Acknowledgement

We would like to thank:

- The Urology Department at La Pitié Hospital in Paris and its chairman Professor F. Richard

for kindly providing logistic assistance for the editing of this book.

We would also like to thank all the contributors for their enthusiastic support and help.
FOREWORD

The great tragedy of science:
The slaying of a beautiful hypothesis by an ugly fact
Thomas Huxley (1825-1895)

These proceedings represent the consensual text and recommendation of the 16 committees that met in Paris at the occasion of the 6th International Consultation on New developments in Prostatic diseases and Prostate Diseases June 24-27, 2005. On behalf of the International Consultation on Urological Diseases (ICUD) and its Steering Committee composed of the representatives of the major urological associations of the world (SIU, AUA, EAU, UAA, CAU, ICS) we would like to thank the chairmen and their committee members for again meeting the highest expectations.

The formula adopted in 1996 and 1999 shows no sign of fatigue with the innovations introduced each meeting. Basically, of course, we stay with our time tested multiprofessional approach under the auspices of the International Agency on Cancer Research, and the International Union against Cancer and advice from the European Organisation on Research and Treatment of Cancer, the American Cancer Society and the International Prostate Health Council that provides access and collaboration with some of the world’s best experts on the disease. The Steering Committee, with support of the International Society of Urology, assures the collaboration of the world’s urological experts on the subject in a truly global endeavour.

The 6th meeting brought us not only an updated present knowledge for the community, but focused on evidence based facts and widely accepted recommendations with a model to define standards for clinical research in the future. In short, a product that can serve as a reference and guide in the different aspects of Prostatic diseases treatment prepared by a 150 member multidisciplinary and international team.

In meeting this milestone, we should not forget that this result was only possible by the advice and guidance of the leading organizations, but also by the enthusiastic support of urologists from more than 20 national organizations.

We want to thank them all personally.

The Editors,
Some of the members of the international committees
Paris - June 24-27, 2005
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P. Abrams *(U.K)*

L. Denis *(Belgium)*,

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It was with particular pleasure, that the delegates to the Fourth International Consultation on Prostate Cancer, held in Paris during the last days of June 2005, welcomed Professor Louis Denis as their Honorary President. As one of the founding fathers of the ICUD, the internationally recognised and universally popular Louis Denis, played a principal role in the establishment of the innovative annual consensus meeting, as the most successful discussion forum available to the Urological Community, worldwide. From its inception in the 1980s and its subsequent recognition by the WHO and UICC, Louis Denis actively promoted the value of the consultation to international urology. The ICUD Board was delighted and honoured, that he accepted the Presidency for 2005.

Louis Denis graduated in 1957 from the University of Ghent, where he completed his medical studies. As a trained sportsman, he won medals in the swimming pool and a bronze medal with the Belgium basketball team in the 1952 University Olympic Games. After residencies at the Antwerp City Hospitals, he moved to the Medical College of Virginia, USA where, under the guidance of his mentor, Professor George Prout, he honed his surgical skills, enjoyed his research activity that gained AUA and EAU prizes and realised an inherent real ability to teach. Most importantly, with Bill Scott’s support, he acquired expertise as a clinical trialist.

In late 1964, however, Louis Denis returned to Belgium, because he was a military man: he retired in 1991 as Lt-Colonel. He was required to help in Operation Red Dragon and joined an American and Belgian assault into Stanleyville, the capital of the North East Belgium Congo, in order to rescue 700 European and American citizens taken hostage by rebels.

With the hostages rescued and military honours awarded, this ‘simple urologist from a little country called Belgium’, a comment he often uses, consolidated his position in the forefront of Belgian urology, with successive appointments as Chief of Urology in the Antwerp Military Hospital and AZ Middleheim Hospital, Antwerp, Professor of Urology, University of Brussels and President of the Medical Board of the Middleheim Hospital. Belgian civil honours, a Knighthood of the Order of the Crown and Commander of the Order of Leopold II, were awards that nationally recognised his clinical and academic prowess.

Contemporaneously, a worldwide recognition of his ability was seen by invitations to present prestigious lectures, the award of honorary degrees and Medical Society Medals, as well as the membership of influential committees and advisory boards. His clinical research was always to the forefront and he contributed substantially to the medical literature with more than 350 peer-reviewed papers, 205 chapters of medical textbooks and the editorship of 50 books. As the European leader, not only in the value and promotion of scientifically sound, randomised, controlled clinical trials, but in the development of transurethral ultrasonography, Louis Denis introduced the international Urological Community to the use of such diagnostic procedures in order to test their potential in the Pan-European screening initiatives for the identification of early cancer of the prostate.
Professor Louis Denis is a renowned figure in international urological affairs, recognised as a founder member of the European School of Oncology in Milan, a former Secretary General and long-time treasurer of the UICC and former President of the EORTC, for which he was able to negotiate a two million euro award from Belgium. Louis Denis, together with the formidable Saad Khoury, Yoshio Aso and the late Gerry Murphy, established the International Consultations in Urological Diseases, global consultations involving multi-professional expertise, which aimed to achieve by consensus, international strategies for the diagnosis and treatment of urological diseases, a concept that has been immensely successful. Through the past decade, he has chaired the International Prostate Health Council, the IPHC, a sort of ‘think tank’, that in the early 1990s, was asked to help to increase the worldwide awareness of prostate disease. With the backing of Council members such as Adolphe Steg, Fritz Schroeder, Peter Boyle, Roger Kirby and Tag Hald, Louis’ IPHC has impressively initiated a range of teaching programmes, organised the Pan-European Screening initiative and promoted the now rapidly growing belief that the growth of prostate cancer can be restrained, possibly even prevented.

‘Europe’s Foremost Free Thinker’ is now retired. ‘So much achieved, but so much more to be done’. As well as appreciating the love and company of his many grandkids, the Emeritus Professor has now assumed another responsibility, that of Director of the Oncology Centre in Antwerp and he continues to travel widely, in the promotion of the Europa Uomo programme, directed to a better relationship between patients and their doctors, attempting to ensure that patients with prostate cancer, worldwide, have ready access to responsible information that will offer some reassurance and a better understanding of their disease and its treatment.

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The Consultation was indeed honoured that the 2005 Presidency was accepted by Louis Denis, a urologist of great skill, an accomplished clinical researcher, sportsman, soldier and exemplary medical diplomat, but most importantly, a wonderful friend and teacher to so many.

Keith Griffiths, ICUD Board Member.
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CHAPTER 1

History of Prostatic Diseases

Chairman

D. Schulteiss (Germany)

R. S. Waldbaum (USA)
Leonardo da Vinci (1452-1519) was the first master of anatomical and medical illustration, although his outstanding work on the anatomy and physiology of the human body was almost unknown to his contemporaries. The incident that he never gave a description of the prostate gland can be explained by the fact, that most of his knowledge was drawn from anatomical dissections of castrated oxen only having a small and atrophic prostate.

The "Tabulae Anatomicae" of the anatomist Andreas Vesalius (1514-1564) from 1538 gave the first illustration of the prostate gland but omitted the seminal vesicles. A more detailed illustration can be found in "De Humani corporis fabrica Libri septem" from 1543.
In his “Dix Livres de la Chirurgie” from 1564 the master of French Renaissance surgery Ambroise Paré (1510-1590) dedicated one chapter to “des chaudes pisses, des pierres et des rétentions d’urine”. He described obstructive urinary symptoms and related them to “carnosities” or “caruncles” deriving from the prostate.

Ambroise Paré even suggested catheters or sounds with sharp ridges on their surfaces designed to remove these “carnosities” or “caruncles” by repeatedly passing these instruments through the urethra.

In his “Tractus de virorum organis generationi inservientibus, de clysteribus et de usu siphonis in anatomia” (1668) the Dutch physician Regnier de Graaf (1641-1673) gave a very detailed and exact anatomical description and illustration of the prostate, the seminal vesicles and the ejaculatory ducts.
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. In his book “A Treatise on the Venereal Disease” from 1786 he illustrated an enlarged middle lobe of the prostate. In his later works he precisely described obstructive symptoms caused by enlargement of the prostate and the resulting effects on the bladder muscularis and of dilation of the upper urinary tract. Hunter also realized that these changes did not occur in castrates.

Jean Civiale (1796-1867) from Paris devised the “kiotome” around 1830 for incision of the obstructing bladder neck. In 1836, his contemporary Louis-Auguste Mercier (1811-1882) introduced several instruments to incise the median bar or even to remove small tissue particles similar to a punch.

In 1874 Enrico Bottini (1835-1903) from Pavia in Italy was the first to apply electric surgery to the prostate. His “Cauterio termo-galvanico” facilitated destruction and incision of a prostate lobe and median bar without producing hemorrhages.
Based on the “Cauterio termo-galvanico” of Bottini several modified galvano-cautery and –incision instruments were suggested by Freudenberg (A), Chetwood (B) and Wishard (C).

Sir Henry Thompson (1820-1904) from London won the prestigious Jacksonian Prize in 1860 with his monography “The enlarged Prostate, its Pathology and Treatment”. He gained reputation as the world’s greatest specialist surgeon after he successfully removed the bladder stone of King Leopold I, King of Belgium, in 1863.

Theodor Billroth (1829-1894) was one of the greatest surgeons of his time and before coming to Vienna he most likely performed the first planned removal of carcinomatous prostatic tissue as partial perineal excision of the prostate in 1867 while still working in Zurich.
George Goodfellow (1855-1910), from Tombstone and Tucson performed the first perineal enucleation of the enlarged prostate in 1891. In 1904 (July and November issue of JAMA) he first reported on 72 cases which he had operated with only 2 fatalities. Many surgeons followed him and contributed various technical aspects to perineal prostatectomy. His definition of a good surgeon was: “A surgeon should have the eye of an eagle, the heart of a lion, and the touch of a woman.”

Eugene Fuller (1858-1930) from New York published suprapubic transvesical enucleation of the prostate in 1895 as performed by him the previous year. He accomplished for the first time not only removal of the intravesical but also of the intraurethral enlargement of the prostate by digital enucleation.

Peter Freyer (1852-1921) from St. Peter’s Hospital in London must have learned about Fuller’s technique of transvesical prostatectomy through a visit of Fuller’s assistant Ramon Guitéras in 1900. One year later Freyer then claimed priority for the technique and by this gave ground to some dispute. Freyer however became the major prostatectomist of the time and deserves credit for popularizing the operation and making it a standard procedure.
During the 1890s men with severe symptoms of prostatic hyper trophy were occasionally castrated. Mansell Moullin from Lon- don described the effect of castration in 1894: “Removal of the testes is followed in a large pro- portion of cases by complete and rapid absorption of the enlarged prostate. The gland entirely dis- appears; nothing is left but a little fibrous mass.” The symptomatic improvement in over a half of patients with an enlarged prostate treated with castration was repor- ted by William White from Phila- delphia in 1895 and 1904.

Searching for alternatives to cas- tration for the treatment of enlar- ged prostate, vasectomy was first- ly suggested by James Ewing Mears in 1890, although Felix Guyon of Paris was also cited as the first to achieve this doubtful distinction. This treatment was en- vogue for a short period of time as it was claimed to be a method with minimal morbidity and great effectiveness. Further applications of this technique soon resulted in less enthusiastic reports (e.g. by Harrison and Wood both in 1900), showing an only 15% improve- ment in micturition. Shortly later the method fell into disrepute.

Hugh H. Young (1870-1945) from Baltimore performed the first radical perineal prostatectomy for prostate cancer on the 7th April 1904. The respective illustrations are taken from a later publication of Young from 1919. In the early 1940’s he reported on 184 patients he had operated with this technique of whom 34 had lived cancer-free and died from unrela- ted disease 5 to 27 years later.
Robert Proust (1873-1935), brother of the famous French author Marcel Proust, was the most important early promoter of perineal prostatectomy in France or even Europe at the beginning of the 20th century. At that time the operation was called “Proustatectomie” in France. The starting point was his doctoral thesis in 1900, which was written under the guidance of Felix Guyon and Joaquin Albarran at the Hôpital Necker in Paris. Later Proust designed a special operating table to put the patient in perfect position for perineal surgery.

As in the US by Young perineal prostatectomy was not only performed in benign disease but even for localized prostatic cancer in France by Joaquin Albarran (1860-1912). Notice wide excision at the bladder neck and anastomosis. These illustrations are taken from the textbook “Médecine opératoire des voies urinaires” published by Albarran in 1909.

Edmond Papin, like Proust working at the Hôpital Necker in Paris, wrote an extensive book of over 200 pages on “Sexual Function after Prostatectomy” in 1908. On the basis of anatomical examinations he analyzed sexual dysfunction after prostatectomy, including 55 documented case reports.
“Prostatectomia suprapubica extravescalis” had already been performed by W. J. van Stockum (1860-1913) from Rotterdam, The Netherlands, in 1908 and published one year later in the German journal “Zentralblatt der Chirurgie”. However, the wide clinical establishment of retropubic approach to the prostate after 1945 must be credited to the Irish surgeon Terence J. Millin (1903-1980), who was working in London.

In 1909 Hugh H. Young (1870-1945) performed the first “cold punch” resection of the median bar of the prostate under direct vision control. In 1913 he already reported on 100 patients treated with this new technique.

James Buchanan „Diamond Jim“ Brady (1856-1917) made money with selling railroad equipment and loved diamonds. Besides from being obese, hypertensive and diabetic he suffered from prostatic obstruction. Hugh H. Young (1870-1945) performed the cold punch on him in April 1912 and his patient later donated the Brady Urological Institute at The Johns Hopkins Hospital.
In 1914 Georges Luys from Paris – depicted here as the great explorer in a sketch of the magazine Chanteclair - reported endoscopic electrocoagulation of the prostate, which he called “forage de la prostate (drilling of the prostate)“.

In January 1926 Maximillian Stern (1873-1946) from New York presented his “resectoscope” before the Genito-Urinary Section of the New York Academy of Medicine on the basis of 46 treated patients. The instrument had two lens systems, one indirect vision for examination and a direct vision lens for bipolar resection.

Joseph McCarthy (1874-1965) from New York incorporated a bakelite non-conducting sheath and his foroblique lens system to improve the Stern resectoscope in 1931. It was the first instrument to move the loop from the bladder towards the instrument as in today’s instruments.
Some alternatives were looked for during that era, e.g. in 1928 the endothermal prostatic excisor of Frederic Foley (1891-1966) from Minneapolis. A conical section of the prostate was burned out with a thin steel music wire under electric current by rotating the instrument.

Finally, the improvements of Stern and McCarthy were united in the classical Stern-McCarthy resectoscope which was then in use for many decades.

Other countries had different and individual developments of TURP. Maximillian Stern came to Berlin in 1927 to present his new resectoscope before the Berlin Urological Society and operated on two patients. As both of them died after surgery the new technique of TUR was not well adopted in Germany initially. Alexander von Lichtenberg (1880-1949, Berlin) realized the importance of TURP and developed his own resectoscope, the “Prostata-Cutor” in 1932, which was later improved as the “Lichtenberg-Heywalt-Elektrotom“.
After World War II several European urologists were trained in the US and transferred the technique of TURP to Europe. One of them was Wolfgang Mauermayer (1919-1994) from Munich, Germany, who designed a famous resectoscope with two light sources and for one-handed use in 1952.

Edward L. Keyes and Russell S. Ferguson from New York City had performed radioorchietomy in several patients since 1932. In the 6th edition of their textbook “Urology” from 1936 they pronounced the “Extension of the life of the patient in comfort, even in the face of widespread metastatic disease”. In some of their patients roentgen castration combined with local irradiation was successful in arresting the primary tumor and the metastatic lesions.

The experimental studies which finally established the knowledge about androgen control of malignant prostatic growth were initiated in 1939 by Charles Brenton Huggins (1901-1997) at that time working in Chicago. He demonstrated that castration in man decreases the height of prostatic epithelial cells in normal prostatic tissue, that testosterone stimulates secretory activity of dogs’ prostatic cells and diethylstilbestrol inhibits this activity. He further proved that acid phosphatase was elevated in metastatic prostate cancer and that castration produced a relief of pain and a stabilizion or regression of local and metastatic osseous lesions.
In the beginning Huggins won a gold medal of the American Medical Association for his work in benign prostatic hyperplasia in 1940 and only a merit for his study on prostate cancer the year after. Finally, these fundamental investigations on the influence of the endocrine system onto the development of a human malignancy were honored with the Noble Prize for Medicine and Physiology in 1966.

R. Paschkis from Vienna devised the first cystoscopic radium applicator in 1911. The radium capsule was situated at the very tip of the instrument and no external fixation of the cystoscope holding it in the correct position was used. In 1913 O. Pasteau and Degrais from Paris reported several cases of prostate cancer which had been successfully treated by the use of radium introduced through a simple coudé gum catheter.

Benjamin Barringer (1877-1953) Chief at Memorial Hospital New York was the first to perform transperineal implantation of radium into the prostate in hundreds of cases between 1915 and 1930; first published in JAMA in 1917. Initially, Barringer used radon-tipped needles introduced through the perineum and left for several hours. Later gold-encapsulated Radon seeds were applied by the same route as permanent implants.
In the 1930’s Barringer also experimented with the open approach for radon seed application already using a template for controlled placement of the seeds as in today’s technique. He even combined the perineal and suprabupic approach for brachytherapy of the prostate.

Immediately after Barringer’s reports Hugh H. Young adopted and investigated various techniques of prostate brachytherapy at his institute in Baltimore.

Young placed needles with Radium tips alternatively intraurethrally and transrectally for short periods of time over several weeks. For this he designed his own radium applicator.
Rubin Flocks (1906-1975) from Iowa State University treated more than 400 prostate carcinoma patients in the 1950’s by injection of a colloidal suspension of radioactive gold into the prostate. Injection was either performed by the closed perineal or the open transvesical route.

Since 1970 Willet F. Whitmore from the Memorial Sloan-Kettering Cancer Center in New York combined open retropubic implantation of permanent Iodine 125 seeds with bilateral pelvic lymph node dissection allowing a more refined treatment.

Hiroki Watanabe from Sendai, Japan, obtained the first clinically useful tomogram of intrapelvic organs via the rectum in 1967. This equipment was used in 400 patients with one examination being accomplished in 15 minutes.
Holm and Gammelgaard from the University of Copenhagen performed the first ultrasound-guided perineal prostatic biopsies in 1982 and first Iodine 125 seed implantation was reported from the same institution in 1983.

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The Assessment and Management of Male Pelvic Pain Syndrome, Including Prostatitis

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The Assessment and Management of Male Pelvic Pain Syndrome, Including Prostatitis

A. J. Schaeffer,


A. INTRODUCTION

The male pelvic pain syndrome, including prostatitis, affects approximately 10% of men and causes significant morbidity and cost. Less than 10% of the patients suffer from acute or chronic bacterial prostatitis, conditions which are well defined by clinical and microbiologic parameters and usually amenable to antimicrobial therapy. Acute prostatitis is characterized by a severe systemic infection and irritative voiding symptoms, responds promptly to antimicrobial therapy, and is usually self-limiting. Chronic bacterial prostatitis may or may not be associated with mild pelvic pain symptoms and intermittent episodes of acute cystitis. Long-term antimicrobial therapy cures approximately 80% of the patients.

The majority of men with “chronic prostatitis” have chronic pelvic pain syndrome (CPPS), which is characterized by pelvic pain, urinary symptoms and sexual dysfunction. The National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) is a reliable means of capturing the symptoms and impact of CPPS. Because the etiology of this syndrome is not known, the evaluation and treatment is varied and, unfortunately, frequently unsuccessful. Because of the substantial emotional and economic impact of this condition, significant research is being conducted which hopefully will lead to a better understanding and management of this condition.

I. DEFINITIONS

Male pelvic pain syndromes describe a combination of infectious diseases (acute and chronic bacterial prostatitis); chronic pelvic pain syndrome; or asymptomatic prostatitis. The National Institutes of Health classification of prostatitis syndromes [1] includes:

1. Category I: Acute Bacterial Prostatitis (ABP) which is associated with severe prostatitis symptoms, systemic infection and acute bacterial urinary tract infection (UTI).

2. Category II: Chronic Bacterial Prostatitis (CBP) which is caused by chronic bacterial infection of the prostate with or without prostatitis symptoms and usually with recurrent UTIs caused by the same bacterial strain.

3. Category III: Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS), characterized by chronic pelvic pain symptoms and possibly voiding symptoms in the absence of UTI. Category III is subdivided into category IIIA (inflammatory) and IIIB (noninflammatory) prostatitis. Pain is the primary symptom distinguishing CP/CPPS from OAB and other LUTS.

Category IV: Asymptomatic Inflammatory Prostatitis, in which evidence of prostate inflammation exists in the absence of genitourinary tract symptoms. It is an incidental finding during evaluation for other conditions such as infertility or elevated PSA.

B. EPIDEMIOLOGY AND PATHOGENESIS

I. EPIDEMIOLOGY

1. METHODS

The International Consultation on Urological Diseases (ICUD) recommendations were designed primarily to evaluate treatment studies, but do not work well for epidemiological studies. To stay true to concepts underlying evidence-based medicine, we began by reviewing the literature following the ICUD rec-
ommendations, using defined criteria for epidemiological studies. Suitable studies were then synthesized to determine the current level of available data and to identify opportunities for further research.

**a) Identification of Studies for Systemic Analysis**

Following the ICUD recommendations, papers published or accepted for publication in the peer reviewed issues of journals were included in this systemic review. Papers published in non-peer reviewed supplements were not included. An exhaustive list was obtained through the major databases covering the last 10 years (e.g. Medline, Embase, Cochrane Library, Biosis, Science Citation Index). Search terms employed included: prostatitis, pelvic pain, epidemiology and survey. We also reviewed the tables of contents of the major journals of urology and other relevant journals for the previous 3 months to take into account possible delay in indexing of papers in the databases. These approaches identified 3,908 references. After reviewing the titles and abstracts, 73 articles were identified for detailed review.

**b) Criteria for Including Epidemiological Studies (Table 1)**

Included studies possessed at least four of the five criteria that have been outlined for epidemiological studies of prostatitis [2].

1. Studies should be population-based. Therefore, case series of referral patients from tertiary care institutions were excluded.

2. A clear case and standardized definition was required. The optimal case definition should bear a reasonable relationship to patients seen in routine clinical practice. In practice, this is often accomplished by choosing a restrictive case definition, such that most experienced clinicians would agree that cases included in the study truly suffer from the condition.

3. It is desirable to incorporate a recognized and validated survey instrument such as the NIH-CPSI [3]. To facilitate evaluation of varied populations the NIH-CPSI has been translated and validated for use in English [3], Spanish [4], Japanese [5], Chinese [6], Malay [6], German [7], Finnish [8] and Korean [9]. However, a recent population-based study found low agreement between physician diagnosed prostatitis and the NIH-CPSI pain measures, suggesting that the index, by itself, may have limited ability to determine the presence or absence of prostatitis [10]. Therefore, use of the NIH-CPSI was considered desirable, but was not required for inclusion in this systematic review.

4. A standard strategy for surveying the population should be used to assure that the participants are likely to represent the overall population. The ideal survey strategy should incorporate a mechanism to verify that cases identified in the survey actually met the case definition.

5. The population studied should be large enough to provide reasonable statistical power for the desired comparisons. It is also important to limit confounding issues such as treatment bias, selection bias and referral bias that pose special problems for studies of tertiary care patients from referral centers.

**2. Result**

**a) Acute and Chronic Bacterial Prostatitis (NIH Categories I and II)**

**1. Prevalence**

We identified no studies on the prevalence of either acute or chronic bacterial prostatitis that met the

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<td>2. Case-definition</td>
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<td>3. Survey instrument</td>
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<tr>
<td>4. Survey-strategy</td>
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<tr>
<td></td>
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<tr>
<td>5. Population size</td>
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* Use of the NIH-CPSI was considered a desirable study characteristic, but this was not required for inclusion in this systematic review.
inclusion criteria. Traditionally, the prevalence of these conditions has been believed to be low based on clinical experience from tertiary care urology practices [11-13]. Recent, population-based studies suggest that the prevalence of bacterial prostatitis might be higher than previously appreciated [14].

2. INCIDENCE

The incidence of bacterial prostatitis may also be higher than previously reported [15]. A recent study evaluated new physician-diagnosed prostatitis cases in a managed care population over a 2-year interval [15]. The incidence of acute or chronic bacterial prostatitis was 1.26 cases per 1,000 men per year, representing an incidence of 102,000 cases per year if these data could be extrapolated to the entire US population.

b) Chronic Prostatitis/Chronic Pelvic Pain Syndrome (NIH Category III)

1. PREVALENCE

We identified 11 studies that met the criteria for inclusion (Table 2). Of these studies seven were from North America [14; 16-21], three were from Asia [6; 22-23], and one was from Europe [24]. The prevalence of prostatitis symptoms (e.g. pelvic pain, urinary symptoms and/or sexual dysfunction) could be compared in eight studies that surveyed varied ambulatory populations including a total of 12,369 men [6; 14; 16; 18; 20-22; 24]. Overall, 816 participants met criteria for symptoms of prostatitis, representing an overall rate of 6.6%. In these studies the prevalence of prostatitis symptoms ranged from 2.2% [20] to 9.7% [18], with a median rate of 6.3%. Three additional studies met the inclusion criteria but were not directly comparable to those summarized above because these studies employed different denominators or different outcome measures [17; 19; 24].

2. INCIDENCE

One study evaluated the incidence of CP/CPPS in a managed care population [15]. The incidence was 3.30 cases per 1,000 men per year, representing an incidence of 267,000 cases per year if these data could be extrapolated to the overall US population.

c) Asymptomatic Inflammatory Prostatitis (NIH Category III)

### Table 2. Epidemiological Studies of Prostatitis

<table>
<thead>
<tr>
<th>Author, Year, Country [Reference]</th>
<th>Population</th>
<th>Number, Age-Range (Years)</th>
<th>Prevalence of Prostatitis-Like Symptoms</th>
</tr>
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<tr>
<td>Collins, 1998, USA [17]</td>
<td>National Ambulatory Medical Care Survey</td>
<td>58,955 visits &gt;18</td>
<td>5% overall Urology: 8% Primary care: 1%</td>
</tr>
<tr>
<td>Mehik, 2000, Finland [24]</td>
<td>Randomly selected</td>
<td>1,832 men 20-59</td>
<td>Lifetime prevalence (incidence) 14.2%</td>
</tr>
<tr>
<td>Nickel, 2001, Canada [18]</td>
<td>Patients of family practitioners</td>
<td>868 men 20-74</td>
<td>9.7%</td>
</tr>
<tr>
<td>Tan, 2002, Singapore [22]</td>
<td>Cross-sectional study</td>
<td>1,087 men 21-70</td>
<td>2.7%</td>
</tr>
<tr>
<td>Kunishima, 2002, Japan [23]</td>
<td>Random sample</td>
<td>502 men 20-79</td>
<td>5%</td>
</tr>
<tr>
<td>Roberts, 2002, USA [20]</td>
<td>Random community-dwelling men, Minnesota</td>
<td>1,541 men 40-79</td>
<td>16% GU pain 2.2% prostatitis</td>
</tr>
<tr>
<td>Calhoun, 2005, USA [14]</td>
<td>Managed care population, Oregon</td>
<td>1,550 men</td>
<td>6.0% or 7.6%, depending on definition</td>
</tr>
<tr>
<td>Daniels, 2005, USA [21]</td>
<td>Community health survey, Massachusetts</td>
<td>1,559 men 30-79</td>
<td>3.9%</td>
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</table>
Asymptomatic inflammation is commonly diagnosed during evaluation of prostate secretions and tissue removed for diagnosis and treatment of prostate disorders and also in patients undergoing evaluation for infertility [25-27]. In one recent report from a managed care population, the incidence of physician-diagnosed asymptomatic inflammatory prostatitis was 0.33 cases per 1,000 men per year [15].

3. COMMENTARY AND CONCLUSIONS ON EPIDEMIOLOGY

Although only a limited number of studies met the evidence-based criteria, these studies support the conclusion that prostatitis is an important worldwide problem that merits additional investigation. The prevalence of prostatitis-like symptoms (defined variously) ranged from 2% to 16%, with a median prevalence rate approximating 7% for chronic prostatitis/chronic pelvic pain syndrome, the most common category.

Prostatitis results in a substantial number of physician visits. Among participants with prostatitis-like symptoms, 60% sought medical help [18]. The odds of a prostatitis diagnosis were thirteen-fold greater at visits to urologists compared with visits to primary care physicians. Patients with prostatitis received antimicrobials 45% of the time compared to 27% of the time for those without genitourinary symptoms [17]. Prostatitis was a diagnosis in 2,000,000 visits annually in the US, including 8% of all visits to urologists and 1% of all primary care physician visits [17]. Patients with symptoms of prostatitis appear to be at increased risk for persistent symptoms and for recurrent episodes. Participants with a previous diagnosis of prostatitis had a much higher cumulative probability of subsequent episodes of prostatitis [16; 28]. Symptom surveys alone may have limited ability to distinguish patients with prostatitis [10]. Clinical evaluation appears necessary to verify that prostatitis is indeed responsible for patients’ symptoms [6].

These studies provide an important foundation for a research agenda. Future studies should be population-based. The case definition should be clear and should have some relationship to clinical practice. Clinical evaluation is necessary to verify that chronic prostatitis is responsible for subjects’ symptoms. It is also important to limit confounding issues, including treatment bias, selection bias and referral bias, that can pose special problems for studies limited to tertiary care patients from referral centers. We need to define the natural history and consequences of prostatitis.

II. PATHOGENESIS

1. METHODS

The ICUD evidenced-based recommendations proved unsuitable for evaluating the pathogenesis of prostatitis. Therefore, we considered prominent studies supporting the major etiologic theories.

2. RESULTS

There is little debate that infection is responsible for acute and chronic bacterial prostatitis. However, there is no consensus on the cause(s) of the other prostatitis syndromes.

a) Risk Factors

Although there are limited epidemiological data, clinical experience suggests that prostatitis may be related to genitourinary tract procedures and manipulation, such as catheterization. An increased rate of ABP related to increased use of TRUS-guided prostate biopsy for evaluation of possible prostate cancer has been found.

A history of UTI appears to be associated with chronic prostatitis (unspecified as to type). For example, the Boston Area Community Health Survey found that 79 (3.9%) of 1559 men aged 30-79 years experienced symptoms of prostatitis [21]. The prevalence of symptoms of prostatitis did not differ significantly by race/ethnicity. However, symptoms of prostatitis increased significantly with age (p=0.0091). The rate was 1.2% among 30-39 year old men, 2.2% among 40-49 year old men, 8.1% among 50-59 year old men, and 7.7% among 60-79 year old men. A history of UTI increased the risk for prostatitis symptoms (p=0.0270). While 12.6% of participants with a history of UTI had prostatitis, only 3.0% of participants without a history of UTI had prostatitis. Multiple logistic regression analyses showed that men with a history of UTI had an odds ratio of 3.80 (95% confidence interval of 1.83, 7.86) of having symptoms of prostatitis compared to men without history of UTI.

b) Acute and Chronic Bacterial Prostatitis (NIH Categories I and II)

Although clinicians accept that bacterial UTI is the cause of category I and category II prostatitis, there
are limited data on the bacterial species associated with these syndromes. Cho and associates completed a retrospective review of 255 inpatients with ABP from 10 hospitals [29]. The most common bacterial species identified were *Escherichia coli* (67%), *Pseudomonas aeruginosa* (13%), *Klebsiella* sp. (6%), and various Gram-positive species (5%). In this respect, the species associated with ABP are very similar to the species associated with acute bacterial UTI in healthy men without urological abnormalities [30].

The bacteriology of CBP has been described in carefully investigated patients from tertiary care institutions [11-13]. Similar to the experience with acute prostatitis, these series report that facultative Gram-negative bacilli (especially *E. coli*) were responsible for the great majority of cases. Recently, reports from clinical series of patients used to support approval of antibiotics for treatment of chronic bacterial prostatitis have reported a preponderance of Gram-positive cocci [31-32]. In these latter series, the median duration of patients’ symptoms was 3.5 weeks [32]. One recent report suggests that cultures suggesting localization of Gram-positive bacteria are not consistent in >90% patients [33]. Thus, the distribution of bacteria causing chronic bacterial prostatitis is currently the subject of active debate.

c) Chronic Prostatitis/Chronic Pelvic Pain Syndrome (NIH Category III)

The major pathogenic theories may be considered in five general categories: infection, voiding or neuromuscular dysfunction, interstitial cystitis, neuropathic pain, and immune dysfunction. Prominent evidence supporting each major theory is summarized in Table 3.

d) Asymptomatic Inflammatory Prostatitis (NIH Category IV)

The causes of asymptomatic inflammation in the prostate and/or seminal fluid are unknown. The mechanisms outlined in Table 3 represent the major theories.

| Table 3. Proposed Pathogenetic Mechanisms in Prostatitis |
|---|---|---|
| Mechanism | Prostatitis Categories | Author, Year, Country [Reference] | Evidence |
| Infection | I, II | Meares (1987), USA [34] | Culture of bacteria in VB3, EPS or semen from patients with category I and II prostatitis |
| | | Weidner et al (1991), Germany [12] | |
| | | Bundrick et al (2003), USA [31] | |
| | | Cho et al (2005), Korea [29] | |
| | | Nickel et al (1994), Canada [38] | |
| | | Hochreiter et al (2000), USA [39] | |
| Voiding or neuromuscular dysfunction | III | Hruz et al (2003), Switzerland [40] | Bladder outlet obstruction (BOO) associated with abnormal urodynamic findings |
| | | Kaplan et al (1996), USA [41-42] | |
| Neuropathic pain | III | Miller et al (2002), USA [43] | Nerve growth factor correlates with pain severity |
| Interstitial cystitis | III | Peeker et al (2002), Sweden [44] | Proposed hypotheses include mast cell activation, defects in the urothelium, autoimmunity, toxic agents, and neuroendocrine-autoimmune interactions |
| Immune dysfunction | III, IV | Alexander et al (1997), USA [48] | Proposed hypotheses include autoimmune reaction, increased levels of pro-inflammatory cytokines, decreased levels of anti-inflammatory cytokines, and T cell proliferation in response to seminal antigens |
| | | Orhan et al (2001), Turkey [49] | |
| | | Ruggieri et al (2000), USA [50] | |
| | | Hochreiter et al (2000), USA [51] | |

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3. COMMENTARY AND CONCLUSIONS ON PATHOGENESIS

In contrast to ABP and CBP, CP/CPPS is defined based on clinical symptoms in the absence of obvious urological causes. Asymptomatic inflammatory prostatitis is diagnosed during evaluation of other conditions. There is no consensus on the cause of either CP/CPPS or asymptomatic inflammatory prostatitis. Proposed pathogenetic mechanisms include: infection, voiding or neuromuscular dysfunction, neuropathic pain, interstitial cystitis, and immune dysfunction. Better understanding of the causes and pathophysiology would facilitate development of better diagnostic strategies and development of specific markers that might facilitate prevention, better diagnosis and management strategies.

C. EVALUATION

I. ACUTE BACTERIAL PROSTATITIS (NIH CATEGORY I)

1. URINE ANALYSIS AND CULTURE

What is the role of urine analysis and culture in the diagnosis/evaluation of ABP?

- In patients presenting with ABP, urine culture is considered the only laboratory evaluation of the lower urinary tract that is required. A midstream urine specimen will show significant leukocytosis and bacteriuria microscopically, and culturing usually shows typical uropathogens.

- A comparative, controlled study evaluated the utility of urinary alpha 1-microglobulin, alpha 2-macroglobulin and albumin in the diagnosis of acute prostatitis in 133 men, and a reference population of 36 without urinary tract infection [52]. The combination of hematuria and absence of urinary alpha 2-macroglobulin is diagnostic for acute prostatitis.

Evidence summary: urinalysis and culture are essential for the diagnosis of ABP. There is evidence that urinary alpha 2-macroglobulin is diagnostic for acute prostatitis. Other urine markers may be of benefit but this is currently unknown.

2. IMAGING

What is the role of radiolabel scintigraphy in the diagnosis/evaluation of ABP?

- In a small prospective study, 10 male patients with prostatitis were compared with 6 males with UTI but without prostatitis to determine whether 111indium labelled leukocytes (ILLs) accumulated in the infected tissue and if uptake responded to treatment [53]. Urinary and blood cultures were also carried out. Scintigraphs prior to antibiotic treatment showed uptake in prostates of all patients with ABP; after treatment, no uptake was noted in 9 out of 10 and 1 out of 10 had markedly decreased uptake. No uptake occurred in prostates of patients with UTI. ILLs could be useful in detecting ABP, especially in clinically ambiguous patients with urological infections.

What is the role of transrectal ultrasound (TRUS) in the diagnosis/evaluation of ABP?

- In a prospective study of 45 patients with a clinical diagnosis of ABP, TRUS was performed upon admission and one month after antibiotic therapy and findings correlated with clinical presentation and evolution of disease [54]. The authors conclude that TRUS does not need to be performed on every patient with suspected ABP (as only 47% had sonographically demonstrable lesions on admission and 61% had lesions improved or disappeared post treatment) but TRUS would be indicated in ABP to exclude the presence of prostatic abscess.

3. SERUM PSA

What is the role serum PSA in the differential diagnosis/evaluation of ABP?

- In a prospective study of 39 men with pyrexia (>38.3 degrees C), serum PSA levels were used to categorize patients according to an initial diagnosis of ABP, pyelonephritis, urogenital infection or fever of unknown origin [55]. All of the 20 cases with pyrexia and elevated PSA were diagnosed and treated as ABP; treatment with antibiotics resulted in significantly reduced serum PSA, fever and normalization of C-reactive protein. The authors recommend PSA as a concise, accurate, rapid and cost-effective tool for identifying ABP.

Evidence summary: no RCTs or systematic reviews found. Application of methods such as scintigraphy, TRUS and serum PSA may further assist in the diagnosis of ABP in addition to the
physical examination and urine culture for patients with ambiguous pyrexia. Based on the small numbers of subjects in the abovementioned studies there is insufficient evidence to recommend their use as a single method for final diagnosis.

II. CHRONIC BACTERIAL PROSTATITIS (NIH CATEGORY II)

1. 4-GLASS TEST AND 2-GLASS PRE- AND POST-MASSAGE TEST (PPMT)

What is the role of the 4-glass and 2-glass test and cultures in the diagnosis/evaluation of CBP?

- In an analysis using the 4-glass test in 50 men with symptomatic prostatitis, anaerobic bacteria were cultivated in high numbers in 18 patients [56]. The authors postulate an association between symptoms and the evidence of these bacteria after antiaerobic therapy.

- In a prospective evaluation of 164 patients with prostatic symptoms, men were categorized by the NIH classification system using segmented urine analysis and culture. The evaluation revealed 38% (64 patients) with category II prostatitis, 7% (12) with category IIIA and 55% (92) with category IIIB [57]. Leukocytes in EPS were detected in only 36% (24) of patients with positive bacterial and chlamydial cultures. The authors conclude that differential diagnosis and therapy based on the results of the 4-glass test and cultures seems to be difficult.

- Using standard techniques including the 4-glass test, the Giessen cohort study demonstrated the evidence of proven CBP in 4.2% of 168 men [58]. This figure is lower than the 7% of 656 patients in the first study 10 years. *E. coli* was the predominant strain.

- Nickel et al conducted a study to evaluate a simpler screening test to assess inflammation, the 2-glass pre- and post-massage test (PPMT), and compare it with the 4-glass test for the initial evaluation of men with a clinical diagnosis of CP/CPPS [59]. A total of 353 men enrolled in the NIH Chronic Prostatitis Cohort (CPC) study with complete values for baseline leukocytes counts and two-day bacterial cultures on the 4-glass specimens were evaluated. A receiver operating characteristics (ROC) curve was constructed to determine the optimal cut point of WBCs in VB3 predicting WBCs in EPS. The PPMT has a strong concordance with the 4-glass test and is a reasonable alternative when EPS is not obtained.

Evidence summary: the 4-glass test is the criterion standard for the diagnosis of CBP. The PPMT is a simple and reasonably accurate screen for bacteria.

2. SEMEN CULTURES

What is the role of semen cultures in the diagnosis/evaluation of CBP?

- A comprehensive survey describes the study results in 40 men with CBP (NIH category II) due to *E. coli* infection and who were treated with a fluoroquinolone [13]. In these patients, semen cultures demonstrated significant bacteriospermia (>10^5/ml) in 21 of 40 men prior to treatment.

Evidence summary: no RCTs or systematic reviews were found. Based on limited evidence, semen cultures were shown to identify significant bacteriospermia in only about 50% of semen specimens from men with CBP.

