite its assumed simplicity.

c) Sexual satisfaction:
All investigators appear to agree that satisfaction with sexual activity is an important outcome in any
clinical trial in sexual dysfunction. Clearly, \textit{the ultimate test of any treatment for sexual dysfunction and for RE in particular is if the patient and his partner are sexually satisfied}. This is the ultimate goal of treatment. Again, however, there is no specific validated tool for this assessment for RE.

Sexual satisfaction has been measured in some studies by various scales [29, 30, 31]. In 1986, Rust and Golombok [32] published on their GRISS instrument (the Golombok-Rust Inventory of Sexual Satisfaction). This instrument has undergone some degree of validation, although it is unclear whether it can be recommended as a fully validated, reliable and reproducible outcome assessment, especially for use in RE trials. Other investigators have used the actual number of attempted intercourse events as indirect evidence of sexual satisfaction [24]. Additional research is certainly indicated in developing a validated patient-reported outcome (PRO) measure for sexual satisfaction in men with RE.

Summary points:

- The outcomes of controlled clinical trials must be assessed using sensitive, reliable and validated instruments. Proper selection of efficacy end points, especially the primary efficacy endpoint, is critical to the success of a clinical trial.
- Primary endpoints should be measured at screening, at baseline (following a run-in period), during the course of the treatment period, and at the end of the treatment period.
- The current Phase 3 endpoints of preference in ED are patient-reported outcomes derived from self-administered questionnaires and from per-event patient diaries.
- The current gold standard questionnaire in ED clinical trials is the International Index of Erectile Function (IIEF). It is a well-known, widely accepted, and extensively validated measure of efficacy for ED and has served successfully as the primary endpoint in several large development programs for drugs intended for the treatment of ED.
- Daily diaries or per-event questionnaires are patient-reported outcome used in ED trials to complement and assist in the interpretation of retrospective questionnaires.
- There is an overall lack of standardized and validated instruments to assess the outcomes of clinical trials in RE. Nevertheless, it is still possible to recommend that controlled clinical trials for treatment of RE should assess efficacy using three basic types of efficacy outcome measures: ejaculatory latency time, ejaculatory control and sexual satisfaction.
- The direct measurement of intravaginal ELT has been criticized by some because it diverts attention toward the chronometer or clock. Such attention to the clock could add bias to the study design, the results may be difficult to interpret, and finally, small increases in IELT may not lead to improved sexual satisfaction. Nevertheless, the objective assessment of intravaginal ELT using the stopwatch methodology still appears useful for conducting clinical trials in PE.
- The patient’s own perception of ejaculatory control is considered to be an important outcome to be assessed in a clinical trial in RE. However, we know of no validated instruments to assess this subjective perception.
- The ultimate test of any treatment for RE is if the patient and his partner are sexually satisfied. Again, however, there is no specific validated tool for this assessment for RE. Additional research is certainly indicated in developing a validated patient-reported outcome measure for sexual satisfaction in men with RE.

V. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

A clinical trial is a research study to answer specific questions about new therapies or new ways of using existing therapies to determine whether new drugs or treatments are both safe and effective. \textit{Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people}. Clinical trials are conducted according to a \textit{protocol}, the study plan on which all clinical trials are based. The plan is carefully designed to safeguard the health of the participants as well as answer specific research questions. A protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study. While in a clinical trial, participants following a protocol are seen regularly by the research...
Clinical trials are an important tool in developing new, safe and effective treatments. **Key features of such trials include adequate sample size to provide a statistically meaningful result and an appropriate statistical analysis plan in place and appropriately executed.** When coupled with good Data Monitoring and Quality Control, this should ensure that a clinical trial demonstrates the utility, or lack of utility, of a new treatment.

Clinical trials are conducted in phases. The trials at each phase have a different purpose and help scientists answer different questions. **In this section, attention will be restricted to Phase 3 clinical trials.** These will be designed and conducted according to the most up-to-date standards of Good Clinical Practice (GCP). In particular, attention will focus on key aspects of the designs and statistical analyses of the data from these studies.

1. **Fundamental trial design considerations for Phase 3 studies**

Phase 3 studies are used to compare at least one treatment with a placebo control group or two or more active treatment groups with each other. While it is now common to see Phase 3 studies arranged in a 2 by 2 factorial design (where the objective is to investigate the interaction between two treatments), the classical Phase 3 study design compares one new treatment with a placebo group. **Assignment of patients to treatment group should be double blinded wherever possible and this assignment should always be randomized.**

There are well-established statistical procedures for the design and analysis of Phase 3 studies. There is no excuse for a Phase 3 study that lacks a clearly defined protocol or analysis plan.

2. **Sample size considerations for Phase 3 trials**

Sample power should be calculated in advance, using the best available estimates of the means and variances of the primary efficacy variables, and anticipated changes associated with treatment. Sample power for Phase 3 trials is traditionally based on estimates of efficacy, not safety. In this respect, while studies may be adequately powered for efficacy, they **may not be adequately powered for detection of low-frequency safety problems.**

Standard formulae are available for the computation of sample power for a clinical trial [33]. In addition, there are available sample size formulas for many commonly used endpoints, measurements, repeated measures, proportions, and survival [34, 35]. Based upon our previous experience with the PDE5 inhibitors, it should now be relatively straightforward to estimate sample size requirements for Phase 3 ED trials. **In the design of these studies it is important to use realistic values for the anticipated treatment effect and standard deviation of the response measure. Many studies turn out to be underpowered because the initial expectations about the treatment effects were much too optimistic.** One should make every effort to ensure that the study is not underpowered.

Both crossover and parallel arm design studies are of statistical validity, as long as they are sufficiently powered. Not surprisingly, the crossover design requires a smaller patient population.

Some trials are designed to establish equivalence between therapies and these require special methods in the calculation of the power [36]. Many of these techniques are included in good sample size calculation software such as NQuery Advisor [37]. Once again there are several web-based power calculation services available that are perfectly adequate.

3. **Statistical analysis issues for Phase 3 studies**

The analysis of Phase 3 studies should normally adhere to the intention to treat principle so as to minimize the effects of possible bias which can arise when only patients who complete the study are included. This principle states that all randomized patients should be included in the analysis in the group that they are randomized to. **Analyzing only the patients who fully complete the study can induce a bias if drop out is not completely at random.** Methods such as carrying the last observation forward are a simple method of adhering to the intention to treat principle. Alternative methods are available if study withdrawal is not random but is associated with treatment or disease status [38]. **This general rule regarding the intention-to-treat population should not be applied to the assessment of adverse events, however, where it may be preferable to report the frequency of side effects only among those who actually received the treatment [39].**

A variety of data analytical methods have been employed in recent ED clinical trials. Although a
detailed discussion of these methods is beyond the scope of this chapter, some general comments and recommendations can be made. To a large degree, the type of statistical method employed depends upon the nature of the research design (e.g. parallel, between-group comparisons versus counterbalanced, crossover designs) and the response variables being analysed (e.g. continuous vs. dichotomous variables).

Given the large number of statistical issues and data analysis considerations, it is essential that a qualified biostatistician be involved in the design and analysis of all clinical trials in ED.

Covariate adjustments or stratification techniques can be used to control for differences between the study groups at baseline in terms of their levels of erectile function or other demographic characteristics (e.g. age, duration of illness). However, covariance analysis should be performed only when specific statistical assumptions are met [40, 41]. In the final efficacy analysis, a limited number of subgroup analyses may be conducted, paying careful attention to the potential lack of power and possibility of Type II errors associated with these analyses [39].

Describing the magnitude of a treatment effect involves both statistical and clinical considerations. Effect size may be calculated using group mean changes from baseline, using percentages of “responders” in the active versus control groups, or using both types of measures. Responder analyses involve prior definition of a response threshold or cut-off. For example, in a multi-centre trial of trans-urethral alprostadil [42] a treatment responder was defined as any individual who completed successful sexual intercourse at least once during the study period. It could be argued that this definition is overly liberal, and not in keeping with current clinical criteria for successful treatment.

Unfortunately, normative population data are lacking to establish response criteria for adequate sexual performance at each age group. In the absence of such data, continued disagreement on the definition of a treatment responder is likely. One approach to the problem of describing treatment effect in ED is to report several measures of treatment efficacy, including both quantitative (e.g. number of successful intercourse attempts) and qualitative (e.g. global satisfaction) indices. This allows for a more comprehensive assessment of the magnitude and consistency of treatment effects.

Finally, as has been seen in the treatment of BPH, meta-analysis may play a role in assessing the direction and magnitude of treatment effects over several independent trials [43, 44]. The method requires careful selection of trials for inclusion in the analysis, based upon pre-determined criteria for assessing methodological adequacy (i.e. randomisation, double-blinding). Results from all eligible trials should be standardised and combined according to strict statistical rules. An odds ratio or relative risk analysis is then performed on the resulting data. Relatively few meta-analyses have been used in the analyses of clinical trial data in ED, although this technique would appear to offer promise in addressing certain issues. As the number of clinical trials of ED increases, it is anticipated that meta-analytical studies will play an increasingly important role in the future.

Summary points:

• Due to the number of statistical and data analysis issues, a qualified biostatistician should be involved in the design and analysis of all clinical trials in ED. Specific issues include the calculation of sample power for the trial, type of statistical model and design to be employed, use of covariate or subgroup analyses, and calculation of effect sizes.

• Describing treatment effect may be best accomplished using multiple endpoints including group means changes from baseline and responder analyses.

• There is no general agreement at present concerning the criteria and appropriate definition of a treatment responder.

• Meta-analysis is a statistical procedure likely to play an increasingly important role in the clinical literature on ED as more trials are published.

VI. OVERALL SUMMARY POINTS: STANDARDS FOR CLINICAL TRIALS

Clinical trial designs, procedures, endpoints and analyses continue to improve in the study of male sexual dysfunctions. For erectile dysfunction (ED), the successful conduct of several major drug development programs now afford us the ability to make recom-
recommendations for certain standards. However, for rapid ejaculation (RE), further research is required before we can make definitive recommendations. The following items comprise the overall summary points from the previous chapter:

Drug development requires a carefully phased approach. Trials at each phase have a different purpose and each phase helps investigators answer a different set of questions. The earliest (Phase 1) studies of a new molecular entity are usually single and multiple-dose safety, tolerability and pharmacokinetic investigations. The critical objective of the Phase 2 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 3 trials, the maximally tolerated dose and the toxic dose(s). Phase 3 trials provide the bulk of the “substantial evidence” towards regulatory approval of a compound.

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 ED. 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 ED will require at least some of these types of investigations.

Results of clinical studies are only interpretable and generalizable when sensitive, reliable, validated outcome assessment instruments are consistently used as primary efficacy endpoints in adequate and well-controlled Phase 3 clinical trials and when these trials are conducted in clearly and consistently defined patient populations.

In general, the study population in clinical trials for ED should be broadly representative of the overall ED patient population. Inclusion criteria should define the patient’s ED as clearly as possible, and should provide minimal duration and severity criteria. Exclusion criteria should be sufficiently strict so as to adequately define the study population and to safeguard the study patients, but not so strict as to limit broad generalizability of study results.

Patient entry criteria for RE should at least contain the following elements: a consistent problem, a sustained problem, a problem causing marked personal or interpersonal distress, and finally, ejaculation prior to, on, or shortly after intromission. However, defining appropriate inclusion and exclusion criteria for RE trial participants continues to evolve. No formal recommendation can be given for a particular “cut-point” for intra-vaginal ejaculatory latency time. A validated patient reported outcome assessment instrument would be helpful in further defining RE severity and developing Phase 3 entry criteria.

The current Phase 3 endpoints of preference in ED are patient-reported outcomes derived from self-administered questionnaires and from per-event patient diaries. The current gold standard questionnaire in ED clinical trials is the International Index of Erectile Function (IIEF). It is a well-known, widely accepted, and extensively validated measure of efficacy for ED and has served successfully as the primary endpoint in several large development programs for drugs intended for the treatment of ED. Daily diaries or per-event questionnaires are patient-reported outcomes commonly used in ED trials to complement and assist in the interpretation of retrospective questionnaires.

There is an overall lack of standardized and validated instruments to assess the outcomes of clinical trials in RE. Nevertheless, it is still possible to recommend that controlled clinical trials for treatment of RE should assess efficacy using three basic types of efficacy outcome measures: ejaculatory latency time, ejaculatory control and sexual satisfaction. We know of no validated instruments that can currently be recommended for either the patient’s subjective perception of ejaculatory control or for sexual satisfaction in men with RE. Additional research is certainly indicated in developing validated patient-reported outcome measures for these response variables.

Due to the number of statistical and data analysis issues, a qualified biostatistician should be involved in the design and analysis of all clinical trials in ED. Specific issues include the calculation of sample power for the trial, type of statistical model and design to be employed, use of covariate or sub-group analyses, and calculation of effect sizes.
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CHAPTER 9

Committee 10

Experimental Models for the Study of Male Sexual Function

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Experimental Models for the Study of Male Sexual Function

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INTRODUCTION

Research in the area of sexual function critically depends on research models. Investigations into the anatomy, physiology, cell biology, biochemistry and pharmacology of sexual function are necessary to develop new therapies for the treatment of human disease. Rarely can these studies be carried out in human patients. Therefore, experimental animal models have been developed to investigate particular aspects of sexual function. Several factors must be considered in the choice of a particular model. Researchers must consider how closely the function being studied resembles the human function, the depth of relevant background data of that species and physiological or behavioral system, whether the method can be standardized and quantified, the technical feasibility of the model, and cost. Often, some compromises must be made with respect to these and other factors. For example, the non-human primate penis may more closely model the human penis for the purposes of studying erectile function. However, cost and animal welfare considerations present major barriers to widespread use of non-human primate models. Rodent models are the most commonly used, largely driven by practical concerns and the huge literature on rodent biology.

It is especially important that researchers choosing to adopt an experimental approach be aware that any given model has strengths and limitations. Some aspects of the model may closely mimic human physiology, while others show significant variance. Further, sexual responses are complex, coordinated functions and it is rare that an experimental model has all components of the function. A particularly complex function, such as ejaculation, is extremely difficult to study in its entirety. A common approach is to study individual components separately.

In this review, the most commonly used models for the study of sexual function are described. The focus is on the technical aspects of the models, not the findings generated using these models. The strengths and limitations of each model are detailed. We also identify aspects of sexual function for which adequate experimental models do not exist. Highlighting these gaps will hopefully stimulate researchers to seek new methods for these areas of investigation.

I. PENILE ERECTION

1. PRESSURE RECORDING IN THE CORPUS CAVERNOSUM

Penile erection is one physiological event of male sexual behavior that, in some aspects, may be considered comparable between mammals [1] The organization of the central and peripheral nervous systems that innervate the penile vasculature and adjoining structures, has been extensively studied in many mammals. Regulatory mechanisms of the erectile smooth muscle from different species are similar to those of human erectile tissues [2-6]

Invasive techniques to measure intracavernous pressure (ICP) provide means for direct estimations of central nervous, or peripheral autonomic or somatic neuronal regulatory mechanisms of erection during various contexts. Thus, copulatory or non-contact erections [7, 8], erectile responses induced by activation of neuronal structures [9-13] or the impact on ICP by systemic or targeted pharmacological intervention [14-18] can be evaluated. Analyses of resting
ICP, duration and amplitude of increases in ICP during an erectile response, rate of increase or decrease in ICP during tumescence and detumescence, and area under the ICP curve, are all measures used to quantify effects of any selected regulatory mechanism of erectile function [19]. Measurement of ICP during stimulation of peripheral nerves, with or without pharmacological modulation of inter- or intracellular signaling mechanisms in the erectile tissue, are commonly described techniques used to study efferent and afferent neuronal pathways involved in the regulation of penile erection [20].

Due to larger anatomical dimensions, animals such as canine or primate breeds have traditionally been used to determine the hemodynamics of penile erection and to record intracavernous pressures during activation of nerves or after administration of pharmacological agents [9, 10, 14, 21-27]. Rats, in many laboratories, have become preferred models for the study of erectile function and dysfunction due to manageable costs of maintenance and convenient handling procedures [28-30]. In vivo rodent models for measurement of ICP in the crus of the corpus cavernosa or in the cavernous body of the penile shaft, have been characterized [8, 11, 12, 15, 16, 31-35]. The lifespan of rats allows for studies of erectile function during physiological aging and characterization of several disease models that resemble pathological states in humans. These factors make this species of interest for investigations of erectile dysfunction [28, 36]. Molecular or gene-based techniques are available and can be used in rats or mice to study erectile function or ED under experimental conditions [29, 37-39].