3. TRANSRECTAL PROSTATIC ULTRASONOGRAPHY

What is the role of transrectal prostate ultrasonography (TRUS) in the diagnosis/evaluation of CBP?

- In a prospective study, 164 patients with prostatic symptoms were evaluated with a variety of diagnostic methods including TRUS, segmented urinalysis and urine cultures, EPS evaluation, and urodynamics [57]. Patients were classified as having category II (CBP) or category IIIA or IIIB prostatitis. TRUS and urodynamics findings were similar in the three groups indicating that differential diagnosis and therapy would be difficult relying on TRUS.

- Imaging may be beneficial in highly selected treatment refractory patients.

Evidence summary: no RCTs or systematic reviews were found. Based on limited evidence, TRUS and urodynamics cannot be relied upon for differential diagnosis of categories of prostatitis.
1. SYMPTOM SCORING, QUESTIONNAIRES AND PSYCHOLOGICAL FACTORS

a) Symptom Scoring and Questionnaires

What is the role of the NIH-CPSI in the diagnosis/characterization of CP/CPPS or evaluation after treatment?

- One systematic review discusses prostate-related pain in patients with CP/CPPS; it includes a discussion of psychological and psychosomatic factors [60]. The consensus is that for evaluation of pain, the validated versions of the NIH-CPSI are recommended for clinical use worldwide.

- A large series of studies were reviewed including double-blind RCTs [61-64], RCTs without verification of double-blind [65-69], and an open-label study [70] using a variety of therapeutic agents to treat CP/CPPS. The NIH-CPSI was the evaluation measure to indicate or negate clinical efficacy. With the exception of two studies, most were small trials involving a total of 30 to 100 patients/controls. Studies are representative of the use of the index for drug trials; only studies reported in English were reviewed.

- A group of studies involved validation of the NIH-CPSI including validation of psychometric properties and translation and linguistic validation [3-4; 7-9; 71-72].

- Three studies focused on a questionable symptomatic difference between type IIIA and IIIB prostatitis patients. Krieger et al [73] demonstrated an increased severity and frequency of symptoms in men with inflammatory CP/CPPS and in two studies Schneider et al [71; 7] demonstrated that NIH category IIIB patients are significantly more symptomatic than category IIIA patients.

- The interaction between CP/CPPS symptoms and urgency/frequency questionnaires (PUF) has been investigated prospectively in 50 patients and correlated with potassium-sensitivity testing [74]. A high rate of PUF scores indicates a questionable overlap of CP/CPPS and interstitial cystitis (aka painful bladder syndrome) symptoms in men.

- A study evaluating the agreement between self-reported physician-diagnosed prostatitis and pain questions from the NIH-CPSI using a randomly selected cohort of men and review of medical records [10] concludes that “while the CPSI is an important evaluative tool for chronic prostatitis, it may not perform well as a diagnostic tool for chronic prostatitis/CPPS. As an evaluative tool, the CPSI provides insight into the severity of symptoms relevant to chronic prostatitis. However, its role as a diagnostic tool is debatable because not all of the questions/scores in the CPSI adequately distinguish between chronic prostatitis and other urological conditions.”

- One study involving 174 patients assessed the responsiveness of the NIH-CPSI to changes over time and attempted to define thresholds for changes perceptible to patients [75]. A six-point decline in NIH-CPSI total score identified an optimal threshold to predict response. Index total and subscale scores were shown to be responsive over time and should be used as a primary endpoint in clinical trials for CP/CPPS.

- A prospective study of symptom follow-up for two years in men with CP/CPPS enrolled in the CPC [76] was completed. The NIH-CPSI total scores of 293 men with complete data showed substantial variations in symptoms. The study provides useful clinical information on the longitudinal course of disease, but also incidentally indicates the merits of the NIH-CPSI in the evaluation process.

1. SEXUAL AND EJACULATORY DISORDERS: SYMPTOM SCORING WITH THE NIH-CPSI OR OTHER INDEX

- Recent data demonstrate a strong association between LUTS and pain/discomfort on ejaculation [77]. The symptom seems to be related to LUTS severity and age.

- Evaluations were conducted in 486 men from the NIH CPC Study to assess the impact of post-ejaculatory pain in men with CP/CPPS [78]. There was some evidence that patients with CP/CPPS who have persistent ejaculatory pain have more severe symptoms.

Evidence summary1: the NIH-CPSI has become the established international standard for symptom evaluation (not for diagnosis) of prostatitis. The index has been shown to be reliable with validated versions in English [3], Spanish [4], Korean [9], German [7], Finnish [8], Japanese [5], Chinese [6].

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1 Other symptom scoring questionnaires (i.e., University of Washington Symptom Score, GPPS, IPPS, ICPPS, PSSI, Stanford Pelvic Pain Symptom Score, and AUA Symptom Scale) that have preceded the NIH-CPSI have not been included in this evaluation.
b) Psychological Assessments

What is the role of psychological factors/psychosomatic aspects in the evaluation of CP/CPPS?

- Two reviews of the psychological/psychosomatic factors associated with CPPS have been published.

- The first review (published in German) [79] states that psychosomatic factors are often neglected in evaluation of CP/CPPS in urologic practice. Diagnostic and therapeutic strategies should address the involvement of somatic and psychogenic factors in the pathogenesis of the syndrome. Personality variables such as somatization, depression, anxiety, hypochondriasis and weak masculine identity play an important role in questionnaire-based studies.

- The second article [60] reviews the hypotheses and data on the psychosomatic causes of pelvic pain in patients with CP/CPPS. The authors underline the current opinion that intraprostatic reflux is the major trigger mechanism for pelvic pain. Psychosomatic factors, psychological stress, hysterical neuroses, hypochondriac reactions and depressive reactions were also judged to be significant causes. In the experience of the authors, the data must be evaluated predominantly by semi-structured interviews, questionnaires and scales, which while considered to be helpful are not indicative and useful in this field. Concerning sexual dysfunction, premature ejaculation, decrease of libido and erectile dysfunction (ED) are considered to be relevant in CP/CPPS patients. The Giessen data provide some evidence that in CP/CPPS patients 42% complain of ED and 26% of premature ejaculation. Furthermore, such conditions lead to reduced frequency of sexual contact. For evaluation, the International Index of Erectile Function (IIEF) is accepted to be the gold standard. Unfortunately, standardized questionnaires for libido disturbances and also for premature ejaculation are not available. For evaluation of pain, consensus is that the validated versions of the NIH-CPSI are recommended for clinical use worldwide.

- The association of impaired quality of life (QOL) with CP/CPPS was evaluated in two separate uncontrolled studies using men from the NIH-CPC study. In 278 men with CP/CPPS, the health-related QOL (HRQOL) instruments revealed lower Mental Component Summary scores than among patients with severe congestive heart failure and diabetes and lower Physical Component Summary scores than the general US male population [80].

In the second report of 463 men with CP/CPPS, depressive symptoms and pain intensity significantly predicted poor QOL [81]. Therefore the authors concluded that CP/CPPS is associated with negative psychological factors and reduced QOL; administration of HRQOL instruments may assist in understanding the impact of disease on patients’ lives. Pain intensity was the most robust predictor of poorer QOL.

- The finding of psychological stress being common in men with prostatitis and symptoms increasing the likelihood of impaired QOL is supported by a Korean study on 1,057 men [82] and in a population-based cross-sectional survey of Finnish men [83].

- In a controlled study, 51 men with CP and a control group of 34 men without any chronic pain condition were evaluated for psychological factors [84]. The scores of CP patients were consistently more elevated than those of controls on hypochondria, depression and hysteria (MMPI) and on somatization and depression (BSI) scales.

Evidence summary: two systematic reviews were found. Evidence from a series of studies in CP patients, some with control comparisons, indicate that depression and psychosocial distress are common among CP patients, calling for careful evaluation and attention to psychological symptoms in fully understanding and caring for these patients.

2. Physical Examinations (DRE, Myofascial Trigger Points, Abdominal Exam)

a) Myofascial Trigger Points and Musculoskeletal Dysfunction

What is the role/value of evaluating myofascial trigger points or possible musculoskeletal dysfunction in patients with CP/CPPS?
• A retrospective uncontrolled study of at least 12 months’ duration of 103 men with pelvic pain involved urodynamics [85]. Pathological tenderness of the striated pelvic muscle was observed in 91 men (88.3%). This myofascial tenderness was virtually always associated with the inability to relax the pelvic floor efficiently with a single or repetitive effort. In 84 men (81.6%), urodynamic evaluation revealed principal findings of hypersensitivity during the attempted voiding period. DRE revealed tenderness in the external urethral sphincter region, a hypertonic sphincter and detrusor-sphincter dyssynergia.

• A controlled study of 62 men with CPPS IIIA and IIIB and 89 healthy controls showed that patients with CPPS had significantly greater pain and tension with palpation by DRE of the psoas muscle and groin [86]. The abnormal pelvic musculature in men with CPPS may contribute to the pain syndrome.

• In an uncontrolled study, 19 men with CPPS who were refractory to other treatments were enrolled in a 12-week biofeedback pelvic floor re-education and bladder training program [87]. A significant improvement was found in all outcome measures.

• In an uncontrolled study 138 men with refractory CPPS were treated with myofascial trigger point release in conjunction with cognitive behavior therapy [88]. More than half of the patients had improvements in pain and urinary scores.

Evidence summary: no systematic reviews or RCTs were found. Primarily, the studies reviewed were uncontrolled, retrospective or treatment outcomes which may implicate a role for tension myalgia in pelvic pain. Currently the benefits of identifying or treating myofascial trigger points or musculoskeletal dysfunction are not known.

b) Digital Rectal Examination and Abdominal Examination

Evidence summary: no systematic reviews, RCTs or clinical trials were found to contribute to the evaluation of these procedures.

3. Urine and Expressed Prostatic Secretion (EPS) for Evaluations

What is the role/value of urine and EPS in the evaluation of men with CP/CPPS?

• An uncontrolled, retrospective reevaluation of a case series of 53 patients and literature review of 59 patients with prostatitis sought to determine the value of the PPMT for diagnosis of prostatitis [89]. The calculated sensitivity and specificity for the PPMT were both 91.1% (102/112 patients); results were similar to those of the 4-glass test, indicating that the PPMT alone would have led to the same bacteriological diagnosis. This test was considered a simple diagnostic tool superior to doing no workup at all.

• A prospective study of 328 patients without urethritis involved microscopic analysis of urine after prostatic massage (VB3) with EPS to assess the significance of leukocyte analysis in VB3 and to give a first hint of the diagnosis of inflammatory CPPS when EPS cannot be obtained [90]. The presence of elevated leukocytes in VB3 predicted the presence of increased leukocytes in EPS with a high certainty: 91.9% sensitivity, 98.9% specificity.

• An uncontrolled, comparative study of 164 patients with chronic male pelvic pain syndrome (including 64 with CBP, 12 with inflammatory CPPS, and 92 with non-inflammatory CPPS) evaluated segmented urinalysis and culture, and TRUS uroflowmetry and residual urine [57]. Leukocytes in EPS were detected in 24 (36%) patients with positive bacterial cultures; TRUS and urodynamics and complaints were similar in all groups. Thus differential diagnosis based on the 4-glass test, cultures and TRUS remains difficult.

• One prospective study compared diagnostic outcomes based on fluid samples to evaluate inflammation in symptomatic patients (without urethritis, acute or chronic bacterial prostatitis) using EPS, VB3 and seminal fluid analysis (SFA) [91]. With EPS alone, 39 of 140 (28%) patients had inflammatory CP/CPPS; however, with NIH consensus criteria (EPS, VB3, SFA) almost twice as many, 52%, had inflammatory disease. In a later study [73] involving 130 men with CP/CPPS (perhaps the same cohort reported above), those with inflammatory diseases had significantly greater severity and frequency of symptoms when evaluated using the NIH consensus criteria.

• A prospective examination of leukocytes and bacteria in EPS, VB3 or semen and correlation with symptom severity in men with CP/CPPS participating in the NIH-CPCRN study [92] evaluated samples from 397 patients. Leukocytes and
bacterial counts as we define them do not correlate with severity of symptoms.

- A comparison of methods of evaluating WBCs in EPS involved 92 CPPS patient samples [93] and quantitatively determined WBC concentration by hemacytometer and staining. This proved superior to the standardized wet mount procedure or gram stain smear, an important consideration for research studies. This result is also supported by an earlier study [94].

Note: The traditional cover slip count of WBCs is easier and more accessible to clinicians in practice and has been used to set historical standards for the definition of traditional prostatitis. However, the counting chamber technique is more accurate but time-consuming.

- One review compared the traditional classification of prostatitis based on evaluation of EPS alone with the new NIH consensus classification that also considers VB3 and SFA findings [95]. For the NIH classification, inflammatory CP/CPPS was diagnosed for subjects with inflammation in their EPS, VB3, or SFA. Subjects without inflammation in any of these three samples were classified in the non-inflammatory group. Thus an optimal diagnostic strategy requires evaluation of VB3 and SFA in addition to the traditional EPS examination. Such precision is necessary for research studies, but whether such precision is important clinically remains unproved.

- A prospective evaluation of 143 patients with prostatitis was conducted to analyze whether the simple PPMT urine culture compares with the results of the 4-glass test [96]. Results were similar, confirming Nickel’s 1997 report [89], and the authors recommend replacing the 4-glass test with the PPMT.

- A case controlled study compared LUTS evaluation in 463 men enrolled in the NIH CPC study with that of 121 age-matched men without urinary symptoms. Leukocyte counts were performed and five-day bacterial cultures on specimens obtained from a standard 4-glass test (VB1, VB2, EPS, VB3) and semen [97]. Men with CP/CPPS had statistically higher leukocyte counts in all segmented urine samples and EPS, but not in semen compared to asymptomatic control men. However, the control population also had a high prevalence of leukocytes. The high prevalence of WBCs and positive bacterial cultures in the asymptomatic control population raises questions about the clinical usefulness of the standard 4-glass test as a diagnostic tool for CP/CPPS.

- One study evaluated a simple screening test to assess inflammation, the 2-glass PPMT, and compared it with the Meares-Stamey 4-glass for the initial evaluation of men with a clinical diagnosis of CP/CPPS [59]. A total of 353 men enrolled in the NIH CPC study had the 4-glass test for baseline leukocytes counts and two-day bacterial cultures. A ROC curve was constructed to determine the optimal cut point of WBCs in VB3 predicting WBCs in EPS. The PPMT has a strong concordance with the 4-glass test and is a reasonable alternative when EPS is not obtained.

- A controlled study evaluated the inflammatory marker prostaglandin E2 (PGE2) and beta-endorphin (natural opioid produced by immune cells at site of injury, which may modulate pain) in the EPS of 70 patients with CP and 8 asymptomatic controls [98]. In symptomatic patients the levels of both substances were similar in categories IIIA and IIIB, and higher than in controls. After treatment with antibiotics or antioxidant phytotherapy the levels of beta-endorphin increased while PGE2 decreased; thus pain in prostatitis may be due to increased prostaglandin production, which may then inhibit local beta-endorphin production.

- A prospective study evaluated peroxidase-positive leukocytes (PPL) and PMN-elastase in EPS and VB3 of 112 consecutive CP/CPPS symptomatic patients to contribute to differential diagnosis between inflammatory category IIIA and non-inflammatory category IIIB [99]. Leukocytes increased in 64 men and did not in 48. PPL and elastase were significantly elevated in the EPS of men with category IIIA CP and cut points were suggested to indicate diagnosis of inflammatory disease.

- A controlled, comparative study evaluated urine markers (antiproliferative factor APF, HB-EGF, EGF) in 41 symptomatic CP/CPPS men, 36 asymptomatic men without bladder disease, and 24 men with IC [100]. APF activity and decreased HB-EGF levels were found in the urine specimens of men with IC vs. CP or controls, but none of the three markers differed between controls and CP/CPPS. Perhaps these markers could be used to distinguish IC from CP/CPPS.
a) Role of C. trachomatis and ureaplasma

- There is one systematic review analyzing the role of C. trachomatis findings in EPS and VB3 in men with CP/CPPS [101]. The major problem, i.e. that diagnostic material passing through the urethra may reflect only urethral contamination, is not resolved.

- A total of 137 symptomatic men with CP/CPPS were evaluated by the 4-glass test, including EPS and VB3 analysis [58]. 31.5% of patients were categorized as having NIH category IIIA and 50% as having NIH category IIIB CP/CPPS. CBP (NIH category II) was excluded in all cases. Occurrence of bacteria in EPS/VB3 did not reflect the typical pattern of CBP. In 24 men U. urealyticum and in one man C. trachomatis was detected in different specimens of the 4-glass test using PCR techniques.

- In 165 symptomatic men with CP/CPPS the 4-glass test was extended for a search for C. trachomatis and U. urealyticum using PCR-testing of semen. Chlamydial infections were established in 12 cases and ureaplasmal infections in 13 cases. There was no correlation between these findings and the NIH prostatitis category of the patient [102].

Evidence summary: no RCTs were found.

- The case studies, including one age-matched controlled study, suggest that the 4-glass test, i.e. microscopic evaluation and culture of EPS and/or VB3 (post-massage urine specimen), can be accurate and an indirect indicator for diagnosis of prostate specific inflammation and infection. The PPMT (2-glass) test is a simple and reasonably accurate screen.

- The detection of U. urealyticum and/or C. trachomatis in 4-glass test specimens does not reflect the identification of causative microorganisms.

b) Autoimmune Markers in Genital Fluids

What is the role of autoimmune markers in evaluation of CP/CPPS?

- A small controlled study evaluated CD4 T-cell proliferative response to seminal plasma in 10 men with CPPS compared to 15 normal controls [48]. T-cell reactivity occurred in 3 out of the 10 CPPS patients but none of the controls, suggesting an autoimmune component to the disease.

- A controlled study of 14 patients with CPPS and 12 normal volunteers examined recall proliferative response of T-cells using purified seminal plasma antigens and autologous dendritic cells to determine if these secretory proteins could be candidate antigens for autoimmune prostatitis [103]. A proliferative response observed in 5 out of 14 patients with CPPS suggests that PSA is a candidate antigen.

- A study of 20 patients with CPPS and 20 age-matched controls evaluated T-cell proliferation response to autologous seminal plasma (SP) and seminal plasma from other individuals [104]. CPPS patients had a statistically greater response to autologous and allogenous SP, thus supporting an autoimmune hypothesis for the disease.

- A prospective controlled study examined immunophenotypic patterns in fractionated urine, EPS and ejaculate of 88 patients with category IIIB CPPS and 100 normal controls [105]. Interleukin, complement and immunoglobulin determinations in serum and ejaculate revealed an inflammatory process in the apparently non-inflammatory (category IIIB) CPPS. Findings of intra-acinar T-rich infiltrates and associated inflammatory reaction may be an advance in defining the disease as caused by an autoimmune component.

- A prospective controlled study of immunophenotypic patterns (IgG, IgA, IgM, IL-1-alpha, sIL02R, IL-6) in ejaculate of 35 patients with category IIIB CPPS and 96 normal controls, and of immunohistochemical detection of T and B lymphocytes in prostate biopsies of 71 patients and 25 controls [106], found intra-acinar T-rich infiltrates and associated inflammatory reaction which may indicate a possible autoimmune component to the disease.

- An uncontrolled, prospective study of 110 men with CP/CPPS category IIIA demonstrated an increase of macrophages (7.6-fold), T-lymphocytes (7.6-fold) and B-lymphocytes (four-fold) in VB3 after prostatic massage compared to VB2 [107].

Evidence summary: no systematic reviews or RCTs were found. Three small but controlled studies provide support for an autoimmune hypothesis of CP/CPPS but at present, the role of this type of characterization is unknown in the evaluation of the disease.
c) Cytokines as Biochemical Markers of Inflammation in CP/CPPS

What is the role of pro-inflammatory and anti-inflammatory cytokines in evaluation of CP/CPPS?

- A controlled study evaluated the levels of nerve growth factor (NGF) and IL-6 compared to IL-8, IFN-gamma, IL-2 and IL-10 in the seminal plasma, as well as correlating results with QOL, in 31 patients with CPPS and 14 controls [43]. NGF correlated directly with pain severity (p <0.01) and IL-10 levels (p <0.04), and IL-6 correlated inversely with pain severity (p <0.03). These results suggest that NGF and cytokines that regulate inflammation (IL-6 and IL-10) may play a role in the pain symptoms experienced by patients with CPPS.

- A controlled study evaluated the levels of IL-8, IFN-gamma, and IL-2 vs. IL-10 in the seminal plasma, as well as correlating results with QOL, in 31 patients with CPPS and 14 controls [108]. IFN-gamma, IL-2 and IL-10 levels were significantly greater in patients with CPPS; IL-10 levels correlated directly with measures of life interference and pain severity.

- A controlled study quantified IL-10 and IL-8 levels in VB3 in 29 randomly selected patients with different types of CP and 11 controls [109]. Levels of IL-10 were significantly higher in 8 patients with clinical symptoms than in the 11 controls or 21 patients with asymptomatic prostatitis; IL-8 was higher in 8 symptomatic and 13 asymptomatic patients than in 7 controls. IL-10 and IL-8 can be detected in VB3 and routine semen and EPS and are important in the etiology of CP.

- An early small controlled study from Japan detected significantly higher levels of TNF-alpha and IL-6 in 6 out of 10 cases of nonbacterial prostatitis (NBP) vs. 11 normal controls; IL-1 beta was detected in only 2 out of 10 cases [110]. The authors conclude that cytokines are useful indicators of NBP.

- In two controlled studies of CP/CPPS, levels of TNF-alpha and TNF-alpha in conjunction IL-1beta were elevated in seminal plasma (18 CPPS patients vs. 8 controls [111]; 20 CPPS patients vs. 10 controls [49]). Other pro-inflammatory cytokines, IL-6 and -8, were also significantly elevated vs. controls [49].

- A controlled study of a total 78 men including CPPS patients (category IIIA, IIIB, IV, and BPH vs. controls) evaluated proinflammatory cytokines TNF-alpha and IL-1 beta in EPS [112]. Increased concentrations of both cytokines were reported in category IIIA as opposed to category IIIB cases vs. controls. EPS of those with category IV, or asymptomatic inflammation, also had increased concentrations.

- In a controlled study from China, TNF-alpha and IL-1 beta levels in EPS were significantly higher in patients with CP with WBC ≥10/HPF and asymptomatic prostatitis (34 patients) vs. those with CP <WBC 10/HPF, 12 with BPH or 8 healthy controls [113]. Therefore, these markers could be used to identify men with CP with high WBC and asymptomatic inflammatory prostatitis.

- In a controlled study from China, TNF-alpha and IL-8 levels in EPS were higher in men with CBP or CPPS category IIIA but lower in CPPS category IIIB and controls [114]. The cut-points of cytokine levels to discriminate CBP or CPPS IIIA from IIIB or controls need further investigation.

In controlled studies the following were reported:

- IL-2 (secreted by T-lymphocytes stimulated by antigen activated antigen presenting cells, resulting in T-cell clonal proliferation) was not detectable in seminal plasma of patients with CP/CPPS [49], whereas

- IL-6 (involved in T-cell activation, growth and differentiation) is significantly increased in seminal plasma of category IIIA and IIIB cases compared to controls [49].

- According to some studies, IL-8 (recruits and activates lymphocytes) had significantly higher concentrations in seminal plasma [49] and EPS [51] of CP/CPPS patients compared to controls, whereas no differences were found in another study [108].

- A controlled clinical study of 207 men with CP vs. 62 controls reported significantly higher levels of IL-6 and IL-8 in seminal plasma of 177 out of 207 (85.5%) CP cases vs. controls [115]. Leukocyte counts had positive results in only 85 out of 177 (48%) of cases. Two cytokines may prove to be markers to identify CP.

Cytokine polymorphisms, differences in DNA sequences, are reported in the literature. However, this is an area of research and exploration that has unknown clinical utility.
d) Association of cytokine concentration with cp/cpps symptoms and/or changes with clinical response to treatment

- In a clinical trial of men with CPPS category IIIB, serum and ejaculate IL-6 levels significantly increased and then dropped again correlating with clinical symptoms [105]. IL-6 levels correlated inversely with pain severity [43] and IL-10 levels correlated directly with measures of life interference and pain severity [43].
- In a controlled comparable study IL-8 and ENA-78 were elevated in the EPS of men with bacterial prostatitis, CPPS category IIIB and category IV; however, there were no appreciable differences to differentiate the categories from one another [39].
- In an uncontrolled study from Russia, TNF-alpha and IL-1-beta levels were elevated in blood serum, urine, ejaculate and EPS of 30 patients with CP before and after 3 to 6 months of treatment with Prostamol-uno [116]. IPSS scores and QOL were assessed. The elevated cytokines returned to "normal value" at 6 months, and this was associated with a 36% decrease in IPSS score and 42% improved QOL.

Evidence summary: one systematic review [117] summarized the status of cytokines as well as other mechanisms in CP/CPPS. No RCTs were found. Based on the several controlled clinical studies available for review it appears that cytokines are currently the subject of extensive research to determine the occurrence and levels associated with categories of CP/CPPS but are not useful for diagnosis or evaluation. The various cytokines are associated with inflammation although they cannot be used to distinguish between symptomatic and asymptomatic cases; levels in genital fluids may vary with patient symptoms although there is some question whether they are associated with pelvic pain. Although cytokines and other inflammatory mediators are frequently elevated in men with inflammatory CP/CPPS, they are also elevated in men with asymptomatic prostatitis. Cytokines are likely to be of benefit in evaluation but the specific role of each, or the balance between pro-inflammatory and anti-inflammatory cytokines, is currently unknown.

4. Ejaculate and Seminal Plasma

What is the value of examining the ejaculate and seminal plasma in evaluation of CP/CPPS?

- There is one review on the relevance of male accessory gland infection for male infertility and prostatitis [118].

a) Ejaculate Findings

- We found predominantly systematic investigations of the Giessen group that compared the inflammatory and infectious status of 168 men with prostatitis syndrome with the results from their previous cohort study in 1992. Ejaculate analysis followed the WHO criteria [58]. Compared with the study 10 years earlier, the proportion of different subtypes of the syndrome remained stable. Using WHO cut-points for leukocytospermia, the inclusion of seminal leukocytes in the diagnostic process did not influence the distribution of NIH category IIIA and IIIB CPPS.

b) Ejaculate Quality

- Secretory parameters of the prostate, seminal vesicles and epididymis in the ejaculate have been analyzed prospectively in 112 men with CP/CPPS [119]. Significant differences, usable for clinical diagnosis, in the levels of the marker enzymes have not been detected in inflammatory or non-inflammatory CP/CPPS patients.
- A prospective investigation of 112 men with CP/CPPS did not demonstrate a negative impact on total sperm count, sperm density, motility, morphology or sperm vitality. Leukocytospermia was not associated with reduced standard semen parameters in either EPS or semen [120].
- In one comparative study of 30 patients with CP/CPPS category IIIB and age-matched controls, ejaculate volume, sperm density, motility and morphology and fructose content were evaluated. Patients with CP/CPPS category IIIB demonstrated a significant reduction of motility and fructose content in seminal plasma [121].

c) Ejaculate Volume

- One systematic review evaluated obstructions of the male reproductive tract caused by accessory gland infections including prostatitis [122]. In 10 of 78 men with infertility, accessory gland infection was revealed by medical history (12.8%). In only two men did transurethral resection of the ductus ejaculatorii (TURED) become necessary following TRUS and cystoscopy, demonstrating the male accessory gland infection as a cause of obstruction of the seminal pathways in prostatitis.


d) **Sperm Morphology**

- In a controlled study, semen analysis for strict criteria on sperm morphology was performed on 34 males with inflammatory CP/CPPS, 18 males with non-inflammatory CP/CPPS and 17 controls. A significantly lower percentage of morphologically normal spermatozoa were found in the NIH category IIIA group as compared to NIH category IIIB and controls [123].

**Evidence summary:** accessory glands, especially the prostate, contribute 70% to the volume of seminal fluid, while less than 5% derives from the testicles. The available data suggest that inflammation associated with CPPS does not significantly alter parameters of sperm quality relevant for male fertility as compared to non-inflammatory CP/CPPS patients and fertile controls.

e) **Ejaculate and Leukocytes**

What is the role of evaluating leukocytes in semen compared to evaluations in EPS in CP/CPPS patients?

- We found no systematic reviews.

- In a study of 140 subjects, 73 men (52%) were classified having inflammatory and 67 (48%) non-inflammatory CP/CPPS following the conventional classification techniques (EPS, VB3, ejaculate). Adding the analysis of any leukocytes in seminal fluid, the combination of EPS and seminal fluid analysis detected 69 of 73 cases (95%) [124].

- In one study, 112 men with CP/CPPS were categorized into inflammatory and non-inflammatory CP/CPPS according to leukocyte analysis in EPS and urine after prostatic massage [99]. Analyzing ejaculate for PPL and PMN-elastase in men with CP/CPPS category IIIA found that PPL and elastase in the seminal fluid were significantly increased. Cut points for both parameters have been suggested using ROC curves.

**Evidence summary:** analysis of leukocytes in seminal fluid improves the classification of CP/CPPS patients in categories IIIA and IIIB. Semen analysis increases the proportion of patients with category IIIA prostatitis. The counting chamber is more accurate than the cover-slip technique for enumeration of WBCs in EPS and semen.

5. **Cystoscopy**

What is the role of cystoscopy in the diagnosis/evaluation of CP/CPPS?

- In a prospective study in 48 men with CPPS category IIIB, cystoscopy revealed bladder neck hypertrophy in 29 men (60%) [40]. This finding was associated with an increased detrusor pressure (pdet) at maximum urinary flow rate (Qmax), decreased Qmax and increased residual urine when compared to 19 men with an apparently normal bladder neck. The authors suggest routine cystoscopy in men with non-inflammatory CPPS and decreased flow rates and residual urine volume who fail to respond to drug treatment.

**Evidence summary:** no systematic reviews or RCTs were found. In the European literature [125], bladder neck obstruction historically has been associated with prostatitis symptoms, but it is not known why bladder neck hypertrophy should cause these symptoms. Endoscopy cannot be suggested as a routine procedure in CP/CPPS.

6. **Imaging Methods of Evaluation**

a) **Transrectal Ultrasound (TRUS)**

What is the role of transrectal ultrasound of the prostate in the diagnosis/characterization of CP/CPPS or evaluation after treatment?

- We found no systematic reviews or RCTs specific to CP/CPPS. Relevant to this evaluation are two reviews [126-127] dealing with TRUS in diagnosis of prostate cancer, in which it was concluded that
  1. no TRUS modalities can replace systemic biopsies in the early detection of prostate cancer; and
  2. sensitivity and specificity values are disappointing in the differential diagnosis, but application of new ultrasound agents for clinical detection and staging are promising.

- One prospective series of case studies [128] showed that sonographic abnormalities are indicative of but not definitive for the presence of CP. Included in the study were 88 men with CP and 53 with prostadynia. Statistically significant prostatic calcifications and unilateral seminal gland abnormalities were present in those with chronic inflammation, but both findings (22% and 11%, respectively) were also present in patients with prostadynia.
• One study used automated analysis of ultrasonographic prostate images (AUDEX) to predict the presence of inflamed prostate tissue in patients with prostatitis [129]. Comparison was made with histological results from those with unambiguously inflamed or noninflamed conditions. A sensitivity of 90.6% and specificity of 64.2% was reached. The prospective positive and negative predictive values for prostatitis were 50% and 94.6%.

• One study used color Doppler and endorectal ultrasonography to evaluate 25 patients with acute prostatic syndrome (APS, 13 acute and 2 chronic recurrent), 7 with asymptomatic chronic prostatitis, 13 with prostate cancer, and 6 healthy controls [130]. Marked color increase indicative of acute inflammation was observed in the 25 men with APS; color was greater than in the normal controls and 8 out of the 9 with cancer. Color intensity matched severity of APS symptoms.

• One study evaluated the presence of abnormal blood flow in patients with CP/CPPS using color Doppler ultrasonography: 53 with inflammation, 80 without inflammation, and 22 healthy controls [131]. Images were scored by two reviewers. Significant blood flow increases in the prostatic capsule (102/133 or 77% patients vs. 4/22 or 18% controls) and diffuse flow throughout the prostatic parenchyma (64% patients vs. 36% controls) were observed. Patients with and without objective evidence of inflammation demonstrated similar abnormalities. CP/CPPS may be associated with abnormal prostate blood flow as demonstrated by this technique.

Evidence summary: no RCTs or systematic reviews were found. Application to differential diagnosis remains debatable and ultrasound features alone cannot be used for final diagnosis. Color Doppler ultrasound may be of some assistance.

b) Nuclear Isotope Scanning

What is the role of nuclear isotope scanning in the diagnosis/characterization or evaluation after treatment of CP/CPPS?

• We found no systematic reviews or RCTs. One prospective study evaluated the value of Tc-99m ciprofloxacin and single photon emission computed tomography (SPECT) in the differential diagnosis of CBP in patients with prostatitis syndrome [132]. The study included 4 normal subjects as negative controls, 2 with acute prostatitis or cystourethritis as positive controls, and 59 patients diagnosed with CBP [21] or CPPS [42] by traditional laboratory tests. Images were read by two radiologists blinded to the microbiological findings. Images showed negative uptake in normal subjects, strong hot uptake in the positive controls and in 13 out of 19 (68%) and 28 out of 40 (70%) of those with CBP and CPPS, respectively. No uptake occurred in 32% of those with positive cultures; therefore the results were false-negatives. Sensitivity and specificity were 85.5% and 82.3%, respectively. Tc-99 imaging might be useful to discern CBP not diagnosed with standard lab tests; its major limitation is the lack of evidence of its diagnostic accuracy (sensitivity and specificity) in larger prospective studies.

c) Magnetic Resonance Imaging (MRI)

In men with chronic prostatitis/CPPS, what is the value of prostate MRI in the diagnosis/characterization of CP/CPPS or evaluation after treatment?

• No systematic reviews or RCTs were found.

• In one study, prostatic MRI was performed in 72 patients including 20 patients with prostate cancer, 20 with BPH, 4 with ABP, 5 with CPB, 19 with chronic nonbacterial prostatitis and 6 symptom-free controls [133]. Two radiologists randomly reviewed images. Accuracy in diagnosis of prostate cancer was 74% (sensitivity 53% and specificity 83%); positive and negative predictive values were 53% and 82%, respectively. Accuracy of diagnosis of cancer was high, but differentiation of bacterial prostatitis from cancer was difficult because the former showed some features similar to those of the latter. Without the integration of clinical data, MRI was insensitive in the differentiation of cancer from other prostatic disorders.

• In one retrospective study of 9 out of 12 patients with histologic chronic prostatitis, the findings at histopathologic examination correlated with metabolic abnormality suggestive of prostate cancer at MR spectroscopic imaging [134]. Metabolic abnormalities from the regions of chronic prostatitis appeared similar to those for
low-, intermediate-, and high-grade cancer. At MRI, chronic prostatitis most commonly demonstrated focal low SI that was not specific for cancer. In one patient, however, the diagnosis of cancer could not be excluded. The study was small and had no comparators or controls.

**Evidence summary:** no systematic reviews or RCTs were found. Based on the limited information in small numbers of patients, and the inability definitively to distinguish CP from prostate cancer, the effectiveness of MRI in the diagnosis/characterization or evaluation of CP/CPPS is currently unknown.

7. **Physiological Methods of Evaluation**

**a) Urodynamic Parameters**

What is the role of urodynamic parameters in the evaluation of CP/CPPS?

- A comparison study of 201 men with LUTS referred for urodynamics and 123 prostatitis patients was conducted. Only 1.6% of CP patients had BOO [135].

- A prospective controlled study evaluated flowmetry, bladder capacity and post voiding residual volume (PVR) in 42 patients with CBP (category II) compared with 42 age-matched control men and 279 men with prostadyinia/non-inflammatory CPPS (category IIIB) [136]. The CBP patients had significantly lower flowmetry parameters than the controls, but CBP and CPPS parameters were similar.

- A urodynamic study of 48 patients with CPPS (category IIIB) revealed 29 (60%) with significant bladder abnormalities [40]. It can be concluded that CPPS patients who do not respond to antibiotics and/or anti-inflammatory drugs may have morphological alterations of the bladder.

**Evidence summary:** no systematic reviews or RCTs were found. These two controlled CTs involved a total of 67 men with CPPS and 80 controls. The results indicate potential for further investigation of thermal sensory tests in the evaluation of CPPS.

**b) Neurophysiological Testing**

What is the role of prostate tissue pressure testing in the evaluation of CP/CPPS?

- A pilot controlled study reviewed intraprostatic tissue measurements under spinal anesthesia in 42 patients with chronic nonbacterial prostatitis and 12 men without urological complaints [139]. Tissue pressure at three points (at 10, 60, 120 minutes) after saline injection was elevated in prostatitis patients compared to controls, and according to the authors probably reflected increased tissue resistance and poor tissue microcirculation status.

**Evidence summary:** no systematic reviews or RCTs were found. In men with CPPS and obstructive voiding symptoms, it is reasonable to consider urodynamic evaluation (e.g. flow rates, PVR, pressure flow studies).

**c) Prostate Tissue Pressure Testing**

What is the role of prostate tissue pressure testing in the evaluation of CP/CPPS?

- A pilot controlled study reviewed intraprostatic tissue measurements under spinal anesthesia in 42 patients with chronic nonbacterial prostatitis and 12 men without urological complaints [139]. Tissue pressure at three points (at 10, 60, 120 minutes) after saline injection was elevated in prostatitis patients compared to controls, and according to the authors probably reflected increased tissue resistance and poor tissue microcirculation status.

- A prospective controlled CT reviewed intraprostatic tissue measurements in 48 patients with CP/CPPS (18 with inflammatory category IIIA and 30 with IIIB) and 12 symptomatic controls [140]. All patients with CP/CPPS had significantly higher pressure at all time points (10, 60, 120 minute) compared with controls (p <0.01); mean
pressure was significantly higher in category IIIA, with >10 leukocytes per HPF, compared with category IIIB, with <10 leukocytes. The study validates initial observations and provides a rationale for differentiating inflammatory and non-inflammatory categories of CP.

**Evidence summary:** no systematic reviews or RCTs were found. Both controlled studies indicate that prostate tissue measurements may be valuable for gaining insights into the pathogenesis of CP/CPPS.

d) Intravesical Potassium Chloride Sensitivity Test

What is the role of intravesical potassium chloride sensitivity testing in the evaluation of CP/CPPS?

- An uncontrolled study of intravesical potassium chloride (KCl) sensitivity was conducted in 44 patients diagnosed with prostatitis [45]. The KCl instillation is known to cause pain in most patients with IC or CP/CPPS, reflecting urinary epithelial dysfunction. Positive KCl tests occurred in 37 out of 44 men (84%), which is almost identical to rate reported for IC (79%).

- A controlled study of intravesical potassium chloride (KCl) sensitivity involved 40 men with CP/CPPS and 6 healthy controls [141]. Although there was a significant increase in pain and urgency scores after KCl instillation, the scores and rates of positive sensitivity (50%) and specificity (63.5%) were not statistically different from the controls.

**Evidence summary:** no systematic reviews or RCTs were found. Based on the observations from the one controlled study, the potassium sensitivity test is not warranted for evaluation of CP/CPPS.

8. SERUM STUDIES

a) Serum PSA Levels

What is the role/value of serum PSA levels in the evaluation (diagnosis and follow-up after therapy) of prostatitis?

- We found no systematic reviews or RCTs.

Pathophysiology of elevated PSA levels in prostatitis is not clearly understood.

- In 72 patients (<50 y.o.) with prostatitis, elevated PSA levels (>4 ng/ml) were found in 5 out of 7 (71%) with acute prostatitis, 2 out of 13 (15%) and 2 out of 32 (6%) with chronic bacterial and nonbacterial prostatitis, and none in those with chronic pelvic pain (prostatodynia). After antibiotic treatment, most patients with bacterial prostatitis had PSA levels decrease to normal [142].

- In 42 patients who had TURs for BPH but no clinical evidence of prostatitis, PSA values significantly correlated with extent of histologically-proven acute or chronic active prostatitis (with inflammatory infiltrate); no correlation with inactive prostatitis was found [143].

- In 700 men who had prostate needle biopsy for elevated PSA or abnormal DRE, 27% had histological evidence of prostatitis: 94% of these had chronic inflammation, 6% acute inflammation, and 0.2% granulomatous changes [144].

- Normalization of serum PSA levels was demonstrated after a full course of antibiotics in patients with clinical acute prostatitis. Failure of PSA levels to normalize in 20% of cases was associated with biopsy-proven prostate cancer [145-146] suggests that significant lowering of PSA after antibiotics occurs in patients who are cancer-negative vs. cancer-positive.

- In 6 cases of clinically diagnosed acute bacterial prostatitis (serum PSA levels 4-13.6 ng/ml), all 6 patients had PSA levels significantly reduced following antimicrobial treatment. PSA levels were also elevated in 6 out of 9 patients with pyelonephritis and 8 out of 18 with fever of unknown origin. These patients had PSA levels decrease after therapy. The authors recommend PSA as a diagnostic tool for ABP [55].

- A prospective control and comparative study of seminal plasma parameters (including PSA) was carried out to evaluate the value of diagnosis and localization of inflammation or infection [147]. The study included 13 patients with chronic prostatitis, 31 with leukocytospermia, and 58 with non-inflammatory diseases as controls. No statistically relevant difference was found in PSA levels; PMN elastase and complement C3 were significantly different in CP patients vs. controls.

- A study including 187 asymptomatic men with elevated PSA who were screened for laboratory signs of prostatitis revealed: 122 were evaluated with 51 (42%) with NIH category IV prostatitis. It can be concluded that screening for category IV prostatitis should be performed in men with elevated PSA to reduce the number of biopsies for cancer [148].
One prospective study included 300 men from a prostate cancer screening program who were evaluated for NIH category IV prostatitis [149]. 32% of the men were in category IV, and PSA levels were significantly higher (2.3) than in men without prostatitis (1.4).

A retrospective study reviewed, scored and associated the extent and aggressiveness of inflammation in prostate specimens (post-TURP or prostatectomy with a pathological diagnosis of BPH and prostatitis) with serum PSA-PSA density [150]. The aggressiveness grade of inflammation in subclinical prostatitis was described as the most important morphological factor responsible for PSA elevation.

A controlled study evaluated 421 patients with CP/CPPS and 122 age-matched asymptomatic control patients to determine if PSA, free PSA, or PSA isoforms could be diagnostic markers for CP/CPPS (NIH categories IIIA and IIIB). Total and free PSA were elevated significantly in CP/CPPS cases and percent free PSA was not significantly different between cases and controls. These minor elevations of total and free PSA are not considered clinically relevant. ROC analysis indicated that these serum biomarkers are not useful markers for CP/CPPS.

Comparison of serum PSA and PSA in EPS

A study of 31 consecutive patients with prostatic disease tested PSA in both serum and prostatic fluid [151]. PSA in EPS was no more specific than serum PSA in evaluating prostatic carcinoma, and there were no statistical differences between prostate cancer, prostatitis and BPH patients.

A controlled study of 62 patients with prostatitis (9 bacterial, 53 nonbacterial) and 22 controls explored the content of lecithin mass and WBCs in EPS and serum PSA [152]. Elevated serum PSA does correlate with the content of WBC in EPS but not with content of lecithin mass or the type of prostatitis.

**Evidence summary:** no systematic reviews or RCTs were found to support determination of serum PSA levels in patients with CPPS.

**b) LH, FSH, Testosterone, Beta-estradiol**

What are the roles of various hormones (LH, FSH, testosterone, beta-estradiol) in the diagnosis and/or evaluation of CP/CPPS after treatment?

We found no systematic reviews or RCTs. We found one placebo-controlled RCT examining the role of mepartricin (40 mg daily for 60 days) for the treatment of CP/CPPS and the relation to hormonal levels (decreasing estrogen plasmatic levels) and clinical improvement [68]. The study was based on the hypothesis that CPPS might be a result of an increased estrogen/androgen ratio, which in turn leads to a reduction of dihydrotestosterone in the prostate epithelium and an increase in estradiol and estrone in the stroma. 26 subjects were randomized into two groups of 13 each. Drug treatment produced a significant symptomatic improvement compared to placebo as evaluated by the total NIH-CPSI scores and pain and QOL domains. Levels of LH, FSH, and testosterone were similar in both groups before and after treatment. 17-beta-estradiol levels were significantly lower in the active drug group after treatment.

**Evidence summary:** based on this single, small sample study there is inconclusive evidence to support the role of LH, FSH, and testosterone in the diagnosis/characterization of CPPS or evaluation after treatment.

c) Immunoglobulins and Antibodies

What is the role of immunoglobulins in the diagnosis and/or evaluation of CP/CPPS after treatment?

We found no RCTs on the identification of immunoglobulins specific to CP/CPPS. One controlled study identified proteins expressed in a prostate cDNA expression library recognized by IgG from sera of patients with CP [153]. The study was originated to identify antigens of the prostate for the development of antigen-specific vaccines for treatment of prostate cancer. Candidate proteins were evaluated in sera from 62 subjects with symptomatic prostatitis and 71 control male blood donors. Two proteins were recognized: MAD-Pro-34, a nucleolar autoantigen, in 6 out of 62 CP patients and 0 out of 71 controls (p =0.008), and NY-CO-7 protein in 9 out of 62 CP patients vs. 3 out of 71 controls (p=0.06). The proteins used could be further investigated but the study demonstrated that only some patients with CP/CPPS have auto antibodies to specific proteins; however, these cannot be used as diagnostic tools.
9. TISSUE SAMPLING

What is the role of prostate histopathology in the evaluation of CP/CPPS?

- A prospective study examined prostate histopathology in 368 biopsies from 97 patients with symptoms of CP/CPPS in order to systematically characterize inflammation [154]. The degree of prostatic inflammation was minimal to absent in 95% of patients; 4% had moderate and 1% severe inflammation. There was no correlation between leukocytes in EPS and the prostate in this population.

- A systematic literature review of articles from 1979-1999, prospective evaluation in two prostatitis research centers, and consensus of experts from the CPCRN were used to develop a histopathological classification for CP inflammation [155]. It was concluded that prostatic inflammation is a common histopathological observation albeit its association with CP/CPPS has not yet been completely defined. The establishment of a standard classification will permit comparison of future studies evaluating, describing or associating the prostatic inflammation with lower GU conditions.

a) Prostate Biopsy Cultures

- In a controlled comparative study of 120 patients with CPPS categories IIIA and IIIB and 60 asymptomatic controls, bacteria cultured from prostatic biopsies did not differ [156]. Therefore use of prostate tissue biopsies for this purpose is not useful for evaluation.

b) Prostate Molecular Biopsy Studies

- One systematic review concerns the role of molecular studies in prostatic biopsies of CP/CPPS patients [157]. The authors indicate that new data recently acquired with molecular techniques may redefine the role of the bacteria identified in the prostatic tissue and involvement in the pathogenesis of the syndrome in a conventional manner. 135 men with CP/CPPS were evaluated with a molecular approach; potential pathogenic bacteria were identified in ~7% of patients.

- Prostate biopsy study using modern molecular techniques (real time PCR) was conducted in 31 men with CP/CPPS proven by standard diagnostic procedures. Bacterial DNA was detected in 8 out of 31 specimens and 3 samples were positive for E. coli infection, demonstrating approximately $10^3$ cfu/ml prostatic tissue [158].

Evidence summary: based on the systematic literature review and consensus report and one biopsy study, prostate biopsies in patients with CPPS may have research benefits.

IV. ASYMPTOMATIC PROSTATITIS (NIH CATEGORY IV)

1. SEMEN ANALYSIS AND CULTURE

What is the role of semen analysis in men with asymptomatic prostatitis presenting with infertility?

- The WHO has suggested requiring two of the following criteria to diagnose male accessory gland infection in men with oligo-, astheno- or teratozoospermia:
  1. history or physical signs of UTI, epididymitis, or abnormal rectal examination;
  2. abnormal urine after prostatic massage (describing the 4-glass test); or
  3. elevated numbers of peroxidase positive WBCs, high numbers of bacteria in semen, C. trachomatis findings, and/or abnormal biochemistry or elevated inflammatory markers in the seminal fluid.

Analysis of prostatic fluid is not recommended

Evidence summary: the suggested classification does not differentiate between prostatitis, epididymitis, and inflammatory alterations of the urethral compartment (chronic urethritis). Elevated WBCs may exert an unfavorable effect on the viability, mobility, and fertilizing capacity of sperm.

- One review [118] analyzes questionable deleterious effects of “chronic prostatitis” on sperm quality in infertile patients based on the literature. The authors suggest that even recent investigations for sperm parameters are contradictory and do not really confirm a negative role of chronic prostatitis for sperm density, motility, and morphology.

- Evaluating the gold standard of leukocyte analysis [159] in semen for leukocytospermia ($\geq 10^6$...
peroxidare positive leukocytes/ml) by immunocyto- logical analysis demonstrated a failure of the peroxidare staining in about the half of the patients.

- Evaluating a total of 112 men with symptomatic prostatitis [120] demonstrated increased numbers of peroxidare positive leukocytes in patients with prostatitis (category IIIA) provided the ejaculate analysis was performed on the same day after lower urinary tract localization studies.

- In a comparison of first urine, midstream urine, and semen samples [160], 51% of the ejaculates demonstrated bacteriospermia. There was no correlation between seminal microbes, raised leukocytes, and pregnancy, however.

- Standard semen analysis has been performed and morphological defects analyzed in 56 infertile men, and the results compared to those of healthy sperm donors [161]. Sperm motility was significantly negatively correlated with leukocyte concentrations in semen.

**Evidence summary:** no RCTs or systematic reviews concerning semen analysis, the use of the 4-glass test, and/or PPMT in category IV prostatitis were found in men diagnosed for infertility. Deleterious effects of proven prostatitis on spermatozoa remain debatable. There are hints at a correlation between a high number of leukocytes and decreased sperm motility. Microorganisms are commonly found in the semen of asymptomatic men without biological relevance.

### 2. ELEVATED PSA, 4-GLASS TEST, PPMT

What is the role of the 4-glass test and/or PPMT in men with asymptomatic prostatitis presenting with elevated PSA in serum?

- In men without symptoms and elevated PSA [162], the presence of acute and/or chronic prostatitis in biopsy specimens may be a contributing factor to PSA elevation. Antimicrobial therapy may normalize PSA; TRUSP biopsy should be performed in cases that do not normalize.

- EPS analysis for increased numbers of white blood cells (>10/HPF) identified 95 men with serum PSA greater than 4.0 µg/ml [163]. After a four-week course of antimicrobials and a nonsteroidal anti-inflammatory agent, PSA in serum was normalized in almost half of the patients.

- 122 asymptomatic men with elevated PSA levels were evaluated for leukocytes in EPS and/or VB3. Men with signs of prostatitis received a four-week course of antimicrobials and were reevaluated after 6 to 8 weeks [148]. In the 51 men with signs of prostatitis, PSA was normalized in 22 patients. Biopsy revealed prostate cancer in 9 of the 29 patients who did not respond to this therapy.

**Evidence summary:** no RCTs or systematic reviews concerning the standardized use of the 4-glass test/PPMT were found. The value of these tests in asymptomatic men with elevated PSA requires further research.

### D. TREATMENT

#### I. ACUTE BACTERIAL PROSTATITIS (NIH CATEGORY I)

ABP can be a serious infection with fever, intense local pain and general symptoms. Septicemia and urosepsis are always a potential risk.

The following factors must be taken in account when treating ABP: potential urosepsis, choice of antimicrobial agent, urinary drainage, risk factors justifying hospitalization and auxiliary measures intended to enhance treatment outcomes [164].

#### 1. ANTIMICROBIAL THERAPY

The choice and duration of antimicrobial therapy for ABP are based on experience and expert opinion and are supported by many uncontrolled clinical studies [165-166]. For initial treatment of severely ill patients, intravenous administration of high doses of bactericidal antimicrobials such as aminoglycosides in combination with ampicillin, a broad spectrum penicillin in combination with a beta-lactamase inhibitor, a third generation cephalosporin or a fluoroquinolone is required until defeverescence and normalization of associated urosepsis (this recommendation is based on treatment of complicated UTIs and urosepsis). Patients who are not severely ill or vomiting may be treated with an oral fluoroquinolone [165-166]. Trimethoprim-sulfamethoxazole (TMP/SMX) is no longer recommended as first line empirical therapy in the guidelines from the Infectious Diseases Society of America (IDSA) [167] and the European Association of Urology.
(EAU) [168] in areas where TMP/SMX resistance for *E. coli*, the most frequent pathogen, is greater than 10% to 20% [169-171]. Low success rates in CBP (see next section) would indicate that it should be reserved for second line oral therapy for ABP as well. Treatment should continue for 2 to 4 weeks [165-166].

2. **Urinary Drainage**

Three choices are available for the management of acute urinary retention in acute prostatitis: suprapubic, intermittent or indwelling catheterization. Suprapubic tube placement has traditionally been advocated for theoretical and practical reasons: it was believed to reduce the risk of prostatic abscess and urethral stricture. This has never been substantiated and many urologists adopt either a single catheterization with trial of voiding or short term small caliber urethral catheterization. A small retrospective series [172] suggested that urethral stenting may provide the same benefits of suprapubic catheterization.

3. **Hospitalization**

ABP can present as a severe infection with a risk of sepsis. Hospitalization is imperative in cases of high fever, vomiting, dehydration, tachycardia, tachypnea, hypotension and other symptoms related to urosepsis. High risk patients (diabetes, immuno-suppressed patients, old age or prostatic abscess) and those with severe voiding disorders should be considered for hospitalization [164].

4. **Auxiliary Measures**

Analgesics and antipyretics are usually indicated. Nonsteroidal anti-inflammatory agents have been suggested for reducing symptoms including fever [164-166]. Alpha-blockers may be considered, particularly in men with moderately severe voiding symptoms, to reduce the risk of urinary retention and facilitate micturition [164-166].

Because of their unique and favorable pharmacokinetic properties and their broad antibacterial spectra, the fluoroquinolones are the agents of choice for the antimicrobial treatment of CBP [165-166; 168-169]. Relatively high doses of antimicrobials are needed and oral therapy is preferred. In CBP, an oral fluoroquinolone should be given for at least 4-6 weeks after the initial diagnosis. After treatment the patient should be reassessed periodically to determine appropriate treatment. Treatment with intraprostatic injection of antimicrobials is not recommended as it is supported only by anecdotal reports [173-174]. In general, therapeuetic results (defined as bacterial eradication) are good in CBP due to *E. coli* and other members of the family Enterobacteriaceae. CBP due to *P. aeruginosa* and Enterococci shows poorer response to antimicrobial therapy [169].

Numerous studies have been performed in the past in patients with CPB, the majority of which are uncontrolled and with a short follow-up period of 4-6 weeks. Since relapse is commonly observed in these patients, only the results of studies with follow-up of at least 6 months should be taken into consideration. In this respect, the most experience has been gathered with ciprofloxacin, although newer fluoroquinolones like levofloxacin, which has improved activity against so-called atypical pathogens, appear to be equally efficacious. Table 4 shows data from CBP fluoroquinolone treatment trials with a follow-up of at least 6 months [31; 175-181]. The combination of antimicrobials and alpha-blockers has been suggested to reduce the high recurrence rate [182] and this combination of two therapeutic regimens could be considered for evaluation in properly designed prospective studies [183].

CBP associated with a confirmed uropathogen that is resistant to the fluoroquinolones can be considered for treatment with trimethoprim-sulfamethoxazole (or other antimicrobials), but the treatment duration should be 8-12 weeks [169]. For treatment refractory patients the following are acceptable treatment strategies:

1. intermittent antimicrobial treatment of acute symptomatic episodes (cystitis);
2. low-dose antimicrobial suppression; or
3. radical TURP or open prostatectomy if all other options have failed.

Many medical and invasive interventions have been proposed to treat CP/CPPS and numerous small,
uncontrolled studies with poorly defined patients and invalidated outcome analyses have suggested efficacy for these interventions [184]. The introduction of an internationally accepted classification system [1] and a validated outcome index, the NIH-CPSI [5], has stimulated the design and implementation of comparable randomized placebo-controlled trials [185-186] that have allowed researchers and clinicians to objectively evaluate evidence based efficacy data as well as compare the various therapies advocated for CP/CPPS.

The following criteria were developed to determine whether a clinical intervention trial in CP/CPPS met strict criteria for an evidence-based treatment recommendation:

1. clearly defined population of CP/CPPS men;
2. randomized placebo-controlled design;
3. validated outcome analyses (NIH-CPSI); and
4. peer reviewed (published in a peer reviewed journal).

1. EVIDENCE-BASED THERAPIES

At the time of the Paris 2005 consensus conference, eleven clinical trials [61-70] met these criteria (Table 5). Since these 11 randomized placebo-controlled trials differ in the number of patients randomized and duration of follow-up but have similar inclusion/exclusion criteria and outcome analyses, we can compare these studies and make some early evidence-based recommendations.

- Antimicrobials cannot be recommended for men with longstanding, previously treated CP/CPPS [64-65]. However, uncontrolled clinical studies suggest that some clinical benefit can be obtained with antimicrobial therapy in antimicrobial naïve early onset prostatitis patients [165; 187].
- Alpha-blockers can be recommended as a first line medical therapy, particularly in alpha-blocker naïve men with moderately severe symptoms who have relatively recent onset of symptoms [62-63; 67]. Alpha-blockers must be continued for over 6 weeks (likely over 12 weeks) [62; 68]. Alpha-blockers cannot be recommended in men with long standing CP/CPPS who have tried and failed alpha-blockers in the past [64].
- Anti-inflammatory therapy is not recommended as a primary treatment [66]; however, it may be useful in an adjunctive role in a multi-modal therapeutic regime [188].

A number of uncontrolled clinical studies have strongly suggested that multi-modal therapy is more effective than monotherapy in patients with long term symptoms [188-189]. Future trials will have to assess such multi-modal therapy. At this time, hormonal therapy cannot be recommended as a
Table 5. The 11 randomized placebo-controlled trials that met the strict criteria defined above evaluated various medical therapies for the treatment of CP/CPPS. The treatment effect is defined as the mean change from baseline in the active treatment group minus the mean change from baseline in the placebo group. A clinically effective treatment should produce a treatment effect of at least 3-4 points (adapted from Nickel et al [189]).

<table>
<thead>
<tr>
<th>Active Agent</th>
<th>Reference</th>
<th>Duration</th>
<th>Patients (n)</th>
<th>Change in NIH-CPSI</th>
<th>Treatment Effect</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Active</td>
<td>Placebo</td>
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<td>Active</td>
<td>Placebo</td>
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</tr>
<tr>
<td>Levofloxacin</td>
<td>Nickel et al. 2003 [65]</td>
<td>6 weeks</td>
<td>35</td>
<td>45</td>
<td>-5.4</td>
</tr>
<tr>
<td>Terazosin</td>
<td>Cheah et al. 2003 [67]</td>
<td>14 weeks</td>
<td>43</td>
<td>43</td>
<td>-14.3*</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>Nickel et al. 2004 [63]</td>
<td>6 weeks</td>
<td>27</td>
<td>30</td>
<td>NR</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Alexander et al. 2004 [64]</td>
<td>6 weeks</td>
<td>49</td>
<td>49</td>
<td>-6.2</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td></td>
<td></td>
<td>49</td>
<td>-4.4</td>
<td></td>
</tr>
<tr>
<td>Tamsulosin + Ciprofloxacin</td>
<td></td>
<td>49</td>
<td>-4.1</td>
<td></td>
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<tr>
<td>Rofecoxib 25 mg</td>
<td>Nickel et al. 2003 [66]</td>
<td>6 weeks</td>
<td>53</td>
<td>59</td>
<td>-4.9</td>
</tr>
<tr>
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<td>49</td>
<td></td>
<td>-6.2</td>
</tr>
<tr>
<td>Pentosan polysulfate</td>
<td>Nickel et al. 2000 [70]</td>
<td>16 weeks</td>
<td>51</td>
<td>49</td>
<td>-5.9</td>
</tr>
<tr>
<td>Finasteride</td>
<td>Nickel et al. 2004 [69]</td>
<td>24 weeks</td>
<td>33</td>
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<td>-3.0</td>
</tr>
<tr>
<td>Mepartricin</td>
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<td>60 days</td>
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<tr>
<td>Quercetin</td>
<td>Shokses et al. 1999 [61]</td>
<td>4 weeks</td>
<td>15</td>
<td>13</td>
<td>-7.9*</td>
</tr>
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</table>

*significant difference between active and placebo (p < 0.05)
NR - not reported
monotherapy [68-69], but should be evaluated in selected patients such as older men with concurrent BPH [68-69]. The early data on herbal therapies, particularly quercetin [61], are intriguing, but a larger multi-center randomized placebo-controlled trial is required before a high level of evidence recommendation can be made on its use.

2. POTENTIAL THERAPIES

Many other medical therapies have been suggested and tested in pilot studies; however, the studies were usually small and uncontrolled. Muscle relaxants [190], Cernilton or bee pollen extract [191-192], saw palmetto [193-194], corticosteroids [195] and allopurinol [196-197] have all been suggested and used but recommendations will have to wait for results from properly designed randomized placebo-controlled trials. Promising approaches employing neuromodulatory, neuroendocrine and immune modulatory agents will require evaluation and randomized controlled trials before their efficacy can be determined.

A number of physical therapies have been recommended, but they also suffer from a lack of prospective controlled data obtained from properly designed controlled studies. Prostatic massage has been the primary therapy for prostatitis since the turn of the century and there has been a re-emergence of interest in its potential [198-199]. Refinement of the prostatic massage therapy (perineal or pelvic floor massage and myofascial trigger point release) has also been suggested as a beneficial treatment modality for patients [88]. Biofeedback [200] and acupuncture [201] also show promise, but like all the other physical therapeutic modalities, require sham-controlled trials before recommendations can be made. Electromagnetic therapy is intriguing and shows interesting results in a small randomized sham-controlled trial [202] and further efforts should be made to test this modality of therapy. Psychological support and therapy has been advocated based on new psycho-social modeling of this syndrome [81].

A number of minimally invasive therapies such as balloon dilation [203-205], neodinium:Yag laser [206], transurethral needle ablation [207-208] and microwave hyperthermia [209-210] and thermotherapy [211] have been suggested. Two trials assessing transrectal microwave hyperthermia [209-210] and one trial assessing transurethral thermotherapy [211] have indicated that these may be better than sham therapy while a trial comparing TUNA to sham [208] found that the efficacy of TUNA in CPPS was comparable to sham treatment. Further assessment of heat therapy employing sham controls, standardized inclusion exclusion criteria and validated symptom outcome measures are recommended. Pudendal nerve blocks or neurolysis surgery [212-213] have been suggested for chronic pelvic pain that can be shown to be secondary to pudendal nerve entrapment. Other surgery such as radical transurethral resection of the prostate and total prostatectomy should not be encouraged or recommended at this time for CP/CPPS since no definitive clinical series or long term follow up has ever been presented.

IV. ASYMPTOMATIC PROSTATITIS (NIH CATEGORY IV)

Therapy is not indicated since these patients by definition are asymptomatic. However, antimicrobial therapy for selected patients with category IV prostatitis associated with elevated PSA (for a complete review of this topic see Kawakami et al [214]) and infertility (for a complete review of this topic see Branigan et al [215]; Yanushpolsky et al [216]) may warrant consideration.

E. EVIDENCE AND RECOMMENDATIONS

1. LEVELS OF EVIDENCE AND GRADING OF RECOMMENDATIONS

A recommended test should be done on every patient during the initial evaluation.

An optional test is a test of proven value in the evaluation of selected patients during a specialized evaluation usually performed by a urologist.

1. EPIDEMIOLOGY

a) Levels of Evidence

1. Approximately 5% to 15% of men have symptoms consistent with CP/CPPS (level 2/3).

2. Asymptomatic inflammatory prostatitis occurs frequently in men evaluated for prostate disorders and less frequently in patients presenting with infertility (level 3).

3. ABP and CBP appear to be less common than CP/CPPS, but we have very limited population-based data on the incidence and prevalence of these conditions (level 3/4).
2. PATHOGENESIS

a) Levels of Evidence

1. Prostatitis syndromes cause substantial morbidity and a large number of physician visits (level 1/2).
2. Although limited data support a number of theories, the pathogenesis of both CP/CPPS and asymptomatic inflammatory prostatitis remain undefined (level 2/3).
3. Risk factors for development of prostatitis appear to include genitourinary tract instrumentation, including prostate biopsies (level 3), and a history of UTI (level 2/3). Other risk factors for development of prostatitis remain undefined (level 3).
4. ABP and CBP are caused by Gram-negative rods (level 1/2) and by Gram-positive cocci (level 3).

b) Recommendation

1. Further studies are needed to define the pathogenesis of all categories of prostatitis (grade A).

II. EVALUATION

1. ACUTE BACTERIAL PROSTATITIS (NIH CATEGORY I)

1. Men with symptoms of ABP should undergo urinalysis and culture/sensitivity. (2:A)
2. Initial imaging of the prostate is not recommended. Ultrasound is indicated if suspicion for prostatic abscess is entertained. (3:B)

2. CHRONIC BACTERIAL PROSTATITIS (NIH CATEGORY II)

1. Traditional 4-glass or 2-glass test for white blood cell count and culture. (3:A)
2. Culture of semen has a low sensitivity but is recommended for evaluation in selected men (e.g. infertility). (3:D)
3. Imaging of the prostate is indicated only in highly selected patients (e.g. treatment refractory). (4:D)

3. CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME (NIH CATEGORY III)

a) Recommended Investigations

1. 4-glass or 2-glass test for WBC count and culture. (3:A)

b) Optional Investigations

1. Flow rate, post-void residual and other urodynamic studies. (3:C)
2. Semen analysis and culture. (3:D)

b) Investigations Which are Not Recommended

1. Serum PSA. (3:B)
2. Potassium chloride sensitivity test. (3:D)
3. Routine imaging of the prostate. (3:D)
4. Test for C. trachomatis and Ureaplasma. (3:D)
5. Cystoscopy. (4:D)

d) Investigational Tests Requiring Further Evaluation

1. Histopathological and molecular microbiological evaluation of the prostate. (3:D)
2. Immune cells and mediators. (3:D)

4. ASYMPTOMATIC PROSTATITIS (NIH CATEGORY IV)

1. No evaluation unless considering antimicrobial therapy for elevated PSA or infertility. (3:C)

III. TREATMENT

1. ACUTE BACTERIAL PROSTATITIS (NIH CATEGORY I)

1. Patients with severe symptomatic febrile acute bacterial prostatitis:
   - aminoglycosides in combination with ampicillin, a broad spectrum penicillin in combination with a beta-lactamase inhibitor, a thrid generation cephalosporin or a fluoroquinolone is required until defeverescence and normalization of associated urosepsis (2:A based on treatment of complicated UTIs and urosepsis),
   - observation/hospitalization, initial parenteral wide-spectrum antimicrobials, and if indicated, bladder drainage. (3:B)

2. The NIH-CPSI instrument should be utilized for symptomatic evaluation and assessment of treatment but not as a diagnostic tool. (3:A)
3. Physical examination of the prostate and other pelvic structures (e.g. myofascial trigger points). (3:B)
4. Psychological evaluation in selected patients may be warranted. (3:B)
2. Prostatic abscess in treatment refractory patients requires drainage. (4:A)

3. Following resolution of severe infection and for less severely ill patients, outpatient oral fluoroquinolones for 2-4 weeks are appropriate. (4:B)

2. CHRONIC BACTERIAL PROSTATITIS (NIH CATEGORY II)

1. Oral fluoroquinolone therapy for susceptible bacteria for 4-6 weeks. (2:A)

2. Trimethoprim-sulfamethoxazole (or other antimicrobials) for fluoroquinolone resistant bacteria. (3:B)

3. Treatment refractory patients:
   - intermittent antimicrobial treatment of acute symptomatic cystitis; (3:A)
   - low-dose antimicrobial suppression; (3:A)
   - radical TURP or simple prostatectomy (as a last resort if all other options have failed). (4:C)

3. CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME (NIH CATEGORY III)

a) Recommended Therapies

1. Alpha-blocker therapy for newly diagnosed, alpha-blocker naïve patients. (1:A)

2. Antimicrobial therapy for newly diagnosed, antimicrobial naïve patients. (4:D)

3. Multi-modal therapy. (4:D)

b) Therapies Which are Not Recommended

1. Alpha-blocker therapy in chronic heavily pretreated patients. (1:A)

2. Anti-inflammatory monotherapy. (1:A)

3. Antimicrobial therapy in chronic heavily pretreated patients. (1:A)

4. Five alpha-reductase inhibitor monotherapy. (1:A)

5. Minimally invasive therapies such as TUNA, laser therapies, etc. (2:A)

6. Invasive surgical therapies such as TURP and radical prostatectomy. (4:D)

c) Therapies Requiring Further Evaluation

1. Heat therapy in the form of microwave. (2:B)

2. Mephartricin. (2:B)

3. Quercetin and other phytotherapies. (2:B)

4. Biofeedback. (3:B)

5. Physical therapy. (3:B)

6. Acupuncture. (3:C)

7. Electromagnetic stimulation. (3:C)

8. Immunomodulating agents. (3:C)

9. Muscle relaxants. (3:C)

10. Neuromodulating agents. (3:C)

11. Pudendal nerve modulation. (3:C)

4. ASYMPTOMATIC INFLAMMATORY PROSTATITIS (NIH CATEGORY IV)

Antimicrobial therapy for selected patients with elevated PSA or infertility warrants consideration. (3:B)
F. REFERENCES


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Committee 15

Summary of
The Assessment and Management of
Male Pelvic Pain Syndrome,
Including Prostatitis

PART II
DIAGNOSTIC WORKUP AND ALGORITHMS

Chair
A. J. Schaeffer (USA)

Members
R. U. Anderson (USA),
J. N. Krieger (USA),
B. Lobel (France),
K. Naber (Germany),
M. Nakagawa (Japan),
J. C. Nickel (Canada),
L. Nyberg (USA),
W. Weidner (Germany)
A. DIAGNOSTIC WORKUP OF MALE PELVIC PAIN SYNDROME, INCLUDING PROSTATITIS

I. INITIAL EVALUATION: RECOMMENDATIONS

II. OPTIONAL EVALUATIONS: UROLOGIC (SPECIALIZED) EVALUATION

III. EVALUATIONS WHICH ARE NOT RECOMMENDED

B. ALGORITHMS

I. ACUTE PROSTATITIS

II. APPARENT RECURRENT “PROSTATITIS”

III. CHRONIC PELVIC PAIN SYNDROME
A recommended test should be done on every patient during the initial evaluation.

An optional test is a test of proven value in the evaluation of selected patients during a specialized evaluation usually performed by a urologist.

I. INITIAL EVALUATION: RECOMMENDATIONS

The initial evaluation should be done on every patient presenting to a physician with symptoms of male pelvic pain syndrome (including prostatitis).

1. HISTORY
An adequate medical history should be obtained focusing on the:

• nature and duration of reported genitourinary tract symptoms,
• previous surgical procedures (in particular, as they affect the genitourinary tract),
• general health issues, including sexual function history,
• medication currently taken by the patient, and
• the patient’s fitness for possible surgical procedures or other treatments.

2. QUANTIFICATION OF SYMPTOMS: NATIONAL INSTITUTES OF HEALTH CHRONIC PROSTATITIS SYMPTOM INDEX (NIH-CPSI)
Severity of symptoms in men with CP/CPPS should be assessed by using the NIH-CPSI. This instrument is a validated questionnaire, completed by the patient, consisting of four questions about pain, three about voiding symptoms, and two about quality of life (QOL). The scores in these three individual domains (pain, voiding and QOL) are combined without weighting to yield the NIH-CPSI total score.

3. PHYSICAL EXAMINATION AND DIGITAL RECTAL EXAM
A focused physical examination should be performed to assess the suprapubic area to rule out bladder distention.

A digital rectal examination (DRE) should be performed to evaluate the anal sphincter tone and prostate gland with regard to approximate size, consistency, shape and abnormalities suggestive of prostate cancer.

In men who may have acute bacterial prostatitis, prostate massage is contraindicated.

In men with CP/CPPS, evaluation of myofascial trigger points may be useful.

4. URINALYSIS AND URINE CULTURE
The urine should be analyzed using a dipstick test, with or without examination of the urinary sediment after centrifugation, to determine if the patient has hematuria, proteinuria, pyuria, or other pathological findings (e.g. nitrite-producing bacteria or glucose).

A conventional 4-glass test or PPMT (pre- and post-prostatic massage urine test) for WBC and bacterial culture is indicated in men with possible CBP, CPPS or selected men with elevated PSA (Figure 1).

Figure 1. The classic Meares-Stamey 4-glass urine test. VB1 (voided bladder 1) is the initial 10 cc of the urinary stream and represents the urethral specimen. VB2 (voided bladder 2) is a midstream from the bladder itself. EPS (expressed prostatic secretion) VB3 (voided bladder 3, the first 10 cc of urine after prostatic massage) are representative of the prostatic microbiologic environment.
**NATIONAL INSTITUTES OF HEALTH CHRONIC PROSTATITIS SYMPTOM INDEX (NIH-CPSI)**

### PAIN OR DISCOMFORT

1. In the last week, have you experienced any pain or discomfort in the following areas?

   - a. Area between rectum and testicles (perineum)
   - b. Testicles
   - c. Tip of the penis (not related to urination)
   - d. Below your waist, in your pubic or bladder area

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<th>Yes</th>
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2. In the last week, have you experienced:

   - a. Pain or burning during urination?
   - b. Pain or discomfort during or after sexual climax (ejaculation)?

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3. How often have you had pain or discomfort in any of these areas over the last week?

   - 0 Never
   - 1 Rarely
   - 2 Sometimes
   - 3 Often
   - 4 Usually
   - 5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

   - 0 None
   - 1 Only a little
   - 2 Some
   - 3 A lot
   - 4 Mostly satisfied
   - 5 Mixed (about equally satisfied and dissatisfied)
   - 6 Mostly dissatisfied
   - 7 Unhappy
   - 8 Terrible

### URINATION

5. How often have you had a sensation of not emptying your bladder completely after you have finished urinating, over the last week?

   - 0 Not at all
   - 1 Less than 1 time in 5
   - 2 Less than half the time
   - 3 About half the time
   - 4 More than half the time
   - 5 Almost always

6. How often have you had to urinate again less than two hours after you had finished urinating, over the last week?

   - 0 Not at all
   - 1 Less than 1 time in 5
   - 2 Less than half the time
   - 3 About half the time
   - 4 More than half the time
   - 5 Almost always

### IMPACT OF SYMPTOMS

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

   - 0 None
   - 1 Only a little
   - 2 Some
   - 3 A lot

8. How much did you think about your symptoms, over the last week?

   - 0 None
   - 1 Only a little
   - 2 Some
   - 3 A lot

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

   - 0 Delighted
   - 1 Pleased
   - 2 Mostly satisfied
   - 3 Mixed (about equally satisfied and dissatisfied)
   - 4 Mostly dissatisfied
   - 5 Unhappy
   - 6 Terrible

---

**Scoring the NIH-Chronic Prostatitis Symptom Index Domains**

- **Pain:** Total of items 1a, 1b, 1c, 1d, 2a, 2b, 3 and 4 =
- **Urinary Symptoms:** Total of items 5 and 6 =
- **Quality of Life Impact:** Total of items 7, 8 and 9 =
1. FLOW RATE RECORDING
Urinary flow rate measurement is useful in the initial diagnostic assessment and during or after treatment to determine response. Because of the non-invasive nature of the test and its clinical value, it should be performed prior to embarking on any active therapy. Maximum urinary flow rate (Qmax) is the best single measure, but a low Qmax does not distinguish between obstruction and decreased bladder contractility.

Because of the great intra-individual variability and the volume dependency of the Qmax, at least two flow rates, both with a volume ideally of >150 ml voided urine, should be obtained. If such a voiding volume cannot be obtained by the patient despite repeated recordings, the Qmax results at available voiding volumes should be considered.

2. RESIDUAL URINE
The determination of post-void residual urine is useful in the initial diagnostic assessment of the patient and during subsequent monitoring as a safety parameter.

The determination is best performed by non-invasive transabdominal ultrasonography.

Because of the marked intra-individual variability of residual urine volume, the test should be repeated to improve precision if the first residual urine volume is significant and suggests a change in the treatment plan.

3. PRESSURE-FLOW STUDIES
This optional test is of proven value in the evaluation of patients prior to invasive therapies or when a precise diagnosis of bladder outlet obstruction (BOO) is important. Pressure-flow urodynamic studies are the only method with the potential to separate men with a low urinary flow rate due to a detrusor underactivity from those with obstruction. This is done by relating the detrusor pressure (pdet) at the time of the Qmax to the maximum flow rate achieved (see committee on Urodynamics).

If patients are found not to have BOO, yet suffer from severe Lower Urinary Tract Symptoms (LUTS), they are less likely to benefit from traditional treatments such as surgery, designed to relieve outlet obstruction. Consequently, it is recommended that these patients have their symptoms treated in an appropriate fashion. Such treatment can consist of therapy aimed at other underlying disease processes, including anticholinergics, bladder behavioral training, biofeedback, etc.

The most important parameter of the pressure-flow study is the pdet at the time of the Qmax.

4. SEMEN ANALYSIS AND CULTURE
There is no conclusive proof of prostatitis exerting a negative effect on spermatozoa, although some studies suggest prostatitis is linked with decreased sperm motility. In general, semen analysis of asymptomatic patients is not indicated.

5. ELEVATED PSA
Evaluation of patients with elevated PSA should follow guidelines for those conditions.

6. IMAGING OF THE PROSTATE BY TRANSRECTAL ULTRASOUND (TRUS) OR COMPUTED TOMOGRAPHY (CT)
Imaging of the prostate is indicated in selected patients who are treatment refractory (e.g. to rule out related disorders such as prostatic abscess or ejaculatory duct obstruction).

III. EVALUATIONS WHICH ARE NOT RECOMMENDED

These tests are not recommended in an otherwise healthy patient with an initial evaluation consistent with prostatitis.

Endoscopy of the lower urinary tract
Serum PSA
Potassium chloride sensitivity test
Test for C. trachomatis and Ureaplasma

DIAGNOSTIC TEST
I. INITIAL EVALUATION: RECOMMENDATIONS
1. HISTORY
2. QUANTIFICATION OF SYMPTOMS: NATIONAL INSTITUTES OF HEALTH CHRONIC PROSTATITIS SYMPTOM INDEX (NIH-CPSI)
3. PHYSICAL EXAMINATION AND DIGITAL RECTAL EXAM
4. URINALYSIS AND URINE CULTURE

II. OPTIONAL EVALUATIONS: UROLOGIC (SPECIALIZED) EVALUATION
1. FLOW RATE RECORDING
2. RESIDUAL URINE
3. PRESSURE-FLOW STUDIES
4. SEMEN ANALYSIS AND CULTURE
5. ELEVATED PSA
6. IMAGING OF THE PROSTATE BY TRANSRECTAL ULTRASOUND (TRUS) OR COMPUTED TOMOGRAPHY (CT)

III. EVALUATIONS WHICH ARE NOT RECOMMENDED
1. ENDOSCOPY OF THE LOWER URINARY TRACT
2. SERUM PSA
3. POTASSIUM CHLORIDE SENSITIVITY TEST
4. TEST FOR C. TRACHOMATIS AND UREAPLASMA
I. ACUTE PROSTATITIS

DEFINED BY
• Febrile illness
• Tender prostate
• Pyuria ± bacteriuria

INITIAL EVALUATION
• Urine culture

TREAT AS ACUTE BACTERIAL PROSTATITIS

VOIDING EFFECTIVELY?

CATHETERIZE

RESPONS TO TREATMENT?

OTHER INVESTIGATION
• Imaging (CT, sonography or MRI) to evaluate for prostate abscess

1. Treatment: Acute Bacterial Prostatitis (NIH Category I)
   • Recommendation 1: Patients with severe symptomatic febrile acute bacterial prostatitis.
     a. Aminoglycosides in combination with ampicillin, a broad spectrum penicillin in combination with a beta-lactamase inhibitor, a third generation cephalosporin or a fluoroquinolone is required until defeverescence and normalization of associated urosepsis (2:A based on treatment of complicated UTIs and urosepsis).
     b. Observation/hospitalization, parenteral wide-spectrum antimicrobials. (3:B)
   • Recommendation 2: Following resolution of severe infection and for less severely ill patients, outpatient parenteral fluoroquinolones for 2-4 weeks are appropriate. (4:B)
2. Attempt gentle passage of small Foley catheter; if unsuccessful, insert a suprapubic drainage tube.
3. Prostate abscess is a rare complication that may require drainage.
II. APPARENT RECURRENT “PROSTATITIS”

**Defined by**
- Recurrent symptoms of pelvic pain and “cystitis”
- Episodic in nature
- With or without prostate tenderness

**Proven urinary tract infection?**

- **Yes**
  - Localization studies
  - **Negative for prostatic infection**
  - **Positive for prostatic infection**
  - Diagnosis Chronic Bacterial Prostatitis
  - Workup for recurrent urinary tract infections
  - **Symptoms resolved?**
    - **Yes**
    - Infection resolved?
      - **Yes**
        - Cured
      - **No**
        - Further treatment
          - Satisfactory response?
            - **Yes**
              - Removal of infective tissue by TURP or open surgery if all other options fail
            - **No**

- **No**
  - Urine culture when symptoms of “cystitis”
    - **Positive**
      - Treat with non-prostate penetrating antimicrobials
      - Treatment - appropriate antimicrobials for adequate time
    - **Negative**
      - Entry from Algorithm III

1. It is important to establish whether the “cystitis” episodes are associated with UTIs. If not, urine culture should be obtained during subsequent symptomatic episodes. If urine cultures are negative, consider CPPS. If cultures are positive, treat with non-prostate penetrating antimicrobials such as nitrofurantoin or a beta-lactam to treat the acute cystitis and preserve the opportunity to identify the pathogen via the 4-glass test.