Whereas numerous investigations in ICP registration models have contributed with substantial amounts of information on the peripheral autonomic control of penile erection, less is known of the neurophysiology and pharmacology of supraspinal and spinal regulatory mechanisms of erectile events [4-6, 20]. During simultaneous registration of ICP, specific techniques for stimulation or administration of drugs at selected areas in the brain or at segments of the spinal cord are available [13, 17, 18, 40-42]. In combination with surgical disruption or pharmacological modification of central or peripheral signaling pathways, the effect on ICP by activities in supraspinal and spinal functional units or specific transmitter systems can be recorded [16, 17, 42].

Most non-behavioral investigations of supraspinal and spinal control of erection are performed in anesthetized ICP registration models. Various anesthetic agents are presumed to exert part of their effects by destabilizing neuronal membranes and / or by interfering with transmitter systems [43], some of which are evidenced or suggested involved in central nervous regulatory mechanisms of penile erection [6]. Reduction in systemic arterial blood pressure and effect on visceral reflex responses induced by anesthetic agents may also indirectly influence erectile responses. Awake ICP registration models must therefore be considered as additional methods to study supraspinal and spinal regulatory functions of penile erection induced by physiological stimuli or pharmacological agents acting at central sites. Procedures to measure ICP in conscious individuals have been characterized and offer means for direct registration of pressure in the corpus cavernosa and data acquisition through directly connected or telemetric modules [7, 8, 16, 19]. Differences in the characteristics of the recorded ICP patterns in rat models, mainly with substantially higher peak pressure values during telemetric recording of apomorphine-induced erections, may represent differences in technical approach, and suggest further comparisons of the awake and anesthetized methods.

Measurement of ICP is typically performed by inserting a hypodermic needle into the body or the crus of the corpus cavernosa. The needle is connected to tubing filled with heparinized saline to prevent clotting. The tubing is attached to a calibrated strain gauge whose output is fed to computerized data acquisition systems or standard chart recorder. A catheter is also placed into an artery in order to measure systemic blood pressure (BP). The data are usually presented as the ratio of ICP over BP. This procedure is necessary because ICP is dependent on both penile vascular mechanisms as well as systemic hemodynamics. The ratio provides a measure that largely reflects penile mechanisms (Figure 1).

2. MEASURING INTRACAVERNOUS PRESSURE DURING EX-COPULA ERECTILE RESPONSE

These erectile contexts mainly evaluate the frequency of the erectile responses. However, erectile dysfunction of the human male is defined as the inability to achieve and maintain penile rigidity. In other words, ED is loss of the quality of erection. Therefore, we should evaluate these erectile responses from the aspect of the quality of the erectile response. Giuliano and Sachs monitored intracavernous pressure with a telemetric recording system [8]. Andersson et al. also measured ICP following subcutaneous injection of apomorphine in the awake condition [16].
They clearly demonstrated that ICP increases of reflexive erection, noncontact erection, apomorphine induced-erection and copulation showed similar patterns. Using these models, it is possible to evaluate their amplitude (ICP) as the quality of the erectile response and to do quantitative analysis of plateau and peak phases separately (Figure 2).

3. Stimulation of the Cavernous Nerve

The vasodilatory innervation of the penis is conveyed by the cavernous nerve [3]. The ICP response to electrical stimulation provides information on the smooth muscle relaxation and nitrergic innervation in the penis. Investigation of penile hemodynamics, synaptic mechanisms, the biochemistry of smooth muscle relaxation and penile pharmacology have been investigated using stimulation of the cavernous nerve [14, 15, 21, 24]. For pharmacological studies, a common approach is to construct a curve of the peak ICP/BP ratio achieved at a range of stimulation frequencies or intensities. A shift of this curve, or change in the maximal pressure ratio indicates the effect of pharmacological agents on penile erections (Figure 3).

4. Stimulation of the Dorsal Nerve of the Penis

The dorsal nerve of the penis (DNP), which carries the somatic sensory information of the glans and the penile skin, constitutes the afferent limb of two neurologically distinct responses: erection and ejaculation [3, 44, 45]. Stimulation of the DNP thus provides a means of assessing the reflex pathways underlying sexual responses. The DNP is constituted by Ad and C sensitive fibers [44], and by few sympathetic postganglionic fibers. These sympathetic fibers have been proposed to be involved in the vasomotor control of the penile skin [45] and may provide a major vasoconstrictor input for detumescence [5, 12]; alternatively, they could modulate the sensitivity of penile afferent receptors [3]. Lastly, the presence of a central reflex from the DNP to the lumbar sympathetic chain has been described [46].
In the rat the DNP cellular bodies have been localized, by axonal tracing techniques [44], in the L6 dorsal root ganglion. A striking sexual dimorphism is here present, with a number of cellular bodies in the male rat that almost doubles that of the female [3, 45]. DNP rat fibers terminate in the spinal cord both in the medial dorsal horn and in the dorsal commissure, with bilateral projections [44, 45]. In particular, it has been shown a direct contact between DNP afferent projections and both cellular bodies and dendrites of motoneurons, innervating the perineal striated musculature [44]. Accordingly, a regulatory role of DNP fibers over motoneurons involved in somatic aspects of sexual reflexes has been postulated [44]. Furthermore, DNP terminal fibers extend to the posterior grey commissure in close proximity to dendrites of preganglionic parasympathetic neurons [47]; this would represent the morphologic substrate for pudendo-parasympathetic reflexes [44].

DNP stimulation has provided electrophysiological evidence for a relationship between the sensory input from the penis and efferent pathways to the penis in the rat [31]. Electrical DNP stimulation evoked long latency (40-150 msec) reflex discharges in postganglionic axons, passing from the major pelvic ganglion into the penile nerves. These reflexes were obtained both in normal and in spinal (T8 spinal cord transection) rats, and were blocked by transection of the pelvic nerves; accordingly, it was concluded that they were mediated by a spinal reflex pathway and efferent neurons in the sacral parasympathetic autonomic outflow. Furthermore, the long reflex latency indicated that a polysynaptic spinal reflex arch was involved. In the same study, it was observed that
DNP stimulation elicited a spinally mediated response in the hypogastric nerve.

DNP has also been used to induce both reflex tonic erections of the penile body, and reflex ejaculatory responses, in acutely spinal transected rats (T8-T9 level) [11, 48] (Figure 4).

Figure 4: ICP increases due to DNP stimulation showing correlation between BS muscle EMG activity and intracavernosal pressure recording in a rat exhibiting BS muscle activity, flips, ejaculations and tonic erections of penile body, upon DNP electrical stimulation. High voltage spikes are constantly associated with flips; early and delayed flips are accordingly observed. From Pescatori et al., 1993 [11].

5. Tonic Descending Inhibition on Sexual Reflexes

The need for a complete spinal transection at a thoracic level in order to easily evoke ex-copula sexual reflexes, long suggested the presence of a tonic descending inhibitory activity arising from supraspinal sites, and projecting to lumbosacral centers [49]. The anatomic site responsible for such tonic inhibitory action on sexual reflexes has been better identified in the rostral pole of the paragigantocellular reticular nucleus, bilaterally located in the oblongata [50]. This area directly projects to pudendal motoneurons and to interneuronal areas of the lumbosacral cord; the medullary lesion required to free sexual reflexes must accordingly be under this inhibitory center, bilaterally [50]. Thus, transection of the spinal cord prior to experiments facilitates spinal erectile reflexes by removing this descending inhibition. Of course, spinal transection precludes examination of supraspinal mechanisms in sexual responses or pharmacological studies. Experimental design requires careful consideration of these factors.

6. Centrally Evoked Erectile Responses

The physiological process of achieving penile erection is dependent on both the peripheral nervous system and the central nervous system (CNS) activation. Thus, centrally evoked penile erection has provided new information on central mechanisms involved in the physiology of penile erection. As a result of these investigations, drugs acting at the central nervous system level are a promising therapeutic target for ED. As an experimental tool, central stimulation methods may elicit penile erection through an activation of wider physiological neural pathway than the cavernous nerve stimulation alone. Centrally evoked penile erection may provide a more physiological and integrated erectile response than peripheral stimulation alone. This method allows for the identification of CNS sites involved in the control of sexual function and potential pharmacological targets. Centrally evoked erection may be elicited by electrical, pharmacological and psychological stimulation.

Typical procedures for these studies use anesthetized rats. However, it is possible to use this technique in awake, behaving animals. Under anesthesia, the animal’s head is mounted in a stereotaxic frame that provides a coordinate system to locate specific brain areas. Small holes are drilled into the skull for placement of electrodes for electrical stimulation, or micropipettes or hypodermic tubing for the administration of drugs. Physiological recordings of ICP and blood pressure are taken during the stimulation. In addition, recordings of peripheral nerve, skeletal muscle activation or other physiological responses may be performed. Following the end of the experiment, the brain is removed and sectioned for histological verification of stimulation sites. For administration of precise quantities of drugs, experimenters have used microliter syringes. These can be mounted directly in the stereotaxic microdrive and inserted into the brain, or be connected by tubing to an implanted hypodermic needle. The latter method allows the use of precise syringe pumps for continuous infusion. Another method is to use micropipettes filled with the drug solution. The drug is injected into the brain by attaching tubing to the end of the micropipette and applying precise pulses of pressurized nitrogen. Visualization of the fluid level in the micropipette with a calibrated microscope allows precise injection volumes in the low nanoliter range [51]. Similar methods can be used in awake behaving animals. The hypodermic needle or micropipette is inserted under anesthesia as described. It is then
glued in place to the skull with dental acrylic. After a suitable recovery period, tubing is attached to the needle or micropipette and connected to a syringe or pressure device outside the cage. In this way, the effects of drugs on behavior can be examined.

7. ELECTRICAL STIMULATION OF THE CNS

The hypothalamus is one of the most important areas modulating male sexual behavior in the CNS. Although numerous studies have indicated important roles of the hypothalamus in sexual motivation and performance, its precise roles in integrating penile erection are still unclear. In this regard, electrical stimulation of the medial preoptic area (MPOA) and paraventricular nucleus (PVN) has been performed and two distinct patterns of penile erectile responses have been separately described following hypothalamic stimulation. PVN and MPOA-stimulated ICP responses exhibited a stable plateau of ICP pressure increase during the stimulation period without contraction of striated penile muscles. [42, 52] However, some hypothalamic stimulations resulted in rhythmic ICP response, which were observed after stimulation, were lower, more variable, and accompanied by significant amplitude variations (“spiky peaks”), due to contraction of striated penile muscles. The latter response more closely resembles ejaculation. The explanation of these two responses is unclear, but may be related to site of stimulation [53].

Bilateral transection of the CN ablated these ICP responses but did not alter striated muscle contraction [54]. Thus, these centrally evoked erectile responses were induced through activation of the cavernous nerve (CN) that is known to be a critical pathway responsible for smooth muscle relaxation and penile erection. Histological studies have clearly demonstrated that there are three projections from the MPOA 1. periventricular, 2. medial forebrain bundle (MFB), and 3. dorsolateral pathway. The anterior hypothalamic area sent fibers through the MFB pathway. Neural fibers from the posterior hypothalamic area go through the periventricular pathway. These data imply that the MPOA and PVN may send efferent fibers through different pathways, furthermore, activation of such different pathway might produce distinct response patterns [53] (Figure 5).

II. PHARMACOLOGICAL STIMULATION

Pharmacological agents induce penile erection through diverse administration methods. Those are systemic (i.e. subcutaneous or intravenous injection) and local (intracavernous, intracerebral and intrathecal injection) administrations. Local administration can be used to identify the site of action of a drug. Centrally evoked erectile responses by pharmacological stimulation are evaluated by measuring frequency of ex-copula penile erection and ICP during erectile response.

An example of the use of pharmacological stimulation is the investigations with apomorphine. Apomorphine is a non-selective D1/D2 receptor agonist with more potent D2-than D1-like activity. Apomorphine given subcutaneously (s.c.), induces penile erection in rats through activation of the central nervous system. The responsible brain area is thought to be the PVN in the hypothalamus, based upon microinjection in this area [55-57]. Recent work suggested that apomorphine affect may also exert an effect at the spinal level [58].

Following subcutaneous injection of apomorphine, erectile responses of rats are observed in freely moving conditions. With penile erection, yawning is observed simultaneously. In general, numbers of this so-called yawn-erection response are counted as an evaluation item. Telemetry models [8, 16] are able to monitor intracavernous pressure in conscious and freely moving conditions. This model can provide us not only frequency but also amplitude of erectile response following administration of apomorphine.

1. LOCAL ADMINISTRATION OF DRUGS (MICROINJECTION)

Microinjection of drugs into the CNS is a means of demonstrating the role of a particular neurotransmit-
erections are elicited by retraction of the penile sheath. In this condition, male animals show phasic erectile responses. Reflexive erections are classified into glans erections and penile body erections («flip»). The glans erections are further classified into three categories: E1, engorgement of the proximal glans only, E2, distention of the distal glans, and E3, flaring of the distal glans («cup»). Flip is defined as dorsiflexion of the penile body. The number of erections, cups, flips, penile response clusters (consecutive responses) and latency from retraction to the first response are usually measured and evaluated [63]. Ex copula erections are generated by spinal reflex mechanisms and modulated by supraspinal control. The oxytocinergic and nitric oxide (NO) systems in the PVN may modulate reflexive erections and non-contact erections [6, 55, 56]. Facilitative actions of dopamine in the MPOA on the penile reflex have also been reported [6, 57]. The MPOA-dopamine pathway is partly responsible for this type of erection through PVN activation.

**IV. URETHROGENITAL REFLEX**

A model has been presented for studying sexual reflexes in anesthetized male and female rats [48]. In urethane anesthetized, acutely spinalized rats, complex coordinated sexual responses can be elicited by a variety of pelvic stimuli, including stimulation of the dorsal nerve of the penis. It was shown that urethral distension is a quantitative and highly reproducible stimulus. Hence, this response has been referred to as the urethrogenital (UG) reflex. In male rats, the UG reflex consists of clonic contractions of the perineal muscles, rhythmic firing in the cavernous nerve, penile erections and ejaculation. Thus, this reflex has been viewed as a model for both penile erection and ejaculatory reflexes. The perineal muscles were all activated simultaneously, as is seen in human climax [64, 66] and in rats during copulation [66]. These perineal muscle contractions resulted in phasic penile erections. The somatic muscle bursts were synchronized with bursts in the cavernous nerve, driven by both pelvic (parasympathetic) and hypogastric (sympathetic) nerve bursting. This reflex can only be evoked from male animals that have high spinal transections or lesions in certain brain areas. A group of neurons in the paragigantocellular reticular nucleus in the brainstem have been
identified as a source of descending inhibitory effects on spinal sexual reflexes in this animal model [50]. This model has been used for studying brainstem and hypothalamic control of sexual reflexes, pharmacological modulation and identification of spinal ejaculatory pattern generators [50, 52, 67-71] (Figure 6).

Figure 6: Bulbospongiousus muscle activity during two successive urethrogenital reflexes. Mechanical stimulation of the urethra resulted in the striated muscle ejaculatory motor pattern. Note the extremely rhythmic bursting activity in the muscle. The response can be elicited repeatedly. From McKenna et al., 1991 [48].

V. NON-CONTACT ERECTION

The penile reflex, which is a spinal level reflex, is under the control of supraspinal regulation. Non-contact erections may be evoked by the presence of an estrous female, and must be centrally mediated [72]. Long-Evans rats are used in this behavioral test. Non-contact erection tests are performed in an observation box that is separated into two halves by a screen divider. The test is started by placing a male rat in one side and an estrous female rat on the other side. The numbers of erections are measured during the observation period. This non-contact erection has been shown to be dependent on olfactory cues from the female. Since this response is mediated by forebrain centers and is not due to tactile reflexive mechanisms, it has been proposed as a model to study centrally driven reflexes, analogous to psychogenic erections.

VI. EJACULATION

Ejaculation is a highly complex, tightly coordinated function with many components. It consists of two main phases, the emission phase and the expulsion phase [73]. The emission phase consists of several individual actions: Contraction of the bladder neck and contraction of the external sphincter. These two actions serve to create a closed space in the prostatic urethra. The contraction of the bladder neck also prevents retrograde ejaculation of seminal fluid into the bladder. The emission phase also consists of ductus deferens contraction for transport of sperm into the urethra, and contraction of the accessory sex gland smooth muscle, which leads to emission of seminal fluid into the urethra. All of these aspects of the emission phase may be reflexly elicited by physiological or electrical stimulation of the dorsal nerve of the penis [74]. The expulsion phase consists of highly regular rhythmic contraction and relaxation of striated and smooth muscles. Studies in experimental animals and spinal cord injured human patients have demonstrated that the entire ejaculatory response is generated within the spinal cord by reflexive mechanisms [75, 48]. The spinal neurons required to generate ejaculation have recently been identified [76]. The spinal reflexive mechanisms are under excitatory and inhibitory control from supraspinal sites [77].