2. Evaluation for Chronic Bacterial Prostatitis (NIH Category II)
   - **Recommendation 1**: Traditional 4-glass or 2-glass test for WBC count and culture. (3:A)
   - **Recommendation 2**: Culture of semen has a low sensitivity but is reasonable in selected men (e.g., infertility). (3:D)
   - Repeat localization culture 3-6 months after completing therapy.

3. Treatment for Chronic Bacterial Prostatitis (NIH Category II)
   - **Recommendation 1**: Oral fluoroquinolone therapy for susceptible bacteria for 4-6 weeks. (2:A)
   - **Recommendation 2**: TMP-SMX (or other antimicrobials) for fluoroquinolone resistant bacteria. (3:B)

4. Failure to eradicate CBP requires long-term antimicrobial management with suppressive or intermittent treatment of acute cystitis or resection of the infected tissue. Radical TURP is effective in only one-third of patients [1] and can cause urinary incontinence; therefore, surgical removal of infected tissue should only be considered as a last resort if all other measures fail.
III. CHRONIC PELVIC PAIN SYNDROME

**Defined as**
- No previous infections
- Persistent chronic pelvic pain symptoms
- With or without LUTS
- With or without prostate tenderness

**Entry from Algorithm II**

**Evaluation**

**Evidence of prostate inflammation?**
- Positive prostatic fluid - WBC or bacteria

**If No**
- Uroflow
- Abnormal: Urodynamics
  - Positive: Treatment for LUTS
  - Negative: Empiric Treatment

**If Yes**
- Bacteria ± WBCs
- Algorithm II

**If Positive prostatic fluid - WBCs only**
- Consider 4-6 weeks of antimicrobial treatment

**If Positive prostatic fluid - Bacteria ± WBCs**
- Optional evaluation
  - Semen analysis and culture
  - Prostate imaging
- Treatment 2

**If Negative**
- Specialized urologic treatments
1. Evaluation for Chronic Prostatitis/Chronic Pelvic Pain Syndrome (NIH Category III)
   a. 4- or 2-glass test for WBC count and culture. (3:A)
   b. The NIH-CPSI (see page 40) should be used for symptomatic evaluation and assessment of treatment
      but not as a diagnostic tool. (3:A)
   c. Physical examination of the prostate and other pelvic structures (e.g. myofascial trigger points). (3:B)
   d. Psychological evaluation in selected patients may be warranted. (3:B)

2. If prostatic fluid tests positive for WBCs but not for bacteria, proceed to antimicrobial treatment as per the
   algorithm above. If prostatic fluid tests positive for bacteria (regardless of the presence or absence of
   WBCs), the patient is positive for prostatic infection as detailed on Algorithm II: Apparent Recurrent “Pro-
   statitis,” and we recommend following the course specified there. It is possible the patient has a positive
   prostatic infection (which can be treated via Algorithm II) as well as non-infective Chronic Pelvic Pain syn-
   drome, in which case both algorithms must be utilized.

3. Treatment
   a. Lifestyle intervention
      i. Diet
   b. Behavioral treatment
      i. Pelvic floor relaxation
   c. Drug Therapies
      i. Alpha adrenergic
      ii. Nonsteroidals
      iii. Analgesic
      iv. Neuromodulating agents
      v. Muscle relaxants
      vi. Immunomodulating agents
      vii. Quercetin and other phytotherapies
      viii. Mepartricin
   d. Additional Therapies
      i. Acupuncture
      ii. Pudendal nerve modulation
      iii. Electromagnetic stimulation
Committee 3A

Epidemiology and Natural History of Benign Prostatic Hyperplasia

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E. Lee (Korea),
R. Sahabudin (Malaysia),
K. Sasidharan (India),
J. Stanford (USA),
T. Tsukamoto (Japan),
L. Zhou (China)
I. INTRODUCTION

II. DESCRIPTIVE EPIDEMIOLOGY

III. RISK FACTORS

1. SEX STEROIDS AND HORMONES
2. GROWTH FACTORS
3. ERECTILE DYSFUNCTION
4. CARDIOVASCULAR DISEASE
5. LIFESTYLE: DIET AND EXERCISE
6. OVERALL SUMMARY

IV. NATURAL HISTORY

1. CLINICAL MANIFESTATIONS OF BPH
   a) Lower Urinary Tract Symptoms
   b) Acute Urinary Retention (AUR)

2. PHYSIOLOGIC MEASURES
   a) Urinary flow rate (usually expressed as the maximal urinary flow rate or Qmax)
   b) Post-void Residual Urine
   c) Pressure-flow Study Parameters

3. ANATOMIC MEASURES (TOTAL PROSTATE VOLUME, CENTRAL HYPECHOIC VOLUME)

4. BIOCHEMICAL MEASURES

5. OVERALL SUMMARY

V. GENETIC MARKERS OF RISK AND PROGRESSION FOR BPH

1. INTRODUCTION

2. BENIGN PROSTATIC HYPERPLASIA (BPH) SUSCEPTIBILITY GENES

REFERENCES
Benign prostatic hyperplasia (BPH) is a histologic condition that is common among older men. BPH ultimately produces its morbidity through lower urinary tract symptoms (LUTS) and outcome events such as acute urinary retention, urinary tract infections, and rarely, obstructive kidney disease. The histologic condition is linked to LUTS and outcome events through incompletely defined mechanisms that involve but are probably not limited to prostate enlargement and bladder outlet obstruction with secondary bladder changes in response to obstruction. Other disease processes that affect the lower urinary tract can produce LUTS, which are not specific for BPH. Similarly, not all men with histologic BPH will have clinical manifestations. Strictly speaking, then, studies of the epidemiology of BPH should focus on the distribution and determinants of the histologic condition. However, the epidemiology of the clinical manifestations of BPH is of much greater relevance to the health of older men. Moreover, documentation of the presence of histologic BPH, or even urodynamic evidence of bladder outlet obstruction, require invasive testing that is usually not practical, particularly in large, population-based epidemiologic studies. Therefore, most epidemiologic studies focus on prostatic enlargement and clinical manifestations suggesting BPH, with the caveat that not all counted “cases” will necessarily have histologic BPH, and that even if they do, the clinical picture may actually be attributable to another cause.

While much has been learned from such epidemiologic studies, there is still much that is not understood. Indeed, despite advances in treatment, the pace of advances in knowledge about causes and risk factors for BPH and its clinical manifestations is not as great as might be hoped. This relative lack of progress might be due to the lingering effects of the historical perspective that BPH is a natural consequence of aging and that its consequences are solely related to quality of life. Alternatively, some of the slow progress may be due to vexing design and measurement issues.

In regards to design, one of the most important issues for future studies is to ensure the alignment of the study population with the epidemiologic question being addressed. For example, it may not be appropriate to rely on subjects recruited from urology practices to generate population inferences. It might be reasonable to use such a sample to characterize patients normally seen by a urologist but even so, one must be concerned about referral patterns that can vary from practice to practice and the particular characteristics that might affect the mix of study subjects. A particularly problematic misalignment is the attempt to draw population inferences from the experience of subjects enrolled in the placebo arms of clinical trials. Selection factors and placebo and Hawthorne effects can all lead to outcomes that would be different than in the general population. The discrepancies between outcomes in the community and those in trial cohorts have been empirically demonstrated [1, 2].
In the search for risk factors for BPH with clinical manifestations, another design issue is the ability to sort out temporal relationships. Comparisons across settings and countries may lead to insights about etiology but may always be suspect because of the ecological fallacy [3]. Equally of concern is the practice of drawing conclusions about the risk of developing signs of BPH based upon cross-sectional data. That is, a man with moderate-severe lower urinary tract symptoms today may have developed them over the past several months or over the past several decades. Clinically, these represent different entities and it is probably of greater interest to identify risk factors for “aggressive” disease as opposed to more indolent forms. This is difficult to do in cross-sectional studies.

In addition to these basic design issues, there are several measurement issues that should be considered. As yet, there is no widely accepted working epidemiologic definition for “clinically important BPH.” That lack of consensus in part reflects the uncertain mechanisms that link the histologic condition with its clinical manifestations. Several studies have highlighted that even the basic prevalence of clinically important BPH is very sensitive to the working epidemiologic decision applied (Figure 1) [4, 5]. Each of the clinical manifestations of BPH is a syndrome, much like heart failure. Each clinical presentation has multiple possible etiologies. However, this situation presents an opportunity in that comparisons of the patterns of these signs and symptoms can give some insight into the underlying pathology. Thus, future studies should not focus solely on LUTS but also assess the constellation of other signs and symptoms related to BPH. And even if not their primary focus, future studies must account for other conditions that might result in LUTS [6]. Finally, studies should consider the spectrum of severity of the signs and symptoms, and not just dichotomize them. By examining them as quantitative traits, there will be increased power to detect associations by avoiding the use of arbitrary cutpoints and consequent misclassification.

This report reviews new data on the epidemiology and natural history of BPH and its clinical manifestations, focusing on new developments since the last International Consultation report on this disease in 2000.

II. DESCRIPTIVE EPIDEMIOLOGY

Since the previous report of this Consultation, additional studies have assessed the occurrence of LUTS in the community setting. In a study conducted in Surahammar, Sweden, [7] all men ages 40-80 years were asked about stress incontinence, post-void dribbling or urgency. If they answered yes to any, they were asked to complete the DAN-PSS. The two-stage design and use of DAN-PSS make it difficult to compare the results to other studies. Andersson, et al

![Figure 1. Prevalence of clinical BPH in men aged 55-74 years based on various different case definitions [39].](image)
[8] surveyed men in two Swedish counties. Among the nearly 40,000 participants, the prevalence of moderate-severe LUTS based on the IPSS increased from 12% in men ages 45-49 years to 38% in men ages 70-79 years. The correlation between IPSS score and age ($r_s=0.25$, $p < 0.001$) was similar to correlations from other population-based studies.

Logie, et al., [9] used the General Practice Research Database from the UK to evaluate the prevalence of LUTS. The investigators used a broad definition of LUTS by identifying any mention of diagnoses, signs and symptoms of LUTS, or BPH; but excluded LUTS mentioned in conjunction with a diagnosis of Parkinson’s disease, diabetes or concurrent urinary tract infection. As with virtually every study, they found a dramatic increase in prevalence with age, from 3.5% for men in their forties to more than 30% for men age 85 years and older. The estimated incidence of these diagnoses increased from about 5 per 1000 person-years among men ages 45-49 years to more than 50 per 1000 person-years among men in their eighties (Figure 2).

These authors’ attention to other diseases that may cause LUTS is somewhat unique in the field despite an emphasis on the importance of this step in diagnostic and treatment guidelines [10, 11]. Data from the baseline recruitment of the Olmsted County Study [6] demonstrate that over ten percent of men in their seventies have a condition other than BPH that could cause LUTS and in 1990, 20% of men in their seventies had a prior surgical procedure on their prostate, which might cause an underestimation of the impact of BPH if judged by measurement of current symptoms alone.

Two large international studies recently reported on the prevalence of LUTS in different populations. Boyle, et al. published prevalence rates from the four centers in the UrEpik study [12]. While there were slight differences across the four centers, there was a remarkable concordance in the age-related increases in prevalence. Similar results were obtained in the Multinational Survey of the Aging Male, [13] with the prevalence of moderate-severe LUTS increasing from 22% among men ages 50-59 years to 45% among men ages 70-80 years.

Several unique populations also have been surveyed in recent years. Tuncay Aki, et al [14] surveyed 257 men from a rural village of Turkey. The prevalence of moderate-severe LUTS, as assessed by the IPSS, increased from 10% among men in their forties to 40% among men age 70 years and older. Campbell conducted a study of Ariaal men in Northern Kenya [15] and found that among the men ages 22 to 96 years, the overall prevalence of moderate-severe LUTS was 49% and that it was higher in the settled men as compared to the nomadic (40% vs. 60%, p=0.05). Age was positively correlated with IPSS in both subpopulations. In a study conducted in New Zealand, Gray, et al [16] found a similar strong relationship of the prevalence of LUTS measured with age in men of European descent but not among men of Maori or Pacific Island descent. The authors suggested that this finding may be due to a “premature aging process” but this notable exception to the nearly universal finding of a direct correlation of LUTS with age deserves further follow-up.

In summary, there have been a number of studies in recent years that have replicated the fairly consistent finding of age related increases in the prevalence of LUTS. There remains some variation in absolute age-specific prevalences across settings and it is difficult to determine whether this variation represents true differences or differences in interpretation of the questions on the IPSS, despite rigorous efforts at
The expansion of studies beyond the use of survey instruments may help disentangle these potential explanations. It is encouraging that several studies have attempted to be more comprehensive in their assessment of LUTS. These studies have highlighted the need to take treatment and secondary causes into account. Moreover, more studies have begun to change their focus to risk (incidence) rather than prevalence. The latter is a good measure for population burden and the number of men who are potentially treatable, but prevalence does not help much with understanding etiology or potential targets for prevention or treatment.

III. RISK FACTORS

The purpose of this section is to review the recent findings on risk factors for clinical manifestations of BPH. In the following paragraphs, new data are summarized on hormonal factors, growth factors, comorbid conditions and lifestyle that have been published since the last Consultation. There have been a number of comprehensive reviews of risk factors for clinical manifestations of BPH including the exceptional review in 1992 by Guess, [17] the most recent summary from the International Consultation, [18] and a recent article by Newhouser et al [19]. For studies published since 2000, we describe the study sample, findings and summarize the state of knowledge for each of these classes of potential risk factors.

1. SEX STEROIDS AND HORMONES

It is well accepted that BPH is androgen-dependent, as castrate men do not develop BPH. Moreover, hormonal therapies are effective in reducing the morbidity associated with this condition. Despite these observations, there has been relatively little data demonstrating a relationship between circulating sex steroid levels, either androgens or estrogens, and clinical manifestations of BPH at the population level. To this end, three studies have been published in recent years that have attempted to assess this association.

The first was based on the Massachusetts Male Aging Study [20]. In this study, 1,709 men were recruited from randomly selected cities and towns near Boston, Massachusetts, in the United States. Baseline blood samples were measured for testosterone, free testosterone, dihydrotestosterone, estrone and estradiol. The cohort was followed up by questionnaire for up to nine years. Men who reported frequent urination or difficulty urinating and were told by a health professional that they had an enlarged prostate or were surgically or medically treated for BPH were considered to have a clinical picture attributable to BPH. There was no association with any of the baseline hormone levels or ratios of hormone levels with this outcome.

Joseph et al. examined data from the Flint Men’s Health Study [21]. They studied a random sample of African-American men, ages 40-79 years, from Flint, Michigan, in the United States. The investigators found that androstenediol glucuronide, estrone sulfate and the ratio of estradiol to total testosterone were all directly associated with prostate volume after adjusting for age; while sex hormone-binding globulin was inversely associated with prostate volume. After further adjustment for body mass index, only sex hormone-binding globulin remained significantly associated with prostate volume. The authors recognized the limits of their cross-sectional design. It may be more appropriate to focus on the age-adjusted associations reported in this study, as adjustment for body mass index may be an example of “over-adjustment.”

Roberts et al [22] examined data from the Olmsted County Study. The study population is a random sample of Caucasian men ages 40-79 years from Olmsted County, Minnesota, in the United States. These men were recruited in 1990 and have been followed biennially thereafter. In the seventh biennial examination, serum levels of testosterone, bioavailable testosterone, and estradiol were measured and compared cross-sectionally with the IPSS, peak urinary flow rate, prostate volume and serum PSA level. There was no clear relationship between any one of the urologic measures and any hormone level alone. There was, however, a strong interaction between bioavailable testosterone and estradiol levels, in that among men with low levels of bioavailable testosterone, there was a monotonic increase in prostate volume across tertiles of estradiol; whereas no association was observed between estradiol and prostate volume among men with higher levels of bioavailable testosterone.

Thus, despite the evidence that histologic BPH is an androgen-dependent condition, there is still little evidence of an effect of hormone levels on clinical manifestations of BPH that is measurable at the population level. The crude observations related to castrated men represent extreme conditions. In less extreme conditions, modest associations may be missed due
to the complicated and redundant pathways and homeostatic mechanisms in sex steroid metabolism. That is, as androgen levels decline, there may be a resulting up- or down-regulation that compensates for these shifts. There is some indirect evidence for this hypothesis in the association in ratio measures in the Olmsted County Study. Moreover, circulating levels of hormones may not be a good indication of intracellular levels where the biologic activity occurs. There may be some hope in sorting out this complex relationship through better-designed longitudinal studies with multiple outcome measures and in looking at the interaction between genes involved in the androgen and estrogen pathways and their interplay with circulating hormone levels.

2. GROWTH FACTORS

As with sex steroids, growth factors are thought to be important in the etiology of histologic BPH. In particular, insulin-like growth factor 1 (IGF-1) is thought to work through a proliferative mechanism and/or anti-apoptotic mechanism [23]. Thus, a number of investigators have attempted to examine the association between circulating growth factor levels and clinical manifestations of BPH at the population level.

Stattin and colleagues [24] performed a nested case-control study within the Northern Swedish part of the MONICA Trial. The investigators identified 60 men who had been treated for a clinical picture attributed to BPH and a set of controls, matched on age, sex and city. The investigators thawed plasma samples that had been frozen at -20ºC for 31/2 years and measured IGF-1 and its primary binding protein IGFBP-3. These investigators found a modest but statistically insignificant trend in the association between IGF-1 levels and a clinical picture suggesting BPH, after adjustment for IGFBP-3. While longitudinally designed, the very small number of men with BPH as they defined it limited their ability to identify trends.

Chokkalingam and colleagues [25] provided further insight by examining data collected as part of a case-control study of prostate cancer in Shanghai, China. For the substudy, cases were comprised of patients admitted to Shanghai hospitals with a diagnosis compatible with BPH. Control subjects were randomly selected from household registration records and found not to have prostate cancer by digital rectal examination and transrectal ultrasonography. These investigators found that plasma IGF-1 levels were higher in cases compared to controls (137.1 ng/ml vs. 122.6 ng/ml, p<0.01), but there were no differences in IGFBP-3 levels. There were, however, strong trends across the tertiles of plasma IGF-1 levels (direct) and for IGFBP-3 levels (inverse after adjustment for age and each other).

Sarma and colleagues [26] examined this association in the Flint Men’s Health Study. They found that prostate volume was not associated with IGF-1 levels but IGFBP-3 levels were directly associated with prostate volume. They found similar results in multivariable models accounting for other factors.

Roberts et al. examined data from the Olmsted County Study [27]. They found that IGFBP-3 levels were inversely associated with age, LUTS, prostate volume and serum PSA level and directly associated with peak flow rate. These associations all disappeared with adjustment for age, however. There was an inverse association between serum IGFBP-3 levels and prostate volume after adjustment for age and IGF-1 levels. This association was not present for symptoms or peak urinary flow rates.

More recently, Oliver and colleagues, [28] in a substudy of control subjects from a case-control study of prostate cancer in the UK found that IGF-1 levels increased with serum PSA level (r=0.14, p<0.001). Moreover, the relationship was stronger in older versus younger men (p=0.05).

Taken together, these results suggest that there is some association between growth factors and clinical manifestations of BPH that is detectable at the population level. It is not clear, however, whether it is the growth factor or its binding protein that is most important, but the data suggest that there may be some dependency between these two. Of interest are the discrepant findings from the Flint Men’s Health Study. As a group, these studies represent methodologic advances for epidemiologic studies of BPH in that they are all population-based rather than clinic or practice based. However, most of the studies to date, with the exception of the Swedish study, have not had a longitudinal component. This makes it difficult to sort out the temporal sequence and therefore cause and effect.

3. ERECTILE DYSFUNCTION

In recent years, several authors have tried to provide further insight into the potential association between clinical manifestations of BPH and erectile dysfunction (ED). Green and colleagues [29] reported on a study of men ages 55-70 years who were identified from patient lists of general practices in the United Kingdom. Of the 4,060 men invited, 2,064 partici-
pated. These men were asked about their ability to attain an erection sufficient for satisfactory sexual activity. Men with ED were compared to those without on the basis of prostate volume and peak urinary flow rate. While age was associated with both ED and prostate volume, these investigators found no association between ED and prostate volume or peak urinary flow rate.

Braun and colleagues [30] identified men between the ages of 30 and 80 years from a population registry of the Cologne region in Germany. Of the 8,000 men contacted, 4,489 participated. Men responded to a survey that assessed sexual function and the IPSS. In contrast to the findings by Green et al., these investigators found an association between sexual function and LUTS severity, for the entire population and within every age stratum.

Boyle and colleagues reported on data from the UrEpik study [12]. The sample was comprised of men between the ages of 40 and 79 years selected in four countries. Participants completed the O’Leary Brief Male Sexual Function Inventory [31] and the IPSS. These investigators found that in all four countries, there was an association between LUTS severity and erectile dysfunction and loss of libido after adjustment for age. These findings were replicated by Chung and colleagues using data from the Olmsted County Study [32]. In this study, all five domains of the Brief Male Sexual Function Inventory were associated with LUTS severity. These relationships persisted with adjustment for age, albeit they were somewhat attenuated.

With the exception of the study by Green et al., most studies have shown an association between ED and clinical manifestations of BPH, even after taking into account potential confounding by age (Table 1). To date, there is no clear explanation of this association, whether through a common pathway or some as yet unmeasured confounding. While these studies were community-based, all were cross-sectional. Longitudinal studies could, perhaps, clarify this relationship.

### 4. CARDIOVASCULAR DISEASE

Other investigators have attempted to provide insights into the relationship between cardiovascular disease and clinical manifestations of BPH. Michel et al [33] studied nearly 10,000 men who had sought treatment for clinical presentations attributed to BPH and were enrolled in a post-marketing study of tamsulosin. These men were sorted as to whether or not they had hypertension on the basis of measured blood pressure, diagnosed, or treated disease. Regardless of how hypertension was determined, there was an association between hypertension and both LUTS severity and peak urinary flow rate that persisted after adjustment for age. The interpretation of these findings in the population context, however, is difficult given the select sample. Weisman and colleagues examined the relationship between a clinical diagnosis of BPH and history of coronary heart disease [34]. They performed a chart review of 702 men seen in a urology practice. Serum PSA level was used as a surrogate for prostate volume after excluding men on medication or with a condition that

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**Table 1. Epidemiologic studies relating lower urinary tract symptoms with sexual dysfunction.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Population</th>
<th>Ages</th>
<th>Participation Rate</th>
<th>ED measure</th>
<th>Clinical BPH measure</th>
<th>Estimate</th>
<th>Strength of Evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green, et al. [29]</td>
<td>Cross-sectional</td>
<td>Patient lists from GP Clinics in UK</td>
<td>55-70</td>
<td>49%</td>
<td>Always able to attain erection sufficient for satisfactory sexual activity (No ED) vs. never able to attain an erection (complete ED) vs. intermediate</td>
<td>TRUS-estimated prostate volume and peak urinary flow rate</td>
<td>No difference across levels of ED</td>
<td>C</td>
</tr>
<tr>
<td>Braun, et al. [30]</td>
<td>Cross-sectional</td>
<td>Age stratified population sample from Cologne, Germany</td>
<td>30-80</td>
<td>56%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boyle, et al. [12]</td>
<td>Cross-sectional</td>
<td>Age stratified population samples from regions of UK, Netherlands, France and Korea</td>
<td>40-79</td>
<td>21% to 77%, by site</td>
<td>Brief Male Sexual Function Inventory</td>
<td>International Prostate Symptom Score</td>
<td>Age- and comorbidity-adjusted odds ratio (OR)</td>
<td></td>
</tr>
<tr>
<td>Chung, et al. [32]</td>
<td>Cross-sectional</td>
<td>Age stratified population sample from Olmsted County, Minnesota, USA</td>
<td>40-79</td>
<td>55%</td>
<td>Brief Male Sexual Function Inventory</td>
<td>American Urological Association Symptom Index (AUASI)</td>
<td>Age-adjusted Spearman rank correlation between AUASI and drive (r = 0.09), erectile function (r = 0.22), ejaculatory function (r = 0.22), problem assessment (r = 0.23) and satisfaction (r = 0.17)</td>
<td>C</td>
</tr>
</tbody>
</table>

*Strength of evidence codes: A= Randomized controlled trial, B= Cohort study or nested case control study, C= Case control or cross-sectional study, D= Ecologic study or Case series/case report.
would alter serum PSA level (n=562). Of the remaining 140 men, 3 of 32 in the low PSA group and 31 of 108 of the high PSA group had coronary heart disease. There was no adjustment for age in these analyses. Moreover, the measurements were of prevalent disease and prostate volume, making the temporal relationships difficult to sort out. Moreover, by recruiting subjects from a referral population, the potential for Berkson’s bias to influence the association was increased.

Meigs and colleagues [20] reported on data from the Massachusetts Male Aging Study. After adjustment for age, these investigators found an inverse association with measured systolic blood pressure and clinical manifestation of BPH.

In summary, based on these studies, there is only weak evidence of an association between clinical manifestations of BPH and cardiovascular disease.

5. LIFESTYLE: DIET AND EXERCISE

In recent years several investigators have attempted to look at lifestyle factors and their association with BPH. Lagiou and colleagues [35] conducted a hospital-based case-control study in Athens, Greece. Case subjects had surgery for clinical problems attributed to BPH and control subjects were selected from the same hospital, matched to the age frequency of prostate cancer cases collected in a parallel study. All men completed a semi-quantitative food frequency questionnaire adapted for the Greek diet. The investigators examined many food items for possible associations. Of these, only added lipids (margarine and butter) and potentially zinc demonstrated an association. Overwhelmingly, the results were negative.

Gass and colleagues [36] conducted a population-based cross-sectional study in Switzerland. Subjects completed a questionnaire that included the IPSS and reported whether or not they had had surgery for BPH. Alcohol intake, coffee intake and smoking habits were also assessed. Their results indicated that alcohol was inversely associated with surgery for BPH, coffee consumption was directly associated and smoking was inversely associated with clinical manifestations of BPH. The lowest prevalence of BPH surgery was noted among men with the heaviest alcohol consumption but no coffee consumption.

Meigs and colleagues looked at a variety of factors in the Massachusetts Male Aging Study cohort [20]. There was a trend towards greater physical activity (more than 860 k/cal/day) being protective against clinical manifestations of BPH. They also replicated the finding of an inverse association with smoking but found no association whatsoever with fat intake or alcohol consumption.

Lacey and colleagues [37] conducted a case-control study in Shanghai, China. They measured physical activity by questionnaire and converted the responses to metabolic equivalents. They found no association with a diagnosis of BPH and physical activity.

Overall, these several studies of lifestyle factors found no clear associations with clinical manifestations of BPH. Some of these negative studies may have been due to the cross-sectional and case-control study designs and the potential ambiguity about temporal relationships inherent in these designs. This limitation can be particularly problematic as activities can be affected by LUTS (need for proximity to rest rooms). Moreover, diet, and in particular fluid intake, may be changed in response to symptoms. Thus, it is still not clear whether the lack of strong associations is because they don’t exist or if there are methodologic issues and/or unmeasured confounders that explain the findings.

6. OVERALL SUMMARY

Over the last four years, there has not been a lot of new information about risk factors for BPH. Much of the work prior to this time used surgical therapy as an outcome. This definition can be problematic as factors related to access to and utilization of care may confound relationships. Moreover, factors that may make surgery a higher risk option could confound relationships as well. Even with the newer studies, many employ designs and methodologies that make it difficult to identify clear-cut associations. Even more so, the complex pathways and potentially mixed phenotypes make it very difficult to identify associations that may reflect risk factors or cause and effect relationships. While somewhat discouraging, this state of affairs actually presents an opportunity for new breakthroughs. Longitudinal studies of subjects with multiple occurrence measures relating to BPH may lead to important new insights about factors that might be related to its pathogenesis.

IV. NATURAL HISTORY

Prostatic enlargement due to histopathologic benign prostatic hyperplasia (BPH) is common in older men. In a significant proportion of these men, BPH
will lead to bladder outflow obstruction (BOO) or other urodynamically characterized abnormalities of the lower urinary tract such as detrusor overactivity, incomplete bladder emptying or even acute urinary retention (AUR). Although BPH rarely presents as a life threatening condition nowadays, it is recognised that it is a slowly progressive condition [38]. Nevertheless, the natural history of BPH is still incompletely described and understood, although our knowledge of the problem has significantly increased since the previous Consultation in 2000. The identification of factors that predict the occurrence of complications or clinical progression has become an important goal of analytic epidemiology because treatment strategies that could help to prevent progression are emerging.

Since there is no generally accepted epidemiological definition of clinically important BPH [39], the natural history is described separately for its various clinical manifestations (symptoms, bother, quality of life, acute urinary retention), pathophysiologic measures (urinary flow rate, post-void residual urine volume, pressure-flow study parameters), anatomic measures (total prostate volume, transition zone volume) and biochemical measures (serum PSA and its derivatives). Additionally, much attention has been given to the analysis of predictive factors for progression, particularly in terms of acute urinary retention (AUR) and the need for surgery or invasive therapy. Rates of surgery or invasive therapy for a diagnosis related to BPH are heavily influenced by capacity of the health care system and therefore problematic for comparing the natural history of BPH across countries.

The available information on the natural history of LUTS and/or BPH is derived from three types of sources:

1. Longitudinal population-based studies.
2. Control groups of men in randomised comparative studies of various treatment modalities.
3. Watchful waiting cohorts.

None of these designs is completely free of bias; the very fact that measurements are taken or questionnaires are administered may modify the disease’s natural history through the Hawthorne effect.

**1. Clinical Manifestations of BPH**

*a) Lower Urinary Tract Symptoms*

The prevalence of moderate and/or severe symptoms as measured by the IPSS has been described in cross-sectional surveys in various populations from many countries around the world [40]. The most important common theme that can be derived from these studies is an age-related increase in the prevalence of moderate to severe LUTS across different cultures.

In recent years, a number of papers have been published that have contributed to knowledge of longitudinal changes and outcomes related to BPH. In 1996, Jacobsen and colleagues [41] reported on longitudinal changes in lower urinary tract symptom severity in the Olmsted County cohort. In follow-up, there was a great deal of movement across categories of symptom severity. For example, of the men with mild symptoms at baseline, 86% and 73% still reported to have mild symptoms at the 18- and 42-month follow-up respectively. At the 18- and 42-month follow-up, 14% and 22%, respectively, of the men who reported mild symptoms at baseline had progressed to moderate to severe symptoms. In the Olmsted county study, an age-related increase of about 0.1 points per age year was noted in initial cross-sectional analyses [42]. Longitudinally, however, an average increase in IPSS (AUASI) of approximately 0.18 (95% confidence interval = 0.13, 0.24) points per year of follow-up was noted [42]. The average annual symptom score slope and variability in slope increased with age at baseline, with considerable within-subject variability (Figure 3).

A 5-year follow-up study has been reported from Austria in men (mean age 52 ± 12 years at baseline) originally participating in a free-of-charge voluntary health examination [43]. Of the eligible men, 53% responded at follow-up. In these men, IPSS had worsened in 50%, improved in 31% and remained unchanged (i.e. exactly the same number of points) in 19%. Moreover, the average IPSS had increased from 4.6 ± 0.05 to 5.5 ± 0.24, or about 0.18 points per year.

In another population-based study, the Krimpen study from the Netherlands, a 4.2 years follow-up has been reported [44]. Of the men, 10% improved (IPSS decreased ≥ 4 points), 20% worsened (IPSS increased ≥ 4 points) and 70% remained the same symptomatically. The average increase was 0.9 points in 4.2 years or 0.21 points per year. Men who were older had a greater increase from baseline during the follow-up period.

The Medical Therapy of Prostatic Symptoms (MTOPS) study was designed to determine whether therapy with the alpha-blocker doxazosin or the 5-
alpha-reductase inhibitor finasteride, alone or in combination, would delay or prevent clinical progression due to benign prostatic hyperplasia [45]. In the placebo arm of the MTOPS study, the incidence of a ≥ 4 points increase in IPSS (AUASI) was 36 per 1000 person-years [46]. At 4 years 14% of the men in the placebo-arm had a ≥ 4 points increase in IPSS. In contrast to the population-based studies, there was a mean reduction of 4.9 points (median 4.0 points) in the MTOPS placebo-group at 4 years. The median baseline IPSS in the MTOPS placebo-group was 17.0. In the Olmsted County study and the Krimpen study median baseline IPSS of 5 (for men aged 40-79 years) [42] and 4 points (for men aged 50-78 years) [47], respectively, was noted. The mean reduction in IPSS in the MTOPS placebo group probably reflects a regression to the mean among MTOPS subjects, who were selected because of higher symptom levels. On the other hand, it can be expected that the rate of progression in terms of a ≥ 4 points increase in symptom score is lower in the MTOPS placebo group than in a population based sample of men with a lower base line mean or median IPSS.

An average increase of about 0.2 points per year of follow-up has thus been found in several population-based studies with different designs. Furthermore, 50-80% of the individual men either improve or remain the same symptomatically after a follow-up of 1 to 5 years. Progression in terms of an increase in symptom severity is seen in 20-50% of the men depending on the definition of progression and the type of population that is studied.

The difference between cross-sectional and longitudinal data indicates that further studies of possible baseline selection bias as an explanation of these differences are necessary. It is already evident that changes as noted in population based studies cannot be extrapolated to placebo cohorts of clinical studies, and vice versa.

b) Acute Urinary Retention (AUR)

The epidemiology of acute urinary retention (AUR) is better understood in recent years and it has even been demonstrated from randomized trials that, probably, a portion of AURs can be prevented [47].

An AUR can occur spontaneously (that is without any external triggering event) or can be provoked by triggers like general or regional anesthesia, non-prostate related surgery, transurethral instrumentation, certain medications that have an effect on lower urinary tract function, excessive fluid (particularly alcohol) intake and sexual activity.

In older studies of the occurrence of AUR the range of the incidence rates has varied widely between 4 and 130 per 1000 person-years [48]. In more recent studies, rates range from about 2 to 18 per 1000 person-years (Figure 4).

Follow-up of the Olmsted County cohort has also provided new information on the occurrence of adverse events in community-dwelling men. Men enrolled in the cohort were passively followed through their medical record for the occurrence of outcomes such as acute urinary retention [48]. For the entire cohort, there were 8,344 person-years of follow-up during which 57 men developed acute uri-
nary retention for a rate of 6.8 per 1000 person-years. While the determination of factors precipitating an episode of acute urinary retention can be difficult through a review of medical records, there are several trends worth noting. Nearly half of all episodes of acute urinary retention in this cohort were associated with surgical procedures; nearly 90% of these were performed under general anesthesia.

The relative risk of AUR appeared to be increased for older men (3.5 to 11.6 times depending on symptom severity), those with moderate to severe symptoms (3.2 times), those with a urinary flow rate less than 12 ml/sec (3.9 times) and those with a prostate volume of more than 30 cm³ as measured by transrectal ultrasonometry (3.0 times). In a multivariate analysis, age at baseline, symptom severity and Qmax were independently predictive of AUR. The number of events among men in whom prostate volume measurements were available was too small to allow assessment of prostate volume in the multivariate analysis.

In the Health Professionals Follow-up Study 6100 men aged 45 to 83 years were followed for 3 years [49]. The data generated in this study could be subject to recall bias. Furthermore there was no information regarding the circumstances surrounding the episodes of AUR. An incidence rate of 4.5 per 1000 person-years was reported. As in the Olmsted County study, the incidence increased with age and symptom severity.

In the Proscar Long Term Efficacy and Safety Study (PLESS), 1367 men with enlarged prostates and moderate symptoms were followed for 4 years on placebo treatment [50]. In this group of men the incidence rate of AUR was 18 per 1000 person years.

The occurrence of acute urinary retention was investigated by Andersen et al. in a pooled analysis of three placebo-controlled, randomized clinical trials of two years of finasteride therapy (5 mg daily) in men with benign prostatic hyperplasia [51]. These studies involved a total of 4222 men with moderately symptomatic BPH: a total of 2113 men received finasteride and 2109 placebo: an incidence rate of 14 per 1000 person years was found.

In the placebo-arm of the MTOPS study an AUR rate of 6 per 1000 person years was noted, lower than the rate of 18 per 1000 person years reported in the previously-published Proscar Long Term Efficacy and Safety Study [47, 50].

Thomas and colleagues reported the follow-up of a cohort of men aged more than 45 years with urodynamically proved bladder outflow obstruction (BOO) who opted not to be treated surgically [52]. Of 1068 men with BOO, 581 were alive at the time of follow-up. Of these men 358 (62%) could be studied. 170 men were followed with watchful waiting for an average of 13.9 years. Of 29 men who failed during follow-up, 7 did so because of an AUR. The incidence rate of AUR therefore was 3.0 per 1000 person-years. Furthermore, in this follow-up study, there was no significant increase in urodynamic bladder outflow obstruction with time; how-
However, a small but significant reduction in detrusor contractility was seen. The authors identified older age at presentation and greater prostate size (as indicated by prostate length on urethral pressure profile) at baseline as the only significant factors that predicted future failure (either AUR or significant symptomatic deterioration leading to surgery).

Verhamme et al reported on a retrospective cohort study in the Integrated Primary Care Information (IPCI) database, a general practice research database in the Netherlands, during the period 1995-2000 [53]. The study population comprised all males aged 45 years or older without a history of AUR. Amongst 56,958 males with a mean follow-up of 2.8 years, 344 AUR cases occurred (incidence rate 2.2 per 1000 person-years). Of these cases 77 (22.3%) were provoked by surgical procedures. AUR was the first symptom of LUTS/BPH in 49% of the AUR cases occurring in men newly diagnosed with LUTS/BPH. Since 49% of AUR cases amongst the LUTS/BPH patients presented with AUR as the first symptom, i.e. without previous contacts with a health care provider, it is clear that earlier patient identification is needed if we aim to reduce the incidence of AUR by means of pharmacological treatment [54]. Presently this type of risk assessment is only possible in men who have seen a health care provider for an assessment.

2. PHYSIOLOGIC MEASURES

a) Urinary flow rate (usually expressed as the maximal urinary flow rate or Qmax)

In an analysis of cross-sectional data from the Olmsted County study the peak urinary flow rate (Qmax) decreased with age [55]. In a longitudinal analysis from the same study, younger men showed a lower percentage decrease per year than older men; men in their 40’s at baseline had a 1.3% per year decrease, whereas men in their 70’s had a 6.5% per year decrease [56]. The age related difference in rate of decrease in the longitudinal analysis is in contrast to the 2% decrease per year that was found to be consistent across all age groups in the cross sectional analysis. In sharp contrast to the decrease seen in the population-based studies, there was a median increase of 1.4 ml/sec in the MTOPS study placebo-group at 4 years [47].

b) Post-void Residual Urine

Post-void residual urine measurements are highly variable and single measurements with long periods in between measurements are not very helpful in the characterization of lower urinary tract function. The occurrence of acute urinary retention as an adverse outcome of BPH can be seen as a special pathophysiologic variant of this phenomenon.

c) Pressure-flow Study Parameters

Thomas and colleagues also reported on serial urodynamic parameters in the natural history study discussed above under AUR [52]. Amongst their 170 men followed with watchful waiting for an average of 13.9 years, pressure-flow studies showed no significant increase in bladder outflow obstruction with time; however, a small but significant reduction in detrusor contractility was seen. The prevalence of detrusor overactivity had increased with follow-up.

In analogy to the other parameters described above it should be clear that results from an analysis of selected clinical cohorts (placebo groups or watchful waiting cohorts) should be interpreted with caution. Extrapolating these results to the general population is inappropriate.

3. ANATOMIC MEASURES (TOTAL PROSTATE VOLUME, CENTRAL HYPOECHOIC VOLUME)

Prostate volume is an important factor in the clinical manifestations of BPH. In general, prostates of men with the LUTS suggesting BPH tend to be larger. Most often total prostate volume is assessed, but with transrectal ultrasound it is also possible to selectively measure the volume of the central part of the prostate [57]. The central part, surrounding the urethra, approximately corresponds to the transition zone of the prostate. It is this part of the prostate that is known to be most prone to histologic BPH [58].