From an experimental point of view, the study of ejaculation is extremely difficult because of its complexity. No model currently exists in which all components are both present and measurable. Ejaculation in awake, behaving animals can be observed in copulatory tests. However, the neural and physiological mechanisms involved are very difficult to measure in such cases and invasive interventions are also problematic. In anesthetized animals, it is not currently possible to elicit all components of ejaculation. However, Pescatori et al. [11] described the possible occurrence of relatively complete reflex ejaculations in acute spinal rats following DNP electrical stimulation. When occurring, ejaculations were constantly associated with flips and with EMG spikes of bulbospongiousus muscle activity. Ejaculated material consisted of few drops of whitish fluid, forcefully expelled, containing spermatozoa; on occasion a seminal plug was observed. For this reason, individual components are studied. For example, the reflex closure of the external urethral sphincter and bladder neck can be studied. Secretion of fluids from the accessory sex glands can be produced by stimulation of peripheral nerves or pharmacological administration.

1. COPULATORY EJACULATION

Ejaculation can be identified in copulatory testing in experimental animals. In particular, copulatory beha-
Behavior in rodents is highly stereotyped. In rats, ejaculation is readily identified by a prolonged intromission with deeper thrusting. After this, the male generally grooms his genitals and ceases sexual behavior for a period of several minutes (postejaculatory interval, PEI). Note that ejaculation in this case is defined behaviorally. True ejaculation, that is, expulsion of semen can be verified by the presence of a seminal plug in the vagina. This is not practical in all experimental situations. In “normal” copulatory situations, the behavioral pattern and seminal expulsion are closely linked. However, in certain situations, after brain lesions and stimulation, pathological models, or with the administration of drugs, the behavioral pattern and seminal expulsion may be disconnected. In these situations, experimenters need to be explicit about the measures being employed.

2. Electroejaculation and Ejaculatory Reflexes

Ejaculation can be induced in man and experimental animals by means of electroejaculation. Typically, a probe containing electrodes is inserted into the rectum. Powerful electrical stimulation induces ejaculation. This method is used clinically for the collection of sperm in patients who are unable to ejaculate, for example spinal cord injured patients [78]. This technique can be used in experimental animals for the collection of sperm or to study ejaculation. [79, 80] The mechanism by which rectal electrical stimulation induces ejaculation is unknown. The technique can be used in anesthetized or unanesthetized subjects. This method may be used to examine pharmacological modulation of ejaculation.

3. Seminal Tract Contraction

Ejaculation can be studied by examining individual components of ejaculation. For example, smooth muscle contraction in the seminal tract can be studied in a variety of preparations. The contraction of the vas deferens in vitro has been one of the most common preparations for studying the pharmacology of smooth muscle. More relevant to the study of ejaculation, seminal vesicle pressure has been measured during copulation and in anesthetized animals following peripheral nerve stimulation and pharmacological treatment [81-82] Seminal emission and contraction of the vas deferens was elicited by stimulation of the dorsal nerve of the penis [74] Both sympathetic and parasympathetic efferents participate in vas contractions. In copulation in the rabbit and rat, contractions of the seminal vesicles have been recorded which are elicited 100 to 300 msec after intromission. Presumably, these contractions were activated by penile stimulation [83-84].

In both anesthetized and unanesthetized animals, the technique is similar. A small incision is made in the apex of the seminal vesicle. A catheter is inserted into the lumen and sutured in place. The catheter is connected to a pressure transducer. Between trials, it is often necessary to flush the catheter with saline to prevent clogging by coagulated seminal vesicle fluid.

4. Bladder Neck Pressure

Bladder neck pressure increases are an essential component to prevent retrograde ejaculation. In the human, bladder neck pressure during ejaculation has been measured at 500 cm of water [85] This can be measured in anesthetized animals by tying in place a catheter connected to a pressure transducer. Pressure increases in response to peripheral nerve stimulation and pharmacological administration can be measured with this method.

5. Seminal Emission

Seminal emission can be measured similar to the methods for recording seminal tract contractions. One method involves placing a catheter into the prostatic urethra. The bladder, vas deferens and seminal vesicle are tied off. The urethra is tied around the catheter. Prostatic secretion thus has no outlet except through the catheter. The rate and volume of prostatic secretion can be measured by marking the movement of fluid within the catheter, which has a known internal diameter. The fluid can be collected for biochemical measurements to determine its composition. Prostatic secretion in response to electrical stimulation of peripheral nerves and drug administration has been measured using this method [86]. Prostatic contractions have also been measured using a video measurement system [87].

6. Striated Muscle Contraction

The expulsion phase of ejaculation is the product of clonic contractions of the striated perineal muscles, which is under somatic control, namely the pudendal nerve. In the rat, striated muscles innervated by the pudendal nerve are the external anal sphincter, external urethral sphincter, coccygeus, internal obturator, ischiocavernosus (IC) and bulbospongious (BC) muscles, being the rat homologue of human bulbocavernosus muscle [45, 88]. The activity of these
muscles during ejaculation can be recorded in copulatory tests or in anesthetized animals using the urethrogenital reflex described above. Retrograde axonal tracing techniques applied to the motor branch of the rat pudendal nerve shown that it leaves the spinal cord at the L5-L6 level [45], while a more recent electrophysiological study reports L6-S1 [88]. Furthermore, the cellular bodies of the pudendal nerve motoneurons have been identified in two interconnected spinal cord nuclei: the dorsolateral and the dorsomedial, that accordingly constitute the rat equivalent of the human Onuf nucleus [45].

In the rat the role of the perineal striated muscles in the ejaculatory reflex has been evaluated by several approaches, that include copulatory/ex-copula observations, electroejaculation, and reflex events [48, 11], described elsewhere in this chapter. What will follow are the distinct roles of IC and BS, as elucidated by electromyography and surgical excision studies.

a) IC muscle

IC is instrumental in producing glans dosiflexions ("flips"), that straighten the rat penis, rendering it suitable for penetration (10-12). Mounts without intromission are accompanied by either strong IC activity with little or no proximal BS activity, or strong proximal BS activity preceding the onset of IC activity. During intromission patterns, IC activity reliably precedes proximal BS activity (13). The IC is activated rhythmically during ejaculation.

b) BS muscle

BS is particularly active in "cups", in ejaculate emission and in properly placing ejaculate into the female cervix. In particular, in copulation and reflexive erection settings, Ejaculations were accompanied by stronger proximal BS activity than were other copulatory events, and were followed by a series of proximal BS and IC bursts lasting for 10-20 seconds [89]. BS ablation results in abnormal ejaculation, leading to a decrease of infertility index [90-92]. Upon bilateral severing of cavernous nerves, rat still presents a residual erectile capability (vascular engorgement of the corpus spongiosum), as the result of BS muscles activity [93].

## VII. HEMODYNAMIC STUDIES OF ERECTION IN HUMANS

Numerous diagnostic tests have been employed to evaluate penile hemodynamics (arterial and venous) in man, including penile plethysmography, penile brachial index, duplex Doppler ultrasonography, dynamic infusion cavernosometry/cavernosography (DICC), arteriography, nocturnal penile tumescence monitoring with RigiScan, and the combined intracavernous injection and visual sexual stimulation test [94-101]. While these tests have varying degrees of usefulness in clinical settings, they may be used for experimental studies of penile erection in humans and pharmacological testing.

### 1. Penile brachial index

The penile brachial index uses a Doppler signal transducer to measure penile blood flow (a value of 0.7 or less indicates arterial dysfunction) and is predominantly used to diagnose arteriogenic erectile dysfunction. However, a normal penile brachial index does not exclude arteriogenic dysfunction because most penile brachial index data are derived from the dorsal arteries, not the cavernous arteries, which are known to have higher flow in the flaccid state [100-101]. Mueller et al. found only a 39% concordance between arteriography and penile brachial index suggesting that this relatively non-invasive test can be non-specific and inaccurate [100]. Intracavernous injection with vasoactive agents in combination with selective pudendal arteriography is considered the gold standard for evaluating penile arterial vascular status. Unfortunately, this diagnostic test is invasive in nature and an expensive study; therefore, it is limited to a small subgroup of patients, such as young patients who sustained pelvic trauma with penile arterial injury who may undergo penile vascularization [96, 97, 99-101].

### 2. Doppler ultrasonography

The simplest and most common erectile function test to detect impaired arterial or venous hemodynamic blood flow parameters is the use of duplex Doppler ultrasonography [101-104]. This relatively non-invasive diagnostic test involves the combination of intracavernous injection of vasoactive agents to induce cavernosal smooth muscle relaxation, the use of visual sexual stimulation, and duplex ultrasonography, which entails high-resolution sonography with pulsed Doppler blood flow analysis to evaluate the penile arterial status. It provides anatomic information regarding the intrapenile arterial anatomy and a real-time assessment of blood flow velocity of the cavernosal arteries. A major advantage of this test is that it clearly delineates the individual cavernous
arteries and simultaneously records the Doppler blood flow. After intracavernous injection, Doppler waveform analysis is done with a 7.5 to 10 MHz probe. Arterial insufficiency is diagnosed if the duplex scan shows an arterial diameter increase less than 25 percent and a peak systolic velocity of less than 25 cm/sec. The criterion of end diastolic velocities of more than 5 cm/sec is used to represent venous leak [96, 98, 100-106]. Additionally, this test can detect abnormalities in the cavernous bodies, such as fibrosis and calcifications (Peyronie’s disease) [104]. Duplex Doppler ultrasonography has been shown to correlate well with arteriographic studies with pulsed Doppler analysis more accurate than selective arteriography for the diagnosis of arteriogenic insufficiency/dysfunction [100]. Therefore, this diagnostic test is used most often to determine arteriogenic or veno-occlusive erectile dysfunction as well as structure abnormalities in the penis. Indirectly, duplex ultrasonography can diagnose veno-occlusive dysfunction, but the standard test is pharmacologic dynamic infusion cavernometry and cavernosography (DICC) [99].

4. Cavernosometry

Cavernosometry involves the placement of a butterfly needle into the cavernosal body for saline infusion and simultaneous intracavernosal pressure monitoring. The corpora cavernosa are infused with warmed, heparinized saline at a flow rate necessary to achieve an erection. Initially, the saline infusion was performed using a pump, but in 1988, gravity cavernosometry was introduced as a simpler, cost-effective method with lower complication rates [107]. The addition of intracavernosal vasoactive agents to achieve more complete smooth muscle relaxation is also used in this setting [108-109]. These methods are followed by infusion of contrast. If the dorsal vein is visualized which is not normally seen in the erect state and the flow rate required to maintain the erection is high, the patient is considered to have venous insufficiency and thus veno-occlusive erectile dysfunction. This procedure has lost favor due to poor long-term results, lack of privacy, fear, increased sympathetic nervous system response, and anxiety in the test setting which all may lead to physiologic veno-occlusive dysfunction. Because of these problems and the complications involved with venous ligation surgery and low success rate, DICC is rarely performed [96, 97, 110].

VIII. PENILE TUMESCENCE MONITORING AND VISUAL SEXUAL STIMULATION

Erectile dysfunction (ED) has been traditionally classified as organic or psychogenic in origin, and these categorizations remain important for therapeutic purposes. Diagnostic modalities have been developed which monitor spontaneous nocturnal penile tumescence/rigidity and erectile response to audiovisual erotic stimulation in an office setting. Historically, nocturnal penile tumescence (NPT) monitoring was the first objective test to study erectile function [111]. In the 1950’s it was recognized that rapid eye movement (REM) sleep periods were accompanied by a recurring cycle of penile erections in men [112]. The value of NPT monitoring is based on the assumption that nocturnal erections utilize the same neural and vascular pathways as sexually stimulated erections. Karacan concluded that NPT values would be diminished or absent in males with organic ED, such as neurological or vascular insufficiency and would be present in psychogenic ED. He also assumed that psychological factors that inhibit erectile function would be absent during sleep. Because nocturnal erections are, for the most part, present in men with psychogenic ED, the use of NPT measurements has been used clinically to distinguish between psychogenic and organic ED. Normally, there are 3 to 5 erectile episodes per night. Each lasting 10 to 25 min and associated with an expansion in penile circumference by 15 to 30 mm [113]. A 20 mm increase in penile circumference represents a full erection and a 26 mm increase or 80% of a full erection is sufficient for sexual intercourse [114]. Nocturnal erections are not affected by recent sexual intercourse and the dream content is not necessarily erotic in nature.

In the 1970’s and early 1980’s, the standard NPT evaluation involved three overnight stays in specially equipped sleeping centers with trained personal to quantitate the number of erectile episodes, maximal penile rigidity, tumescence, and the duration of nocturnal erections. In 1985 the RigiScan (Timm Medical Technologies, Eden Prairie, MN) device was introduced that allowed men to be analyzed in the home settings as well as in the office with the capability to measure penile circumference and rigidity continuously [115]. This is a multicomponent instrument comprised of a microcomputer and a logging unit. The logging unit is secured around the patient’s leg at bedtime and has two wire loops that record
changes in penile circumference and rigidity. One loop is placed around the base of the penis and another at the tip of the penis proximal to the coronal sulcus. Every 15 secs, the circumference is measured and compared to the patient’s baseline reading. Every 3 mins, rigidity is measured by radial compression applied to each loop [113]. When the circumference increases by more than 10 mm, rigidity monitoring is increased to every 30 secs. When no linear displacement occurs, rigidity is 100% and for each 0.5 mm of loop shortening that occurs, rigidity measurement is decreased by 2.3% [113]. A normal NPT test is defined as three to six erections per 8 hr or an average of 0.375 erections an hr with a change in penile circumference of at least 30 mm at the base and 20 mm at the tip of the penis and a rigidity of at least 70% sustained for at least 10 minutes [116-118]. Greater than 70% rigidity is considered adequate for vaginal penetration, whereas less than 40% rigidity represents an insufficient erection for intercourse. Any rigidity measure between 40-70% correlates with various degrees of penile flaccidity.

Clinically, NPT testing is recommended for confirmation of men with a high clinical suspicion of psychogenic ED, in medico-legal cases to rule out malingering, preoperatively to document poor rigidity, and in men with normal hormonal and vascular evaluation (i.e., intermittent ED; situational problems; acute onset of erectile failure; relationship or other stressors; young men with ED without risk factors and especially if unresponsive to Viagra). In patients with obvious organic disease of the penile vascular bed, an NPT test will rarely alter management and therefore, is not recommended. In men with other forms of sexual dysfunction such as penile sensory loss or anorgasmia, NPT is also not indicated (Figure 7).

An obvious limitation of the RigiScan device is that normal potent men may demonstrate an absence of erectile activity 15% to 20% of the time while sleeping [119]. Several external factors unrelated to erectile physiological mechanisms, such as aggressive dreams, depression, sleep disorders, alcohol intake, medications (psychotropic drugs), and smoking may produce aberrant patterns in sleep and corresponding erectile activity, leading to false-negative results [120-124]. Additionally, RigiScan technology primarily determines radial rigidity, which may not directly equal axial rigidity, a measure that is more closely related to the ability to have sexual intercourse [125-126]. Sparse RigiScan data exists on age-adjusted normal erectile performance; therefore, it is difficult to assess normative erectile data obtained from various age groups [127]. In cases where a patient is suspected of having psychogenic ED, a normal NPT study both in a sleep lab or with RigiScan may confirm the diagnosis and suggest a functionally intact neurovascular axis. An abnormal test may need to be validated with other more sensitive diagnostic studies. Taken all together, NPT monitoring devices offers a relatively inexpensive, minimally invasive means of objectively testing erectile function; but should be used in conjunction with clinical, diagnostic, and laboratory information in determining a man’s erectile status.