Prostate volume is associated with age. The cross-sectional analysis of the population-based Olmsted County study has shown that among men aged 40-79 years, total prostatic volume increases approximately 0.6% per year of age, while central hypoechoic part of the prostate increased 2.3% per year [59].

In the longitudinal analysis of the same study an increase of 1.6% per year of follow-up was seen on average. Furthermore, men with larger prostates at baseline had a greater growth rate than men with smaller prostates [60].

In a population based cross-sectional study of men aged 55-75 years in Rotterdam, the Netherlands, Bosch et al have shown that total prostate volume increased 2% per year of age, whereas the central hypo echoic part of the prostate increased 3.5% per year of age [57].
In the MTOPS study’s placebo group, prostate volume increased by a median of 18% after 4 years, or 4.5% per year [46]. The mean baseline volume in the MTOPS placebo group was 35 cc, compared to 29 cc among Olmsted county men. This difference may explain the faster growth rate in the former study.

In spite of the interesting information from these studies, it remains unclear what proportion of men actually exhibit a growing prostate. In an analysis of prostate volumes measured longitudinally in the population-based Krimpen study among men aged 50-78 years, intra- and inter-observer variability of the transrectal ultrasound measurement was taken into account in order to define a “true” change in prostate volume [61]. In this study a true change in volume was considered to exist if there was a minimal absolute change of 10 cc or a minimal relative change of 26%. Based on these two different approaches and using the planimetric method of volume measurement, a real increase in prostate volume after a follow-up of 4.2 years is found in 22.6% or 16.3% of the men using the 26% cut-off or the 10cc cut-off, respectively. The 26% cut-off can detect a true increase with greater sensitivity than the 10 cc-cut-off. Irrespective of the cut-off, only a small percentage of men have a real decrease in prostate volume (<1.5%).

4. BIOCHEMICAL MEASURES

A number of cross-sectional studies have examined the correlation between serum prostate-specific antigen (PSA) and age, and between serum PSA and prostate volume. In one study, 16 men without BPH showed a PSA doubling time (PSAdt) ranging from 54 ± 13 years at age 40 to 84 ± 13 years at age 70, whereas doubling times ranged from 2± 13 years at age 40 to 17± 5 years at age 85, for 20 men with BPH [62]. In the same study, 18 men with prostate cancer were studied; those with local/regional disease had doubling times of 2.4 ± 0.6 years.

Cross-sectional data from the Olmsted County study have suggested that PSA increases 4% per cc of prostate volume and that serum PSA concentration is directly correlated with patient age and prostate volume, which are in turn correlated with each other [63].

In an analysis of longitudinally determined PSA values in men without prostate cancer from the Krimpen study, an increase of 5% in serum PSA per year of increasing age was found [64]. PSA has been identified as a proxy for prostate volume in men in whom prostate cancer has been excluded or is at least unlikely [65, 66]. This impression has been based on the analysis of data from clinical cohorts of men. These studies seem to indicate that an enlarged prostate (i.e. volume more than 30 cc) is very likely if serum PSA is 1.5 ng/ml or higher. PSA performs better in the estimation of prostate volume than digital rectal examination (DRE). The validity of this approach has been confirmed for men in the community [67]. Unfortunately, it is not possible to accurately estimate prostate volume based on the serum PSA level and patient age in individual men [66].

5. OVERALL SUMMARY

An average increase in IPSS of about 0.2 points per year of follow-up has been found in several population-based studies with different populations and designs. Furthermore, 50-80% of the individual men either improve or remain the same symptomatically after a follow-up of 1 to 5 years. Progression in terms of an increase in symptom severity is seen in 20-50% of the men depending on the definition of progression and the population being studied.

In the longitudinal analysis of the Olmsted County cohort, an increase of 1.6% in prostate volume per year of follow-up was seen on average. Furthermore, men with larger prostates at baseline had a greater growth rate than men with smaller prostates. In several studies, the central hypoechoic part of the prostate increased faster than the total prostate volume. PSA has been identified as a proxy for prostate volume; but, unfortunately, it is not possible to accurately estimate the prostate volume based on the serum PSA level and patient age in individual men.

An analysis of data from clinical cohorts and population-based data has shown that age at baseline, symptom severity, Qmax and prostate volume are predictive of the risk of AUR. Since about 50% of all new AUR cases among men with LUTS attributed to BPH present without previous contacts with a health care provider, it is clear that earlier patient identification is needed to reduce the incidence of AUR by means of pharmacological treatment. Presently this type of risk assessment is only possible in men who have seen a health care provider for an evaluation.
1. INTRODUCTION

Benign prostatic hyperplasia (BPH) is common among aging men. A better understanding of its pathogenesis is evolving, particularly from the development of molecular epidemiological studies of similar complex diseases. BPH is multifactorial and heterogeneous in its potential causes, which may include environmental, endocrine and genetic factors. The study of the interactions between genes and multifactorial diseases has expanded in recent years. DNA polymorphisms in genes involved in hormone synthesis, signaling and metabolism may, therefore, be involved in these changes. Furthermore, identification of the genetic determinants of age-related changes in the prostate could provide insights for risk assessment, prevention and new therapeutic targets.

2. BENIGN PROSTATIC HYPERPLASIA (BPH) SUSCEPTIBILITY GENES

Age-related changes in the size of prostate gland and associated lower urinary tract symptoms are variable. A large proportion of older men have prostate enlargement while only a few show prostate involution. The age-related prostate enlargement is due to benign prostatic hyperplasia marked by the development of fibro-muscular (mesenchymal) nodules that occur in the periurethral gland with associated glandular (epithelial) hyperplasia. The process takes years, with the first microscopic changes of BPH beginning at about age 35. The incidence of histologic BPH is fairly consistent across national and ethnic groups, with the prevalence of BPH increasing with age in all male populations. The etiopathogeny of BPH remains unclear. A disruption in the endocrine/autocrine-paracrine prostatic homeostasis, involving growth factors and steroid hormones, is likely a key factor. These molecular alterations may contribute to the pathogenesis of BPH and could be enhanced by specific biologic susceptibility or genetic predisposition in association with exposure to environmental factors.

Several specific etiologic hypotheses have been put forward based on histologic, hormonal [68, 69] and age-related changes resulting in an increase in the stem cell population and a decrease in cell death. There are two factors necessary for BPH to occur: the presence of dihydrotestosterone (DHT) and aging. The importance of DHT in prostate growth after puberty has been shown in patients with congenital deficiency of 5-a reductase, the enzyme responsible for conversion of testosterone to DHT [70]. Affected males have ambiguous genitalia at birth, but at puberty the availability of normal levels of testosterone causes [71] normal virilisation, functional erections, and ejaculation. The low levels of serum DHT, however, result in a vestigial prostate that never develops BPH.

The effects of aging on the prostate are manifold. Serum testosterone levels decrease due to decreased stimulation of Leydig cells and increased conversion of testosterone to estrogen in the peripheral tissues and the prostate [72, 73]. The relative roles of androgens and estrogens in inducing BPH are complex and not completely understood. It is known that patients with genetic disorders of androgen function have poor prostatic growth and that castration prior to puberty prevents BPH. Castration in patients who already have clinical manifestations of BPH has little therapeutic effect. A probable explanation is that androgens are required for the initiation and probably for progression of BPH, but not for its maintenance. The role of estrogen may be to initiate stromal hyperplasia, which, in turn, induces epithelial hyperplasia through androgen-induced mediators, such as growth factors. Prostate Growth Factor (PrGF) was the first growth factor isolated from prostate; it induces proliferation of fibroblasts and was subsequently identified as basic Fibroblast Growth Factor and renamed fibroblast growth factor-2 (bFGF/FGF2) [74]. Ultimately, endocrine pathways may only be permissive in BPH pathogenesis, influencing the prostatic microenvironment to modulate the direct mediators, peptide growth factors. The fibroblast growth factor family contains at least 14 members, including acidic (FGF1) and basic fibroblast growth factor (FGF2), keratinocyte growth factor (FGF7) [75] and FGF8, which are possibly involved in both normal and abnormal prostatic growth.

Although distinct receptors have been identified and described with high affinity for FGF1, FGF2 and FGF7, all members of the fibroblast growth factor family can signal through common tyrosine kinase receptors. Four independent genes (FGFR1, FGFR2, FGFR3 and FGFR4) encode for four FGF receptors with several isoforms, which share 50%-75% homology. However, fibroblast growth factors are not the only growth factors involved in BPH pathogenesis, as studies of gene expression in BPH have shown the
involvement of genes related to prostatic embryology, angiogenesis, and inflammatory cytokines as well [76, 77].

The possible role of familial factors in the development of BPH has been established, and a heritable form of BPH has been suggested with a dominant Mendelian transmission for a gene found in 7% of men with BPH (89% lifetime penetrance), providing the most likely explanation for familial aggregation of clinical manifestations of BPH with an early age of onset [78]. Recently, Pearson and colleagues have shown that a family history of clinical manifestations of BPH significantly enhances the risk of LUTS and surgery for BPH among family members [79].

Few allelic variations have been studied in men with BPH. Some genetic polymorphisms affecting androgen receptor or metabolism genes or growth factor pathways or alpha 1-adrenoceptor gene variants have been studied for associations with BPH. The frequencies of the different alleles of the alpha 1a-adrenoceptor polymorphism were not different between patients with BPH and normal subjects and did not provide any evidence to support the hypothesis that the alpha 1a-adrenoceptor gene is associated with BPH [80]. In another study, a variant NQO1 allele was slightly more frequent in benign prostatic hyperplasia patients but did not correlate with a significant risk for BPH [81]. It has been suggested that variability in an AR gene CAG repeat influences the development of symptomatic BPH, particularly in predicting obstructive urinary symptoms [82].

Cussenot and colleagues have also correlated AR gene CAG repeat length with age related prostate weight. The results showed a correlation between an increasing AR gene CAG repeat length and a lower risk for prostate overgrowth. These data support the hypothesis that AR gene CAG repeat length predicts BPH risk. Moreover, it has also been demonstrated that polymorphisms in CYP17 enzyme gene, involved in testosterone synthesis, are also correlated with the risk of BPH [83]. Conversion of testosterone to its major intraprostatic metabolite, dihydrotestosterone (DHT), is catalysed by the enzyme 5alpha-reductase type 2. The fact that different alleles of the 5alpha-reductase type 2 gene may be associated with different levels of 5-alpha-reductase activity and thereby perhaps BPH and prostate cancer risk has motivated studies of ethnic variation in the allelic distribution of this gene. Two main polymorphisms in the 5-alpha reductase gene have been studied. On the one hand, the VL89 mutation, which replaces valine at codon 89 with leucine, reduces 5alpha-reductase activity. On the other hand, the AT49 mis-sense substitution results in an alanine residue at codon 49 being replaced with threonine. Increased conversion of testosterone to dihydrotestosterone catalysed by the AT49 variant has been considered as a significant contributor to the incidence of prostate cancer in about 8% of African-American and Hispanic men in the US. Regarding BPH, no clear correlation with 5-alpha reductase polymorphisms have been establish with BPH risk [83, 84], but these polymorphisms change the power of inhibition of the enzyme by the 5-alpha reductase inhibitors finasteride or dutasteride [85]. Recently, investigators have shown that a specific polymorphism in the fibroblast growth factor for FGF8: FGFR4, as well as a transforming growth factor-beta 1 gene polymorphism could be both associate with the likelihood of prostate enlargement [86, 87].

Based on these findings, it would appear that genetic mechanisms can explain at least some component of BPH initiation and progression, justifying future studies that may lead to new therapeutic approaches based on pharmacogenomics.

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CHAPTER 3

Committee 3B

Epidemiology of Benign Prostatic Hyperplasia in Asia

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Traditionally in East Asian countries, socio-cultural atmosphere of accepting lower urinary tract symptoms (LUTS) as a natural part of aging process has been dominant. However, countries like Japan or Korea are quickly becoming an “aging society” and the ever-growing public interest in their health and well-being, public awareness towards BPH has been increasing rapidly along with the number of patients who visit hospitals seeking medical care for voiding symptoms. Thus, it can be expected that BPH will soon become a major issue with regard to public health and welfare in these countries, as is already the situation for many western countries.

I. PREVALENCE OF BPH

a) Histologic or Autopsy Prevalence

There have been no Asian studies about the presence of histologic BPH on a surgical specimen or, in the case of autopsy series, in whole prostates removed after death from men not dying of prostate conditions since 2000. In BPH patients, racial differences in cellular composition in Caucasian-American (CA), African-American (AA), and Japanese (JP) men were studied by Aoki et al. The stained cores were quantitatively analyzed for the percentage of the area with different cellular composition (stroma (S), epithelium (E), epithelial lumen (L), and glandular component (E + L = G)), using computer-assisted color imaging. The mean percent area density of S, E, and L in the prostate of CA men was 84.2, 12.1, and 3.8%, respectively; for AA, 84.4, 12.4, and 3.2%; for JP, 77.4, 15.2, and 7.5%. The S/E ratio is significantly lower in JP than in CA men. The S/G ratio is significantly lower in JP than in CA and AA men (Table 1). Overall, JP contained more glandular lumen and less stromal component than that of CA and AA. CA and AA showed no significant difference in cellular composition [1].

b) Clinical Prevalence

There is no globally accepted clinical definition of BPH, and, thus, clinical prevalence and incidence rates must be viewed in the context of the definitions chosen by the investigator. In 1996, Masumori et al. compared prostate volume and peak urinary flow rate in Japanese and American men 40 to 79 years old. Prostate volume and peak urinary flow rate were measured in eligible Japanese men and results were compared to those of a randomly selected American cohort. According to their data, mean prostate volume averaged 20.3 ± 10.6 ml. in Japanese and 29.6 ± 13.4 ml. in American men, while predicted cross-sectional increases with age decade were 1.5 and 5.5 ml, respectively. Peak urinary flow rate was higher but the decrease with increasing age was greater in Japanese men. Therefore, prostate volume is larger and the increase with age is more pronounced in American than in Japanese men (Figure 1). However, Japanese men may have a higher peak urinary flow rate and greater cross-sectional decrease with age[2]. Looking at the data from Korean men in a community-based study in 1998, the prevalence of LUTS among Korean men may actually be similar to that of westerners. According to the results of a community-based study, 23.2% of Korean men 50 or older complained of moderate to severe degree of LUTS (IPSS ≥ 8) likely to be associated with BPH based on evaluation with IPSS questionnaire.
Table 1. Cellular Component of the Prostates among Three Races

<table>
<thead>
<tr>
<th></th>
<th>CA</th>
<th>AA</th>
<th>JP</th>
<th>P value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHOLE PROSTATE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroma (%)</td>
<td>84.2 (1.9)</td>
<td>84.4 (1.5)</td>
<td>77.4 (1.2)</td>
<td>0.0042*</td>
</tr>
<tr>
<td>Epithelium (%)</td>
<td>12.1 (1.4)</td>
<td>12.4 (1.3)</td>
<td>15.2 (0.8)</td>
<td>0.1529</td>
</tr>
<tr>
<td>Epithelial lumen (%)</td>
<td>3.8 (0.6)</td>
<td>3.2 (0.3)</td>
<td>7.5 (0.5)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>S/E ratio</td>
<td>9.3 (1.5)</td>
<td>8.4 (1.4)</td>
<td>5.4 (0.4)</td>
<td>0.0730**</td>
</tr>
<tr>
<td>S/G ratio</td>
<td>7.2 (1.2)</td>
<td>6.6 (1.1)</td>
<td>3.6 (0.3)</td>
<td>0.0281***</td>
</tr>
<tr>
<td>TRANSITION ZONE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroma (%)</td>
<td>79.9 (2.9)</td>
<td>83.6 (2.2)</td>
<td>75.5 (1.3)</td>
<td>0.0481¶</td>
</tr>
<tr>
<td>Epithelium (%)</td>
<td>15.3 (2.3)</td>
<td>13.1 (1.8)</td>
<td>16.6 (1.0)</td>
<td>0.3903</td>
</tr>
<tr>
<td>Epithelial lumen (%)</td>
<td>4.9 (0.8)</td>
<td>3.2 (0.5)</td>
<td>7.9 (0.5)</td>
<td>&lt;0.0001§</td>
</tr>
<tr>
<td>S/E ratio</td>
<td>8.3 (1.6)</td>
<td>10.3 (2.6)</td>
<td>5.4 (1.4)</td>
<td>0.0956¶</td>
</tr>
<tr>
<td>S/G ratio</td>
<td>6.2 (1.2)</td>
<td>7.6 (1.6)</td>
<td>3.2 (0.2)</td>
<td>0.0329+</td>
</tr>
<tr>
<td>PERIPHERAL ZONE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroma (%)</td>
<td>88.5 (1.6)</td>
<td>85.0 (2.5)</td>
<td>78.9 (2.0)</td>
<td>0.0070***</td>
</tr>
<tr>
<td>Epithelium (%)</td>
<td>8.9 (1.2)</td>
<td>11.9 (2.1)</td>
<td>14.0 (1.3)</td>
<td>0.0741**</td>
</tr>
<tr>
<td>Epithelial lumen (%)</td>
<td>2.6 (0.6)</td>
<td>3.2 (0.5)</td>
<td>7.0 (0.8)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>S/E ratio</td>
<td>15.7 (3.4)</td>
<td>10.8 (1.7)</td>
<td>7.5 (1.7)</td>
<td>0.0637**</td>
</tr>
<tr>
<td>S/G ratio</td>
<td>12.5 (2.7)</td>
<td>8.3 (1.3)</td>
<td>5.4 (1.5)</td>
<td>0.0383**</td>
</tr>
</tbody>
</table>

S/E ratio, storoma-to-epithelial ratio; S/G ratio, storoma-to-glandular ratio; grandular component, stroma + epithelium.

Data presented as the mean with standard error in parentheses.

*JP p<0.01 vs. CA/AA, **JP p<0.05 vs. CA, ***JP p<0.05 vs. CA/AA, ¶JP p<0.01 vs. AA, §JP p<0.05 vs. CA, JP p<0.01 vs. AA, +JP p<0.05 vs. AA


Figure 1. Destination of prostate volume and maximum flow rate for participants in community-based study in Shimamakimura, Japan and Olmsted County, USA. (Data published in Masunori, N., et al: Japanese men have smaller prostate volumes but comparable urinary flow rates relative to American men: results of community based studies in 2 countries. J Urol, 155: 1324-1327, 1996)
Assessing by the age group, the prevalence of LUTS were 17.7%, 23.3%, and 35.3%, respectively, in those who were 50-59 years, 60-69 years, and 70 or older [3]. The comparison of prevalence of moderate to severe LUTS among various countries is shown Table 2A and 2B, based on the published data until 1999.

c) Racial Differences

To identify differences in prevalence of symptomatic BPH between different ethnic groups residing within metropolitan Kuala Lumpur, IPSS, Qmax and prostate size were measured from 575 volunteers aged 50 and above. The prevalence of moderate to severe lower urinary tract symptoms (LUTS) in Malays, Chinese and Indians were 70%, 59% and 50%, respectively (p=0.004). The mean prostate size was 25.1cc. There is no significant difference in term of maximal flow rate and prostate size among Malays, Chinese and Indians in Malaysia [4].

d) Medical Care

Because Japan is a rapidly aging society and men aged 55 or older are expected to increase from 15 million in 1995 to 21 million in 2010, the number of patients receiving treatment for BPH is increasing. Terai et al. analyzed several nationwide health statistics by the Ministry of Health and Welfare of Japan. The cross-sectional surveys revealed that the estimated total number of patients receiving treatment increased from 202,000 in 1987, to 335,000 and 590,000, respectively, in 1995 and 1998. Approximately 73-80% of patients were men aged 65 years or over and 94-98% were 55 years or older. The incidence of prostatectomies remained relatively stable at 50,000/year (3.0-3.8 prostatectomies /1,000 men aged 55 or over). The total cost of BPH therapy nearly doubled between 1988 and 1998. The total value of the market for medical therapy increased from 30-40 billion yen in 1989 to more than 80 billion yen in 1998. The application of alpha-blockers increased from 243,000 men (70% of all patients) in 1995 to 452,000 (77%) in 1998, whereas the number of patients taking antiandrogens, plant extracts and antispasmodic agents/ Ca antagonists (for pollakisuria), respectively, remained relatively stable at 60,000-70,000, 180,000 and 300,000 [5].

Table 2A. Prevalence of moderate to severe lower urinary tract symptoms among various countries.

<table>
<thead>
<tr>
<th>Country</th>
<th>Mode of evaluation</th>
<th>Age</th>
<th>No. of subjects</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>AUA-7</td>
<td>40-80</td>
<td>2,119</td>
<td>28</td>
</tr>
<tr>
<td>Canada</td>
<td>AUA-7</td>
<td>50-70</td>
<td>508</td>
<td>23</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>IPSS</td>
<td>55-74</td>
<td>502</td>
<td>30</td>
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<tr>
<td>Japan</td>
<td>AUA-7</td>
<td>55-87</td>
<td>961</td>
<td>27.6</td>
</tr>
<tr>
<td>Korea</td>
<td>IPSS</td>
<td>50-70</td>
<td>514</td>
<td>23.2</td>
</tr>
</tbody>
</table>

Table 2B. Prevalence of moderate to severe lower urinary tract symptoms according to age group in various countries.

<table>
<thead>
<tr>
<th>Countries</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50-59 years</td>
</tr>
<tr>
<td>USA</td>
<td>31</td>
</tr>
<tr>
<td>Canada</td>
<td>15</td>
</tr>
<tr>
<td>France</td>
<td>8</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>26</td>
</tr>
<tr>
<td>Japan</td>
<td>29</td>
</tr>
<tr>
<td>Korea</td>
<td>18</td>
</tr>
</tbody>
</table>

† Examine for subjects 70-74 years old † Examine for subjects 70 years or older
(Data published in Jeong MK. Epidemiology of BPH. Lee HM, editor; Textbook of benign prostatic hyperplasia. The Korean Prostate Society. 2004, pp 95-104)
e) Symptom Severity

International Prostate Symptom Score (IPSS) has been widely accepted to use in the research of LUTS and BPH. To evaluate linguistic validity of the Japanese version of International Prostate Symptom Score (IPSS) and BPH Impact Index (BII), the translation was performed by Homma et al. The developers generally approved the translation, but had 2 major concerns in the Japanese version: 1) “how often” in every sentence of English version was not translated into Japanese, and 2) the Japanese expression in the response choices of QOL index should be more emotional. The former concern was compromised by placing a sentence at the beginning of the questionnaire explaining that the response should be considered in frequency [6]. They also evaluate psychometric properties of the Japanese version of International Prostate Symptom Score (IPSS) and BPH Impact Index (BII). It was not significantly affected by age, symptom severity, institution type, or whether the patients were asked symptoms during the last week or during the last month. Japanese translations of IPSS and BII were shown to be reliable, valid and one-dimensional instruments in the Japanese patients. They would be equivalent to the original English questionnaires [7].

Masumori et al. evaluated the IPSS and QOL score of 235 outpatients having lower urinary tract symptoms and 242 participants in a community-based study of Japanese men aged 50 to 79 years old. Although the proportion of outpatients in the severe IPSS category (IPSS 20 to 35) was greater than that in the participants of the community-based study in each age decade, the proportion in the moderate IPSS category (IPSS 8 to 19) in both groups overlapped each other. On the other hand, the distribution of QOL scores was considerably different, with only a small portion of overlap in each age decade (Figure 2). Although scores for both voiding symptoms (incomplete emptying, intermittency, weak stream, and hesitancy) and storage symptoms (increased frequency, urgency, and nocturia) were significantly greater in outpatients than in study participants in each age decade, the difference was more obvious for voiding symptoms than for storage symptoms [8].

The approximate 50% of sixth and seventh decade males, classified to the middle level of symptom in Japan [9]. Their study focused on elucidating changes of the lower urinary tract symptoms (LUTS) and changing of voiding condition with aging in the subjects, who offered the health checks. They evaluated urinary function in 225 Japanese males (age 20-79), estimated IPSS, QOL score, uroflowmetry, residual urine. QOL scores, IPSS, prostate volume and residual urine were significantly increasing related to age, and advanced age was associated with a decline of voiding volume and Qmax.

Comparison of QOL scores and IPSS criteria demonstrated a significantly positive correlation with incomplete emptying and a weak stream. A significant negative correlation was found between the QOL score and Qmax. The distribution of middle level of symptom, divided by clinical guideline for BPH, significantly increased with age.

In 1999, data from community-based studies were published from Korea. It was reported that 27.8% of Korean men between the age of 40 to 89 have BPH when applying diagnostic criteria of enlarged prostate with size of 20 g or larger and IPSS of 8 or higher [10]. In another study, the prevalence of BPH in Korea was assessed to be 21.8% by implementing diagnostic criteria of enlarged prostate on digital rectal exam, maximum flow rate of 15mL/sec or lower, and IPSS of 8 or higher [11].

When assessed by the age group, the prevalence of BPH in Korea were 3.6%, 12.6%, and 24.1%, respectively, in those who were in their sixth, seventh, and eighth decade.

In Malaysia, 18.9 % and 39.6 % of the men voluntary participated the study were severely and moderately symptomatic, respectively. The mean peak flow rate of the subjects was 15.4 ml/s. 20.9 % and 55.2 % of the subjects had peak flow less than 10 ml/sec and 15 ml/sec, respectively. The prevalence of symptomatic benign prostate enlargement (BPE) was 39.3 %. The prevalence increased 8 % per decade from 41.7 % for men aged 50 to 59 to 65.4 % for men aged 70 or more [4].

f) Nocturia

Nocturia is one of main symptoms of patients with BPH, although it is not specific. Homma et al. studied the relationship of nocturia with the IPSS in men with lower urinary tract symptoms due to BPH in 219 consecutive Japanese men. The results indicate that the nocturia score is least specific to symptoms associated with BPH or least sensitive to the thera-
Figure 2. Destination of QOL scores for participants in community-based study and outpatients having LUTS in each group in Shimamaki-mura, Japan

peutic effect on symptoms. This finding may be related to the high nocturia score in the age matched control population [12]. Similar results were obtained from the study of 505 newly diagnosed patients with symptomatic BPH [13]. Patient age, score of urgency, and functional bladder capacity were each significantly associated with nocturia.

Tamsulosin therapy and TURP significantly reduced the number of episodes of nocturia in 17.9% and 32.2% of patients, respectively. These rates of improvement were lowest for nocturia among the seven individual symptom scores. They also examined the prevalence of and risk factors for nocturia in Kurashiki city and the surrounding area, a rural area in Japan [14]. They collected data on 4568 men as well as 1949 women who participated in a multiphasic health screening. Overall, 1856 individuals (28.5%) answered that they arose to urinate at least twice during the night. This rate increased with age from 16.5% in individuals younger than 50 to 60.0% in those older than 69. Surprisingly, gender was not associated with nocturia. In male individuals, BPH was an independent positive risk factor (OR 1.35). Hypertension (odds ratio [OR] 1.64) and DM (OR 1.70) were other independent positive risk factors for nocturia. On the other hand, current smokers who smoked 20 or more cigarettes per day were less likely to have nocturia than non-smokers (OR 0.72).

**g) Bother, Interference, and Health-related quality of Life**

Bother and interference with activities of daily living caused by each factor of LUTS are not equal. To investigate which factors are most bothersome to preoperative patients with BPH a total of 423 newly diagnosed patients and 388 preoperative patients with symptomatic BPH were evaluated. Japanese patients with BPH generally suffer from weak stream, feeling of incomplete emptying and nocturia in all disease phases. Frequency is problematic for newly diagnosed patients and urgency is problematic for preoperative patients as well. Symptom-specific QOL of BPH patients cannot be estimated by physically measurable variables [15].

In Malaysian men with clinical BPH, the commonest bothersome symptoms were nocturia (56 %), frequency (50.4 %) and sense of incomplete voiding (43.5 %). A good correlation was found between the total symptom score and the single disease-specific quality of life question (r=0.69, p<0.001). The correlation between IPSS and peak flow rate (r=-0.22, p<0.001) and prostate volume (r=0.11, p=0.009) was weak. There was no correlation between IPSS and age (r=0.06, p=0.17) [4].

**h) Urethral Function**

Nakai et al. examined the potential correlation between urethral function and LUTS in Japanese men with BPH. There was a positive correlation between hesitancy and detrusor bladder neck dyssynergia (P = 0.0011) and between incomplete emptying and low bladder neck pressure at maximum cystometric capacity (P = 0.0425). The hesitancy proved to have no correlation with bladder neck opening time.

Urodynamic evaluation of urethral function was beneficial for attributing LUTS to clinical BPH. Among various parameters, detrusor bladder neck dyssynergia (P = 0.0011) was the most specific to clinical BPH, suggesting it to be a situation where a steep rise in bladder neck pressure or prostatic urethral pressure remains greater than the increasing intra-vesical pressure, resulting in sustained difficulty in opening the bladder neck and subsequently the subjective sensation of hesitancy [16].

**i) Clinical BPH and PSA**

Mean serum PSA increased with age, and the correlation of PSA and prostate volume was determined to be statistically significant in each cohort of age. A correlation coefficient ranged from 0.315 to 0.439 from the data of 218 Japanese patients confirmed to have BPH by histological examination [7]. Gupta et al. compared the relationship between serum prostate specific antigen (PSA) and indexes of prostate volume in Japanese men with the one in white men. PSA, total prostate volume and transition zone volume increased almost linearly with age.

On univariate regression with age with each successive decade total prostate volume increased by 10.65% (95% CI 5.4 to 16.2), transition zone volume increased by 20.84% (95% CI 11.84 to 30.56) and the transition zone index increased by 3.1% (95% CI 1.66 to 4.57). On multivariate analysis the PSA-total prostate volume relationship was statistically independent of age. The study suggested that Japanese men might produce or release more PSA per unit prostate volume than white men (Figure 3) [18].
There have been reports of analytical studies addressing the polymorphism of several genes relating to BPH in Japan since 2000. The CYP17 gene (CYP17) codes for the cytochrome P450c17alpha enzyme, which mediates two key steps in the sex steroid synthesis. There is a polymorphism (a T-to-C substitution) in the 5′-untranslated region, which may influence the transcription level of CYP17 mRNA. Habuchi explored the association between CYP17 polymorphism and a risk of BPH in a Japanese population. There was a significant difference (P < 0.05) in the genotypes between BPH patients and male controls. Men with the A1/A1 CYP17 genotype had an increased risk of BPH (odds ratio (OR), 2.44; 95% CI = 1.26-4.72) compared with those with the A2/A2 genotype [19]. They also focused on the association of polymorphisms in the 3′-untranslated region (3′UTR) of the vitamin D receptor (VDR) gene with BPH in Japanese men. There were significant differences in the CC versus TC + TT genotype distribution between BPH patients and male controls (P=0.041). Males with the TC or TT genotype had a 1.51-fold increased risk of BPH (95% CI=1.02-2.24, P=0.041) compared with those with the CC genotype, therefore suggesting the dominant effect of the TGFB1 T allele on development of BPH [22].

II. GENE POLYMORPHISM

Transforming growth factor-beta 1 (TGF-beta1) plays a significant role in regulating the proliferation and apoptosis of prostate epithelial and stromal cells. Li explored the association between the T (Leu) to C (Pro) polymorphism at codon10 of the TGF-beta1 gene (TGFB1) and the risk of BPH in 221 patients and 303 male controls in Japan. Insulin-like growth factor-I (IGF-I) also plays an important role in prostate growth, hyperplasia, and carcinogenesis. Circulating IGF-I levels may be modulated by a genetic cytosine-adenine (CA) repeat polymorphism in the promoter region of IGF-I. The 19-CA-repeat allele (19-allele) was more frequently observed in BPH patients compared with the controls (BPH versus control: P=0.001). Compared with non-carriers of the 19-allele, men homozygous for the 19-allele had a significantly increased risk of BPH (age-adjusted odds ratio (aOR) = 3.53, 95% CI = 1.32-9.46, P=0.012), and those heterozygous for the 19-allele also had an intermediate increased risk of BPH (aOR = 1.66, 95% CI = 1.14-2.43, P=0.009). The 19-allele of IGF-I appears to increase the risk of BPH with a gene dosage effect in the Japanese population [24].
Levi et al. have considered trends in mortality from benign prostatic hyperplasia (BPH) over the last decades in Europe and, for comparative purposes, the USA and Japan. Between the early 1950s and the late 1990s, overall mortality from BPH in the European Union (EU) fell from 5.9 to 3.5 per million, and the decline since the late 1950s was over 96%. Comparable falls were observed in the USA and Japan, and BPH mortality rates in the late 1990s were lower than in the EU (1.8/106 in the USA, 1.4 in Japan) [25].

In Japan, Seki et al. conducted a questionnaire survey concerning the prevalence and preference with regard to various types of surgical treatment for benign prostatic hypertrophy (BPH), in order to gather preliminary data that may be helpful for standardizing the surgical treatment of BPH in Japan. The questions dealt with the type and volume of surgical treatment experienced previously, and the treatments which had been performed in each institute during 2000. Of the 155 institutes to which the questionnaire was sent, 70 responded (45% response rate). TUVP (transurethral vaporization of the prostate by thick-loop) was second to TURP (transurethral resection of the prostate) both regarding the volume of the surgical treatment that had been experienced previously, and the volume that had been performed during 2000. TURP was recognized as the most preferred treatment with regard to both cost effectiveness and overall usefulness, while TURF (transurethral radiofrequency thermotherapy) was preferred both for safety and reduced invasiveness, and open surgery for efficacy. Minimal invasive surgical treatment, such as TUVP, followed by ILCP (interstitial laser coagulation of the prostate) and TUMT (transurethral microwave thermotherapy) was recognized as the most preferable treatment for dealing with the prevalence from now on at general hospitals [26].

Because some Asian countries are rapidly becoming aging society and men aged 55 or older are continuously increasing. In Japan, the total value of the market for medical therapy increased almost twice from in 1989 to in 1998. In the community-base series, Asian men have much smaller average prostate volume than Caucasian-American or African-American people. On the other hand, Japanese contains more glandular tissue and less stromal component than Caucasian-American or African-American does. In Japanese men, total prostate volume and transition zone volume increased almost linearly with age. Japanese men might produce or release more PSA per unit prostate volume than white men.

The clinical prevalence of LUTS among Asian men seems to be similar to that of westerners. In Malaysia, the prevalence increased 8 % per decade from 41.7 % for men aged 50 to 59 to 65.4 % for men aged 70 or more. However, there is no significant difference in term of maximal flow rate and prostate size among Malays, Chinese and Indians in Malaysia.
In Japan, the studies focused on nocturia have been published. The results indicate that the nocturia score is least specific to symptoms associated with BPH or least sensitive to the therapeutic effect on symptoms. Patient age, score of urgency, and functional bladder capacity were each significantly associated with nocturia.

There were some analytical studies to address the polymorphism relating BPH. The polymorphism in several genes is associated with an increased risk of BPH. However, there were not enough data indicating the difference the incidence of specific gene polymorphism between in Asian men and other races. Additionally, no polymorphism is specific for BPH so far. Further studies are necessary to determine which polymorphism is definitive the symptomatic BPH.

REFERENCES

Tuberculous Prostatitis has been depicted as a rare disease in most of the case reports published [1, 2]. However, these reports do not reflect the true incidence since evidently many cases remain without reporting or diagnosed in many endemic pockets and susceptible groups especially in developing countries. The survey of currently accessible literature discloses a global distribution of its occurrence. Cases of tuberculous prostatitis have been reported from a number of countries such as India, Pakistan, Bangladesh, Cuba, Spain, Russia and Japan [3-8].

There are discernible indications that increase in infection with the human immunodeficiency virus (HIV) will escalate the incidence of tuberculous prostatitis [9,10]. HIV effectively blunts the cell-mediated immunity, the principal host defence against infection with mycobacterium tuberculosis and thus aiding and abetting the resurgence of the disease in many parts of the globe [11]. Recently a higher incidence of granulomatous prostatitis was found in patients who had been treated with intravesicle Bacillie Calmette-Guerin [12-14].

The issue of modes of tuberculous involvement of the prostate has generated divergent views. Two proposed routes of dissemination are haematogenous and direct intracanalicular extension or combination of both. There is overwhelming clinical, experimental and autopsy evidence indicating haematogenous route as the principal mode of tuberculous involvement of the prostate [15].

In developing countries where the disease has endemic pockets and patients seek medical redress with pronounced urogenital disease, an intracanalicular route of prostatic involvement should be reckoned as a distinct possibility. Analysis of such cases clearly discloses renal, ureteral and vesical disease stigmata, whereas there is no such consistent association when the prostate acquires tuberculosis exclusively through haematogenous routes. Documentation of tuberculous prostatitis does not differ drastically from tuberculous lesions elsewhere in the body. The traditional methods such as direct microscopy, and culture of the materials harvested from the lesions are validated investigations and assumes importance when histological picture is equivocal.

Clinical recognition of tuberculous prostatitis remains elusive in a fair number of cases and the disease is disclosed histologically only after transurethral resection or prostatic enucleation for prostatic hyperplasia and accidently in biopsies of the prostate [16, 17]. Symptoms of cases belonging to this subset are rather non-specific and merge with those produced by benign prostatic hyperplasia. Many patients in this group do not volunteer any previous history of tuberculosis nor bear any categorical stigmata of the disease. On going tuberculosis activity in the prostate produce a variety of symptoms such as urinary frequency, urgency, dysuria, bloody ejaculate and haematuria. These symptoms are more pronounced when prostatic urethra is involved through descending infection from concurrently infected bladder and upper tracts.

In Indian sub-continent where tuberculosis is endemic in many areas, tuberculosis is reckoned as one of the possible causes haematospermia and as well as refractory prostatitis. However, in one retrospective study in Japan of 107 patients with haematospermia by Jinzas, Noguchi and Hoska there was only one case of documented genital tuberculosis [18].

Previous history of pulmonary tuberculosis or tuberculous epididymo-orchitis can be extracted in some cases of tuberculous prostatitis and provide strong circumstantial clue for a clinical diagnosis. Tuberculous epididymo-orchitis may precede tuberculous prostatitis by several years or simultaneously coexist. This concomitance is more evident in the regions of significant disease prevalence such as India Evaluation of the male factor in infertile men infrequently discloses genital tuberculosis. A very recent study by Dhole revealed a history of urogenital inflammation in 5 – 12 % of men attending infertility clinics [19]. Spontaneous prostato-rectal fistulization due to entrenched tuberculosis of the prostate is an uncommon manifestation of the disease [20-21]. The rarity
of its reportage in literature is, perhaps, no true reflection of its occurrence. There is unpublished data emanating from few Indian centers indicating its incidence more frequent than literature would indicate [22]. Some of the tuberculosis afflicted prostates by virtue of their nodularity and induration may simulate adenocarcinoma of prostate on digital rectal examination [23]. However, the coexistence of carcinoma and tuberculosis of the prostate is extremely rare [24].

In recent literature there has been increasing stress on the value of CT and sonography in the documentation of intra and periprostatic events such as non specific and specific abscesses [25, 26]. Their utility in the diagnosis of advanced urinary tract tuberculosis has also been emphasized [27] (Figures 1, 2). Sonographic features of prostatic abscesses run generally parallel to CT findings. The echographic images of a prostatic abscess consist of hypoechoic cystic lesions inside an enlarged prostate [28].

The advent of cross-section imaging has dented to some extent the reliance on cystourethrography as the principal imaging modality in the diagnosis of tuberculosis of the prostate. There has also been some criticism in recent years of the non specific character of cystourethrography. Conventional cystourethrography, however, in selected cases continues to extract exquisite details of many intraprostatic events which tuberculosis engender. These include the depiction of intra prostatic cavitations, periprostatic tracks and overt prostatic-rectal fistulization (Figure 3). Few recent reports have described MR appearance of tuberculosis of the prostate [29]. Diffuse radiating streaky low signal intensity lesion in the prostate (watermelon skin sign) on T2 weighted images are presumably specific for tuberculosis of the prostate and not seen in carcinoma of the prostate [29].

Tuberculosis of the prostate shows adequate response to 6 months triple drug regimen of rifampin, ethambutol and isoniazid [30]. In earlier literature there was stress on relatively protracted course of chemotherapy stretching over 9 months for tuberculosis [31]. However, subsequent literature is replete with reports recommending shorter courses [32 – 33].