Recently, visual sexual stimulation (VSS) with erotic video stimulation and RigiScan testing has been compared to more traditional methods of monitoring penile erection such as NPT and pharmacological vasoactive injections to differentiate psychogenic from organic ED [128-130]. In a study by Allen and colleagues, anxiety and increased sympathetic stimulation caused an inaccurate response to pharmacologically induced erections as measured by penile duplex ultrasonography when compared to NPT testing [130]. Of note, visual sexual stimulation studies had similar specificity in diagnosing psychogenic ED compared to the better-established tests used to measure vascular penile status such as duplex ultrasonography with intracavernous pharmacological injection [128-130]. For this reason, VSS is commonly used in conjunction with RigiScan in order to mimic the sexual situation as closely as possible in a clinical setting and estimate the patient’s erectile capability through a similar mechanism that exists in a sexual encounter. This method allows the clinical researcher to collect patient data over multiple visits using RigiScan monitoring in the office setting combined with VSS in order to diagnose an organic or psychogenic origin of ED.
The use of audiovisual sexual stimulation by virtual glasses allows for partial isolation from the surrounding environment thus reducing test-related stress or anxiety and has been documented to significantly promote more complete cavernosal smooth muscle relaxation and penile erection [132-136]. Clinical studies with VSS and the new oral PDE 5 inhibitors and sublingual centrally acting agents for the treatment of ED, have confirmed the efficacy of this non-invasive method of measuring erectile function in men [131, 133-137]. The combination of RigiScan technology and VSS in case-controlled studies allows for objective measurements of the penile erectile response in patients treated with placebo and active drug. The limitations expressed earlier do not affect the use of RigiScan for drug evaluations on radial rigidity and tumescence with VSS because all erectile parameters measured are compared to placebo, and therefore the inherent limitations are circumvented. Data is also available supporting the benefits of audio-visual sexual stimulation with virtual glasses to negate the anxiety factor involved in more invasive diagnostic tests such as duplex ultrasonography and DICC [131,136]. Recently, Ugolini and colleagues [138] reported that there is a limited need to select erotic visual material to be provided to heterosexual men with the purpose to promote psychogenic erections, provided that the sexual orientation of the specific individual (heterosexual versus homosexual) is taken in account, and that no extreme contexts (incest, sadomasochistic or related themes) are included (see also fig. 15). These data caution that the identification of appropriate erotic visual stimuli for each patient needs to be performed before each session for a more reliable assessment of erectile responses.

In summary, visual sexual stimulation combined with RigiScan technology can be used as an alternative assessment for cost-effective, minimally invasive, and reliable screening of the erectile response. Similar methodologies are currently used in clinical drug trials to determine the efficacy of new pharmacological agents for the treatment of ED.

IX. METHODS FOR ASSESSING SEXUAL MOTIVATION IN ANIMALS

1. ASSESSMENT OF SEXUAL MOTIVATION

Studies of human subjects have typically used questionnaires together with retrospective or diary reports of the actual occurrence of sexual behavior in order to assess subjects’ sexual motivation following various hormonal or pharmaceutical manipulations. Obviously, such interviews are not feasible in studies using animals. The majority of studies of animal sexual behavior assume that sexual motivation is high if the investigator observes the species-specific consummatory aspects of mating in tests conducted in a home cage or other small compartment. In male subjects this would include approach of a sexually receptive stimulus female, mounting—including neck grip in certain species, pelvic thrusting, penile erection, intromission and ejaculation-related behaviors. In female subjects this would include the receptive sexual behaviors (e.g., lordosis in rodents; standing behavior in ungulates and non-human primates; passive acceptance in carnivores) that facilitate penile intromission leading to ejaculation and the deposition of sperm in the female’s vagina. Most investigators would agree that the motivation of a subject, be it male or female, to approach a conspecific for the purpose of mating is best assessed under circumstances in which the target animal has complete control over whether or not he/she will approach and interact with the opposite-sex stimulus animal. This is especially true in studies of female subjects in so far as males are typically larger in body size and are more sexually assertive than females. Accordingly, Frank Beach [139] was among the first investigators to establish procedures for assessing females’ ‘proceptive’ sexual behavior (reflecting their motivation to initiate sexual interaction with a male) by giving the female full control over whether she approached and interacted sexually with a stimulus male. Other investigators have assessed the motivation of female rats to approach a sexually active male that was either restrained behind a wire mesh screen [140] or tethered in a corner of a cage [141]. A similar approach has been used in studies carried out using dogs [142] and female rhesus monkeys [143]. More recently, a paced mating paradigm has been widely used to assess the motivation of female rats to approach and receive mating stimuli from a male.

2. LEVEL CHANGING AS AN INDEX OF SEXUAL MOTIVATION IN BOTH SEXES

Another simple modification of the standard apparatus for studying rodent sexual behavior involved the addition of a second level that was connected to the ground level by inclined ramps. In an initial study using such a bi-level apparatus [144] ovariectomized
female rats that received ovarian hormones showed significantly more level changes/test than controls given no hormones when confronted with a sexually active male. Level changes can thus be an index of females’ ‘proceptive’ sexual motivation. Likewise, this same apparatus has also been used to assess sexual motivation in male rats and mice. For example, Mendelson and Pfaus [145] showed that male rats’ level changing behavior increased significantly across a series of tests when subjects were tested in the presence of an estrous, but not in the presence of an anestrous stimulus female. The ability of stimuli from an estrous female to augment level changing was attenuated by making male rats peripherally anosmic [146], implying that males’ motivation to seek out the female resulted from their attraction to volatile estrous odors. Further evidence that level changing reflects males’ sexual motivation is provided by the observation [147] that male rats showed significantly less level changing behavior within a few minutes following ejaculation with an estrous female (i.e., during the post-ejaculatory interval). Male rats also showed significantly less level changing behavior in the presence of an estrous female when they were treated with dopamine (DA) receptor blockers [148], implying that the activation of DA neurons normally augments masculine sexual motivation and reward (Figure 8).

### 3. OPERANT ASSESSMENT OF SEXUAL MOTIVATION

Some of the earliest studies to assess rats’ sexual motivation were carried out using a straight runway [149-151] in which subjects’ latency to approach a sexually active stimulus animal in a goal box was taken as an index of motivation. Although some useful results have been obtained using this method, running speeds can be influenced by a variety of factors in addition to subjects’ sexual motivation. This factor reduces the usefulness of this simple method. Another approach has been to require rats of either sex to press a lever in a Skinner box in order to gain access to a sexually active, opposite-sex conspecific [152]. Again, although useful data were collected using this method, subjects’ operant responses occurred at a low rate under a continuous reinforcement schedule, and when the opposite-sex animal became available the resulting sexual interaction disrupted the operant lever pressing much more than after delivery of a food pellet of opportunity to lick a water spout (more typical rewarding stimuli in Skinner box testing). Everitt and co-workers [153] improved on this procedure by providing a conditioned secondary reinforcer (a red light) that was initially associated by male rat subjects with access to an estrous female which dropped into the male’s compartment from an overhead location. This procedure led to high levels of lever pressing by male subjects in order to turn on the conditioned stimulus. Although some interesting data were obtained using this method, it also has its disadvantages: (1) Much pretraining is needed in order for subjects to acquire the task, and (2) various surgical, endocrine, or pharmaceutical manipulations may influence task performance by affecting subjects’ motivation to lever press for the conditioned stimulus as opposed to the unconditioned sexual stimuli per se.

As a compromise between the insensitive method of measuring runway approach latencies and the tedious method of training animals to press a lever for access to a goal stimulus, numerous investigators have chosen to assess subjects’ preference to approach and interact with one of 2 stimuli different social stimuli that are tethered in the opposite ends of a 3-compartment box or in the goal boxes of a T- or Y-shaped maze. The method has also been adapted so that volatile odors from conspecifics are presented instead of physical access to these stimuli. In other instances, subjects are allowed to choose between approaching and investigating anesthetized stimulus animals.

![Figure 8: Rats in a level change apparatus. From Mendelson and Gorzalka, 1987][144]
Such an approach has been used to assess the preference of rats [154-155], hamsters [156], and ferrets [157] and mice [158] for same- versus opposite-sex conspecifics. It has also been extensively used [159] to establish the roles of neuropeptides including vasopressin and oxytocin in the establishment of monogamous pair bonding in prairie voles of both sexes. Paredes and Baum [160] used operant performance in a T-maze to assess the effects of excitotoxic lesions of the sexually dimorphic preoptic/anterior hypothalamic region on the preference of male ferrets to approach same- versus opposite-sex conspecifics. More recently this method and was adapted so that volatile odors from same- versus opposite-sex conspecifics could presented in an air-tight Y-maze, with the aim of establishing the role of body odorants in heterosexual mate recognition in ferrets of both sexes [161]. Tests of a subject’s preference for one type of stimulus over another (e.g., body odors emitted when air is blown over an anesthetized breeding male versus an anesthetized estrous female ferret) involved training sessions over 3 consecutive days. On each day subjects would be given 8 ‘free’ trials in which they were placed in the start box of the Y-maze whereupon the choice (male vs female odor) and latency to approach one of the goal boxes was recorded. After all but the last free trial, subjects would receive a ‘guided’ trial in which the Y-maze arm leading to the stimulus freely chosen on the previous trial was blocked off, thereby ‘guiding’ the subject to the non-preferred stimulus. In this way subjects were frequently reminded of the availability of the opposite stimulus to the one most recently chosen in a free trial. Statistical analyses were carried out on the choice (% trials to the male vs female stimulus) and the latencies to approach each type of stimulus averaged over a total of 24 free trials. This method has effectively revealed effects of endocrine status [162], sexual experience, and peripheral anosmia [161] on ferrets’ heterosexual odor preferences (Figure 9).

4. CONDITIONED PLACE PREFERENCE (CPP)
TESTS TO ASSESS INCENTIVE VALUE OF MATING EXPERIENCE

One standard way to assess the rewarding characteristics of drugs of abuse (e.g., heroin, cocaine, amphetamine) is to demonstrate that the administration of a particular drug in a compartment (distinctive because of its color, odor, and/or floor texture) which was initially not preferred by a subject (typically a rat or mouse) causes the subject to prefer that compartment as a result of repeated pairing of its physical features with receipt of the drug [163]. Baum and Miller [164] adapted this approach to show that male rats will learn a CPP for the opportunity to mate with an estrous female and that the expression of this CPP was significantly attenuated by castration and by administration of the opioid receptor antagonist, naloxone. Others [165] extended this finding by showing that naloxone blocked the CPP otherwise established by placing male rats into distinctive environments immediately after achieving ejaculation with an estrous female. In addition, female rats also acquire a CPP as a result of repeated pairing with a sexually active male [166].

Most recently, Paredes and co-workers [167-168] showed that female rats established a stronger CPP when they were allowed to pace their mating behavior with a male than when the male paced the rate of their sexual contacts. These studies were carried out in a 3-compartment box in which the central chamber was painted gray. One side chamber was painted white and had wood chips on the floor whereas the other was painted black without wood chips on the floor, and its walls were moistened with 2% glacial acetic acid to give it a distinctive odor. Rats were given a 30 min. pretest during which the time they spent in each of the three compartments was recorded and a ‘preferred’ chamber was specified. Subsequently, during daily tests #1, #3, and #5 all subjects were simply placed alone in the preferred

Figure 9: Diagram showing a Y-maze used to assess partner as well as odor preferences in ferrets. Air is drawn over stimulus animals that are either anesthetized (right goal box; odors only) or tethered (left goal box; odor, visual, and auditory cues) in the goal boxes, and the subject (shown in the start box) is allowed to choose between the 2 arms of the Y maze, thereby indicating a preference for one stimulus over the other. Adapted from Kelliher and Baum, 2001 [161]
compartment for 30 min. By contrast, during tests #2, #4 and #6 subgroups of these female subjects were placed in an adjacent chamber and allowed either to engage in paced mating (female-paced mating; see above) or to mate with a male with no opportunity to avoid him (male-paced mating) until ejaculation occurred whereupon each subject was immediately placed for 30 min. in the initially non-preferred chamber of the CPP apparatus. One day after the sixth conditioning session all subjects were again allowed to roam freely throughout the CPP test apparatus, and the time spent in each compartment was recorded. Based on these observations, a preference scores were calculated as the percentage of time spent in the initially non-preferred compartment both before as well as after either female- or male-paced mating had occurred. Statistical analysis showed that females showed a significant post-conditioning increase in the percentage of time spent in the compartment into which they were placed after mating experience only if they had been able to pace their interactions with the stimulus male (Figure 10).

![Figure 10: A rat being tested in a conditioned place preference apparatus. Photo courtesy of Raul Paredes.](image)

**X. MICRODIALYSIS**

Microdialysis is a unique technique that can be used to measure neurotransmitters in the CNS in vivo [169, 170]. This method is applied to investigation of the central mechanism of copulatory behavior and penile erection from the aspect of the central pharmacology. We can apply this interesting technique to measure various neurotransmitters during copulatory behavior and ex-copula erectile responses with or without systemic or local drug administrations [171-174]. Microdialysis methods make it possible to determine effects of alterations of neurotransmitters in specific brain area during sexual responses. The principle is that a small probe is placed into a tissue of the body. The tip of the probe is covered with a small patch of microdialysis membrane. This allows passage of small molecules across the membrane. The inerior of the probe is perfused with physiological buffer solution. Small molecules diffuse into the dialysis fluid and can be analyzed. The system also allows drugs to be dissolved in the dialysis fluid and they diffuse out to affect the tissue. This technique is commonly used in brain tissue, but it can also be used in other tissues, such as measuring nitric oxide release in the penis. For brain studies, a guide canula is inserted into the target brain area stereotaxically. The dialysis probe is inserted 24 hours before the experiment. The animal is able to move freely while connected to the microdialysis line. The target brain area is dialyzed continuously during experiments. Dialysis samples from a specific brain area are collected periodically. The samples are analyzed with high-performance liquid chromatography [HPLC]. After experiments, the position of the tip of the probe has to be confirmed histologically.

Measuring neurotransmitters during copulatory behavior or the erectile response: Elevations of some neurotransmitters were observed during copulatory behavior and erectile response [173, 175, 176]. These included dopamine, nitric oxide [NO] and their metabolites. These findings strongly suggested that these neurotransmitters might have important roles in the central integration of the copulatory behavior and penile erection.

Application of this technique allows us to measure changes of neurotransmitters in specific brain areas and observe copulatory behavioral or erectile responses simultaneously following drug administration. The work of Melis and colleagues done using this technique has provided us with important information about the central roles of NO in the hypothalamus [174]. They administrated various drugs that could modulate NO and other neurotransmitters systemically or locally [i.e. PVN, third ventricle], then measured the changes of neurotransmitters and observed ex-copula erectile responses.

Sato et al, used another sophisticated drug administration method to observe changes of copulatory behavior and ex copula responses corresponding to alternation of NO in the hypothalamus [177]. Drugs were dissolved in Ringer’s solution. The drug solution was infused into the target brain areas via the
microdialysis probe. This method of drug administration via a microdialysis probe may produce less stimulatory pressure than the microinjection method. Although microdialysis-technique has some limitations (e.g. the volume sampled by the dialysis probe is not precisely known), this experimental model is useful for investigation of relationship between pharmacological changes in specific brain area and behavioral changes [169, 170, 172, 174, 175].

XI. DISEASE ANIMAL MODELS OF ERECTILE DYSFUNCTION

Our understanding about the molecular mechanisms involved in the physiology of penile erection has advanced significantly in the last decade as a direct result of the use of animal models to study aberrant erectile mechanisms in various pathological situations. The purpose of this sub-chapter is to evaluate experimental disease animal models used to study ED and further our understanding of species choice and end points associated with each animal model.

1. SPECIES CHOICE

The available animal models for the in vivo study of ED, as opposed to in vitro studies on excised tissues, are rodents, specifically the laboratory rat. Although the dog [178, 179], cat [180, 181], rabbit [182, 183], mouse [184, 185], and even the monkey [186, 187], have been employed for investigating the physiology of erectile function and the effect of vasoactive drugs on this process, the rat remains the predominant experimental animal species where ED has been documented. This choice of species was essentially based on the traditional application of the rat for laboratory studies, the ample literature on copulatory behavior, the relatively short life span, similar anatomy to the human penis, the considerable costs involved with larger animals, and the availability of rat-specific molecular probes. It is likely that the mouse may become a useful complement, because of the numerous knockout and transgenic animals that may be applied for the study of ED, and to a lesser extent, the rabbit, for alternative models of diabetes, hypercholesterolemia, and to harvest large amount of penile tissue for in vitro studies.

2. HYPERTENSION

Erectile dysfunction and hypertension are widely acknowledged to be associated, however, rigorous studies combining experimental approaches to these conditions are lacking [189-202]. The animal model of hypertension most widely used to assess erectile function is the spontaneously hypertensive rat (SHR) [188-194]. Although more limited in scope, studies have also demonstrated that the more severely pathological stroke prone SHR (SHR-sp) rat has markedly decreased erectile response relative to the normotensive Wistar Kyoto (WKY) rat [195]. There are other rat strains with primary or genetic hypertension (e.g. Prague Hypertensive, Genetically Hypertensive and Milan Hypertensive) that have not yet been characterized with respect to erectile function status.