Prostatic tuberculous abscesses will require decompression. In selected cases some of them can be sonologically targeted and transcutaneously aspirated. However, transurethral deroofing is the most appropriate form of therapy in most of the abscesses.
The tenacious content and multi loculated character of some abscesses make the transcutaneous route rather ineffective. Prostate-rectal fistulas, a rare complication of tuberculosis of the prostate, spontaneously close in most of the instances after the institution of chemotherapy. Few larger and refractory ones, however, will require surgical closure and reinforcement with omental interposition [34].

Tuberculous prostatitis generally has no pernicious portents and is managed adequately by medical therapy and appropriate surgical intervention when indicated. The disease contour, however, is adversely impacted when it occurs in conjunction with infection with immuno deficiency virus (HIV) and long term survival is exceptional in such cases [22].

REFERENCE

22. Personal data and unpublished communication.

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Committee 5

Lower Urinary Tract Symptom: Etiology, Patient Assessment and Predicting Outcome from Therapy

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<td>IV. PHYSICAL EXAMINATION</td>
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Historically, the term "prostatism" was applied to almost all symptoms which referred to micturition in the older man. The term unfortunately implied that the cause of the problem was the prostate which, in later years, was found clearly not to be the case in many instances. The term Lower Urinary Tract Symptoms (LUTS: Abrams, 1994) has been adopted as the proper terminology to apply to any patient, regardless of age or sex, with urinary symptoms but without implying the underlying problem. "Prostatism" was initially divided into "irritative" and "obstructive" symptoms, but it became obvious that there was a poor correlation between so-called "obstructive" symptoms and urodynamic diagnosis of bladder outlet obstruction and also between so-called "irritative" symptoms and a urodynamic diagnosis that related to definable abnormalities seen during filling/storage. Additionally, the term "irritative" implied, to some people, an infectious or inflammatory process. Thus, the division of LUTS into "filling/storage symptoms and emptying/voiding symptoms" was suggested (Abrams, 1994), (Table 1).

LUTS replaced the term "prostatism" in the mid 1990s yet the urological community has continued to misuse the term "BPH".

The terminology with respect to prostate characteristics has also changed. Abrams (1994) was the first to suggest a reconsideration of the use of the term "BPH" and a redefinition of terminology. He pointed out that BPH was a histological diagnosis that had been shown to occur in 88% of men older than 80 years. He added that, in some patients, the prostate gland enlarged, and this condition should be distinguished from BPH and referred to as benign prostatic enlargement (BPE). In approximately half of patients with BPE, he stated that true bladder outlet obstruction resulted, a condition which should be termed benign prostatic obstruction (BPO). “BPH”

### Table 1. LUTS

<table>
<thead>
<tr>
<th>FILLING / STORAGE</th>
<th>EMPTYING / VOIDING</th>
<th>POST VOIDING SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>Hesitancy</td>
<td>Post-micturition Dribbling</td>
</tr>
<tr>
<td>Urgency</td>
<td>Straining to Void</td>
<td>Feeling of Incomplete Emptying</td>
</tr>
<tr>
<td>Nocturia</td>
<td>Poor Stream</td>
<td></td>
</tr>
<tr>
<td>Urgency Incontinence</td>
<td>Intermittency</td>
<td></td>
</tr>
<tr>
<td>Stress Incontinence</td>
<td>Dysuria</td>
<td></td>
</tr>
<tr>
<td>Nocturnal Incontinence</td>
<td>Terminal Dribbling</td>
<td></td>
</tr>
<tr>
<td>Bladder / Urethral (Pain)</td>
<td>Absent or Impaired Sensation</td>
<td></td>
</tr>
</tbody>
</table>
was previously an all encompassing term that included prostate size, benign prostate histology and all filling/storage or voiding/emptying symptoms thought related to the prostate pathophysiologically in the adult male. The current terminology recognizes the imprecise and misleading implications of the previous usage of this phrase. The terminology related to the prostate is currently expressed as follows:

- **BPH** - Benign Prostatic Hyperplasia. This term is used and reserved for the typical histopathological pattern which defines the condition.
- **BPE** – Benign Prostatic Enlargement. This refers to prostatic enlargement due to a benign cause, generally histological BPH. If there is no prostatic histologic examination available, then the term is presumptive of a benign cause for enlargement, usually assessed by digital rectal examination.
- **BPO** – Benign Prostatic Obstruction. This is a form of bladder outlet obstruction (BOO, see below). This term may be applied when the cause of the outlet obstruction is BPE, due to a benign cause, generally histological BPH.
- **BOO** is a term for any cause of bladder outlet obstruction, and defined by urodynamics. It should be noted that there are other causes of “BOO” than prostatic enlargement (Table 2).
- “LUTS suggestive of BPO”, recommended by the WHO-sponsored consultation on “BPH”, is the generic phrase to describe elderly men with filling/storage or voiding/emptying problems likely to be caused by an obstructing prostate.

The relationship between BPE, LUTS, and BPO can be pictured simply (Figure 1) or in a more complicated fashion (Figure 2).

The 5th International Consultation on “BPH” (Abrams et al 2001) and the International Continence Society’s 2002 Terminology Report has emphasized the importance of using the terms BPH/BPE and BPO/BOO correctly (Abrams et al 2002).

By putting male LUTS into proper context, with respect to the range of lower urinary tract dysfunctions (LUTD), the clinician has a better chance of understanding the causes of a man’s symptoms and focusing management accordingly.

We have tried to use these terms consequently and trust that it will make it easier to communicate the patient’s lower urinary tract and prostate status, thereby facilitating management.

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**B. LOWER URINARY TRACT SYMPTOMS**

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**I. DEFINITION OF SYMPTOMS**

LUTS are equally bothersome to men and women. Lower urinary tract symptoms (LUTS) greatly affect the quality of life (QOL). These symptoms are not specific to prostatic obstruction in men and are almost as common in women [Boyle et al 2003].

The term “Lower urinary tract symptoms” is used to describe patients’ urinary complaints without implying a cause (Abrams 1994). Lower urinary tract symptoms were defined by the standardisation subcommittee of the International Continence Society (ICS) in its latest report in February 2002 (Abrams et al. 2002).

LUTS are the subjective indicators of a disease or change in conditions as perceived by the patients, carer or partners and may lead him/her to seek help from health care professionals. Symptoms may either be volunteered or described during the patient interview. They are usually qualitative.

In general, lower urinary tract symptoms cannot be used to make a definitive diagnosis. However LUTS can also indicate pathologies other than lower urinary tract dysfunction, such as urinary infection. The clinician will make his/her best efforts to exclude other causes of LUTS.

Lower urinary tract symptoms are categorized as storage, voiding, and post micturition symptoms (Table 1).

1. **Storage symptoms** are experienced during the storage phase of the bladder, and include daytime frequency and nocturia.

   *Increased daytime frequency* is the complaint by the patient who considers that he/she voids too often by day. This term is equivalent to “pollakisuria” used in many countries.

   *Nocturia* is the complaint that the individual has to wake at night one or more times to void.

2. **Voiding symptoms** is the complaint of a sudden compelling desire to pass urine, which is difficult to defer.

   *Urgency* is the complaint of any involuntary leakage of urine.
Table 2. Causes of BOO

<table>
<thead>
<tr>
<th>Intraluminal</th>
<th>Mural</th>
<th>Extramural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethral stones</td>
<td>Bladder neck stenosis</td>
<td>BPE</td>
</tr>
<tr>
<td>Urethral neoplasms</td>
<td>Urethral strictures</td>
<td>Prostatic carcinoma</td>
</tr>
<tr>
<td>Foreign bodies</td>
<td>Meatal strictures</td>
<td>Penile clamps</td>
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<tr>
<td>Prolapsed ureterocele</td>
<td>Urethral neoplasms</td>
<td></td>
</tr>
</tbody>
</table>

From Frymann and Abrams (2000)

Figure 1. The diagram shows the three basic features of LUTS/BPO: Symptoms, enlargement and obstruction. These overlap but are independent variables determining the nature of the clinical situation. From Hald T.

Figure 2
In each specific circumstance, urinary incontinence should be further described by specifying relevant factors such as type, frequency, severity, precipitating factors, social impact, effect on hygiene and quality of life, measures used to contain the leakage, and whether or not the individual seeks or desires help because of urinary incontinence.

**Stress urinary incontinence** is the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing.

**Urgency urinary incontinence** the complaint of involuntary leakage accompanied by or immediately preceded by urgency. Although the ICS 2002 term is urge urinary incontinence it was recognized in a 2004 ICS standardization workshop that this had been an inadvertent mistake and urgency urinary incontinence is a better term.

**Mixed urinary incontinence** is the complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing. This form of UI is only likely to occur after prostatectomy.

**Enuresis** means any involuntary loss of urine. If it is used to denote incontinence during sleep, it should always be qualified with the adjective “nocturnal”.

**Nocturnal enuresis** is the complaint of loss of urine occurring during sleep. This is an important, although rare symptom in older men, as it may indicate high pressure chronic retention (Abrams et al 1978)

**Continuous urinary incontinence** is the complaint of continuous leakage, and only found after prostatectomy.

2. **BLADDER SENSATION** can be defined, during history taking, into four categories.

- Normal: the individual is aware of bladder filling and increasing sensation up to a strong desire to void.
- Increased: the individual feels an early first sensation of filling and then a persistent desire to void.
- Reduced: the individual is aware of bladder filling but does not feel a definite desire to void.
- Absent: the individual reports no sensation of bladder filling or desire to void.

3. **VOIDING SYMPTOMS** are experienced during the voiding phase.

- Slow stream is reported by the individual as his perception of reduced urine flow, usually compared to previous performance or in comparison to others.
- Splitting or spraying of the urine stream may be reported.
- Intermittent stream (Intermittency) is the term used when the individual describes urine flow which stops and starts, on one or more occasions, during micturition.
- Hesitancy is the term used when an individual describes difficulty in initiating micturition resulting in a delay in the onset of voiding after the individual is ready to pass urine.
- Straining to void describes the muscular effort used to initiate, maintain or improve the urinary stream.
- Terminal dribble is the term used when an individual describes a prolonged final part of micturition, when the flow has slowed to a trickle or dribble.

4. **POST MICTURITION SYMPTOMS** are experienced immediately after micturition.

- Feeling of incomplete emptying is a self-explanatory term for a feeling experienced by the individual after passing urine.
- Post micturition dribble is the term used when an individual describes the involuntary loss of urine immediately after he has finished passing urine, usually after leaving the toilet (onto his clothes).

II. **LUTS IN THE COMMUNITY, IN RELATION TO AGE**

Lower urinary tract symptoms (LUTS) are fairly common in young men. In a prospective study, 85 men with LUTS (18 to 45 years old) were investigated to determine the cause of LUTS in young men and whether noninvasive testing and symptoms scores are useful in deciding which patients to evaluate with videourodynamics (Nitti et al. 2002). Mean AUA scores were total 19.3, voiding 10.8 and storage 8.5. Videourodynamic diagnoses were primary bladder neck obstruction in 40 (47%) cases, dysfunctional voiding in 12 (14%), impaired contractility in 8 (9%), “sensory urgency” in 7 (8%), detrusor overactivity alone in 5 (6%), detrusor overactivity during filling and detrusor underactivity during voiding in 1 (1%), external detrusor-striated sphincter dyssynergia in 1 (1%) and normal in 5 (6%). Of these patients, 9 could not void during urodynamics and in 6 (7%) no urodynamic diagnosis was made. Thus LUTS in young men have a variety of underlying
causes. Videourodynamics was not considered helpful in patients with a normal or nondiagnostic study or “sensory urgency” only but was an extremely helpful diagnostic test in men with abnormal uroflow and high voiding scores.

The prevalence of LUTS increases with age such that a large proportion of men aged >70 years, may have them. In the Netherlands, France, UK, Korea, the prevalence of lower urinary tract symptoms in men and women was studied by a population-based, cross-sectional survey (Boyle et al. 2003). The percentages of men and women with an IPSS of 8–35, indicating moderate to severe symptoms, were, respectively, 20.7 and 18.0 (the Netherlands); 19.2 and 12.6 (France); 25.1 and 23.7 (UK); and 16.2 and 19.9 (Korea). The percentages of men and women with moderate to severe symptoms were by age group, respectively, 10.6, 15.5 (4049) ; 19.0, 18.2 (5059); 30.5, 23.8 (6069) ; and 40.4, 28.7 (7079) . Among those aged 40–49 the main differences between men and women were in the questions about frequency of urination during the day and being able to hold back urine. Among the older groups, men reported more symptoms on all questions apart from urination at night and difficulty in holding back urine, both of which were equally prevalent among men and women. The overall prevalence of LUTS was high and showed no marked cultural variation. Prevalence increased with age, with severe LUTS being more common in older men. Women reported similar levels of the symptoms traditionally associated with LUTS in men. In each age group there were no major cultural differences in the frequency of LUTS. There were differences with age between men and women; younger men had a lower prevalence of LUTS than younger women but older men a much higher prevalence than older women.

In Japan an epidemiologic population-based investigation on LUTS has been performed (Homma et al. 2005). Self-administered questionnaires pertaining to micturition were mailed to 10,096 men and women aged 40 years or older who were family members of randomly selected households. 4,570 responses were available for the analysis (men 46.0%). The average age was 60.6 years for both genders (range 40-100). Urinary frequency (≥8 micturitions per daytime/ ≥11 micturitions per daytime) was reported by 50.1%/11.3%, and nocturia (≥1 micturition per night/≥3 micturitions per night) was reported by 69.2%/13.5%. The proportion of cases experiencing symptoms (≥once per week/ ≥once a day) was 27.0%/19.8% for decreased urine stream, 17.8%/12.0% for “feeling of residual urine”, 2.2%/1.0% for bladder pain, 14.0%/8.0% for urinary urgency, 8.9%/5.3% for urgency incontinence and 8.0%/3.9% for stress incontinence. The prevalence increased with age and was generally greater in men except for stress incontinence. Daily activities were negatively influenced by urinary symptoms in 14.7%. More specifically, the influence was felt on mental heath (10.2%), vitality (10.1%), physical activities (7.1%), work/house chores (5.9%), and social activities (4.0%). The number of problematic symptoms was 2.0 on average. The most problematic and prevalent symptoms were nocturia (38.2%), daytime frequency (19.3%), stress incontinence (14.5%), urgency (10.4%), urgency incontinence (9.8%), and reduced urinary flow (6.6%). Despite a negative impact by LUTS only 18.0% of individuals had visited physicians. Prevalence of LUTS was generally higher in men and the aged population. Appropriate management and treatment should be encouraged by increasing publicity of urinary problems.

In Sweden, the prevalence of LUTS was estimated in different age groups of men 45–79 years old by a large population-based study (Andersson et al 2004). 18.5% and 4.8% of the men were moderately or severely symptomatic; the prevalence of at least one symptom was 83%. LUTS were strongly age-dependent, with 1.8% of severe symptoms among men aged 45–49 years and increasing to 9.7% among those 75–79 years old. Frequent urination was the most common symptom among men aged<70 years and nocturia among those aged>70 years. Symptoms like hesitancy, poor flow and intermittency were highly correlated with each other (Spearman coefficients 0.56–0.60). There was a high correlation between the IPSS and a poor score for quality of life resulting from the bothersomeness of LUTS (r=0.70).

Among symptomatic subjects, 36% reported a poor quality of life (fairly bad, very bad or terrible). Only 29% of symptomatic subjects (IPSS>7) reported that they had been diagnosed previously for their urinary problems, and only 11% received medication for that. In Sweden, irrespective of the reasons, it is apparent that few men seek help for their urinary symptoms. Only a third of symptomatic men reported that they had been diagnosed for urinary problems previously. This issue emphasizes the important need for better public education and awareness of the relatively high prevalence of LUTS in society.
CONCLUSIONS

- Precise internationally agreed definitions exist for LUTS and indeed for LUTD and for BPH/BPE/BPO. Their widespread adoption will increase the ease of communication and the transparency of the published literature.

- There is good quality (Level 1) evidence that LUTS are relatively common in the community, with an increasing prevalence with age. It is important to note that the prevalence is little affected by gender, suggesting the possibility that many men’s and women’s LUTS have similar aetiologies. There is also evidence that that many men with LUTS do not seek help despite having bothersome symptoms (level 2).

III. STORAGE SYMPTOMS

From the ICS-“BPH” study (Donovan, et al.,1996; Peters, et al. 1997; Abrams, et al. 1997), it was shown that the more prevalent symptoms were voiding symptoms, but the more bothersome symptoms were the storage symptoms, with the exception of post micturition dribbling (Table 3). Terminal dribbling was seen in 94%, reduced stream in 93%, intermittency 88%, hesitancy 83%, and incomplete emptying 81%. The five most bothersome symptoms, however, defined by the portion of men who reported the bother was at least “a bit of a problem” were post-micturition dribbling 84%, urgency incontinence 84%, nocturnal incontinence 81%, miscellaneous incontinence 81%, and urgency 80%.


Although voiding symptoms are most prevalent, storage symptoms are clearly the most bothersome to the patient and interfere to the greatest extent with daily life activities, having a considerable negative effect on quality of life. Urgency, frequency and urgency incontinence may cause social embarrassment or isolation and nocturia may disturb sleep and induce fatigue or irritability during the daytime (Peters, et al. 1997; Sagnier, et al. 1995; Debeau, et al. 1995; Calais, et al. 1997).

Table 3. A Summary of the prevalence and troublesomeness of LUTS, listed in decreasing rank order, from Fryman and Abrams, 2000

<table>
<thead>
<tr>
<th>Rank</th>
<th>Storage Symptom</th>
<th>Voiding Symptom</th>
<th>Storage Symptom</th>
<th>Voiding Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Terminal dribbling</td>
<td>Post micturition dribbling</td>
<td>Urge incontinence</td>
<td>Nocturnal enuresis</td>
</tr>
<tr>
<td>2</td>
<td>Reduced stream</td>
<td>Nocturnal incontinence</td>
<td>Intermittency</td>
<td>Misc. incontinence</td>
</tr>
<tr>
<td>3</td>
<td>Intermittency</td>
<td>Urgency</td>
<td>Hesitancy</td>
<td>Urgency</td>
</tr>
<tr>
<td>4</td>
<td>Incomplete emptying</td>
<td>Frequency</td>
<td>Nocturia</td>
<td>Incomplete emptying</td>
</tr>
<tr>
<td>5</td>
<td>Urgency</td>
<td>Strain to continue</td>
<td>Strain to start</td>
<td>Reduced stream</td>
</tr>
<tr>
<td>6</td>
<td>Nocturia</td>
<td>Post micturition dribbling</td>
<td>Pain in bladder</td>
<td>Strain to start</td>
</tr>
<tr>
<td>7</td>
<td>Repeat urination</td>
<td>Strain to continue</td>
<td>Repeated urination</td>
<td>Dysuria</td>
</tr>
<tr>
<td>8</td>
<td>Frequency</td>
<td>Pain in bladder</td>
<td>Dysuria</td>
<td>Strain to continue</td>
</tr>
<tr>
<td>9</td>
<td>Strain to continue</td>
<td>Frequency</td>
<td>Strain to continue</td>
<td>Hesitancy</td>
</tr>
<tr>
<td>10</td>
<td>Urge incontinence</td>
<td>Urge incontinence</td>
<td>Strain to continue</td>
<td>Intermittency</td>
</tr>
<tr>
<td>11</td>
<td>Frequency</td>
<td>Urge incontinence</td>
<td>Frequency</td>
<td>Hesitancy</td>
</tr>
<tr>
<td>12</td>
<td>Dysuria</td>
<td>Frequency</td>
<td>Stress incontinence</td>
<td>Intermittency</td>
</tr>
<tr>
<td>13</td>
<td>Pain in bladder</td>
<td>Stress incontinence</td>
<td>Frequency</td>
<td>Stress incontinence</td>
</tr>
<tr>
<td>14</td>
<td>Misc. incontinence</td>
<td>Stress incontinence</td>
<td>Frequency</td>
<td>Stress incontinence</td>
</tr>
<tr>
<td>15</td>
<td>Stress incontinence</td>
<td>Stress incontinence</td>
<td>Frequency</td>
<td>Stress incontinence</td>
</tr>
<tr>
<td>16</td>
<td>Nocturnal incontinence</td>
<td>Stress incontinence</td>
<td>Frequency</td>
<td>Stress incontinence</td>
</tr>
</tbody>
</table>

Table 4. Lower urinary tract symptoms (LUTS) in community samples and in patients with LUTS admitted to a urologic clinic. From Jepsen and Bruskewitz, 2000

<table>
<thead>
<tr>
<th></th>
<th>COMMUNITY SAMPLE (%)</th>
<th>LUTS PATIENT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=423</td>
<td>N=2119</td>
</tr>
<tr>
<td></td>
<td>&lt;60/60-69/&gt;70yr</td>
<td>40-49/50-59/60-69/&gt;70ys</td>
</tr>
<tr>
<td><strong>VOIDING SYMPTOMS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weak stream*</td>
<td>30/37/52†</td>
<td>35/34/39/44†</td>
</tr>
<tr>
<td>Strain start*</td>
<td>18/17/12</td>
<td></td>
</tr>
<tr>
<td>Strain continue</td>
<td>23/22/25</td>
<td>12/15/13/15</td>
</tr>
<tr>
<td>Hesitancy*</td>
<td>53/47/49</td>
<td>14/18/20/19</td>
</tr>
<tr>
<td>Intermittency*</td>
<td>44/53/53</td>
<td>18/25/29/32†</td>
</tr>
<tr>
<td>Incomplete emptying*</td>
<td>32/35/34</td>
<td>16/17/23/23†</td>
</tr>
<tr>
<td>Terminal dribble*</td>
<td>79/78/73</td>
<td></td>
</tr>
<tr>
<td>Postmicturition dribble</td>
<td>44/40/42</td>
<td>37/43/44/36</td>
</tr>
<tr>
<td><strong>STORAGE SYMPTOMS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>29/43/34†</td>
<td>34/36/35/35≠</td>
</tr>
<tr>
<td>Repeated voiding</td>
<td>24/28/27</td>
<td>12/11/18/11</td>
</tr>
<tr>
<td>Nocturia*</td>
<td>7/15/43†</td>
<td>16/29/42/55†</td>
</tr>
<tr>
<td>Urgency</td>
<td>44/51/64†</td>
<td>28/32/42/46†</td>
</tr>
<tr>
<td>Urge incontinence</td>
<td>13/26/41†</td>
<td>36/46/56†</td>
</tr>
<tr>
<td>Stress incontinence</td>
<td>8/14/14</td>
<td>23/25/24/22$</td>
</tr>
<tr>
<td>Miscellaneous incontinence</td>
<td>4/9/12</td>
<td>16/20/22</td>
</tr>
<tr>
<td>Bladder pain</td>
<td>15/14/19</td>
<td></td>
</tr>
<tr>
<td>Dysuria</td>
<td>22/15/13</td>
<td>5/6/7</td>
</tr>
</tbody>
</table>

* Question in the International Prostate Symptom Score (American Urological Association) Questionnaire
† Significant correlation with age
≠ Within 2 hours
$ Wet clothing
1. STORAGE LUTS AND THEIR ETIOLOGIES

A brief summary of the etiology of these symptoms follows, recognizing that the major symptoms are mostly a manifestation of the overactive bladder syndrome [Abrams et al 2002]. Theories regarding the pathophysiology of this, and its possible relationship to bladder outlet obstruction, are considered subsequently.

a) Frequency

There is surprisingly little objective data on frequency in the normal population. Abrams (1997) cites two papers and personal experience in considering normal diurnal frequency to be between 3-7 voids per day. Jepsen and Bruskewitz (2000) consider the normal 24-hour urinary frequency as 8, that more than 3-hours between successful voids is normal and that less than 2-hours is abnormal.

Diary data in men and women vary. One study of asymptomatic men and women showed that females tend to void more often (median 8 vs. 7 voids per 24 hours) and at lower mean volumes (Mueller et al 2005). Latini, et al used a 24 hour diary to study voiding habits in 284 asymptomatic men. They found that subjects voided a median of 7 times per 24 hours (Latini et al 2004). They also reported that even in asymptomatic men the number of daily voids correlated with the IPSS. Furthermore they cautioned against using a cutoff of 8 daily voids to define abnormal urinary frequency since diary variables depend on patient characteristics including age and race and also on climatic and social factors. The mechanisms of increased urinary frequency are characterized as follows:

- Normal voided volumes. This is approximately 300-600 ml. in the adult. If an individual has normal voided volumes then increased frequency must be due to an increased intake resulting in increased output. This may be due to the following:
  - Polydipsia, osmotic diuresis, or an abnormality of antidiuretic hormone production (diabetes insipidus)

- Reduced voided volumes. This implies that the bladder capacity under general or regional anesthesia would be normal but the voided volumes are consistently small, <300 ml. The causes of which include the following:

---

Table 5. Prevalence of bother from lower urinary tract symptoms in community samples, from Jepsen and Bruskewitz, 2000

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any degree of problem (%)</td>
<td>More than quite a problem (%)</td>
</tr>
<tr>
<td></td>
<td>N = 423</td>
<td>all</td>
</tr>
<tr>
<td></td>
<td>&lt;60/60-69/&gt;70 yr</td>
<td></td>
</tr>
<tr>
<td>Voids symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weak stream</td>
<td>79/73/71</td>
<td>28</td>
</tr>
<tr>
<td>Strain start*</td>
<td>79/71/71</td>
<td>23</td>
</tr>
<tr>
<td>Hesitancy*</td>
<td>76/71/67</td>
<td>24</td>
</tr>
<tr>
<td>Intermittency*</td>
<td>72/68/63</td>
<td>23</td>
</tr>
<tr>
<td>Incomplete emptying</td>
<td>80/77/72</td>
<td>28</td>
</tr>
<tr>
<td>Terminal dribble</td>
<td>81/75/77</td>
<td>31</td>
</tr>
<tr>
<td>Postmicturitional dribble</td>
<td>84/85/82</td>
<td>34</td>
</tr>
<tr>
<td>Storage symptoms</td>
<td>62/65/64</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>76/72/70</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>75/73/72</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>77/80/81</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>77/85/84</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>67/56/73</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>75/81/84</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>68/74/73</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>73/68/79</td>
<td>21</td>
</tr>
</tbody>
</table>

*Question in the American Urological Association Symptom Problem Questionnaire.
°Wet clothing
From Jepsen and Bruskewitz, 2000.
- detrusor overactivity
- significant residual urine volume (emptying failure)
- non-inflammatory causes of increased bladder sensation including tumor ingrowth
- inflammatory bladder conditions
- fear of urinary retention (i.e., in the older male patient who experiences hesitancy increasingly as the bladder fills and who compensates by voiding frequently)
- fear of incontinence (i.e., patients with stress incontinence after prostatectomy and/or detrusor overactivity who note their problem increases with increasing bladder volume)
- psychogenic, other than fear of urinary retention or incontinence

• Reduced structural bladder capacity. In this case the bladder capacity is smaller than normal under regional or deep general anesthesia and results in consistently small voided volumes. The reduction in capacity may be due to:
  - fibrosis, non-infectious cystitis/inflammation, post-pelvic irradiation fibrosis, previous bladder surgery

b) Urgency, urgency incontinence and the overactive bladder

Urgency is defined as a sudden compelling desire to pass urine which is difficult to defer (Abrams, et al. 2002). It is the primary driver of frequency, nocturia unrelated to polyuria, and, when it is correlated with detrusor overactivity that cannot be suppressed, urinary urgency incontinence. (Figure 3) (Chapple, et al. 2005; Chapple and Wein, 2005). An earlier definition included the fact that the desire was compelling, to avoid either leakage or pain (Abrams, et al. 1998); many feel that fear of leakage should be reinserted in the definition. Urgency is the prime symptom of the overactive bladder symptom syndrome (urgency, with or without urgency incontinence, usually with frequency or nocturia in the absence of infection or other obvious pathology (Abrams, et al. 2002). One shortcoming of this definition is that it leaves out patients with grossly impaired or no sensation but with urinary incontinence due to an involuntary detrusor contraction.

The prevalence of the symptoms of overactive bladder has been established in large population-based surveys in the U.S.A. (Stewart, et al. 2003) and in Europe/Scandinavia (Milsom, et al. 2001). Data from both studies indicate that approximately 17% of the adult population have symptoms suggestive of overactive bladder, and that approximately one-third of these patients have urinary urgency incontinence, while the other two-thirds do not. The prevalence of overactive bladder rises with age in both sexes, another piece of evidence that symptoms which characterize this symptom syndrome cannot be due solely to the presence of an enlarged and/or obstructing prostate (Figure 4). On a relative basis, urinary urgency incontinence is more common in women than in men (Figures 5 and 6).

Urginary urgency is not the same as “urge”, which can be defined in the urinary sense as “the desire to void” or “the need to void.” ‘There is some debate as to whether urinary urgency is merely an extreme form of the strong desire to void. Current thinking is that urgency is a separate and pathological symptom; however, patients with OAB can have both normal storage sensations and urgency, and not every one of their micturition cycles is associated with urgency. By its definition, urgency is episodic and there is little or no degradation in the sensation. Thus, “scales” that attempt to define the intensity of urgency may be at odds with the definition if urgency is a sensation that is either there or not. The physiological sensations of the first sensation of filling, normal desire to void and strong desire to void can, however, vary in intensity, also some measurement of the intensity of urgency may be useful in assessing symptom severity and the outcome of therapy of OAB. Chapple’s diagrams (Figures 7 and 8) provide an understandable visual interpretation of how urgency drives the symptoms of frequency and nocturia, in the absence of nocturnal polyuria and, in the absence of the ability to abort an involuntary contraction, urgency related incontinence. The ability to defer micturition is one of the keys to the definition of urgency. This might vary depending on the circumstances of the individual, i.e., the availability of bathroom facilities, whether at home or at work and the level of distraction. Urgency episodes are pathological and they result in either small volume voids and reduced and variable inter-void intervals or urgency incontinence. The time from the onset of the urgency episode to the void or the incontinence episode is generally short and may be referred to as the “deferment time” or “warning time”. The period between episodes of urgency can also be measured and termed the refractory or urgency free interval. The factors which influence whether incontinence occurs or not can be
Urgency Drives the Other Symptoms of OAB

Figure 3.
1. Proven direct effect
2. Effect correlated with urgency but inconsistent due to multifactorial etiology of the symptom

Chapple C. ICI poster, 2004

Figure 4

Figure 5
Figure 6

Figure 7. Schematic of the relationship between bladder volume and desire to void during the normal micturition cycle. During the normal cycle, desire to void is intermittent and increases with bladder volume. The cycle terminates with a void that may or not be associated with strong sensation.

Figure 8A. A schematic of the effect of urgency on the micturition cycle. During an urgency episode, the desire to void increases abruptly, resulting in a void and shortening the intervoid interval, and reducing the volume voided. Therapy can eliminate urgency episodes and thus normalize the inter-void interval.

B. A diagram of two micturition cycles terminated by voids associated with urgency episodes. A refractory period, defined as the interval between voiding and the next urgency episode, can be measured and may be affected by therapy. A warning or deferral time can also be measured as the time from the onset of urgency to voiding.
summarized as follows:

• pelvic floor and urethral sphincter tone
• mobility
• toilet access
• timing of sensation (i.e., if sensation delayed or impaired because of neurologic disease/injury, then incontinence is more apt to occur)

Urgency affects nocturia as well, but successful treatment of urgency is not well correlated with nocturia reduction. The reason is that nocturia (see separate section on nocturia) is related not only to nocturnal overactive bladder but also may be related to other factors discussed in more detail later, for example: nocturnal polyuria, non-urological sleep disorders and congestive heart failure.

Urgency is, therefore, the pivotal clinical symptom in overactive bladder as it is the driver for frequency, non-polyuria related nocturia, and urgency incontinence. It is also a surrogate end-point for patients having better “control.” There is no evidence to support the hypothesis that there is a continuum between the normal desire to void and urgency. A strong case can be made, however, for the suggestion that the definition of urgency be further qualified by adding phrase “for fear of leakage” which was previously in the definitions but abandoned at the time of the last revision of terminology. The ICS Standardization Committee, unfortunately, has compounded the problem by suggesting that synonymous terms for overactive bladder include urgency/frequency syndrome and urge syndrome (Abrams, et al. 2002). One circumstance that warrants discussion is that the difference between the terms urgency and urge may not translate into other languages.

c) Nocturia

Nocturia can be caused by any of the problems listed above as causing diurnal frequency. However, in addition, nocturnal polyuria can be a significant causative factor. This is often due to the re-absorption of edema fluid in patients with congestive cardiac failure, when they recline. Nocturia may also be due to loss or reduction of antidiuretic hormone production at night: the reversal of the diurnal pituitary rhythm. Below there is more detailed discussion on the aetiological factors responsible for nocturia.

d) Pain

This may be due to inflammation, infection, malignant or pre-malignant bladder conditions, painful bladder syndrome including interstitial cystitis, or pelvic pain syndrome including prostatitis. None of these have any particular relationship to BPH, BPE, BPO. Prostate cancer can invade the posterior bladder base and cause nerve entrapment/irritation in the pelvis.

e) Impaired or absent sensation

This may be due to a variety of neurological diseases or injury or to the effects of chronic bladder overdistention.

2. PATHOPHYSIOLOGY OF URGENCY, DETRUSOR OVERACTIVITY AND OVERACTIVE BLADDER: THEORIES AND OBSERVATIONS RELEVANT TO BPH, BPE, BPO

In the past, the sensation of urgency, the occurrence of urgency incontinence and the occurrence of incontinence without sensation in a patient with neurological disease or injury were all assumed to be due to what we now call detrusor overactivity (DO). This is undoubtedly the case with the latter two phenomena, but urgency without incontinence is able to exist without demonstrable DO on a urodynamic study, although the two are often associated. Whether urgency with or without DO represents a purely sensory phenomenon or an aborted, but not recorded, inappropriate micturition reflex remains to be seen.

In any case, the following list includes the relevant theories regarding the pathophysiology of OAB, DO and urgency. Source references, exclusive of the individual ones cited, can be found in Nordling, et al. (2001), Morrison, et al. (2005) and Mostwin, et al. (2005). Only some of these bear potential relevance to BPH, BPE, or/and BPO. They are indicated with an asterisk.

a) Neurogenic

Loss of inhibition or increased afferent input at any level of the nervous system can result in OAB (de Groat, 1997; Chancellor and Yoshimura, 2002) (Figures 9 and 10). Evidence supporting this includes:

• Reduced suprapontine inhibition
• Damaged axonal paths in spinal cord
• Increased LUT afferent input
• Loss of peripheral inhibition
• Enhancement of excitatory neurotransmission in the micturition reflex pathway

Figure 9. Neurogenic Etiology of Overactive Bladder. After De Groat W.C Urology, 1997; 50 (Suppl. 6A) :36-52
The DO seen in various supraspinal and spinal pathologies (Wein, 2002).

- Local anesthetic injected into the prostate in patients with DO inhibits the DO (Chalfin and Bradley, 1982). Trans-urethral microwave therapy and alpha blockers have been hypothesized to act upon prostatic or prostatic urethral sensory receptors.

- Capsaicin, a neurotoxin for unmyelinated C-fiber afferents, inhibits DO when given intravesically (Andersson, et al. 2005)

- BPO is associated with a positive ice-water test (a spinal reflex) in the majority of patients. This is abolished by capsacin (Chai, et al. 1998)

- Neuroplasticity following obstruction has been hypothesized to occur by a variety of mechanisms, resulting in spinal reflexes which may persist after the initial stimulus has been removed (Steers, et al. 1990, Steers, et al. 1991, Steers and de Groat 1998, Spitzbergen, et al. 1998, Steers, et al. 1999). In some models, nerve growth factor (NGF) has been shown to be elevated in bladder tissue and to revert to base levels when the obstruction is
relieved, and NGF blockade prevented the neural and micturition alterations.

- It is interesting to compare the results of various types of therapy on symptoms recorded in the ICS male questionnaire (Figure 11) (Donovan, et al. 1999). It is clear that at least in this study, the therapies that would be expected to ablate periurethral or prostate tissue produced the greatest reduction in storage symptoms, which would suggest to some, since the urodynamic results of surgery are greater than those produced by the minimally invasive non-drug therapies, but both ablate tissue, that a neurologic mechanism is involved.

- During filling/storage, Andersson (2004) suggests (see article for supporting references) that acetylcholine and other neurotransmitters may be released from the urothelium and increase afferent nerve activity by exciting receptors in the urothelium or suburothelium. Presumably either the release or the increased sensitivity would be hypothesized to be heightened in patients with OAB/DO.

- Andersson (2004) also suggests that a neuronal “leak” of acetylcholine may occur during filling/storage, causing enhanced myogenic activity (“micromotions”) similar to those hypothesized by Turner and Brading (1997) and previously described by Coolsaet (1993) (see 1st bullet “myogenic” below).

- Gillespie (2004) has proposed that the inappropriate augmentation of autonomous myogenic activity or the failure of inhibitory inputs are possible causes for DO/OAB. He proposes that autonomous activity, non-micturition contractions and phasic sensory discharge are features of the normal bladder during filling and that these basic mechanisms, generating and modulating autonomous activity are different from those involved with micturition. The possible aetiological factor, could be regarded as “myogenic” and links the two principle aetiological theories.

b) Myogenic

There is some evidence to suggest a myogenic cause for OAB / DO:

- Partial obstruction in an animal model causes patchy detrusor denervation, increased spontaneous action potentials and activity, and increased cell to cell conduction, allowing small foci of activity to spread into localized or synchronous contractions of portions of the bladder wall, increasing intravesical pressure and/or stimulating sensory receptors (Turner and Brading, 1997; Sibley, 1997; German, et al. 1995; Speakman, et al. 1987; Andersson, 1990) (Figure 12).

- In approximately 25 percent of patients with BPO, the response of muscle strips from the bladder dome to norepinephrine is changed from inhibitory (beta effect) to excitatory (alpha effect) (Perlberg and Caine, 1982).

c) Structural

DO has been reported to be associated with a distinct ultrastructural (EM) pattern known as complete dysjunctional (EL-Badawi, et al. 1993). This has been hypothesized to occur with aging in some individuals and be responsible for DO in the absence of obstruction (El-Badawi, et al. 1997).

d) OAB Symptoms, BPH, BPE, BOO, BPO: Other Observations

It has often been assumed that the pathophysiology of LUTS in the older man is the result of BPO associated with BPE, presumably because all of these phenomenon increase with age. Girman, et al. (1995) and Barry, et al. (1993) looked at the correlation of maximum flow rate, prostate volume and symptom score. There were no statistically significant correlations. Nitti, et al. (1994) also failed to find either clinical or statistical correlations between the severity of bladder outlet obstruction based upon pressure flow urodynamic studies and LUTS. In the male, LUTS may be associated with BOO, but neither storage nor voiding symptoms are diagnostic of urodynamic obstruction (Figure 13). The situation seems complex and in those with BOO, both neurologic and myogenic mechanisms (Figure 12) have been suggested (see above) and many are summarized in Figure 14 (adapted from Steers).

3. THE PREVALENCE OF STORAGE SYMPTOMS

The AUA symptom index (IPSS) was originally introduced in 1992, a symptom index specifically designed for what was called “BPH” at that time. In the years that followed, the questionnaires were administered to samples of men and women, however, it became obvious that there is indeed a lack of specificity for lower urinary tract symptoms attributed to BPO/BPE. Now the IPSS is suggested to be neither gender specific nor disease specific, as symptomatology found in men and women are similar (Lepor and Machi, 1993; Chancellor and Rivas, 1993; Chai, et al., 1993). Lepor and Machi (1993)
Figure 11. Responsiveness of the items in the ICSmale questionnaire to interventions (watchful waiting, minimally invasive therapies, and TURP) (Donovan et al 1999)

Figure 12. Myogenic Theory. Turner WH, Brading AF. Pharmacol Ther. 1997; 75:77-110

Partial denervation alters smooth muscle

↑ Excitability

↑ Ability for activity to spread between cells

Coordinated myogenic contractions and increased bladder pressure
administered the IPSS to 101 men and 99 women between 55-79 years of age attending a general health symposium with no emphasis on genitourinary disease. The mean symptoms scores were 6.9 for men and 7.7 for women. When divided into “obstructive” and “irritative” scores, their respective “obstructive” scores were 2.7 and 2.9, and the “irritative” scores 4.2 and 4.8, not significantly different. This argues for an age related rather than obstruction related etiology for LUTS in at least a substantial portion of patients. It is certainly conceivable that BPE/BPO could contribute or exacerbate this age related process and of course it is highly likely that it is related as an etiologic factor to LUTS, but certainly not in all, and maybe not even the majority, of cases. Homma, et al. (1994) studied 168 men and 101 women who had no spontaneous complaints. Ages ranged from 34-84. Symptom distribution is shown in Tables 6 and 7, and in Figures 15 and 16. Nearly all symptoms increased with age, but it is interesting that there is a substantial incidence of storage symptoms in men with very small prostates (less likely to have obstruction) and in women with no prostates at all!