A small number of investigations have also assessed the impact of secondary hypertension. DOCA-salt treatment, aorto-iliac balloon injury, experimental passive cigarette smoke inhalation, and increased alcohol consumption all in normotensive rats have produced concomitant hypertension and erectile dysfunction [195-198]. However, there have been no investigations, which provide evidence causally-linking the hypertension-associated abnormalities with specific erectile dysfunction mechanisms. Studies to date have established that in hypertensive models there are substantial differences in vascular structure, function and morphology, neurogenic signaling, and in susceptibility to various erectolytic stimuli. For example, the penile vasculature of the SHR, compared to normotensive rats, has been shown to have a substantial structural upregulation, characterized by an overall narrowed vascular lumen and thicker medial wall, increased adrenergic sensitivity, as well as increased corpus cavernosal fibrosis [188-190]. Finally, there have also been differential responses to various antihypertensive drug treatments in hypertensive animals with increases, decreases or no change in erectile function being observed [189,191-193, 199, 202]. Based on our well-established conceptual understanding of erectile physiology it is likely that alterations occur at the neuronal, vascular, and structural level, although the specific pathophysiological mechanisms generating ED remain to be determined.

3. AGING

The initial reports on ED in the aged rat were based on the assessment of the decay of copulatory behavior [200, 203]. Since the first report on the decrease of the erectile response associated with aging to electrical field stimulation (EFS) and vasoactive agents, this system and both end-points have been the method of choice to measure this condition and numerous investigations have confirmed this approa-
ch [204-211]. Aging-related ED in the rat, as well as in men, results essentially from a loss of compliance of the corpora cavernosa due to progressive fibrosis and loss of endothelial and smooth muscle, combined with a decrease of nitric oxide synthase (NOS) content and/or activity [204, 207-216]. In this sense, it is fundamentally a vasculogenic type of ED [213-217]. For this reason, the aging rat has been applied to measure the potential application of gene therapy with cDNA constructs that encode proteins either affecting directly smooth muscle relaxation or countering the deterioration of this tissue with age [206-208, 211, 212, 218-221].

Different rat strains, such as Fischer 344, Sprague Dawley, and Brown Norway have been reported to experience 30-40% reductions in the MIP/MAP value starting as early as 8-10 months of age, although the most significant decreases are observed at ages over 20 months with a 70% decrease at 30 months of age [204, 206, 207, 209, 211, 212, 218]. The Brown Norway rat is a species which exhibits a combination of primary and secondary testicular failure that more closely resembles human reproductive aging and erectile function and is therefore the species of choice to study age-related erectile function [222]. Future studies on agents affecting aging-related ED should expand the simple mean intracavernosal pressure (MIP) / mean arterial pressure (MAP) values to include the area under the erectile curve or complete erectile response curves to different electrical voltages or frequencies and to various doses of vasoactive agents in order to better define the efficacy of treatments in correcting the underlying alterations of cavernosal smooth muscle in ED (Figure11).

4. DIABETES

This model has been utilized by the same group to investigate both the effects of diabetes and of aging in the rat electrically evoked erections. In a study with streptozotocin-induced diabetes, electrically evoked erections were compared at 1, 3 and 6 months in diabetic and control rats [230]. At 3 and 6 months diabetic animals exhibited a significant decrease of latency for erection and a slower phase of detumescence, when compared with age-matched controls. These observations would be consistent with a decreased adrenergic tone, as suggested also by findings of both norepinephrine depletion [231] and nerve growth factor levels alteration [232] in the corporal bodies of diabetic rats. In this study it was also shown a trend for a lower developed intracorporal pressure in the 6 month diabetic group.

Figure 11: ICP increase in response to CNS stimulation, acetylcholine and CGRP administration in young and old rats. The left hand panel shows the age-related response to one stimulation/intensity. The right hand panel shows the shift in the dose response curves with age. From Bivalacqua et al., 2003 [211].

Another study compared a group of 8-month-old animals (being at this age sexually mature), with a group of 27-month-old rats, i.e. an age that represents the typical life span of the laboratory rat, approximately corresponding to 75 years of age in humans [213]. Aged rats showed a significantly slower elevation of the intracavernosal pressure, and a significantly prolonged detumescent phase, in comparison with the adult rats. The intracavernosal pressure rise in response to electrostimulation was less pronounced in the aged group, although in a non statistically significant manner. Aged corporal tissues showed at light microscopy degenerative signs of elastic fibers, and when norepinephrine precontracted they required a 3-fold increase of papaverine concentration to achieve full relaxation, compared to adult tissues.

Numerous epidemiological, clinical, and basic science studies have shown a strong correlation between ED and diabetes mellitus (DM). Animal models of
diabetic-associated ED that reproduce the etiology and pathophysiology of type 1 and 2 (NIDDM) DM is complicated due to the difficulty of reproducing in an animal a combination of neuropathy and vasculopathy. However, since the vast majority of diabetic patients have vasculogenic ED [223-225], there is little divergence in the response of both aging- and diabetes-related animal models to therapy aimed to correct the underlying smooth muscle defects at both the cavernosal trabeculae and arteries [226, 227]. In diabetes, in common to vascular disease in general, the molecular mechanism for the impairment of smooth muscle relaxation appears to involve impairments in nitric oxide synthesis, neuropathy, oxidative stress and fibrosis, caused by reactive oxygen species and advanced glycation end products, irrespective of whether they originate from hyperglycemia or other causes [228-234]. The first rat models proposed for the study of diabetes-related ED were the congenitally diabetic BB/WOR rat, displaying insulin-dependent type 1 diabetes, and the BBZ/WOR rat, with NIDDM or type 2 diabetes. The BB/WOR rat exhibits severe neuropathy in somatic, sympathetic, and parasympathetic nerves without the compounding angiopathy associated with human diabetes [235]. The copulatory behavioral testing and the study of sexual reflexes confirmed the severe neuropathy associated with ED in the BB/WOR rat [235]. Additionally, these diabetic animals exhibit considerable decreases in penile reflexes, indicative of peripheral neuropathy, but did not show any impairment of the cavernosal-nerve mediated erectile response at 3-5 months of diabetes [236, 237]. Therefore, this animal model can be used to determine the contribution of neuropathy alone to diabetic-related ED [236-238]. Further studies are needed to define whether more prolonged diabetes in the BB/WOR rat would eventually result in vasculogenic ED, denoted by either EFS or injection of vasoactive drugs. In contrast, the streptozotocin (STZ)-induced diabetic rat, where the drug is injected to different strains of adult rats in a single intravenous or intraperitoneal injection at doses varying from 35 to 60 mg/kg, is associated with a 40-50% reduction in the erectile response to EFS and in sexual performance [239-247]. STZ-diabetic rats exhibit both neuropathy and vasculopathy in the penile vascular bed; however, the drug is rather toxic and carcinogenic, with severe body weight loss and androgen deficiency making this a model of insulin-dependent type 1 diabetes. Similar criticisms can be made in reference to the alloxan-induced diabetic rat with ED, however, alloxan does not cause severe androgen deficiency like STZ [234, 248-251].

To our knowledge there are no experimental studies in any animal model for ED associated with the most prevalent type of diabetes in men, type 2 NIDDM. It is very important to define in experimental animals of type 2 NIDDM whether these animals exhibit impairments in erectile function and whether pharmacological or gene therapy approaches are effective in correcting diabetic-related ED.

Moreover, it is important to discern the effects of insulin resistance and hyperglycemia at the endothelial and smooth muscle level from those caused by other metabolic alterations present in type 2 NIDDM. Therefore, experimental studies to measure erectile status to EFS and copulatory behavior in animals that are widely accepted as models of insulin resistance and type 2 NIDDM such as the Zucker (fa/fa) rat, Cohen diabetic rat, Psammomys obesus (Israeli sand) rat, or in mice models of insulin resistance are warranted at this time in order to determine the pathophysiological mechanisms involved in type 2 NIDDM [252-257] (Figure 12).

5. HYPERCHOLESTEROLEMIA

Hypercholesterolemia and subsequent atherosclerosis are well-recognized risk factors for the development of vasculogenic ED [280-282]. It is important to realize that hypercholesterolemia-associated ED in men is multi-factorial in nature and is usually compounded by other vascular risk factors such as smoking, age, and diabetes.

Obstruction of the internal pudendal and common penile and cavernosal arteries by atherosclerotic lesions is associated with ED in men. The first animal model of ED due to atherosclerotic vascular disease was developed in the rabbit to mimic the atherosclerosis that is present in human hypo-iliogastic and penile vascular beds.

In this study, rabbits underwent balloon de-endothelialization of the aorto-iliac arteries and received a 1.6% cholesterol and 4% triglyceride diet for eight weeks and resulted in severe, moderate, and minimal luminal occlusion of the ilio-hypogastric arteries and impairments in endothelium-dependent cavernosal smooth muscle relaxation and agonist-induced penile erection with papaverine [106-108]. Recently, this model has been modified by feeding the rabbits a low-level (0.3%) long term (80 wks) cholesterol-enriched diet (without accelerating the disease process by endothelial denudation) that led to more severe atherosclerotic vessel disease in the iliac arterial tree and subsequent augmentation of the pelvic nerve stimulated erectile response [286].
Animal models of hypercholesterolemia-associated ED have demonstrated that impairments in erectile function cannot be entirely explained by arterial hemodynamic abnormalities. Vascular modifications with hypercholesterolemia in both the rabbit and rat occur at the level of

1) a reduced inflow of blood to the penis as a result of atherosclerotic plaques in the penile and pelvic vessels,
2) impairments in endothelium-dependent corporal smooth muscle relaxation,
3) fibrosis and degeneration of the cavernosal endothelial and smooth muscle cells,
4) hypoxia of the corpus cavernosum with alterations in intracellular organelles (loss of mitochondria),
5) decrease in number and size of non-myelinated axons as well as atrophy of axons,
6) a reduction in NOS containing nerve fibers, and
7) increase in corporal collagen deposition [283-290]. For these reasons, the hypercholesterolemia rabbit and rat have been used as models of ED to determine the potential application of gene therapy with cDNA constructs and proteins either affecting directly endothelium-dependent corporal smooth muscle relaxation or counteracting the destruction of cavernosal nerve fibers [288,289]. Therefore, hypercholesterolemia-associated atherosclerosis of the iliac and penile arteries as well as the penile vascular bed in these animals closely simulates the pathological conditions present in men.

6. CAVERNOUS NERVE INJURY

ED is highly prevalent after pelvic surgery, especially radical prostatectomy as a result of injury to the neurovascular bundle (cavernous nerves) [291]. Over the past two decades, cadaveric dissection, anatomic modeling and animal studies have outlined the pathway of the cavernous nerves in the pelvic plexus [292-297]. The animal model of cavernous nerve injury (CNI) most widely used to assess the effects of neurotomy on cavernosal architecture and molecular mechanisms involved in ED is the cavernous nerve resection and cavernous nerve freezing rat models. Through a lower abdominal midline incision, the posterolateral area of the prostate is exposed on both sides and the major pelvic ganglions and cavernous nerves are identified. The cavernous nerves either unilaterally or bilaterally is either sharply divided with knives to remove a segment of nerve, cauterized, or froze using a thermocouple [298-305]. The bilateral CNI model most closely mimics the circumstances of post radical prostatectomy patients because the cavernous nerve has been damaged or severed and erectile function lost [300]. The unilateral CNI model is best suited to study the process of nerve regeneration and what influence this process has on recover of erectile function.

Figure 12: Impairment of ICP responses to cavernous nerve stimulation in the diabetic rat. From Bivalacqua et al., 2003 [247]
ED observed post radical prostatectomy is most likely attributed to changes in the endothelium and smooth muscle cells from a loss in neural integrity. The absence of neural input to the penis after CNI in the rat results in 1) cavernosal smooth muscle apoptosis, 2) alterations in the endothelium and smooth muscle, 3) decrease in neuronal NOS nerve fibers in the penis and pelvic ganglia, and 4) alterations in growth factors [298-305]. Since the development of the CNI rat model, a more thorough understanding of the importance of at least partial innervation of the penis has helped delineate the pathophysiological sequences involved in the development of post radical prostatectomy ED. Additionally, it has led to the potential development of new more effective pharmacological agents and gene therapy approaches for the treatment of ED associated with radical prostatectomy [299, 302, 306-308].

7. CNS LESIONS

The effect of specific brain lesions can be used to estimate erectile function and copulatory behavior in the male rat. In general, copulatory behavior or ejaculatory responses are observed to determine the physiological functions of damaged brain areas or neural pathways. These experiments help define the function of selective brain nuclei/region on erectile function [309-321].

Removal of the neocortex provides little information on specific cell groups contributing to male copulatory behavior. In regards to electrolytic lesions of targeted brain regions, electrodes are inserted in target areas stereotaxically. Lesions are made with sufficient current strength (1-2 mA) and durability of stimulation (30-60 sec) and subsequent male copulatory behavior is determined. However, the disadvantage of this method is that it eliminates both cell bodies in the area and neural fibers passing through the brain area of interest. Chemical lesions of specific brain regions have been utilized with neurotoxic substances applied for this purpose, in particular, kainic acid, ibotenic acid, 6-hydroxydopamine (6OH-DA), and para-chlorophenylalanine (pCPA). 6OH-DA is an agent that has selective neurotoxic properties for catecholaminergic neurons, pCPA depletes serotonergic neurons in the CNS, and ibotenic acid destroys nerve cell bodies but not neural fibers. Additionally, afferent or efferent fibers from specific brain regions are transected with a knife. In this method, it is possible to estimate each physiological function of both afferents and efferents from specific brain lesions. Therefore this method is better to study the integrative relationship between the nuclei in the CNS. However, afferent and efferent fibers from a nucleus contain various neural fibers that may assume different physiological roles (Figure 13).

Figure 13: Effects of brainstem lesions on male sexual function. The figure shows a cross section of the brainstem at the level of the rostral medulla. The thin lines outline electrolytic lesions. On the left in the lower portion are shown lesions that were effective in removing tonic inhibition of male sexual reflexes. On the right and midline show lesions that were ineffective. Figure from Marson and McKenna, 1990 [50].

Transection of the spinal cord has also been studied in rodents and used to investigate spinal control of penile erection, penile reflexes, and ejaculation [309, 310]. Specific limitations to these methods are that interpretation of behavioral changes following brain lesions is not simple. Depending on the damaged part of the nucleus, behavioral changes or erectile responses are different. In addition, it is difficult to decide whether those behavioral changes are due to damage to the cell bodies in the area or neural fibers passing through this area. For example, the MPOA is considered to be the brain center of copulatory behavior and penile erection. This central area integrates sexual stimulation and transmission of excitatory and inhibitory information to other brain areas or spinal centers, and the severity of impairment of copulatory behavior depend on the damaged areas of the MPOA. Therefore, it is difficult to interpret whole animal physiology after selective brain nuclei/regions because of the redundancy in the CNS.

Specific disease animal models using brain lesions are still in the process of development. Some disease models have been proposed such as models of Parkinson’s disease and spinal cord injury. Substantia nigra lesions using 6-OH-DA has been proposed as an experimental model to study ED associated with Parkinson’s disease, however, the model has not pro-
duced consistent results [320]. A spinal cord injury (SCI) model of ED has also been utilized following transection of the spinal cord at various levels and results from these studies documented that ex-copula responses were enhanced after SCI [309, 321-324]. Specific brain lesion models of ED for the study of sexual behavior and function are not widely accepted as disease models because of the inherent limitations and should be the focus of research in the future.

8. ALCOHOL AND SMOKING

Various illicit and non-illicit recreational drugs have been implicated in sexual dysfunctions. The most notable of such drugs are alcohol and smoking. Excessive use of alcohol may lead to ED acutely or chronically in men however the underlying pathophysiological mechanisms are unknown at this time [325]. The use of an animal model to study the pathophysiology of alcohol-associated ED in the peripheral and central nervous systems as well as the penile vascular bed has been lacking. Ethanol and its metabolite acetaldehyde have been shown to significantly impair both contraction and relaxation of rabbit corpus cavernosal smooth muscle in vitro [326, 327]. Additionally, acute intraperitoneal injection of high doses of ethanol resulted in a reduction in both yawning and penile erection in response to subcutaneous apomorphine [328]. Future experimental studies are warranted to determine what affect low and high doses of ethanol, short and long-term exposure to ethanol, ethanol’s influence on hormones such as testosterone, and possible mechanisms of action that lead to impairments in cavernosal smooth muscle cell function and peripheral and/or central nervous system dysfunction are necessary.