Chute, et al. (1993) reported on the evidence of LUTS thought secondary to BPO in the Olmstead County population. This included men 40-79 years old who were randomly selected and excluded only because of prostate cancer or prior surgery, bladder cancer or prior surgery, other bladder or urethral disorder, urological conditions that could affect voiding, severe cognitive disorders, inability to void in a standing position, and need for dialysis. The storage symptoms evaluated were nocturia, urgency, and frequent urination within 2-hours. Only the first two showed increasing prevalence with age. The prevalence and the percentage of men reporting these symptoms to be more than a bit bothersome, stratified by the various age groups, were as follows: age 40-49; nocturia 16% and 13%; urgency 28% and 15%; for ages 50-59, nocturia 29% and 17%; urgency 32% and 21%; for ages 60-69, nocturia 42% and 29%; urgency 42% and 27%; for ages 70 and over, nocturia 55% and 35%; urgency 46% and 31%. Frequency did not show an age relation, and the corresponding percentage of men with frequency, occurring more than rarely, and those reporting frequency to be more than a little bothersome, stratified by various age groups, is as follows: ages 40-49, 34% and 12%; ages 50-59, 34% and 15%; ages 60-69, 36% and 16%; ages 70 and over 35% and 16%.

The prevalence of detrusor overactivity and its correlative symptom, urgency, increases with age, but the addition of prostatic obstruction does seem to further increase its occurrence. Detrusor overactivity is found to be present in about 50-65% of patients with BPE/BPO. The notion that obstruction is at least partially responsible was supported by the fact that a 62% and 69% incidence of DO in patients with BPO was reduced to 35% and 31% respectively, after relief of outflow obstruction by transurethral prostatectomy (Abrams, et al., 1979; Andersen, et al., 1980). Urodynamic testing in 211 men with LUTS showed that approximately 30% did not have urody-

**Figure 13. Symptoms related to male lower urinary tract dysfunction**

BOO= bladder outlet obstruction; Sx= symptom
Figure 14. Potential Etiology of Overactive Bladder in Men with Bladder Outlet Obstruction (BOO)

- Partial denervation
- Ischemia
- Detrusor muscle

OUTLET OBSTRUCTION

- Supersensitivity to ACh
- Reduced response to intramural nerve stimulation
- Increased electrical coupling between cells
- Hypertrophy/hyperplasia
- Instability of membrane potential
- Altered intracellular Ca^{2+} regulation
- Hypertrophy of afferent and efferent neurons
- Expression of nerve growth factor
- Reorganization of spinal micturition reflex (C-fiber mediated)
- Altered Na^{+} channel expression/function

OVERACTIVE BLADDER

BOO= Bladder outlet obstruction. Adapted from Steers WD. Rev Urol. 2002;4 (suppl 4): S7-S18

<table>
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<th>Age</th>
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<td>42%</td>
<td>54%</td>
<td>68%</td>
<td>77%</td>
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<td>16%</td>
<td>18%</td>
<td>23%</td>
</tr>
<tr>
<td>Frequency</td>
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<td>13%</td>
<td>19%</td>
<td>32%</td>
<td>62%</td>
</tr>
</tbody>
</table>

Homma et al. 1994 [81].

Table 7. Prevalence of urinary symptoms related to age. Women.

<table>
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<th>50-59</th>
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<td>19</td>
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<td>12</td>
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<tr>
<td>Weak stream</td>
<td>17%</td>
<td>19%</td>
<td>26%</td>
<td>40%</td>
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</tr>
<tr>
<td>Urgency</td>
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</tr>
<tr>
<td>Frequency</td>
<td>13%</td>
<td>15%</td>
<td>11%</td>
<td>30%</td>
<td>33%</td>
</tr>
<tr>
<td>Nocturia</td>
<td>8%</td>
<td>15%</td>
<td>26%</td>
<td>55%</td>
<td>58%</td>
</tr>
</tbody>
</table>

Homma et al. 1994 [81].

Figure 15. Prevalence of urinary symptoms in men with prostates < 20g (Homma et al 1994)
namic evidence of obstruction. The symptomatology in these patients was related to detrusor overactivity and low detrusor strength or speed (Coolsaet and Block, 1986). However, age-matched men without lower urinary tract symptoms have been found to have a prevalence of detrusor overactivity between 25% and 63% (Andersen, et al., 1978; Jensen et al., 1984). Interestingly, detrusor overactivity was reported by Jones and Schoenberg (1985) to be present in 38% of women over the age of 65. This observation is compatible with later observations which report comparable IPSS symptom scores in aging women to those in age-matched men (Lepor and Machi, 1993; Chai, et al., 1993; Chancellor and Rivas, 1993). Urodynamic studies fail to give a functional explanation to this observation (Madersbacher, et al., 1999).

The ICS “BPH” Study (Donovan, et al., 1996) was conceived because, as stated, “little evidence exists to suggest which individual symptoms are related to BPH, BPE, or BPO, and there is no clear concept of which groups of symptoms should be used to identify or measure patients with these conditions.” It should be noted that were the study to be titled presently, the title would be different as views as on the use of the term “BPH” have changed. However, the original name of the study has been retained, with the thought being that everyone interested would understand what the study was designed to investigate. Ultimately, 1,256 patients >45 years of age who presented to urology departments in twelve countries with symptoms and possible BPO were recruited. A substudy was performed of a population based group of men, in which all ambulatory men age 40 years or over registered with a rural general practice in the United Kingdom were invited to complete the questionnaire, and this resulted in a sample of 423 individuals. The results are shown in Table 8. In the ICS “BPH” study the general pattern of a positive association with age is not evident, except for the symptoms of nocturia and urgency incontinence in the ICS “BPH” patients. In the community sample, there was an expected age gradient for the majority of urinary symptoms. The authors speculate that the increasing incidence of nocturia is due to the increasing occurrence of nocturnal polyuria secondary to occult cardiac failure. They further speculate that the increase in urgency incontinence is probably due to the relationship between detrusor overactivity and age. The ICS “BPH” patients considered their symptoms to be more bothersome much more frequently than those in the community sample. From the standpoint of symptomatology, it is particularly interesting to examine the prevalence of the symptoms in the community sample of registered general practice patients who were not consulting a urologist. It is of course possible that many or most of these patients had

Figure 16. Prevalence of urinary symptoms in women (Homma et al 1994)
BPH/BPE/BPO (singly or in any combination). However, until this is proven, one can only conclude that such storage symptoms as urgency, frequency, and nocturia are compatible with a diagnosis of BPH/BPE/BPO but by no means specific or even strongly suggestive of any of these.

Thomas, et al. (2005) followed neurologically intact men diagnosed with detrusor underactivity during voiding who opted initially for no specific treatment. Of the ones who attended for repeat assessment and who had not died in the interim, 84% remained untreated with a mean follow up time of 13.6 years. Initially, 20% of these also had urodynamic DO : at follow up, this increased to 48%. However, the symptom of urgency, present initially in 26% of men, increased to only 34%. The mean age of presentation was 57.5 years and at follow up 70.9 years. Thomas, et al. (BJUI 2005) also followed a group of men initially diagnosed with bladder outlet obstruction who opted for a conservative approach and attended for repeat assessment. The mean follow up time was 13.9 years in those who had not died in the interim. The urodynamic indices of obstruction and the specific voiding symptoms did not change. Nocturia increased from a mean of 1.7 to 2.0 (p=0.022), but the percentage of men reporting symptoms of urgency, frequency and urinary urgency incontinence did not change significantly. However, the occurrence of detrusor overactivity on urodynamic study, increased from 35% to 70% (p<0.001). The mean age of presentation was 56.9 years and in follow up 70.8 years.

Thomas, et al. (2004), looked also at the natural history of lower urinary tract dysfunction following transurethral resection of the prostate for bladder outlet obstruction (Figure 17). They followed a population 60.5 years of age at presentation and 74.1 years at follow up. The mean follow up time was
14.3 years and mean time since surgery was 13.0 years. Although, there was significant resolution of DO in the short term, at follow up, 64% of patients demonstrated DO compared with 40% at original presentation. Interestingly, only 31% complained of urgency, compared with 51% at presentation. Their observations would all support the association of at least DO with aging but, oddly enough, less so with the reported symptom of urgency. The reappearance of DO following outlet ablation also is compatible with a neurologic phenomenon, i.e., regrowth or re-establishment of sensory afferents in the prostatic urethra or prostate itself or perhaps of a central nervous system change with age?

1. INTRODUCTION

Nocturia is defined as the complaint that the individual has to wake at night one or more times to void (Van Kerrebroeck et al, 2002). In view of the high prevalence especially in elderly people it still is considered sometimes as a normal part of ageing (Chasens, 2003). As such, nocturia is an important but often still neglected element of LUTS in male patients. However, where voiding once at night still might have no major impact on sleep and as a consequence quality of life, nocturia episodes of two or more may significantly affect quality of life. Moreover in the majority of patients, the symptom of nocturia has a multifactorial pathophysiological background that complicates the analysis and hence the therapeutic approach as multi-component therapy may be necessary (Abrams and Wein 2002).

2. PREVALENCE AND IMPACT

Nocturia is a common symptom in men with an increasing incidence from 50 years onwards (Schatzl, 2000).

The prevalence ranges from 10% in the general population above 20, but will rise to 16% above 40, 29-60% at age 50 or more and will reach up to 55% in men over 70 reaching 70-91% for those age 80+ years. There may be differences among different countries depending probably on the local habits and toileting facilities (Van Dijk, 2002). The increasing prevalence is largely due to age-related conditions that underlie the pathophysiology of the condition. The symptom has also been associated with several chronic medical conditions, such as hypertension, diabetes, and cardiovascular disease (Rembratt et al 2003).

Especially in frail elderly people with gait and balance disorders and other risk factors, the risk for falls is increased by the necessity to wake up at night to void (Stewart, 1992). Nocturia also has been shown

IV. NOCTURIA

1. INTRODUCTION

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Especially in frail elderly people with gait and balance disorders and other risk factors, the risk for falls is increased by the necessity to wake up at night to void (Stewart, 1992). Nocturia also has been shown
to have adverse effects on quality of sleep (Asplund, 1992) and as a consequence on quality of life (Asplund, 2005). Especially the first part of sleep is very important and hence the decrease of the hours of undisturbed sleep until the first nocturia episode appears to be an important contributing factor in the impact on quality of life (Jennum, 2002).

The complaint of nocturia is often not only bothersome for the individual, but also for the partner. In older men, the symptom of nocturia often occurs together with other LUTS and/or other symptoms in the framework of the overactive bladder syndrome. However, the symptom of nocturia as such does not suggest a specific diagnosis, although benign prostatic obstruction is a major cause of nocturia (Johnson, 2003).

3. Pathophysiology

The pathophysiology of nocturia, especially in elderly males, is often multifactorial and related to a combination of two or more of the primary causes, all of which increase with age. Three major causes can be identified: a primary sleep disorder, polyuria (24 hour or nocturnal) and low voided volumes, usually as a component of overactive bladder syndrome or prostatic obstruction (Weiss, 2000).

• Although elderly people spend more time in bed, the total sleep time decreases and reduces sleep efficiency. Also older people have more frequent awakenings during the night and have difficulties falling asleep again (Stanley, 2005). Furthermore, sleep disordered breathing and sleep apnoea have been associated with nocturia and nocturnal incontinence in the elderly (Umlauf, 2004). The exact mechanisms however are still unknown.

• Polyuria, especially nocturnal polyuria, is a major cause of nocturia. The proportion of 24-hour urine produced at night increases with age (Miller, 2000). Whereas in young healthy individuals, the proportion of urine produced at night is less than 30%, this percentage can increase up to 50% in the frail elderly (Rembratt, 2003). The nocturnal urine production can be increased due to mobilisation of excess volume caused by peripheral oedema related to venous insufficiency and/or congestive heart failure. However there is some evidence that an abnormality in the secretion and/or action of arginine vasopressin at night plays a role in this phenomenon (Asplund, 1991).

• In older men, benign prostatic obstruction, often in combination with detrusor overactivity, results in reduced voided volumes and increased micturition frequency. This occurs due to the combination of incomplete bladder emptying, and involuntary detrusor contractions, reducing the volumes voided.

• Hence an increase in the frequency of nocturnal micturitions is a well-established element of LUTS in males (Johnson et al 2003). Therefore although LUTS suggestive of BPO is considered an independent risk factor for nocturia, other independent age-related changes in the bladder may contribute to nocturia in older men (Homma et al 2002).

4. Diagnostic assessment

A specific algorithm (Figure 18, Wein 2002) based on pathophysiological mechanisms has been developed by the ICS Standardisation Committee (Van Kerrebrouck et al 2002).

As a nonspecific cause, sleep disorders must be mentioned and should be excluded or treated prior to further lower urinary tract evaluation. As the symptom of nocturia can be the consequence of a too high urine production with 24 hour polyuria, nocturnal polyuria or a combination of both, drinking behaviour should be studied and preferably recorded in terms of the amounts and types of fluid, as well as timing of drinking. Since bladder problems must be considered as a third contributing factor, the analysis of nocturia may be complex.

The cornerstone to further analysis is the completion of a frequency-volume chart with the length of night time stated, that is the period in bed with the intention to sleep, until waking with the intention of arising (Saito, 1993). It is obvious that the time spent in bed will be relevant to the total number of nocturia episodes. It can also be useful to have a look at the timing of nocturia episodes since this may relate to the pathophysiological background. Increased venous return tends to produce nocturia episodes earlier during the night while some form of sleeping disorders or bladder problems may rather cause nocturia episodes in the second part of sleep.

History taking of other urinary symptoms and medication used are important elements to elucidate the problem.

In view of the increasing incidence of the symptom with age, one can question whether nocturia in elderly men is part of the normal aging process. However
not all men above a certain age will develop nocturia. The bother and impact on quality of life (QoL) will depend on the individual but in general bother will increase as the number of nocturnal voids increases (Asplund, 1992). Scoring systems may be used to quantify the impact on quality of sleep or the overall quality of life. A recently developed nocturia-specific quality of life score (N-QOL) may be a useful tool in this respect (Abraham et al, 2004) and has become one of the modules of the International Consultation on Incontinence Questionnaire (ICIQ) (Avery et al 2004).

**5. Treatment**

In view of the bother and impact on quality of life, treatment for nocturia must be considered with the aim to at least relieve the severity/frequency of the symptom by reducing or abolishing the nocturia episodes.

Treatment of nocturia in males must be based on the identification of all potential pathophysiological mechanisms involved. No specific data are available on combined interventions, but it is obvious that a combination of several therapeutic approaches may be beneficial. These include behavioural strategies, therapy for medical and sleep disorders, drug therapy or any combination of these.

Evidence is lacking on the effects of behavioural strategies such as altering/reducing fluid or sodium intake, or leg elevation for oedema. Modifying fluid and food intake that might lead to altering urination at night might equally affect the impact of nocturia on sleep and minimize the risks for example, of falls. Timing of antidiuretic therapy in the afternoon may reduce volume overload at night by evacuation of urine before going to bed to sleep (Reynard et al). Data are lacking on the effect of treatment for sleep apnoea with continuous positive airway pressure on nocturia, but the condition must be treated because of the potential side effects. There is also a place for other treatments of disturbed sleep.

Several options for specific drug therapy for nocturia are available. If detrusor overactivity is one of the main contributing factors, antimuscarinic therapy should be considered. Currently limited data are available as to the impact of LUTS/BPO treatment.
on the relief of nocturia. There is some indication that the combination of an alpha-adrenoreceptor antagonist in combination with a 5 alpha-reductase inhibitor may be preferable (Johnson et al 2003). In one study similar results, in terms of effect on nocturia, were published for the alpha1-AR antagonist (tamsulosin) and surgical treatment (Yoshimura et al 2003).

An important number of publications present the beneficial results of exogenous AVP (desmopressin or DDAVP) for the treatment of nocturia. Also, in a large group of men, significant results have been published showing a significant reduction in nocturia episodes and increases in mean duration of first night-time sleep episode (Mattisson et al 2002). A major concern related to DDAVP treatment in elderly patients may be the possibility of fluid retention and hyponatremia. However with strict biochemical control this may be a very effective therapy for bothersome nocturia.

V. VOIDING SYMPTOMS

The term voiding symptoms refers to those symptoms experienced by the patient during micturition: slow stream, splitting or spraying of the stream, interrupted stream (intermittency), hesitancy, straining to either initiate, maintain or improve the urinary stream and terminal dribble (Abrams, et al 2002).

The term “obstructive symptoms” and “prostatism” are still sometimes misused, but in modern terminology the descriptive terms voiding symptoms as part of Lower Urinary Tract Symptoms should be used (Abrams, 1994).

A distinction should be made between storage symptoms and voiding symptoms, the latter related to the time that the individual is evacuating urine. As there is a poor relation between these voiding symptoms and obstruction it is advised to no longer refer to these symptoms as “obstructive”. The term “emptying symptoms” is equivalent to voiding symptoms.

Voiding symptoms can be related to bladder outlet obstruction, impaired detrusor contractility or a combination of the two. In most individual patients it is impossible to relate symptoms to pathophysiological mechanisms or to the urodynamic findings. In terms of objective urodynamic assessment, statistically significant, but clinically insignificant correlations between symptoms and urodynamic parameters of obstruction, could only be established for the symptoms of hesitancy and weak stream (Abrams et al 1978). Postvoid dribble is so common among men without prostatic problems that it is of little value as a discriminator, and is not a voiding symptom, but should be included with feeling of complete emptying as a post-micturition symptom. Straining is a symptom with little relation to obstruction (Reynard 1995). The overall conclusion in most of the relevant literature is that voiding LUTS cannot predict which pathology is present. Hence from symptoms alone, it is not possible to diagnose bladder outlet obstruction nor any of the other pathophysiological mechanisms (Sirls 1996). However, scoring systems have been based on these symptoms in community populations (Brasso et al 1994).

The lack of significance of voiding symptoms is not surprising as, in the case of limited bladder capacity, voiding symptoms can be the consequence of small volume voids. Moreover in patients with detrusor overactivity, a suppressed involuntary contraction may result in voiding symptoms because of the inability to generate a voluntary detrusor contraction in an attempt to empty the bladder. In this instance slow flow results from a small voided volume. Therefore, similar voiding symptoms may occur in situations of overactive detrusor as well as of underactive detrusor.

C. PATIENT ASSESSMENT

This section on clinical assessment includes:

• History taking, frequency-volume charts and symptoms scores
• Physical examination
• Urinalysis
• Biochemical testing
• Postvoid residual urine
• Imaging of the lower urinary tract
• Endoscopy of the lower urinary tract

The American Urological Association (AUA Practice Guidelines Committee, 2003), the European Association of Urology (Madersbacher, et al., 2004)
and the 5th International consultation on BPH (Resnick, M., 2001) highly recommend that a detailed medical history should be taken focusing on the urinary tract and aiming at identifying conditions, other than benign and malignant disorders of the prostate which may be responsible for LUTS. Such a recommendation is based on experts' opinion and no evidence to support such policy can be found in the peer-review literature other than the guidelines themselves. Possible causes of urinary symptoms include benign disorders of the bladder, such as acute bacterial cystitis, squamous metaplasia of the bladder, bladder stones, etc) (Badawi and Langbein, S., 2005; Cruz, 1999; Kojima, et al., 1997; Porru, et al., 2005) and urethral disorders such as urethral stenosis (Serrano-Brambila, et al., 2003), malignant conditions of the urinary bladder (urothelial tumours) and conditions outside the LUT such as CNS (multiple ischemic lesion of the brain) (Seim, et al., 2005) and spinal cord (lumbar disc protrusion) (Yamanishi, et al., 1998). The symptomatic diagnosis of any of the described conditions inside and outside the LUT does not necessarily establish a cause-and-effect relationship with LUTS as more than one pathologic condition may coexist in the pathophysiology of the storage and voiding symptoms. The evidence of co-morbidities may be of importance not only in the diagnostic phase but also when management and treatment of LUTS is considered. [Level of evidence 4, Grade of recommendation D].

II. FREQUENCY-VOLUME CHARTS

Frequency-volume charts (FVC) have become an important part of the evaluation of LUTS. Most experts would agree that these charts provide invaluable information about a number of symptoms including urinary frequency, urgency, incontinence episodes, and voided volume. In fact some symptoms, like nocturia, cannot be properly evaluated without a chart. Frequency-volume charts are critical for the distinction between nocturnal overactive bladder and nocturnal polyuria, two common causes of nocturia. Despite this the structure, content and duration of chart keeping for the evaluation of MLUTS has not been standardised. There are a number of parameters that can be assessed by the FVC, including: total number of voids 24/hours, total number of daytime (awake) voids, total number of nighttime voids, total fluid intake, total voided volume, maximum, minimum and mean voided volume, number of urgency episodes, and number of incontinence episodes. Although, if data on urgency and incontinence episodes is requested then the ICS (Abrams et al 2002) would determine the instrument as a bladder diary.

FVCs have been shown to be reproducible and more accurate when compared with the patient's recall (Larsson, et al, 1992; McCormack, et al, 1992; Wyman, et al, 1998; Blanker, et al, 2000; Groutz, et al, 2000). For example, it has been shown that for nocturia, 51.5% of men were inaccurate in their estimation of the number of episodes per night (Jaffe, et al, 2002). Furthermore, men who perceived their nocturia as more severe, tended to overestimate their nocturnal voiding frequency, and those who perceived their nocturia as less severe, tended to underestimate it (Jaffe, et al, 2002). However, recommendations for diary length in men vary considerably, including 24 hours (Gisolf, et al, 2000), 3 days (Robb, 1985), or 7 days (Russell, et al, 1994; Abrams, et al 1996). This inconsistency may be explained by the fact that previous investigations have analyzed only the reproducibility and correlation of data.

Homma et al (2002) determined that the optimal length of a diary varies according to the parameter assessed and the precision and sensitivity required. In addition, if one is trying to assess change, the baseline parameter (e.g. number of voids, incontinence episodes) will affect the length of the diary needed to detect a certain change. They concluded that a 7 day diary is a reasonable option for most patients with incontinence. Ku, et al (2004) concluded that a 7-day diary may be satisfactorily maintained by patients with incontinence and LUTS, and is a valid tool for symptom evaluation. However, record keeping for 7 days was found to increase patient burden and they suggest that the number of days required to evaluate voiding symptoms should be reduced.

The majority of information collected on FVCs or bladder diaries has been used to establish baselines or to study patients with OAB or incontinence. Gisolf, and colleagues (2000) reported on the reliability of frequency volume charts to study men with LUTS suggestive of BPO. Patients reported on frequency volume charts for 3 periods of 24 hours. The authors found correlations between diary data and IPSS questions pertain to frequency and nocturia. They also found that data obtained from a single 24-hour diary was no different that that obtained from three 24-hour diaries.
Most studies have used paper diaries to collect information. Quinn, et al (2003) compared the use of electronic and paper diaries in a crossover study on patients with OAB. They concluded that the comparability of data collection, suggested that the electronic diary is an appropriate alternative to a paper-based method for assessing the symptoms of OAB, while ease-of-use ratings appeared to support the electronic diary as an acceptable alternative.

### III. SYMPTOM SCORES

Symptom scores have been used in male LUTS for a variety of purposes:
- to assess symptom severity
- to examine the relationships between clinical measures/tests results and scores from symptom and quality of life questionnaires
- to predict the response to treatment
- to assess the outcomes of treatment

Specific symptoms scores have been evaluated and are discussed below:
- **IPSS** Symptoms and QoL impact of LUTS
- **ICIQ-SF** Symptoms and QoL impact of urinary incontinence
- **ICIQ-MLUTS** Symptoms and bother of LUTS and UI
- **Dan PSS** Symptoms and bother of LUTS and UI
- **OAB-q** Symptoms and QoL impact of OAB

Over the past two decades symptoms scores have become a routine part of the evaluation of lower urinary tract symptoms (LUTS). Symptoms scores have been used to quantify LUTS in terms of both prevalence and severity, verify the influence of LUTS upon quality of life, including sexual function, and determine the therapeutic efficacy of various treatments. In addition it is important that symptom scores have a wide applicability across a number of different cultures and languages. In an ideal setting, symptoms scores should also help to determine the underlying etiology of LUTS (e.g. bladder outlet obstruction, detrusor overactivity, impaired detrusor contractility, etc.) however this is made difficult by the fact that different conditions can produce similar or even identical symptoms. A number of different symptom scores have been proposed to assess the type and severity of LUTS associated with BPO. Each has advantages and disadvantages, and it is clear that the worldwide use of such indices has helped in evaluating symptoms, treating patients, and communicating findings globally. Furthermore, attempts to develop new and better indices are constantly improving our understanding of LUTS and the conditions that cause them. Three questionnaires with a high level of psychometric validity and reliability, are the International Prostate Symptom Score (IPSS), the International Consultation on Incontinence Questionnaire Male LUTS module (ICIQ-MLUTS), previously known as the ICSmale questionnaire now known as the ICIQ-MLUTS, and the Danish Prostate Symptom Score (DAN-PSS). Although each was designed with the same purpose, only 5 symptoms are common to all 3: incomplete emptying, urgency, decreased stream, frequency and nocturia.

### 1. THE INTERNATIONAL PROSTATE SYMPTOM SCORE (IPSS)

The IPSS is the most commonly used tool to evaluate LUTS suggestive of BPO. In 1992 Barry et al. reported that the American Urological Association-7 (AUA-7) Symptom Index was a valid short questionnaire useful in the diagnostic work-up of voiding symptoms (Barry et al 1992). Subsequently it was adopted by the World Health Organization (WHO) and renamed the International Prostate Symptom Score (IPSS) after adding a disease-specific quality of life score (Mebust et al 1991). The IPSS was developed to examine how patients with “BPH” perceived their symptoms and how symptoms affected their lives. It was also created as a tool to give clinicians a uniform and reproducible method of assessing symptoms and facilitate comparisons of results in clinical studies (O’Leary et al 1992). Initially the goal was to develop a short, practical, self-administered, clinically sensible index with excellent psychometric properties to capture the severity of urinary symptoms related to “BPH” (Barry et al 1992). The committee (the American Urological Association Measurement Committee) reviewed previously published indexes as well as unpublished indexes from pharmaceutical companies conducting research on treatments designed to alleviate BPO, and developed a list of questions which covered all symptom domains that they felt were appropriate. Only patients who investigators felt clearly had “symptomatic BPH” were enrolled in the initial testing of the questionnaire. After a second validation study using a shorter, revised questionnaire which con-
tained questions that correlated with global bother questions, the committee decided on the seven question where each symptom was rated as 0-5 based on increasing severity.

The IPSS includes seven questions covering incomplete emptying, frequency, intermittency, urgency, weak urinary stream, hesitancy, and nocturia. Each question can be answered on a scale of 0 to 5 (ranging from “not at all” to “almost always”). The symptom index is the sum of the seven scores and, therefore, ranges from 0 to 35 points. Additionally, one question concerning the patient’s quality of life with LUTS may be answered on a scale of 0 (“delighted”) to 6 (“terrible”). Statistically, the index was shown to be internally consistent, and highly reliable and to accurately discriminate “BPH patients” from controls. Furthermore, symptoms were able to be classified as mild (AUASS ≤ 7), moderate (AUASS 8-19), and severe (AUASS ≥ 20 severe) based on sensitivity cutoffs for “BPH patients” and specificity cutoffs for controls (Barry et al 1991).

The IPSS has subsequently been used routinely in clinical practice and has been used extensively in clinical studies to evaluate the prevalence of LUTS and “symptomatic BPH” (Tuncay et al 2003; Anderson et al 2004) and also to assess the effects of various pharmacological, minimally invasive and surgical treatments for LUTS /BPO. It has many advantages as it is self-administered (and thus efficient, less time consuming and without interviewer bias), sensitive to change and generalizable to different populations and socio-economic groups (Netto and Lima 1995; Netto et al 1997; Quek et al 2002; Ganpule et al 2004). In addition, in cases where self-administration is not possible (visual impairment and illiteracy) interviewer administration is an acceptable substitute, however the mode of administration should remain consistent in a given patient (Netto and Lima 1995: Barry et al 1995; Plante et al 1996; Cam et al 2004). IPSS scores increase with age as would be expected. Young asymptomatic men (age 50 or less) tend to have low scores (Moon et al 1997; Cam et al 2004). IPSS scores increase with age as would be expected. Young asymptomatic men (age 50 or less) tend to have low scores (Moon et al 1997; Cam et al 2004). However, with increasing age IPSS has been shown to increase even in men without voiding complaints suggesting that mild to moderate LUTS may be considered a “normal” consequence of aging and do not necessarily cause patients to complain (Van Haarst et al 2005).

The IPSS has been shown to be sensitive to change. Barry, et al (1995 b) calculated the clinically significant changes in the score by examining patients’ rating of treatment which ranged from markedly, moderately or slightly improved, through unchanged to worse. Those who had no improvement had a reduction of 0.7 points; those who rated slight improvement had a mean reduction of 3.0; moderately improved reduced by 5.1 points; and markedly improved reduced by 8.8 points. A much greater decrease in symptoms was necessary to elicit the same self-rating of improvement among patients who started with higher baseline levels, thus minimal perceptible difference were powerfully influenced by baseline scores. A change of at least 3 points is considered indicative of a meaningful change.

One of the major criticisms of the IPSS is the fact that it is not disease or condition specific. While it is a useful tool for judging the severity of LUTS suggestive of BPO, and evaluating therapeutic outcomes (compared to baseline in individual subjects) it is not, however, a diagnostic tool for benign prostatic obstruction (de la Rosette, et al, 1998). LUTS are multifactorial and bladder outlet obstruction, motor and sensory abnormalities of the detrusor, impaired detrusor contractility, urethral function, habits and lifestyle are all potential causes of the same or similar symptoms. Multiple studies have shown that the IPSS is not correlated with urodynamic obstruction (Nitti et al, 1994; Yalla, et al, 1995; van Venrooji, et al, 1995; Ko, et al, 1995; Sirls, et al, 1996; Madersbacher, et al, 1997; Eckhardt, et al, 1997). It also correlates poorly with free urinary flow rate, prostate size, and the amount of post void residual urine (Barry, et al 1993). In addition, the IPSS is not strongly correlated with prostate volume as determined by transrectal ultrasonography (Madersbacher, et al, 1997; Yano et al, 2004). Aged-matched women have similar scores as men (Lepor and Machi, 1993; Chancellor and Rivas, 1993; Chai, et al, 1993), another indication that the IPSS is not disease or condition specific. Furthermore it has been shown to accurately describe LUTS, to be a good indicator of the degree of bother and the effect on quality of life of LUTS ON WOMEN! (Scarpero, et al, 2003).

Another criticism of the IPSS is that it does not assess the symptom of urgency incontinence, one of the most bothersome of the LUTS suggestive of BPO. Urgency incontinence is an important symptom, particularly in regard to therapeutic outcomes in BPO patients. The prevalence of this symptom was also reported as common by the ICS-“BPH” study group and was higher in men with bladder outlet obstruction than in those without (de la Rosette, et al, 1998).
CONCLUSIONS

There is level 1 evidence to suggest that the IPSS is a useful tool to assess LUTS suggestive of BPO and to assess change from baseline after treatment. The IPSS is sensitive to change, and the larger the change, the more is the impact on bother. There is also level 1 evidence that the IPSS it not disease or condition specific and that the symptoms that are measured are not necessarily associated with BPH, BPE, or BPO. Finally, one other shortcoming of the IPSS is that it does not include the symptom of urgency incontinence, a prevalent and highly bothersome symptom in men with LUTS with or without BPO.

Recommendation: Grade A

2. The International Consultation on Incontinence Questionnaire: ICISmale LUTS (ICIQ-MLUTS, Previously ICS Male)

The ICISmale questionnaire resulted from the International Continence Society “Benign Prostatic Hyperplasia (ICS “BPH”) study” (Donovan, et al, 1996; Witjes, et al, 1997; Abrams, et al, 1997; de la Rosette, et al, 1998; Donovan, et al, 2000). Unlike the IPSS which compared patients with “clinically defined BPH” to non-urological control patients, in order to evaluate the ability of the questionnaire to discriminate, the ICISmale questionnaire (now renamed the ICIQMLUTS as part of the ICIQ modular questionnaire: www.iciq.net). was assessed by comparing patients visiting urological clinics who had urodynamically proven bladder outlet obstruction with community based men. When the ICISmale was initiated, it was intended that a scoring system would be devised in terms of relationships with urodynamically confirmed bladder outlet obstruction (Abrams, et al, 1997). However, early investigations indicated that this would not be possible because only the symptom of urgency incontinence had any statistically significant correlation and that was with detrusor overactivity, even with the power of study due to a relatively large number of patients (1,271) (de la Rosette, et al 1998). This is similar to what has been found with the IPSS, even though the ICISmale questionnaire was derived from patients who had urodynamically investigated bladder outlet obstruction. This led the authors to conclude that: “there are objective methods that quantify both urine flow rate and bladder outlet obstruction. In addition, there are valid and reliable methods to quantify the presence of LUTS. These methods measure different aspects of the clinical condition that should be viewed separately in the evaluation and treatment decision of the patient presenting with LUTS [de la Rosette, et al 1998].” Unlike the IPSS, the ICIQ MLUTS (long form ICISmale) questionnaire does assess a number of incontinence symptoms.

The ICIQMLUTS long form questionnaire contains 22 questions on 20 urinary symptoms, and, for most questions, the degree of bother that the symptom causes (Donovan, et al, 1996). It has exhibited acceptable levels of validity, reliability and sensitivity to change following a range of treatments including surgery, minimally invasive therapies and drug treatments (Abrams, et al 1997; Donovan, et al, 1999; Vandonink, et al 2003). After factor analysis, the long version has now been largely replaced by a scored short-form the ICIQMLUTS formerly termed the ICISmale-SF (Donovan, et al, 2000). It also continues to be used to assess LUTS in men and the results of minimally invasive therapies and drug treatments (Joshi, et al 2002; Joshi, et al, 2003a; Joshi, et al, 2003b; Gacci, et al, 2003). The ICIQMLUTS consists of 14 questions; 5 assessing voiding symptoms, 6 assessing incontinence symptoms and 1 question each on frequency, nocturia, and quality of life (Donovan, et al 2000). The ICIQMLUTS may be divided into a voiding subscore (ICISmaleVS) and an incontinence subscore (ICISmaleIS). Thus it is primarily a questionnaire for the assessment of the occurrence and bothersomeness of a wide range of LUTS in men.

The scientific committee which met at the end of the 1st International Consultation on Incontinence in 1998 supported the idea that a universally applicable questionnaire should be developed, that could be widely applied both in clinical practice and research. The hope was expressed that such a questionnaire would be used in different settings and studies and would allow cross-comparisons, for example, between a drug and an operation used for the same condition, in the same way that the IPSS has been used. An International Consultation on Incontinence Questionnaire (ICIQ) Advisory Board was formed to steer the development of the ICIQ, and met for the first time in 1999. The project’s early progress was discussed with the Board and a decision made to extend the concept further and to develop the ICIQ Modular Questionnaire. The first module to be developed was the ICIQ Short Form Questionnaire for urinary incontinence: the ICIQ-UI Short Form. The ICIQ-UI Short Form has now been fully validated and published (Avery, et al, 2004). Given the
intention to produce an internationally applicable questionnaire, requests were made for translations of the ICIQ-UI Short Form at an early stage, for which the Advisory Board developed a protocol for the production of translations of its modules. The ICIQ-UI Short Form has been translated into 30 languages to date. In addition to the ICIQ-UI Short Form, twelve modules have been adopted which are direct (unchanged) derivations from already published questionnaires. As described above, the ICIQ-MLUTS is derived from the ICs

CONCLUSION

The ICIQMLUTS long-form (ICs) and the ICIQMLUTS (ICs) have a high level of psychometric validity and reliability. The ICIQ-MLUTS is derived from the ICs, and has a 10 point bother question after each symptom question. There is level 1 evidence to suggest that the ICIQ-MLUTS is a useful tool to assess LUTS suggestive of BPO and to assess change from baseline after treatment. Furthermore, it does take into account symptoms of incontinence and it may be divided into voiding and incontinence subscores. It has not yet had the same widespread use in clinical practice to date as has the IPSS.

Recommendation: Grade A

3. THE DANISH PROSTATE SYMPTOM SCORE (DAN-PSS)

This questionnaire was designed in Denmark to measure the presence and severity of LUTS and, in a separate assessment, to measure the degree to which men are bothered by each urinary symptom (Hald, et al, 1991; Meyhoff, et al, 1993). The DAN-PSS was initially intended for use in “the BPH patient” without serious complications such as recurrent urinary tract infections, bladder stones, renal impairment, acute or chronic urinary retention etc.” The questionnaire consists of 12 questions pertaining to a variety of LUTS including hesitancy, weak stream, incomplete bladder emptying, straining to void, frequency, nocturia, urgency, dysuria, post void dribbling, stress and urgency incontinence. Each question is graded from 0 (not present) to 3 (e.g. highest level of severity or always). For each symptom, the patient is then asked how much of a problem the symptom is (0- no problem; 1-small problem; 2- moderate problem; 3- severe problem). A composite score is achieved by the multiplication of the ‘symptom’ by the ‘bother’ score, with a total range of 0 to 108 (Hald, et al, 1991; Meyhoff, et al, 1993). The DAN-PSS has excellent test-retest reliability, content and construct validity and is able to discriminate between patients with LUTS suggestive of BPO and those without (Brasso, et al 1994; Hansen, et al, 1995). The DAN-PSS has also been shown to be appropriately responsive to change after surgery and medical therapy (Hansen, et al, 1994; Hansen, et al, 1995; Pannek, et al, 1998). A computer version of this questionnaire has been validated and patients are said to appreciate the new version more than the paper version (Flyger, et al, 2001).

The DAN-PSS may be subdivided into an “obstructive” and an “irritative” part. Schou, et al claimed that with a cutoff point of 6 for the “obstructive” part the DAN-PSS is able to discriminate men with bladder outlet obstruction from men without significant obstruction (Shou, et al, 1993). However, a subsequent study showed no correlation of the DAN-PSS (or “obstructive” subscore) with obstruction measured by standardized pressure-flow analysis (Pannek, et al, 1998). Furthermore that study showed that neither the preoperative DAN-PSS nor the IPSS score could sufficiently predict the success or failure of transurethral prostate resection.

Recommendation: Grade B.

4. SYMPTOM SCORES – SUMMARY

A variety of symptoms scores have been described to assess patients with LUTS suggestive of BPO. The IPSS, ICIQ-MLUTS (long and short forms), and DAN-PSS have been the most tested and found to be reproducible, valid, reproducible, and sensitive to change from therapy. The IPSS has been the most widely

CONCLUSION

The DAN-PSS is a psychometrically valid and reliable tool for the assessment of LUTS suggestive of BPO. It is unique from other indices in that it multiplies the severity of symptoms by the degree of bother. Thus severe symptoms with no bother will contribute zero to the total score. It considers a variety of symptoms including incontinence. There is limited level 1 evidence to suggest that the DAN-PSS is a useful tool to assess LUTS suggestive of BPO and to assess change from baseline after treatment, with most studies coming from Denmark.

Recommendation: Grade A
used (in many countries and languages), but neglects the symptom of urgency incontinence, a symptom that produces significant bother. The ICIQMLUTS (ICSmale-SF) is slightly longer, but takes into account the symptom of urgency incontinence, and in fact may be divided into voiding and incontinence subscores. To date, it has not been as widely used as the IPSS, but may see more widespread use as part of the ICIQ Modular Questionnaire. The DAN-PSS has been mostly used in Denmark. Because LUTS are multifactorial, none of the symptoms scores are condition specific and none are able to consistently predict obstruction. This has led to the conclusion that these valid and reliable methods, to quantify the presence and severity of symptoms and the objective methods that quantify urine flow rate and bladder outlet obstruction, measure different aspects of the clinical condition, and should be viewed separately in the evaluation and treatment decision of the patient presenting with LUTS (Eckhardt, et al, 2000). Symptom scores and a functional assessment provide the optimal way to appreciate the “total picture” of the male with LUTS.

IV. PHYSICAL EXAMINATION

A general physical examination with a specific attention to the presence or absence of a distended bladder, excoriation of the genitals secondary to urinary incontinence, evidence of urethral discharge and a focused neurological examination is also highly recommended. Digital rectal examination (DRE) of the prostate is currently performed to excluded the presence of locally advanced prostate cancer, although its specify and sensitivity is low (Chodak, et al., 1988), to evaluate anal sphincter tone which is often decreased in neurogenic patients (Agarwal and Rosenberg, M. L., 2003) and to estimate prostate size although DRE is known to underestimate prostatic volume as compared with trans rectal ultrasound or magnetic resonance imaging (Roehrborn, et al., 2001). Prostate volume has been recently associated with the risk of BPH progression (McConnell, et al., 2003) and response to treatment (Boyle, et al., 1996). Occasionally tumours of the anal canal can be diagnosed while performing DRE of the prostate.