Chronic heavy smoking is a well-recognized risk factor for vasculogenic ED and vascular disease in general, and is usually compounded by other risk factors such as diabetes [329]. The common pathophysiology at the molecular level of all these conditions is probably related to oxidative stress, which in smoking is caused by compounds present inuffed tobacco smoke [330, 331]. Despite its epidemiological relevance for ED, only two experimental animal studies have been published. The first one reported an acute impairment of the EFS erectile response by exposure of dogs to tobacco smoke generated by allowing cigarettes to burn without puffing during this procedure, which obviously did not reflect the sustained oxidative stress exerted by chronic smoking, but rather the acute effects on blood pressure of nicotine and other compounds [332]. In the second study performed on young and aged rats, animals experienced daily whole body exposure (1 hour/day) in chambers for 6 weeks to smoke exposure (1 hour/day) in chambers for 6 weeks to smoke generated in the same fashion, followed by a 3-day washout, but despite the considerable hypertension and decrease in penile NOS, no ED was observed by EFS [197]. This was assumed to be due to the comparative resistance of the rat to vascular disease, and the inadequacy of "passive" smoking to mimic chronic smoking in humans.

Future studies will probably require longer periods of exposure (2-3 months) and particularly the use of elaborate puffing machines that allow studying the effects of chronic mainstream smoking with predominant contact with the animal’s nose. This “active” smoking will be based on inhalation of smoke generated at much higher combustion temperatures, and therefore with oxidative products more resembling those derived from actual smoking in humans. An animal model that closely simulates the conditions present in chronic cigarette smoking is warranted at this time due to the lack of scientific data on the direct effect of smoking on erectile function.

9. HYPOGONADAL

Data exists to support a critical role for androgens in the maintenance of the mammalian erectile response [258, 259]. Testosterone is recognized to be a crucial modulator of male sexual behavior, however, the exact role of this hormone in male erectile function remains undetermined. In the rat, dog, and rabbit animal models, androgens particularly testosterone appears to act at the level of the penile vascular bed, as well as in portions of the central and peripheral nervous system to mediate erection [260-270]. Effects of castration on sexual function are evaluated by observation of copulatory behaviors, penile reflex, and erectile response electrical stimulation of the cavernous nerve. Particularly in the rat model, androgens act centrally to support copulatory behavior and peripherally to maintain constitutive NOS activity, a-adrenergic stimulation, and support the veno-occlusive mechanisms. Thus the erectile response in the rat is androgen dependent [264, 270-278]. Castrated rats have a reduction in erectile response to cavernosal nerve stimulation 24 hrs after castration and maximal reduction after 1 to 2 wks [262]. Androgens appear to exert regulatory control of penile erection at the level of the hypothalamus in that castrated rats have a reduction in apomorphine-induced penile erection and reductions in copulatory.
behavior [265]. Castrated rats have been used as models to study veno-occlusive dysfunction because cavernosal sinusoidal smooth muscle fails to fully relax and blood flow continues during erection in castrated rats, suggesting the failure of veno-occlusion [271, 272].

An additional method to study androgen deficiency in the rat has been to remove the adrenal gland. Adrenalectomy results in a decline in penile erection in the rodent to values similar to those found in castrated animals [261]. The rat adrenal gland secretes little androgens so that after castration, androgens are virtually absent in the peripheral blood and erections are lost [279]. Whereas in men, the adrenal cortex secretes androstenedione and dehydroepiandrosterone sulfate (DHEA) which can be converted into testosterone and dihydrotestosterone in the periphery and may be sufficient to sustain the erectile response after orchectomy in men. Therefore, in men who have undergone orchectomy, the adrenal gland may sustain the androgens necessary for normal erectile function.

Despite these reports of the importance of androgens in the erectile response of laboratory animals, the role of androgens in the maintenance of the human erectile response remains controversial. There does not seem to be a strong cause and effect relation between peripheral blood androgen concentrations and erectile function; even in severely hypogonadal men, the erectile response is not always lost, and testosterone treatment of hypogonadal men with ED does not necessarily restore impaired erectile function [258]. Therefore, until the exact role of androgens (testosterone) is delineated in the maintenance of penile erection in man, the hypogonadal animal model of ED may be best utilized as a model of veno-occlusive ED.

1. PARAMETERS OF MALE COPULATORY BEHAVIOR

a) Precopulatory behavior: Male rats sniff and investigate females’ perineal regions as a precopulatory behavior. This behavior is an investigation (recognition) process for the female and probably augments sexual excitation. Copulation may not occur without this precopulatory behavior, because of insufficient sexual stimulation received by the female.

b) Mounting and Intromission: Male rats mount the females dorsally and from the rear. Males show pelvic thrusting during a mount. However, the penis does not insert at every mount. Penile insertion may entail an extended series of very brief genital contacts (200-400msec) before ejaculation occurs. Without females’ lordosis (arched-back posture), the male’s ability to achieve intromission is reduced significantly. It is difficult to see intromissions of rats because of their very brief insertion. Thus, intromission refers to the skeletal motor patterns associated with penile insertion.

c) Ejaculation: Ejaculation occurs after several intromissions. At ejaculation, male rats show a longer-intromission period, grasp more strongly the female’s back with forelimbs and freeze for a couple of seconds just after ejaculation.

d) Postejaculatory behavior: Postejaculatory interval (the interval from ejaculation to the resumption of copulation) is several minutes in some species of rats (Wistar, Sprague Dawley rats). During this refractory period, male rats show genital grooming and little locomotion, and do not show any interest in sexual stimulation from estrus female.

2. MEASURES OF MALE COPULATORY BEHAVIOR

a) Mounting: The most common measure of mounting activity is a simple count of the number occurring, during the interval between the first mount and the ejaculation. Increase of this parameter may result from males’ greater sexual motivation.

b) Intromission: Less useful is simple count of the number of intromission occurring in the time limited test. The relative number of mounts (NM) and intromissions (NI) is commonly referred to as the intromission ratio. The ratio NI/ (NM+NI) is most useful measure. This measure is sensitive to male erectile capacity or penile sensitivity. However, this ratio is also reflects the female’s behavior; hyporesponsive female will decrease this ratio.
c) Ejaculatory and post ejaculatory interval: The behavioral measures of ejaculation include the number of intromissions preceding ejaculation and ejaculatory latency. The numbers of intromissions of these measures are considered to assess the ejaculatory threshold. The total copulatory potential of the male may be measured by number of ejaculations occurring within a time limited test. Each post ejaculatory interval is commonly measured by post ejaculatory mount latency and the post ejaculatory intromission latency.

3. TEST CONDITIONS

Many situational factors affect measures of copulatory behavior. Those are females’ estrus condition, time of day, size of test chamber, compatibility of male and female. Meisel and Sachs [63] proposed as a hypothetical criterion for test duration may be “two ejaculations plus the subsequent post ejaculatory period, with a time limit of 30 minutes for first mount, 30 minutes for each ejaculation latency, and 15 minutes for each post ejaculatory interval.” Most rodents are nocturnal animals. Males are more likely to copulate during dark phase than during the light phase. Thus most investigators performed sexual behavior test during dark phase.

XIII. VASCULAR SMOOTH MUSCLE CELLS IN VITRO AS A MODEL SYSTEM IN SEXUAL MEDICINE RESEARCH

Throughout the circulation, vascular smooth muscle cells (VSMC) exhibit remarkable structural and functional diversity and phenotypic heterogeneity. In part, this diversity is hypothesized to be due to plasticity of each type of smooth muscle cell in response to physical and chemical stimuli in the microenvironment. It may also be that the smooth muscle diversity found in adult blood vessels, has a fundamental developmental basis. That is, the site of origin and/or type of disease state may be a key component dictating the phenotype and response characteristics of the cells. Normally their function is to control vascular tone by contracting and relaxing but during disease, drug treatment or aging they may dedifferentiate, produce extracellular matrix, and invade or migrate through the vessel wall. For example, it is widely known that aortic intimal VSMC involved in the vascular remodeling following endothelial injury are phenotypically distinct from their medial counterparts. In fact, these intimal cells can resemble immature, dedifferentiated VSMC with fewer contractile proteins and myofilaments. Some investigators have hypothesized that intimal cells share similarities in morphology and gene expression with fetal or embryonic VSMC, or cells growing in culture. In contrast, in the intact vessel medial VSMC express a differentiated profile of proteins associated with contractile function and the synthesis and maintenance of extracellular components of the vessel wall (Table 1).

<table>
<thead>
<tr>
<th>Table 1. General Tissue Culture Issues</th>
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<tr>
<td>• Removal of cells from 3-D architecture</td>
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<tr>
<td>• Growth ‘platform’</td>
</tr>
<tr>
<td>• Selection bias (enzymatic digestion, explant)</td>
</tr>
<tr>
<td>• Primary, passaged or immortalized cells</td>
</tr>
<tr>
<td>• Efficiency of plating (survival)</td>
</tr>
<tr>
<td>• Growth factor stimulus</td>
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<tr>
<td>• Phenotypic change</td>
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<tr>
<td>• Presence of physical factors</td>
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<tr>
<td>• Presence of chemical factors</td>
</tr>
<tr>
<td>• Rate of cell division (cell cycle)</td>
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<tr>
<td>• Cell density</td>
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<tr>
<td>• Degree of cell confluence</td>
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<tr>
<td>• Stage of induced quiescenceÆgrowth</td>
</tr>
<tr>
<td>• Degree of genetic heterogeneity</td>
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In the past two decades, investigators striving to model the biological diversity of vascular smooth muscle cells during normal development, natural aging and in disease conditions have made substantial use of in vitro experimentation. However, important and widely acknowledged considerations in researching vascular smooth cell biology via an in vitro tissue culture approach are the advantages and disadvantages. Some of these (Table 1) relate to the overall experimental conditions of cell preparation or tissue culture conditions that are relevant to any cells grown in vitro rather than factors specific to VSM cells. In particular, preparation of primary cell cultures from tissue samples is noteworthy.

Other methodological factors are specific to the properties of the cells being used. In the field of sexual medicine a ‘tissue culture’ approach to the study of penile vascular smooth muscle has been used but to a more limited extent.
Tissue culture-based sexual medicine research has focused predominantly on the major cell type of the human corpus cavernosum, the vascular smooth muscle cell. The studies have characterized certain cellular functions (e.g. contractile and relaxant effects via vasoactive factors and potassium channels) and structures (e.g. gap junctions, extracellular matrix production) although there have also been some very innovative approaches involving tissue reconstruction. It is important to recognize that a conceptual framework which uses findings from tissue culture studies must take into account a number of issues. In particular, even when using primary cultures of penile vascular smooth muscle cells the origins of the cells extracted must be recognized. Furthermore, by removing the cells away from their in vivo environment with respect to: (i) the three dimensional architecture, (ii) the hemodynamic stimuli provided by the circulation and (iii) the paracrine influences of the autonomic nervous system and endothelial cells, the interpretation of the results becomes the most significant component of the experimentation. For example, not only can there be substantial phenotypic heterogeneity between cells taken from the corporal sinusoids, helicine arteries, cavernous or pudendal arteries but the interaction of these cells with the adjacent endothelium, blood borne factors or the nerves may be markedly different. Thus, interpretation of findings must reflect an understanding of the balance between the advantages and disadvantages of the methodology.

1. Advantages to Assessing VSMC in Vitro

There is no doubt that regardless of the field of interest, tissue culture allows for enhancement of a number of methodological considerations such as:

i) isolation and control of experimental variables,

ii) greater ease of proximal targeting of chemical and physical stimuli,

iii) ability for single or multi-cellular cell imaging/analysis of ion fluxes or membrane potentials,

iv) characterization of phenotypic and morphological changes in response to various stimuli,

v) gene transfection studies and (vi) more discrete analysis of cell cycle regulation and signal transduction pathways. Many of these properties (see Table 2) can be assessed more extensively in the in vitro setting without the ‘unknown’ confounding influence of other factors. In some instances, such as the characterization of gap junctions or ion channels the in vitro approach provides the main, if not only, approach to assessing the function of these very specific cellular processes. Thus, assessment of VSMC in vitro can be a very useful model system for investigating, in a stepwise manner, the regulation of various properties, functions and structures particularly at the biochemical and molecular level (Table 2).

<table>
<thead>
<tr>
<th>Table 2. Specific Culture Properties of VSMCs</th>
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<tbody>
<tr>
<td>• Density at confluence</td>
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<tr>
<td>• Cell size/ hypertrophy</td>
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<tr>
<td>• Degree of polyploidy</td>
</tr>
<tr>
<td>• Rate of cell proliferation</td>
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<tr>
<td>• Contractile properties</td>
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<tr>
<td>• Apoptosis / necrosis</td>
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<tr>
<td>• Extracellular matrix production</td>
</tr>
<tr>
<td>• Invasiveness</td>
</tr>
<tr>
<td>• Migration</td>
</tr>
<tr>
<td>• Growth factor production</td>
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<tr>
<td>• Vasoactive factor production</td>
</tr>
<tr>
<td>• Response to chemical and physical stimuli</td>
</tr>
</tbody>
</table>

2. Limitations of Tissue Culture-Based Experimentation

On the other hand, there are a number of methodological considerations that limit the in vitro approach particularly as a result of the difficulty of recapitulating the in vivo environment such as: (i) selection bias of cells following enzymatic digestion or organ culture/explant method (i.e. damage to, necrosis or apoptosis of certain cells leaving behind a more stress-resistant population of cells), (ii) loss or change in numbers of receptors, proteins and enzymes as a result of the switch from the in vitro to in vivo environments, (iii) the loss of the three-dimensional microenvironment removes the relationship between VSM cells, endothelium, nerves and the circulation, (iv) the marked change of cellular phenotype during in vivo to in vivo transition. It may be that these limitations are part of the reason why sexual medicine researchers have not fully embraced tissue culture methodology as a model system as much as have investigators in other areas of cardiovascular research (e.g. hypertension, atherosclerosis).
3. Specific research topics

There have been numerous areas of research that have used tissue culture approaches using penile tissue to characterize various cellular structures and functions. The Christ group has been particularly strategic in developing an understanding of the processes that regulate and are regulated by gap junctions [334, 337, 338-340, 351, 364, 375]. In addition, Christ and others have well established culture models to examine potassium channels both in the native state and following gene transfection [336, 341, 344, 352-354, 359]. Other investigations have assessed the contribution of various signalling pathways although there has been particularly focus on the cyclic nucleotides, cAMP and cGMP [348-350, 362, 365, 377, 379]. In vitro approaches using both animal and human cultured penile VSMC have been used to assess the response to changes in various vasoactive substances (NO, ET, VIP, PACAP, NE, ACh) and growth factors [332, 345, 346, 352, 358, 368, 368, 374, 378, 380, 381]. Surprisingly, despite that smooth muscle cells are intimately associated with the regulation of their own microenvironment little research has been done in the area of regulation of extracellular matrix by vascular smooth muscle (30, 31). In vitro model systems would provide an excellent means of assessing VSMC production of collagen as well as the enzymes involved in extracellular matrix degradation (matrix metalloproteinases (MMPs) such as collagenases, stromelysins, gelatinases, and membrane-type metalloproteinases). A number of other aspects of genital VSMC biology have also received less attention or are only known becoming areas of research interest (see below).

4. Characterization of novel genes associated with smooth muscle cell differentiation

Tissue culture methodology allows for the development of unique human or animal smooth muscle cells clones with, for example, differential capacities to convert from a noncontracting-synthetic phenotype to a contracting-nongrowing phenotypes. In fact, investigators have cloned several novel genes that are expressed as these cells differentiate and appear to be associated with the transition. DNA microarray technology also allows for genome-wide characterization of smooth muscle cell phenotypes. This area of research is forthcoming in the field of sexual medicine [356, 357].

5. Signalling pathways in culture human corpus cavernosum

Validated primary cultures of smooth muscle cells from human and rabbit penile corpus cavernosum, were used to assess the presence and activity of Rho-kinase, an enzyme involved in the Ca2+-sensitizing pathway in smooth muscle cells. Previously, in animal studies, inhibition of this enzyme was shown to elicit penile erection by relaxing cavernosal smooth muscle. In the study by Rees et al [370] Rho-kinase was demonstrated in the cultured corpus cavernosal smooth muscle cells both by indirect immunofluorescence and Western blotting and could be inhibited by Y-27632, in a concentration-dependent manner. These results demonstrated for the first time expression and activity of Rho-kinase in human penile cavernosal smooth muscle cells and suggest that these cells can provide a cellular model for the study of enzymes involved in Ca2+-sensitizing pathways.

6. Genital tissue reconstruction using cells in culture

Congenital and acquired abnormalities of the genitalia would benefit from the availability of transplantable, autologous corpus cavernosum tissue for use in reconstructive procedures. A range of surgical procedures have been used to restore genitalia although the scope of the intervention is often limited due to the scarcity of penile tissue. Experimental studies have demonstrated that it may be possible to seed primary cultures of human corporal smooth muscle cells, obtained during penile prosthesis implantation, onto biodegradable polymer scaffolds or directly, to aid the formation of differentiated corpus cavernosum smooth muscle in vitro and in vivo [347, 366]. A difficult issue is that although smooth muscle and endothelial cells are the major components of erectile tissue, reconstitution with connective tissue and nerves is needed required to attain normal anatomical and functional corpora. These studies suggest that the reconstitution of other components of erectile tissue may be achieved in the future using tissue engineering techniques.

7. Summary and conclusions

Of the approximately 50 research articles assessed for this brief review the majority have focused on specific research topics of particular groups of investigators. Research in the area of smooth muscle biology in female sexual function and dysfunction is noticeably lacking. Thus, the methodological
approach of tissue culture does not appear to be ready to take on a larger burden within the research strategy of sexual medicine scientists, at least in part, this is likely due to the substantial number of methodological considerations and difficulties in interpretation. Regardless, the tissue culture approach provides a viable and efficient means of addressing key research questions particularly at the biochemical and molecular level. It is not surprising that this model system falls back in utility in studies trying to assess structures and functions that require the in vivo three dimensional architecture and microenvironment.

XIV. BRAIN IMAGING OF SEXUAL AROUSAL IN HUMANS

1. INTRODUCTION

It has been more than a decade since it was appreciated that changes in regional cerebral blood flow (rCBF) during experimentally modified psychological activation, as occurring in emotional processes, can be measured by functional neuroimaging approaches [384, 385]. The most used techniques are positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

For many years the knowledge of the central nervous system (CNS) areas involved in sexual arousal, and generally in sexual behavior, was mainly dependent on animal data [386]. Animal models are notably insufficient to understand human sexual behavior where, for instance, cognitive aspects play a crucial role. The availability of neuroimaging techniques opened the possibility of investigating for the first time central nervous system correlates of sexual arousal in humans.

2. POSITRON EMISSION TOMOGRAPHY (PET)

By means of radioactive ligands, PET can detect regional cerebral blood flow, metabolic changes, as well as density and binding of several neurotransmitter receptors. The underlying principle is that a radioactive isotope emitting positrons (β+ particles with a mass equal to an electron but with a positive electrical charge) is integrated into a biological molecule and injected intravenously. Following activation of a specific brain region, the local regional cerebral blood flow increases and the emitted positrons interact with electrons of neighboring atoms, producing photons. These photons may be detected by an array of camera detectors placed around the subject’s head [385].

3. FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI)

fMRI uses the magnetic resonance approach of perfusion-based signal intensities of the brain. Activated areas of the human brain show localized increases in blood flow that exceed increases in oxygen consumption; accordingly, the oxygen content of venous blood increases. The magnetic susceptibility of oxyhemoglobin and deoxyhemoglobin differs slightly. Consequently, blood can be used as an endogenous contrast agent, as the transient changes in MR signal that accompany these hemodynamic events can be recorded with rapid MRI methods. fMRI allows one to localize functional brain activation with an accuracy of millimeters and a temporal resolution of seconds [384, 385]. In particular, compared with PET, fMRI has higher signal-to-noise ratios, enabling superior temporal correlation between brain activation and peripheral response [387].

4. METHODOLOGICAL CONSIDERATIONS

Neuroimaging investigations of emotional processes need specific requirements concerning inclusion criteria and subjective/objective assessments of sexual arousal. Further considerations pertain to the appropriate stimulus selection, when addressing exploration of CNS correlates of sexual arousal.

Inclusion criteria and subjective/objective assessments of sexual arousal: Evaluated subjects should share the same dominant hemisphere; characteristically, right handed individuals are selected. When investigating emotional processes subjective cognitive response is desirable, to verify how the administered stimulus in fact evoked the target emotion. Ideally, this subjective response should be collected immediately following stimulus administration, minimizing the cognitive component of memory recall. Such a cognitive task would also warrant the presence of attention of the volunteer during the stimulus administration. Furthermore, an objective assessment of the evoked emotion is highly desirable. Specific to the investigation of sexual arousal, measures of penile tumescence in men and of vaginal lubrication and/or blood flow variations in women would fulfill such need [388, 389]. Lastly, it is well appreciated that sexual arousal is androgen dependent [390]. Accordingly, it would be desirable to know the hormonal milieu of the investigated population.

Stimulus selection and paradigm design: In imaging studies, several issues need to be addressed in devi-
sing a suitable paradigm design, in order to reliably measure CNS correlates of sexual arousal in humans.

A crucial step is the identification and precise definition of a study stimulus effective in inducing the target emotional response, namely sexual arousal. It is generally accepted in the sexological literature that material of overtly sexual or pornographic nature constitutes a good source of stimuli for a subjective sexual response [391]. The sexual response’s biological equivalents (i.e., lubrication, erection) may also be objectively measured [388, 389]. Furthermore, several studies have shown that film clips are more potent in inducing subjects’ emotional response, compared to slides or images [392-394]. Notwithstanding this, explicit erotic film clips may induce in the viewer, besides sexual arousal, several other emotional reactions, as for instance curiosity, attention, shame, etc. Therefore, preliminary validation of visual stimuli for emotional content is strongly advisable.

Functional neuroimaging investigations rely on the flow-dependent signal difference between baseline and stimulated behavioral conditions. This ‘subtractive’ study paradigm aimed at investigating brain areas associated to sexual arousal should include the following three stimulus categories:

a) target stimuli: film clips with a high value of both the affective dimension of pleasure and of sexual arousal, and being of a clearly sexual nature;

b) positive control stimuli: film clips with a high value of the affective dimension of pleasure, but with a medium-low level of sexual arousal;

c) neutral stimuli: film clips with relatively neutral values of both the affective dimension of pleasure and of sexual arousal.

According to the IAPS standardization procedure [395, 396], pornographic film clips fulfill the requirements of target stimuli, non-professional sport clips fulfill those of positive control stimuli, and film clips featuring interior or exterior settings fulfill those of neutral stimuli. A recent study investigated both if the subjective sexual arousal induced by erotic film clips differed in men and women. This study examined if the arbitrary selection of positive control stimuli and neutral stimuli were in fact fulfilling such criteria, in terms of emotional content [397, 398]. It emerged that it is not possible to preliminarily define which visual stimulus constitutes an appropriate positive control stimulus or a neutral stimulus, as their emotional rating is widely overlapping. Erotic film clips resulted in reactions distinct from the other two types of clips (sport clips and indoor-outdoor film clips) because of high scores of the investigated dimensions of pleasure and arousal. However, a striking gender difference emerged: while men scores grouped these clips in a well-defined high pleasure - high arousal cluster, women scores conversely produced a wide clip distribution, with some erotic clips perceived as unpleasant, and with others overlapping the scores of control film clips. While the erotic film clips used in such study have been extracted by men-directed movies, it has been reported that women’s subjective responses may vary, according to the gender of the erotic movie director [389]. Accordingly, women directed erotic movies may prove to be more appropriate in inducing sexual arousal in women for the purpose of neuroimaging investigations. It was also further confirmed that it is of paramount importance to assess upfront the sexual orientation of the tested subjects (heterosexual vs. homosexual), and not simply to assume it. This study accordingly underscored that studies aimed to investigate sexual arousal by means of erotic, control and neutral visual stimuli need a preliminary validation of such stimuli for emotional content, proposing a “ad hoc” validation process [397, 398] (Figures 14, 15).

5. OVERVIEW OF RECENT NEUROIMAGING STUDIES ADDRESSING CNS CORRELATES OF SEXUAL AROUSAL IN HUMANS

Several PET and fMRI investigations recently addressed CNS correlates of sexual arousal in men and women [399-403] (Table 3), and two studies explored the effect of apomorphine SL on brain activation patterns in psychogenic ED patients, using sexually explicit film clips (21, 22) (Table 4). These studies vary, sometimes widely, in terms of paradigm design, and comparative evaluations may be difficult to drawn. Nonetheless, some general conclusions may be drawn (Tables 3, 4).

6. HEALTHY MEN AND CNS NEUROIMAGING CORRELATES OF SEXUAL AROUSAL

The work of Arnow et al. [403] appears particularly rigorous in terms of paradigm design, including subjective and objective assessment of sexual arousal. When penile tumescence was used as a regressor, they found the right insula/subinsular region, including the claustrum, as the largest and most significant region of activation. Such findings are very
Table 3. Characteristics of PET and fMRI investigations addressing CNS correlates of sexual arousal in healthy men and women [385, 394, 399-403], and in two hypogonadal male patients [402].

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Population</th>
<th>Visual stimuli</th>
<th>Subjective sexual arousal</th>
<th>Objective sexual arousal</th>
<th>Activated CNS areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stokerus</td>
<td>PET</td>
<td>8 healthy males 21-25 yo</td>
<td>y</td>
<td>y</td>
<td>erotic tumescens</td>
<td>geographical thoroughness penile plethysmography and serum testosterone inferior temporal cortex bilaterally right insula and right inferior frontal cortex left anterior cingulate cortex</td>
</tr>
<tr>
<td>Redouté</td>
<td>PET</td>
<td>9 healthy males 21-39 yo</td>
<td>y</td>
<td>y</td>
<td>erotic tumescens</td>
<td>geographical thoroughness penile plethysmography and serum testosterone</td>
</tr>
<tr>
<td>Bocher</td>
<td>PET</td>
<td>10 healthy males 24-35 yo</td>
<td>y</td>
<td>y</td>
<td>erotic tumescens</td>
<td>geographical thoroughness penile plethysmography and serum testosterone</td>
</tr>
<tr>
<td>Park 2001</td>
<td>fMRI</td>
<td>12 healthy men and 2 hypogonadal men 21-25 and 29-35 yrs</td>
<td>y</td>
<td>y</td>
<td>none</td>
<td>Likert-type rating scales for sexual arousal and penile erection</td>
</tr>
<tr>
<td>Park 2001</td>
<td>fMRI</td>
<td>6 healthy women 25-41 yo</td>
<td>y</td>
<td>y</td>
<td>erotic tumescens</td>
<td>Likert-type rating scales for sexual arousal and penile erection</td>
</tr>
<tr>
<td>Arnow</td>
<td>fMRI</td>
<td>14 healthy men 18-30 yo</td>
<td>y</td>
<td>y</td>
<td>erotic tumescens</td>
<td>Likert-type rating scales for sexual arousal and penile erection</td>
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Table 4. Characteristics of two PET and fMRI investigations addressing the effect of apomorphine SL on brain activation patterns in psychogenic ED patients [404, 405].

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Population</th>
<th>Visual stimuli</th>
<th>Subjective sexual arousal</th>
<th>Objective sexual arousal</th>
<th>Activated CNS areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hagemann</td>
<td>PET</td>
<td>12 psychogenic ED men 25.41 yrs</td>
<td>yes</td>
<td>y</td>
<td>erotic tumescens</td>
<td>none</td>
</tr>
<tr>
<td>Montorsi</td>
<td>fMRI</td>
<td>6 healthy men and 10 psychogenic ED men 7 and 49 yrs mean age</td>
<td>yes</td>
<td>y</td>
<td>erotic tumescens</td>
<td>none</td>
</tr>
</tbody>
</table>

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similar to the PET studies of Stoleru et al. [399] and of Redoute et al. [403]. The insula is involved in visceral sensory processing, and is activated also following vibrotactile stimulation. The authors suggest that the claustrum/subinsular activation during visually induced sexual arousal may reflect cross-modal transfer of visual input to imagined tactile stimulation (19). Other areas activated during penile tumescence were: hypothalamus and the striatum (caudate nucleus and putamen), well known to be involved in sexual response, both in animals and in humans; and the anterior cingulate cortex (specifically BA24 and BA 32). The anterior cingulate is linked to attentional processes, and areas BA 24 – BA 32 are involved in modulating autonomic and endocrine functions, including gonadal and adrenal secretions (23). The right middle temporal and middle occipital gyri (BA 37/19), involved in visual processing were also activated[402] (Figures 16, 17).

Differences in experiment design may explain the very few activations observed by Arnow et al. at block analyses, compared with the activations found by Stoleru et al. with the same analyses in their PET study. Namely, the positive control clips (sport scenes) of the Arnow study may have been more effective compared with the humor conditions of the Stoleru study [395]. Other experimental design differences may account for the substantially different activation regions between the Arnow and the Park study. The latter in particular did not include a positive control stimulus in its study paradigm (Figures 18, 19).

7. TESTOSTERONE AND CNS NEUROIMAGING CORRELATES OF SEXUAL AROUSAL IN MEN

It is well documented that neurons in the midbrain, hypothalamus and amygdala contain receptors for gonadal hormones, and that through such areas androgens regulate sexual behavior and motivation [390].

Stoleru et al. found correlations between levels of plasma testosterone drawn after film presentation,
Figure 16: Average penile turgidity and button presses for 11 subjects for video 1. Button A was pressed to indicate sexual interest, Button B was pressed to indicate onset of erection and Button C was pressed to indicate loss of interest. The onset and durations of the three different video conditions, erotic, sports and relaxation (R), are indicated below the turgidity trace. From Arnow et al., 2002 [402]

Figure 17: Turgidity-correlated brain activations obtained from a random effects analysis of 11 subjects. Red–yellow colour scale indicates regions that exhibit significant correlations with behavioural measures of penile turgidity. These colour maps have been superimposed on the average T2-weighted and stereotaxically normalized brain volume. (A) SPM99 surface reconstruction depicting projections of activations on the right side of the brain. (B) Axial section depicting the largest brain activation observed in this experiment in the right insula and claustrum. (C) Axial section illustrating activation in left caudate/putamen and right middle temporal/right occipital gyri (BA 37/19). (D) Axial section depicting cingulate gyrus activation. (E) Coronal section illustrating activation in the right hypothalamus. From Arnow et al., 2002 [402]

Figure 18: Coronal section demonstrating brain regions where rCBF was linearly correlated with levels of perceived sexual arousal. (a) Anterior cingulate gyrus; (b) head of caudate nucleus; (c) claustrum and (d) putamen. Section is located 4 mm rostral to anterior commissure. Height threshold: $z = 4.40$, $P < 0.0001$, uncorrected. Right is to the right. From Redoute et al., 2000 [403]
and activation-deactivation areas during visual sexual stimulation [399]. A positive correlation was noted for the right middle occipital gyrus (a37) and the right inferior frontal gyrus (a45). Conversely, four regions on the left hemisphere [inferior parietal lobule, inferior frontal gyrus (a46 and a10), and gyrus frontalis medialis] exhibited a negative correlation with testosterone plasma levels, suggesting that testosterone modulates negatively their activity level [399].

Park et al. in their fMRI study showed that in hypogonadal patients decreased brain activities can be restored with testosterone supplementations [400]. They in fact included in their series also two hypogonadal impotent patients. Following 3 months testosterone supplementation, patients were then rechallenged with fMRI. They both showed increased CNS activities. These were striking in the one patient that started with the lower testosterone level, and at three months was better normalized by hormonal supplementation. In this case inferior frontal, cingulate gyrus, insula, corpus callosum, thalamus, globus pallidus, and inferior temporal areas were now significantly activated upon visual sexual stimulation, similarly to normal volunteers.

8. PSYCHOGENIC ED MEN EXPOSED TO APOMORPHINE SL AND CNS NEUROIMAGING CORRELATES OF SEXUAL AROUSAL

Very recently, two studies assessed the impact of apomorphine SL administration to men with psychogenic ED in CNS correlates of sexual arousal [404, 405]. Both were randomized, double blind, placebo-controlled studies, and both used as active compound apomorphine SL 4 mg.

Hagemann et al. evaluated 12 psychogenic patients in a parallel design PET study, also monitoring penile radial rigidity [404] (RigiScan device). All patients when challenged with erotic movies showed significant increases in regional cerebral blood flow (rCBF) in the inferior frontal cortex bilaterally, and in the rostral anterior cingulated; while cerebral activity decreased in both inferior temporal cortices. Following apomorphine SL further increases in rCBF were detected in the right superior prefrontal area, and a >60% rigidity was recorded in 4 of the 6 men receiving the active treatment.

Montorsi et al., through a crossover fMRI study, evaluated 10 psychogenic ED patients [405]. During erotic movie viewing, it was noted that, compared to normal controls, psychogenic patients exhibited a significant activation in the cingulate gyrus, frontal mesial and frontal basal cortex, bilaterally. In these patients, apomorphine SL normalized the activation of the above areas, while increasing the extension of the activated networks, and activating foci in the nucleus accumbens, hypothalamus and mesencephalon. Furthermore, the right hemisphere was significantly more activated than the contralateral one. During fMRI, eight of the ten patients demonstrated penile erection when challenged with apomorphine SL.

9. FINAL CONSIDERATIONS AND FUTURE PERSPECTIVES

Neuroimaging investigations of sexual arousal in humans are capable of record activation of brain areas in response to visual erotic stimuli. The different results reported by different authors may reflect differences in paradigm design. Only few studies utilized the three stimulus categories: study (erotic) stimuli, positive control stimuli, and neutral stimuli. In particular, in none of the available studies there has been a preliminary validation for emotional content of the used visual stimuli. The neuroimaging techniques PET and fMRI appear very promising for helping to elucidate many aspects of human sexual behavior.

10. CONCLUSIONS

A large number of models exist for the study of male sexual function. Each model has both strengths and limitations. Practical considerations have led to a great reliance on rodent models. These have the advantage
of cost, ease of handling and a large foundation of biological knowledge. The disadvantage of rodent models is that they do not always accurately reflect human physiology and pathophysiology. Therefore, validation of any given model must be assessed for a particular application. The utility of these models is amply demonstrated by the great expansion of our understanding of male sexual physiology in recent years. Future challenges will be to develop more practical models for functions such as sexual desire, ejection and refinement of models of pathophysiological conditions, such as Type II diabetes.

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SEXUAL MEDICINE
SEXUAL DYSFUNCTIONS
IN MEN AND WOMEN

EDITORS
T.F. Lue - R. Basson - R. Rosen -
F. Giuliano - S. Houry - F. Montorsi

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International Society of Urology (SIU)
International Society for Sexual and Impotence Research (ISSIR)
Edition 2004
FOREWORD

The first International Consultation on Erectile Dysfunction held in Paris, France July 1999 was a milestone in the history of scholarly research in men’s sexual function and dysfunction. The proceedings of the Congress, ”Erectile Dysfunction: 1st International Consultation on Erectile Dysfunction” has become the most quoted reference on men’s sexual dysfunction in the world.

The ensuing years have seen an explosion of interest in both men’s and women’s sexual function and dysfunction. There are numerous scientific articles reporting topics from molecular biology to epidemiology to surgical treatments from all corners of the world. The Second International Consultation inherited this great tradition and expanded the agenda to cover and update the knowledge related to function and dysfunction of both genders. This proceeding is thus correctly named “Sexual Medicine” with the first volume dedicated to men’s sexual function and dysfunction and the second to women’s sexual health and dysfunction.

The more than 200 members of the 19 committees are all internationally known scholars and experts from the 5 continents of the globe. This marvelous proceeding is the product of 4 preparatory meetings, 4 days of presentations, debates and discussions in Paris and numerous hours of hard work of the committee members and their committee chairpersons. Besides the committees on male-specific conditions such as penile prosthesis, Peyronie’s disease and penile reconstruction, all other committees are charged to address issues related to both men and women. Therefore, there is a welcomed huge expansion on the findings of research related to women’s sexual function and dysfunction in this book. Although the common theme is an update on the science and expert opinion, individual committees have the freedom to add different flavors to its style and content- making it a truly world effort in this endeavor. Although evidence-based medicine is the guiding principle in selecting and analyzing articles, consensus expert opinion and geographic, religious and cultural factors are also taken into consideration in forming the recommendations.

Besides updated information on both men’s and women’s sexual health issues and dysfunction, several notable topics are new to this book. These include: 1) Quantitative research vs. evidence based medicine; 2) Male Sexual Dysfunction Scale (MSDS) - an important project commissioned by the International Consultation; 3) a brief psychosexual evaluation questionnaire which gives the clinicians a user-friendly tool to properly evaluate the psychosexual aspect of the patient; 4) brain imaging; and 5) greatly expanded coverage of sexual dysfunction in women.

This tremendous world-wide task would be impossible without the vision of the International Consultation, the generous support of various organizations and industry and the flawless coordination by Professor. Saad Koury and his staff. We are also indebted to the important contributions from all committee members and chairpersons and the 4 vice chairs of this Congress: Drs. Francois Giuliano, Raymond Rosen, Rosemary Basson and Francesco Montorsi.

A. Jardin - T.F. Lue
Some of the members of the international committees
Paris - June
Editors

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1. Definitions, Classification and Epidemiology of Sexual Dysfunctions

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CATANIA J. U.S.A.
FUGL-MEYER A. Sweden
FUGL-MEYER K. Sweden
LAUMANN E. U.S.A.
LEWIS R. U.S.A.
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LEVINE S.B. U.S.A.
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OSWALDO R. Brazil
PLAUT M. U.S.A.
WYLIE K. U.K.

3. Educational, Socio-Cultural and Ethical Aspects of Sexual Dysfunctions

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DEAN J. U.K.
FOURCROY J. U.S.A.
GINGELL C. U.K.
KINGSBERG S. U.S.A.
KOTHARI P. India
OKUYAMA A. Japan
RUBIO AURIOLES E. Mexico
UGARTE F. Mexico
VELA NAVARRETE R. Spain
WAGNER G. Denmark

4. Economical Aspects of Sexual Dysfunctions

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JAROW J. U.S.A.
KIMOTO Y. Japan
MIRONE V. Italy
RICHTER S. Israel
SCHMIDT A. S.Africa
SHABSIGH R. U.S.A.
YAFFE L. U.S.A.

5. Clinical Evaluation and Symptom Scores of Sexual Dysfunctions

BRODERICK G. U.S.A.
CLAYTON A. U.S.A.
CUZIN B. France
DEROGATIS L. U.S.A.
HATZICHRISTOU D. Greece
LITWIN M. U.S.A.
MEULEMAN E. The Netherlands

6. Standards for Clinical Trials in Sexual Dysfunctions: Research Designs and Outcomes Assessment

DONATUCCI C. U.S.A.
GLINA S. Brazil
GUESS M. U.S.A.
HEIMAN J. U.S.A.
HIRSCH M. U.S.A.
HYDE J.S. U.S.A.
MONTAGUE K. U.S.A.
MONTORSI F. Italy
SEGRAVES R.T. U.S.A.
WYLIE M. U.K.

7. Physiology - Pathophysiology of Female Sexual Function

GIRALDI A. Denmark
GOLDSTEIN I. U.S.A.
KADIOGLU A. Turkey
MARSON L. U.S.A.
NAPPI R. Italy
PFAUS J. Canada
SALONIA A. Italy
TRAISH A. U.S.A.
VAN LUNSEN R. The Netherlands
VARDI Y Israel

8. Priapism, Peyronie's Disease and Penile Reconstructive Surgery

AKKUS E. Turkey
ALTER G. U.S.A.
JORDAN G.H. U.S.A.
LEBRET T. France
LEVINE L.A. U.S.A.
MULHALL J. U.S.A.
PEROVIC S. Serbia
PRYOR J. U.K.
RALPH D. U.K.
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9. Disorders of Orgasm in Male and Female, Ejaculatory Disorders in Males

ABDO C. Brazil
HULL E. U.S.A.
INCROCCI L. The Netherlands
LEVIN R. U.K.
MCMAHON C. Australia
MESTON C. U.S.A.
PERELMAN M. U.S.A.
ROWLAND D. U.S.A.
WALDINGER M.D. The Netherlands
XIN Z.C China
10. Experimental Studies of Sexual Functions and Dysfunctions Including Brain Imaging Studies

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11. Physiology, Molecular Biology of Erectile Function and Pathophysiology of Erectile Dysfunction

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12. Endocrine Aspects of Male and Female Sexual Dysfunctions including Hormonal Treatment

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14. Pharmacological Treatment of Erectile Dysfunction

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15 Future Treatment Target

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16. Female Sexual Desire and Arousal Disorders and Sexual Pain Disorders: Pathophysiology and Treatment

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Robert J. Krane, my mentor, my professor, my chairman, my friend. You left us too young. How do I describe you to people who never knew you? To put it simply, Bob Krane was a visionary. At a time when the word "sex" wasn't used publicly by anyone over 30, and no one would dare complain of impotence, Bob had the vision to see that erectile dysfunction was a real problem which affected men deeply, and deserved medical attention. He took it upon himself to learn more, and brought what we now know as sexual medicine to Northeastern United States.

I met Bob when I started as a resident at Boston University School of Medicine. At that time Carl Olsson was chair of the department. When Carl left for Columbia, Bob was a natural to take over the department. At that time he became the youngest chairman of Urology in the U.S.

Right from the beginning Bob had a sense that the practice of the future was one of specialization. His right hand man was Mike Siroky, who specialized in neurology. Bob had flown to Texas to learn from Brantley Scott himself how to implant this newfangled device, the penile prosthesis. I had always been interested in flow, but Bob turned to me one day and declared, I was to become the world's expert in penile vascular function. I had no idea to what he was referring, but I said yes.

Bob raised the funds to fly in Vaclav Michal, the developer of the penile microvascular arterial bypass procedure, from Czechoslovakia. Vaclav showed me his technique in Boston and I trained with one of our local vascular surgeons after he left. Thus started our first clinic for sexual dysfunction in 1978, although we couldn't call it that. It was named the New England Male Reproductive Center, avoiding the words sex or erectile dysfunction, but we no longer were restricted to just sex therapy to treat our patients. We added into the mix penile implants and penile revascularization surgery.

During that time we found funding sources to open a basic science lab, with Inigo Saenz de Tejada as director. Bob knew that an academic practice needed hard science to back it up. In 1988 in Boston we co-chaired the International Society for Impotence Research, as the ISSIR was known then. By then Bob had friends around the world and was known as a brilliant physician and witty, thoughtful friend. Many of the world's most renown scientists in the field of impotence were Bob's personal friends, and attended this meeting.
Over the years we learned the various therapies to treat erectile dysfunction. At the same time our basic science researchers under the directorship of Abdul Traish and Noel Kim discovered the role of nitric oxide in smooth muscle relaxation facilitating erection. Bob Krane encouraged research and looking beyond the obvious. Over the years we had fellows from around the world visit us or train with us. In Bob's absence we continue with this model.

Everywhere we travel we find friends of Bob and Bambi's.

Bob's gift to us was this vision of which I spoke. The ordinary needed embellishment, the average needed education, the picture needed to extend into the future. This image of Bob helps to explain his extraordinary ability to bring out the best in people. It also helps to explain his driving passion that helped bring the field of sexual medicine to where it is today.

After helping to found the ISIR and chairing the 1988 meeting, Bob went on to be president for 4 years ED consultation.

This year marks the 25th anniversary of the clinic started so long ago by Bob Krane to treat impotence, then erectile dysfunction and now sexual medicine. Along the way he trained scores of residents, many fellows and hundreds of health care professionals as he traveled the world. It is fitting that we remember him to today at the this consultation on sexual dysfunctions.

This is the legacy Bob leaves us. Never settle for what is, when we can learn so much more. Ask questions. Talk to people. Make friends. In the world Bob was born into talking about sex was taboo. Now we proclaim to the world that every human being has a right to health including sexual health.

Bob's special legacy to me was his allowing me to follow my passion. Today this gift continues to live as I am attempting to follow that vision and create a department of sexual medicine. But everywhere I look I see and hear Bob—in his family's faces, in his friends' conversations, in his former students' research and in myself whenever I have a new idea.

You left us too young, but thank you Bob for all you have left for us to do, and thank you for the giving us the passion with which to do it. We shall follow in your footsteps and leave carry it through to the next generation.

Irwin Goldstein
CHAPTER 11 Committee 12A Endocrine Aspects of Men Sexual Dysfunction
A. Morales (Canada), J. Buvat (France), L.J. Gooren (Netherlands), A.T. Guay (USA), J.M. Kaufman (Belgium), Young C. Kim (Korea), H.M. Tan (Malaysia), L.O. Torres (Brazil)

CHAPTER 12 Committee 8 Priapism, Peyronie’s Disease, Penile Reconstructive Surgery
J. Pryor (U.K), E. Akkus (Turkey), G. Alter (USA), G. Jordan (USA), T. Lefebvre (France), L. Levine (USA), J. Mulhall (USA), S. Perovic (Serbia), D. Ralph (U.K), W. Stackl (Austria)

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John J. Mulcahy (USA), E. Austoni (Italy), J H. Barada (USA), H. Ki Choi (Korea), W. J.G. Hellstrom (USA), S. Krishnamurti (India), I. Moncada (Spain), D. Shulteiss (Germany), M. Sohn (Germany), H. Wessells (USA)

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CHAPTER 16 Committee 15 Future Treatment Targets
K-E Andersson (Sweden), A. Argiolas (Italy), A. Burnett (USA), K.K Chen (China), T.M Mills (USA), W. D. Steers (USA)

CHAPTER 17 Summary of the Recommendation for Men

3 SEXUAL DYSFUNCTIONS IN WOMEN

CHAPTER 18 Committee 6B Standards for Clinical Trials in Sexual Dysfunctions of Women: Research Designs and Outcomes Assessment
J. R. Heiman (USA), M. K. Guess (USA), K. Connel (USA), A. Melman (USA), J. S. Hyde (USA), T. Segraves (USA), M. G. Willie (U.K)

CHAPTER 19 Committee 7 Physiology of Female Sexual Function and Pathophysiology of Female Sexual Dysfunction
I. Goldstein (USA), A. Giraldi (Denmark), A. Kadigilu (Turkey), H.W van Lunsen (The Netherlands), L. Marson (USA), R. Nappi (Italy), J. Pfaus (Canada), A. Salonia (Italy), A.M. Traish (USA), Y. Vardi (Israel)

CHAPTER 20 Committee 12B Endocrine Aspects of Female Sexual Dysfunction
S.R. Davis (Australia), A.T. Guay (USA), J.L. Shifren (USA), N.A. Mazer (USA)

CHAPTER 21 Committee 9B Women’s Orgasm
C.M. Meston (USA), E. Hull (USA), R.J. Levin (UK), M. Sipski (USA)

CHAPTER 22 Committee 16 Women’s Sexual Desire and Arousal Disorders and Sexual Pain
R. Basson (Canada), W.C.M. Weijmar Shultz (Netherlands), Y.M. Binik (Canada), L.A. Brotero (USA), D.A. Schenbach (USA), E. Laan (Netherlands), W.H. Utian (USA), U. Wesselsmann (USA), J. Van Lankveld (Netherlands), G. Wyatt (USA), L. Wyatt (USA), S. Leiblum (USA), S. E. Althof (USA), G. Redmond (USA)

CHAPTER 23 Summary of the Recommendation for Women

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EVIDENCE - BASED MEDICINE OVERVIEW OF THE MAIN STEPS FOR DEVELOPING AND GRADING GUIDELINE RECOMMENDATIONS.

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/cebmb/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 (i.e. therapy, diagnosis, differential diagnosis/symptom prevalence study).

The Oxford Center for Evidence-Based Medicine Website: http://minerva.minervation.com/cebmb/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 inte-
gration of individual clinical expertise with best available exter-
nal clinical evidence from systematic research. Without the for-
mer, practice quickly becomes tyrannised by evidence, for even excellent external evidence may be inapplicable to, or
inappropriate for, an individual patient: without current best evi-
dence, 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; gene-
ralisability; 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 gui-
deline 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** (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 were 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 state-
  ment 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 proce-
dure). 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 diffe-
rence, 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 recommen-
dation, for example, if the therapy is prohibitively expensive,
  dangerous or unethical. Grade A recommendation can fol-
  low from Level 2 evidence. However, a Grade A recom-
  mendation 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 stu-
  dies or ‘majority evidence’ from level 2/3 studies or Dephi
  processed expert opinion. Grade C recommendation is
given when expert opinion is delivered without a formal ana-
lytical process, such as by Dephi.
• **Grade D** “No recommendation possible” would be used
  where the evidence is inadequate or conflicting.

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 interven-
tions. 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 recom-
mendations 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 recom-
mandation, 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 perfor-
ance and cost effectiveness, and also factors such as patient
preference.

P. Abrams, S Khoury, A. Grant 19/1/04
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