In conclusion, the level of evidence for recommending DRE in the diagnostic workup is weak considering the causative role of benign prostatic enlargement (BPE) for LUTS [Level of evidence 4, grade of recommendation D], a higher level of evidence exists for the estimation of prostate volume in the managing LUTS patients [Level of evidence 1, Grade of recommendation A].

V. URINALYSIS

Urinalysis is not a single test, complete urinalysis includes physical, chemical, and microscopic examinations. Dipstick urinalysis is certainly convenient but false-positive and false negative results may occur [19]. It is considered an inexpensive diagnostic test able to identify patients with urinary tract infection (UTI) as indicated by the presence of leucocyte esterases and nitrites, although infection may exist in the absence of pyuria and, in the elderly population, pyuria may develop in the absence of UTI [19]. Microscopic haematuria can be easily identified by dipsticking because of the presence of haemoglobin. The detection of haematuria is important because the condition is associated with a 4-5% risk of diagnosing urological disorder or malignancy within 3 years [20]. Because of the high prevalence of urinary tract infection (UTI) and the increase of LUTS in the presence of UTI, all guidelines on the management of patients with LUTS suggestive of BPO, and urinary incontinence, endorse the use of urinalysis in primary care management [Gerber et al 1997; Roehrborn et al 2001]. [Level of evidence 4, Grade of recommendation A].

VI. BIOCHEMICAL TESTING

1. SERUM CREATININE

Epidemiological studies in community dwelling men have shown the absence of any association between BPO / BPE / BPO and chronic kidney disease (Rule, et al., 2005) suggesting that screening for renal function is not justified in patients with LUTS (Rule, et al., 2005). Such recommendation has been recently endorsed by the American Urological Association in their guidelines on “BPH” (AUA Practice Guidelines Committee, 2003). Diabetes or arterial hypertension appear to be the most important cause of elevated serum creatinine in men with proven BPO and renal failure (Gerber, et al., 1997). Recently, data from the MTOPS study showed that the risk of developing de novo renal failure in men with LUTS is low (less than 1 %) suggesting that is not necessary to monitor renal function in patients with LUTS / BPO (McConnell, et al., 2003). Nevertheless, most nation-
al and international guidelines (Madersbacher, et al., 2004; Roehrborn, et al., 2001) still recommend measuring serum creatinine judging that the cost of missing a diagnosis of renal failure outweighs the expenditure of screening for renal function (Gerber, et al., 1997). [Level of evidence 4, Grade of recommendation D]

2. PROSTATE SPECIFIC ANTIGEN

There is no consensus as to the measurement of prostate specific antigen (PSA) in patients with LUTS. The rationale for measuring PSA is twofold: to screen for prostate cancer (Noel, 2000), and to measure a parameter with prognostic value for the progression of BPH and the response to treatment (Boyle, et al., 1996; McConnell, et al., 2003). Screening for prostatic cancer is a major reason why men over 50 of age will consult their family doctor or a urology clinic. Prostate Specific Antigen (PSA) has been primarily used in the diagnosis and treatment of prostatic cancer since its introduction in the 1980s; however it is also produced by benign prostatic epithelial cells and many patients with LUTS / BPO might have a raised PSA. The question as to whether PSA is a proxy for prostate volume, as suggested in LUTS patients, or a marker for prostate cancer is unresolved. Evidence to support both views can be found in the peer-review literature. A recent paper from Catalona’s group suggests a relationship between initial PSA level and subsequent prostate cancer detection with a stepwise increase in cancer detection rate (from <1% to 58%) in patients with <1.0 ng/ml, 1.1-2.5, 2.6-4.0, 4.1-10.0 and >10 ng/ml PSA value in over 26,000 patients enrolled in a screening programme (Antenor, et al., 2004). In the same year, Thompson published data on prostate cancer prevalence from the prostate cancer prevention trial (Thompson, et al., 2004) confirming a stepwise increase in the risk of having a prostate cancer in patients with serum PSA from ≤0.5 to 4.0 ng/ml but showing the limitation of the current threshold of 4.0 ng/ml. Change of PSA threshold from 4.0 to 2.0 ng/ml has been proposed but no consensus exists yet (Wilson and Crawford, E. D., 2004). Therefore the discussion on the clinical benefit of PSA testing for prostate cancer screening is not settled yet (Crawford, 2005; Stamey, et al., 2004). All guidelines suggest a cautious use of PSA in the diagnostic workup of patients with LUTS because of the low specificity of PSA for the diagnosis of prostate cancer (Noel, 2000) although it remains the best available tool for prostate cancer screening (Crawford, 2005). When PSA is considered as a screening tool for prostate cancer, most guidelines suggest that it is used only in patients with a life expectancy of 10 year or longer (AUA Practice Guidelines Committee, 2003; Madersbacher, et al., 2004). The European Urology Association (Madersbacher, et al., 2004), the American Urological Association guidelines (AUA Practice Guidelines Committee, 2003) on “BPH” suggested that the benefit and risks of PSA testing should be discussed with the patient. PSA testing is recommended in men with LUTS and a life expectancy of over 10 years in whom the diagnosis of prostate cancer would change the management of patient’s voiding symptoms. The committee on initial evaluation of LUTS of the 5th WHO International Prostate Consultation also supported this practice (Chatelain et al 2001).

Serum PSA is also a surrogate of prostate volume. The Longitudinal Baltimore Study of Aging showed evidence for a clear increase in the risk of prostate enlargement in each cohort (from 40 to 69.9 years) with increasing serum PSA levels (Wright, et al., 2002). PSA is also a strong predictor of the risk of acute urinary retention and the need for surgery in men with LUTS (McConnell, et al., 2003). Laniado et al (2004) has also recently tested the hypothesis that PSA level could be used to predict the presence or absence of bladder outlet obstruction, evaluated by pressure flow studies. In patients with LUTS, those with a PSA more than 4 ng/ml are significantly more likely to have some degree of BOO. Conversely patients with PSA less than 2 ng/ml have a 33% risk of BOO (Laniado, et al., 2004).

The level of evidence for PSA as a screening tool for prostate cancer, as a proxy for prostate volume and a prognostic parameter for BPE progression is high [Level of evidence 2, Grade of recommendation B].

VII. POST-VOID RESIDUAL URINE

Interestingly, PVR tends to increase with age suggesting a progressive voiding dysfunction (Rule, et al., 2005). In daily practice, PVR is often used to assess patients presenting with LUTS, although the pathophysiology of elevated PVR is not generally well understood and its interaction with BOO and detrusor underactivity is complex.

The standardization of terminology of lower urinary tract functions defines post void residual (PVR) as “the volume of urine left in the bladder at the end of micturition” providing a qualitative description with-
out addressing the issue of normal and abnormal values. The rationale for measuring post voiding residual (PVR) urine in men with LUTS is twofold: to diagnose significant residual urine volume/chronic urinary retention as a possible cause of symptoms, and to treat high residual urine volumes as they are considered to be associated with an increased risk of urinary tract infection and to an increased risk of urinary retention.

No consensus exists as to the relation between PVR and UTI. In the standard patient the evidence is controversial (Abrams P et al 2001; Bosch, 1995), and the negative role of large residuals has been largely derived from experience in paediatric, elderly, diabetics and neurogenic patients (Beylot, et al., 1982; Grosshans, et al., 1993; Lidefelt, et al., 1989; MacGregor and Williams, C. J., 1966; Merritt, 1981). Large residual urine has been considered a bad prognostic factor for disease progression although, in the standard patient, the evidence suggest that renal failure, acute retention and UTIs are uncommon in men with large, chronic residuals (Bates, et al., 2003). No factors are available to identify patients, with significant residual urine, who are at risk for progression (Bates, et al., 2003).

Following the described evidence, both the 5th International Consultation on BPH and the AUA define measurement of PVR as a optional test in primary care management for the standard patient (AUA Practice Guidelines Committee, 2003; Chatelain, C et al 2001) although the test is recommended in some national and international guidelines (Madersbacher, et al., 2004; Roehrborn, et al., 2001). No data are available to define normal versus abnormal PVR values, the International Consultation on BPH defined a range of 50 to 100 ml as the lower threshold to define abnormal PVR (Abrams et al., 2001). Both the AUA and the EAU guidelines suggest a threshold of 300 ml to identify patients at risk of unfavorable outcome following LUTS / BPO treatment (AUA Practice Guidelines Committee, 2003; Madersbacher, et al., 2004).

Post voiding residual can be measured by in-and-out catheterization (preferably under ultrasound control) to confirm that the bladder is empty (Stoller and Millard 1989)or by ultrasonography (Holmes, 1967). More recently, a dedicated ultrasound system has been developed for automatic measurement of PVR, thereby improving the accuracy over catheterization (Coombes and Millard, R. J., 1994; Marks, et al., 1997) which has been largely abandoned in clinical practice.

The level of evidence for the measurement of post voiding residual in the standard patient with LUTS is weak and it is mainly based on experts’ opinion [Level of evidence D, Grade of recommendation D]

### VIII. IMAGING

Imaging of the upper and lower urinary tracts has been used for several years as part of the diagnostic assessment of men with LUTS related to BPO (de Lacey, et al., 1988). Nowadays the routine use of upper urinary tract imaging by means of intravenous urography or renal ultrasound has not been considered as a first line test in most LUTS / BPO diagnosis guidelines. Imaging can be used to screen for upper and lower urinary tract disorders (hydronephrosis, lithiasis, neoplasms, diverticula, etc.), and to assess prostate morphology and size. However, many urologist do not take images of the upper urinary tract routinely because tumours and kidney stones or failure are no more frequent in men with LUTS related to BPO than in healthy men (Thorpe and Neal, D., 2003). However renal ultrasound should be considered as the imaging modality of the upper urinary tract in patients with LUTS and an history of upper urinary tract infection or urolithiasis, or haematuria or renal insufficiency (Roehrborn, et al., 2001). Lower urinary tract imaging should be performed to assess prostate size and shape, asymptomatic bladder neoplasms, diverticula, stones and wall thickness when clinically indicated.

Prostate volume can be estimated from the suprapubic approach with sufficient accuracy. However, the advantage of transrectal versus suprapubic ultrasound (TRUS) imaging is the possibility of evaluating prostate morphology and transitional zone index (TZI). Choi et al (Choi, et al., 2002) showed an higher mean TZI value and IPSS value in Korean men compared with Caucasian and Hispanic cohorts, they confirmed a relationship between TZI and LUTS and suggested the possible relationship between the higher TZI observed in Korean men (despite a lower mean prostate volume) and the greater severity of LUTS in this population.

At present there is no evidence to recommend TRUS as a valuable tool for detecting early prostatic cancer or to exclude prostate cancer in men presenting with LUTS, and it should be used to guide accurate needle placement during transrectal prostate biopsy (Brawer et al 2001). Currently prostate ultrasound (transrectal or transabdominal) should be considered as optional test in the management of patients with
LUTS / BPO. It may be an appropriate test when minimally invasive therapy or surgical operations are considered.

The size and shape of the prostate and the presence of an intravesical lobe clearly evaluated by ultrasound should be considered when selecting patients for transurethral microwave heat treatment (TUNA) or other minimally invasive therapy as well as for the selection of transurethral prostatic incision (TUIP) versus transurethral prostatic resection (TURP) (AUA Practice Guidelines Committee, 2003). Magnetic resonance imaging or computer tomographic images are alternative methods for lower urinary tract imaging and have somewhat greater precision than transrectal or transabdominal ultrasonography, but their higher cost and the lower availability of machines limits their usefulness and their use in the community setting (Jacobsen, et al., 2001). Three dimensional ultrasonography is under investigation and preliminary data suggests that it is superior to 2-D TRUS in the prediction of the resected weight at TURP(Kanao, et al., 2004).

**Bladder Wall Thickness and Bladder Weight**

The observation of detrusor/bladder hypertrophy in the aging male is a thousand years old (Abu Ali Al-Hussain Ibn Abdallah Ibn Sina (981 – 1037 AD) but only “recently” in 1810, did Hunter relate bladder hypertrophy to obstruction.

Bladder wall thickness (BWT) is a variable that has been used to assess BOO non-invasively. The postulated rationale is that prostatic obstruction is associated with detrusor hypertrophy leading to increased bladder wall thickness (Elbadawi, et al., 1993). Animal models confirm that detrusor hypertrophy decreases after release of obstruction (Saito, et al., 1996). However, detrusor hypertrophy and increased BWT may be related to detrusor overactivity also. Furthermore, an increase in BWT may result not only from smooth muscle hypertrophy but also from the increase in fibrous tissue and collagen that occurs with both age and obstruction (Inui, et al., 1999). BWT is currently measured by ultrasonography and suffers the limitations of such technique. A suprapubic approach is currently used in males and a transvaginal one in females. In a given patient, the value of BWT also depends on bladder distension. As the bladder is filled the bladder wall is stretched, thus reducing BWT (Kaefer, et al., 1997).

Beyond a certain volume the variation of BWT for a given change of bladder volume may be lower than the resolution of the imaging technique. To overcome this a bladder thickness index can be calculated, which standardises BWT with respect to bladder volume. Alternatively BWT can be measured at a fixed bladder (150ml) (Manieri, et al., 1998).

Ultrasound measurements of BWT appears quite promising, but the technique has not been thoroughly tested. The correlation between BWT and BOO is of interest and may also have some clinical validity; it certainly served as a proof of concept of the relation between morphology and function in this area. Further research is needed to understand whether ultrasound measurement of BWT may be a valuable parameter to monitor the effect of LUTD on the urinary bladder. At present, measurement of BWT remains a promising research issue of limited use in clinical practice unless automated ultrasound systems are made available reducing interobserver variability. The level of evidence for the imaging of upper and lower urinary tract is weak and it is mainly based on experts’ opinion [Level of evidence 3, Grade of recommendation C]

**IX. Endoscopy of the Lower Urinary Tract**

Endoscopy of the lower urinary tract provides information regarding comorbidities of the urinary bladder and urethra which can be responsible for LUTS or may change the management of patients with prostate disorders. As far as the prostate is concerned, endoscopy provides as estimation of prostate size by evaluating prostate length, morphology of the prostate and of the bladder neck. Because of the low prognostic value of bladder endoscopy for the diagnosis of BOO (Shoukry, et al., 1975), the test remains optional in all the reports examined (AUA Practice Guidelines Committee, 2003; Chatelain et al 2001; Madersbacher, et al., 2004; Roehrborn, et al., 2001). So far this test is not recommended in the initial evaluation of patients with LUTS but is usually appropriate in men with a history of microscopic or gross haematuria, urethra stricture, bladder cancer, or prior lower urinary tract surgery. It can also be used as an optional test to identifies whether surgery or another form of invasive therapy was suitable in men with severe LUTS (AUA Practice Guidelines Committee, 2003). It should not be performed in patients scheduled for watchful waiting or medical therapy.
The level of evidence for the use of endoscopy in the standard patient with LUTS is weak and it is based on a single study [Level of evidence 3, Grade of recommendation D]

D. URODYNAMICS

I. INTRODUCTION

Urodynamics may be performed for various reasons. In clinical research the main aim is to gather knowledge about the diseases encountered: i.e. to ensure that medical practice is knowledge-based. For clinical urodynamic assessment the main aim of urodynamics is to guide therapy and improve outcomes: its ability to do this has to be judged from the evidence provided by trials and cohort studies. When a condition is first widely encountered, there is a phase in which clinical research is crucial in order to generate new knowledge. For example, following the widespread expansion in the indications for radical prostatectomy, when the reasons for post-operative urinary incontinence were imperfectly understood, many articles dealing with clinical research into the mechanisms and risk factors for incontinence were published. Once the etiology had been established, the debate shifted to whether routine clinical urodynamics should be limited to selected difficult cases or performed more widely. Because urodynamics remains the only way of establishing objectively the pathophysiological situation, urodynamic evaluation always remains necessary in, at least, the difficult cases.

Since the last International Consultation on “BPH” (Abrams et al 2001), there has been some evolution of views about the urodynamic evaluation of lower urinary tract symptoms (LUTS) in men with possible benign prostatic obstruction. This topic is updated in the present report, which is based mainly on publications from 2000 onward. Recent efforts to improve non-invasive methods of urodynamic measurement, so as to reduce patient burden and make urodynamic evaluation more practical, are reviewed more extensively. Prostate cancer and its sequelae were not considered in any of the previous consultations on prostate problems. In this report therefore the field of urodynamic investigation and assessment, as performed before and after prostate cancer and its treatment, is reviewed for the first time at an International Consultation. We have attempted to include all relevant publications without regard to date.

Men in middle or old age present with lower urinary tract symptoms (LUTS) that may be, but are not necessarily, related to prostatic changes such as benign or malignant enlargement and obstruction. LUTS may be due to dysfunction anywhere in the complicated mechanical and neural control system that allows normal function and comprises lower urinary tract function. The aim of urodynamics – according to most textbooks – is to reproduce the symptoms while making measurements that will reveal their cause. Because the number of possible causes is in principle very large, and urodynamics is currently quite limited in its power to reveal them, it is frequently useful to go beyond the mere reproduction of the symptom and to document the complete function of the LUT in both filling and voiding phases. Thus for example, if cystometry is performed to ascertain the cause of incontinence, and if incontinence is indeed demonstrated during the filling phase, it is still wise to complete filling and examine the voiding phase also, because unsuspected abnormalities may contribute to the incontinence, or may reveal urethral obstruction, poor voiding, elevated residual urine, or possible neuropathy, and may change the interpretation of the symptoms, alter the presumed diagnosis, or change the choice of treatment.

For a comprehensive description of how urodynamics is performed and interpreted the last International Consultation should be consulted (Abrams et al 2001). In this chapter we shall focus on the urodynamic assessment of voiding and in particular the diagnosis of bladder outlet obstruction (BOO).

II. DIAGNOSING BLADDER OUTLET OBSTRUCTION: PRESSURE-FLOW STUDIES

1. Introduction

It is now accepted that, although symptomatic management of LUTS is important, obstruction associated with benign prostatic enlargement (BPE) is equally important, since it may lead to disease progression and occasionally cause harmful effects on the bladder and the kidneys (Flanigan et al 1998; Lu et al 2000; Brierley et al 2003). Thus assessing bladder outlet obstruction (BOO) is an important part of the evaluation of men with LUTS. The currently accepted ‘gold standard’ measure of BOO is the pressure-
flow study (PFS) of voiding (Abrams et al 2001, Abrams et al 2002). In fact pressure-flow studies are the basis of the definition of obstruction and therefore remain the only objective means of establishing or ruling it out.

2. PRESSURE-FLOW STUDIES

For a pressure-flow study, intravesical pressure ($p_{ves}$) and abdominal pressure ($p_{abd}$, usually obtained intrarectally) are measured during voiding, simultaneously with the flow rate in the external stream. The detrusor pressure ($p_{det}$) is calculated by subtracting $p_{abd}$ from $p_{ves}$. The results of three typical studies are shown in Figures 19, 20 and 21.

The PFS contains information about urethral resistance (i.e. possible obstruction) and detrusor contractility. Several fundamental classes can be distinguished.

Urethral resistance classes:
- low detrusor pressure and normal flow rate = unobstructed
- high detrusor pressure and low flow rate = obstructed

Detrusor contractility classes:
- low detrusor pressure and low flow rate = weak detrusor contraction (detrusor underactivity)
- high flow rate at high detrusor pressure = abnormally strong detrusor contraction

Numerous ways of making these descriptions quantitative have been suggested. The International Continence Society recommends judging obstruction (in men) from the nomogram shown in Figure 20, (Griffiths et al 1997). A point representing the value of the maximum flow rate $Q_{max}$ and the corresponding detrusor pressure $p_{det}\cdot Q_{max}$ is plotted on the nomogram, and falls into one of 3 regions, unobstructed, obstructed or equivocal, consistent with the urethral resistance classes just described. The equivocal ‘grey’ zone allows for normal physiological variation and measurement errors.

Even without the ICS nomograms, a patient can be placed in one of the three zones by calculating the bladder outlet obstruction index (BOOI, Lim and Abrams 1999):

$$BOOI = p_{det}\cdot Q_{max} - 2 Q_{max},$$

with $p_{det}\cdot Q_{max}$ in cm H$_2$O and $Q_{max}$ in ml/s:

- unobstructed: $BOOI \leq 20$ cm H$_2$O
- equivocal: $BOOI = 20$ to 40 cm H$_2$O
- obstructed: $BOOI \geq 40$ cm H$_2$O

Other variables (e.g. URA [Griffiths et al 1989] DAMPF [Schafer 1995]) also provide a continuous classification of urethral resistance or obstruction. Partly because of the natural variability of voiding studies, they have not proved noticeably more useful in practice than the simple ICS nomogram.

3. RELIABILITY OF URODYNAMICS IN MEN WITH LUTS

a) Variability and reproducibility of urodynamic measurements

In the previous consultation (Abrams et al 2001) it was concluded that random variations of about 9-14 cm H$_2$O in pressure measurement, and about 0.4-2 ml/s in maximum flow rate occur. In repeated studies during the same session there is usually a systematic decrease of up to 4 cm H$_2$O in detrusor pressure and 0.4 ml/s in maximum flow rate. These variations have little clinical importance: they cause only 10-16% of patients to change classification on the ICS or similar nomogram, and in all but about 1% the change is only by 1 class (e.g. from equivocal to unobstructed or from obstructed to equivocal). A urethral catheter appears to be associated with slight changes in flow rate, although it is not certain that these changes are due just to the catheter. A catheter of size 8 French gauge seems to be acceptable.

More recently, Klausner et al [2002] examined the effect of catheter size on assessment of bladder outlet obstruction, in 31 pts with LUTS suggestive of BPO. Using 5 French and 10 French catheters in random order, they observed that the 10 French catheter caused a decrease in $Q_{max}$ and an increase in $p_{det}\cdot Q_{max}$ indicating a detectable obstructive effect over and above that of a 5 French catheter. On the Abrams-Griffiths nomogram, 10 of the 31 pts (32%) were categorized as obstructed with the 10 French catheter but not with the 5 French. Overall 17 of the 31 went from a less to a more obstructed category when the 10 French catheter was used. The authors’ conclusion was that 10 French catheters should be avoided because of their obstructive effect.

Some centers perform pressure-flow studies with their patients standing, and others with them seated. Unsal and Cimentepe [2004] compared flow rates and residual urine in the 2 positions, in 44 men with LUTS suggestive of BPO and 44 healthy men. No
Figure 19. A typical pressure-flow study in an unobstructed individual. Satisfactory data quality is suggested by similar fine structure in the pves and pabd signals and by satisfactory cough tests before and after voiding. However, regular waves in pabd indicate rectal contractions. The resulting periodically negative values for pdet should be viewed as artefacts. The green circles mark the maximum flow rate Qmax and the detrusor pressure at maximum flow, pdetQmax.

Figure 20. Pressure-flow study in an obstructed individual. Qmax is low and pdetQmax is elevated to over 100 cm H2O (see red circles), indicating bladder outlet obstruction. The negative value of the abdominal pressure before voiding suggests a slight artefact due to incorrect levelling of the transducers.

Figure 21. Pressure-flow study with intermediate values of maximum flow rate and detrusor pressure at maximum flow (yellow circles). Small rectal contractions are visible in pabd and therefore also in pdet as downward deflections.
significant position-dependent differences in the maximum or average free flow rate, or in PVR measured by ultrasound, were found. A limitation is that the order of the observations was not clearly described, so that there may be a confounding order effect.

In 1999 Tammela et al [1999] reported on pressure-flow studies of 3 consecutive voids in 216 men with symptoms possibly associated with benign prostatic obstruction. All were measured with no catheter present in the urethra. The mean value of the detrusor pressure at maximum flow rate ($P_{\text{det}} \cdot Q_{\text{max}}$) decreased significantly in successive voids, from 71 to 66 to 63 cm H$_2$O. Correspondingly, the proportion of patients classified as obstructed by the Abrams-Griffiths nomogram fell from 67 to 64 to 59%.

Kranse and Van Mastrigt [2003] in 131 unselected male patients, observed less pronounced systematic variations from one pressure-flow study to the next, but considerable random variability. In 35% of patients the classification of obstruction based on the ICS nomogram changed between measurements. They investigated the possible causes of this variability by ingenious statistical methods and concluded that it was not due to random measurement noise but to real physiological changes in bladder and urethral function. They pointed out that the variability of pressure-flow studies was therefore not a disadvantage, but a reinforcement of their importance as the only means to study bladder outlet resistance, detrusor contractility, and their physiological variations.

Using their results, if one amalgamates the unobstructed and equivocal classes on the ICS nomogram, as is often done, and takes the second test as the standard, then the sensitivity and specificity for obstruction of the first test are 81% and 83% respectively and the overall accuracy is 82%. These figures represent the intrinsic variability of obstruction. (Similar figures would be obtained if the first test were taken as the standard.) Similar calculations based on data of Sonke et al [2000] yield an overall accuracy of 83%, and sensitivity and specificity of 74% and 86% respectively. These figures are very similar to those of Kranse, despite criticism of the technical quality of the measurements (see editorial comments following Sonke article [2000]).

Two recent studies have reported on the variability in men of other urodynamic variables. Ockrim et al (2001) compared variability of the observation of detrusor overactivity in 60 men with LUTS (mean age 67 y) and 35 men with spinal cord injury (mean age 39 y). In men with LUTS the apparent prevalence of detrusor overactivity decreased from 72% to 63% to 48% in three successive filling cystometries, performed on the same occasion. Similarly, the mean maximum detrusor pressure during detrusor overactivity decreased from 41 to 34 to 25 cm H$_2$O. Bladder volume at first, normal, and strong desire to void and cystometric capacity all increased significantly from the first to the third cystometry, by 14 – 25 ml. These observations of systematic changes in successive cystometries are consistent with those in neurologically normal women [Griffiths, et al., 2005]. Unfortunately the random intra-subject variations were not reported, but they are probably even larger than the systematic ones [Griffiths, 2005]. In contrast, in men with spinal cord injury, none of these variables changed significantly in successive cystometries, except possibly for maximum detrusor pressure during overactivity, which showed a barely significant decrease of 4 cm H$_2$O (5%). Thus, for example, detrusor overactivity was observed in 100% of the spinal-cord injured men in all 3 cystometries, while the mean cystometric capacity was 310, 308 and 307 ml respectively. Similar consistent results were obtained by Ho et al [DATE] examined the reproducibility of 2 consecutive urodynamic studies in a neurologic population.

To summarize, in neurologically intact men there is both systematic and random variability of urodynamic variables, which is due to real physiological changes in the behaviour of bladder and urethra. The variability is much less pronounced in those with serious neurological disease at spinal level, suggesting that supraspinal control is responsible for much of the normal variability.

b) New interpretations of urodynamic measurements

Some new mathematical approaches to the interpretation of studies of pressure and flow, based on computer manipulation of urodynamic variables, have been proposed. [Porena et al 2003; Valentini et al 2003] They are intended to reproduce more closely the underlying physiology than existing methods, but it is not yet clear how well they succeed in this nor whether they will offer more reliable interpretation.

4. DETRUSOR CONTRACTILITY IN MEN WITH LUTS

Detrusor contraction strength during voiding (an aspect of detrusor contractility) can be judged from
another nomogram due to Schäfer (Figure 23) On the basis of $p_{\text{det}}Q_{\text{max}}$ and $Q_{\text{max}}$ it classifies contraction strength in one of 4 classes, from very weak to strong (later subdivided to yield a finer graduation). Again the same classification can be obtained by calculating the bladder contractility index (BCI, Abrams 2004), also known as projected isovolumetric pressure PIP; or the detrusor coefficient DECO, which is almost identical (Tan et al 2004).

$$\text{BCI} = p_{\text{det}}Q_{\text{max}} + 5Q_{\text{max}}, \text{ with } p_{\text{det}}Q_{\text{max}} \text{ in cm H}_2\text{O and } Q_{\text{max}} \text{ in ml/s:}$$

- very weak: $\text{BCI} \leq 50 \text{ cm H}_2\text{O}$
- weak: $\text{BCI} = 50$ to $100 \text{ cm H}_2\text{O}$
- normal: $\text{BCI} = 100$ to $150 \text{ cm H}_2\text{O}$
- strong: $\text{BCI} \geq 150 \text{ cm H}_2\text{O}$

It is now widely recognized that impaired detrusor contractility can cause poor flow rate, incomplete emptying, and corresponding symptoms, even in the absence of urethral obstruction, [Abrams, et al., 2001; Griffiths, 2004] and that this is especially likely in the frail elderly. [Resnick and Yalla, 1987]

A detrusor contraction of normal strength can produce either a high detrusor pressure or a high flow rate (depending on the urethra), but not both at once. A weakly contracting detrusor can produce neither a high flow rate nor a high detrusor pressure. Thus to assess detrusor contraction strength both pressure and flow rate have to be considered. It is particularly important to understand that a low detrusor pressure does not necessarily represent a weak detrusor contraction unless the flow rate at that moment is also low. As described above, the simplest method of assessment is to calculate the bladder contractility index (Abrams 2004) or DECO (Tan, et al 2004) during voiding at the moment of maximum flow, given above:

Equivalently the values of $p_{\text{det}}Q_{\text{max}}$ and $Q_{\text{max}}$ can be plotted on a nomogram that shows the strength categories (Figure 21).

Detrusor contraction strength can be estimated more reliably by measuring the isovolumetric detrusor pressure during a mechanical stop test, [Tan et al 2003; Tan, et al 2004] i.e. by eliminating the possibility of flow altogether.

Another aspect of contractility is the ability to sustain the detrusor contraction until the bladder is empty. Failure to do so leads to residual urine, and indeed Zhang et al [2003] have suggested that, in men with suspected BPO, residual urine volume is more closely related to a weak detrusor contraction than to urethral obstruction. The prevalence of weak detrusor contraction has not been much studied, but Thomas et al [2004] found that among a large series 2066 of neurologically intact men with LUTS, 224 showed detrusor underactivity (defined as a detrusor pressure at $Q_{\text{max}} < 40 \text{ cm H}_2\text{O}$, with $Q_{\text{max}} < 15 \text{ ml/s}$). In a series of 196 patients with and without prostatic obstruction, treated or otherwise, they found no evidence to suggest that detrusor contractility declined in long-term obstruction, nor to suggest that relieving the obstruction surgically improves the contractility. [Al-Hayek, et al 2004]

Overall, however, research activity in the field of detrusor contractility remains limited, presumably because there is no obvious pharmacological way to improve poor contractility. Discovery of a drug that noticeably improved detrusor contraction would revolutionize this field.

### 5. Why Urodynamic Pressure-Flow Studies Are Not More Widely Performed

In spite of the above, urodynamic pressure-flow studies are not widely performed in routine clinical practice. One reason is the perceived invasiveness and morbidity of urodynamics. [Porru et al., 1999] A second is the perceived lack of clinical utility in improving outcomes – for example by better patient selection. In addition, assessment by methods of this sort is strongly influenced by costs and reimbursement.

The objective morbidity of urodynamic studies is low [Klingler et al., 1998; Bombieri et al., 1999; Porru et al., 1999] although temporary dysuria is common (33 to 76%). Bacteriuria is found in up to 8% and symptomatic infection in 0.5 - 4%. Mild macroscopic haematuria (6%) [Porru et al., 1999] and post-investigational urinary retention (5% in men with obstruction, Klingler et al., 1998) have also been reported. Subjective morbidity may be due to factors such as embarrassment, which might make the test not only unpleasant, but also unreliable. Scarpero et al [2005] reported on the expectations and experience of 78 men and 88 women undergoing urodynamic testing. Men expected little or no embarrassment, which might make the test not only unpleasant, but also unreliable. Scarpero et al [2005] reported on the expectations and experience of 78 men and 88 women undergoing urodynamic testing. Men expected little or no embarrassment, which might make the test not only unpleasant, but also unreliable. Scarpero et al [2005] reported on the expectations and experience of 78 men and 88 women undergoing urodynamic testing. Men expected little or no embarrassment, which might make the test not only unpleasant, but also unreliable.
Figure 22. ICS pressure-flow nomogram: showing the three pressure-flow curves from figures 9, 10 and 11.

Figure 23. The voids of Figures 9, 10 and 11 classified for detrusor contractility by the Schäfer nomogram. The position of the maximum flow point (coloured dots) in the 4 bands indicates the strength of the contraction (VW = Very Weak, W = Weak, N = Normal, S = Strong). The strengths for these 3 voids are Normal, Normal and Weak respectively.
1. INTRODUCTION

Because of the above drawbacks to invasive urodynamics, attempts have been made to assess BOO non-invasively. Various methods have been used both singly and in combination. Single measures can be broadly divided into 4 categories:

- Symptoms and symptom scores
- Ultrasound derived parameters including prostate size and shape
- Uroflowmetry
- Non-invasive bladder pressure measurements (via a penile cuff or a condom catheter).

What can reasonably be expected of non-invasive surrogate measures of obstruction? Pressure-flow studies (PFS) themselves are not perfect. Repeated measurements in one subject give quite variable results, especially in patients with an intact nervous system, who form the majority of those with LUTS. Clearly the association of any surrogate with obstruction can never be better than the association of one pressure-flow determination with another in the same patient. The intrinsic accuracy of classification appears to be about 80% [Sonke et al., 2000; Kranse and Van Mastrigt, 2003], limiting sensitivity and specificity to about 80% if both are maximized simultaneously.

In this section the various tests will be reviewed with the aim of obtaining the sensitivity and specificity of each test in predicting BOO, although frequently only a correlation coefficient is provided. As far as possible, positive and negative predictive values are avoided since they are affected by the prevalence of BOO, which may vary considerably across the studies assessed. It has to be realised that the sensitivities and specificities quoted assume that PFS have 100% accuracy, which stated above is not the case!

Male patients with LUTS are one of the commonest problems seen in the urology clinic. Although the symptoms are commonly associated with benign prostatic obstruction (BPO), symptoms may be related to an ageing bladder or a combination of BPO and aging. Other types of bladder outlet obstruction, due for example to bladder neck hypertrophy or urethral stricture, may also cause LUTS. In the assessment of patients with LUTS the initial step is to differentiate LUTS suggestive of BPO from LUTS not associated with BPO. This is often done by digital rectal examination although its accuracy in assessing the size of the prostate is poor. [Meyhoff et al., 1981] Prostate size can be measured more accurately with transrectal or transabdominal ultrasound. [Loeb et al., 2005] Patients without BPE have been defined as having a prostate volume of less than 20 ml (grams), [Garraway et al., 1993] but this certainly does not mean that prostates larger than 20 ml are necessarily obstructive, nor that prostates smaller than 20 ml are necessarily non-obstructive. [Hirayama et al., 2002]

2. SYMPTOMS AND SYMPTOM SCORES

As the earlier section on LUTS, their Aetiologies and Assessment demonstrated, LUTS and, in particular, voiding symptoms, lack any worthwhile specificity for BPO. This has been confirmed in large trials such as the International Continence Society- “BPH” study [de la Rosette et al., 1998] and summarised by the last International Consultation on BPH. [Abrams et al., 2001].

Eckhardt et al (2001) examined a cohort of 565 men with LUTS suggestive of BPO. 301 men (53%, 66 ± 7 years of age) had obstruction, and 264 men (47%, 66 ± 8 years of age) had no clear obstruction on conventional criteria (Schäfer grade ≤ 2, equivocal or unobstructed on ICS nomogram). Obstruction grade was not associated with symptoms, but decreased contractility, reduced bladder capacity and detrusor overactivity were weakly associated with some symptoms. All associations were weak, even when statistically significant in this large group, and no correlation coefficient exceeded 0.2 in magnitude.

Symptom scores are reviewed earlier in this chapter and, like individual symptoms, have weak associations with urodynamically proven BPO.

In spite of their weak relationship with urodynamic parameters, in particular obstruction, because symptom scores such as IPSS can be assessed easily and non-invasively they are still useful tools. However, neither individual symptoms nor symptom scores should be used for the diagnosis of BPO or as the only guide for further management of patients with LUTS. To do so may lead to undertreatment of patients with BPO or overtreatment of those without it (Level 3 evidence, but Grade A recommendations due to the large volume of evidence).
3. **Ultrasonic Assessment of the Prostate**

TRUS is the imaging modality used most frequently to assess prostate volume and it is more accurate than DRE [Loeb, et al., 2005]. MRI provides an even more accurate estimation of prostate volume and can more easily detect drug-induced changes in volume. [al-Rimawi et al 1994].

The relationship between total prostate volume and BOO has been investigated in several studies. A retrospective study involving 521 patients showed a weak but statistically significant correlation of prostate size and BOO (r=0.32, p<0.001). [Rosier and de la Rosette, 1995] The sensitivity and specificity for BOO of a prostate volume greater than 40 ml were 49% and 32% respectively. In another study of 525 patients there was a similarly weak correlation between prostate volume and BOO (r=0.28, p<0.001). [Eckhardt et al, 2001].

With the failure of total prostate volume alone to diagnose BOO, attempts have been made to diagnose BOO using the prostate shape and relative proportions of the different zones of the prostate. The zonal anatomy of the prostate consists of 3 zones: a central zone, a transitional zone (TZ) and peripheral zone. [McNeal, 1988] The transitional zone is the major site for the development of benign prostatic hyperplasia (BPH) leading to BPE, and is affected to a greater extent than the peripheral zone by medical treatment with finasteride [Tempany et al., 1993] and dutasteride, [Roehrborn et al, 2002] with correspondingly greater effect on Qmax. [Tewari et al, 1995; Roehrborn et al., 2002]

TZ index (the ratio of TZ volume to total prostate volume) is more strongly correlated with symptoms (r =0.75, p=0.001) and Qmax (r=-0.71, p=0.001) than prostate volume alone, but it is only moderately correlated with a critical measure of obstruction (detrusor pressure at Qmax; r=0.43). [Kaplan et al., 1995] and several investigators have concluded that it is not clinically useful for judging obstruction. [Lepor et al., 1997; Witjes et al., 1997; Kurita et al., 1998]

**a) Prostate shape**

Though size is important, shape may be equally or more important in predicting BPO. One way of assessing it is by using transrectal ultrasound (TRUS) to measure the anterior / posterior and the transverse diameter and to calculate the “presumed circle area ratio” (PCAR). The PCAR represents how closely the transverse ultrasound image of the prostate approaches a circular shape.

The ratio tends toward one as the prostate becomes more circular. The PCAR showed a stronger correlation with BOO than TZ index (r=0.487, P<0.0001, versus r = 0.331, P<0.005). The sensitivity and specificity for BOO of a PCAR value > 0.8 were 77% and 75% respectively, [Kojima et al., 1997] only a little smaller than the limit imposed by intrinsic variability of obstruction. It has been shown by Watanabe et al (1975) that when the ratio is greater than 0.75, BPO is likely. Similar findings were seen in a smaller study [Desai, 1999]. It seems clear that the more circular the prostate the more likely there is to be BOO.

In conclusion, these measures do show a consistent and definite, although weak, correlation with the diagnosis of BOO (see above). The relative size of the transition zone and the “circularity” of the prostate appear to improve the association with BOO, although the level of evidence (3) is not sufficient to allow a recommendation for the routine use of TRUS to assess prostate volume or shape to be used for the diagnosis of BOO/BPO.

**b) Intravesical prostatic protrusion on transabdominal ultrasound**

Intravesical Prostatic Protrusion (IPP) is another way of using prostate shape to predict BPO. The postulated rationale is that, as the prostate enlarges, it protrudes into the bladder, distorting the proximal urethral funneling and leading to BOO. [Ohnishi et al, 1985] IPP is usually measured by transabdominal ultrasound in the mid-sagittal plane. [Yuen et al, 2002] IPP is the distance from the tip of the protruding prostate to the base at the circumference of the bladder. [Chia et al, 2003; Tan and Foo, 2003], see Figure 24.

It is graded according to severity: grade 1 (5mm protrusion), grade 2 (5-10mm) or grade 3 (>10mm) [Chia et al, 2003]. As the measurement of IPP is affected by bladder volume, it is suggested that it should be measured at a comfortably full bladder volume of 100 to 200ml. [Yuen et al, 2002]. The test/retest reliability of this technique has not been published to date.

The relationship of IPP to BOO is such that, as the IPP grade increases, the severity of BOO also increases. In one study, 79% of patients with IPP grade 1 were not obstructed, but 94% of patients with IPP grade 3 were obstructed. [Chia et al, 2003] The positive predictive value of IPP grade 3 for BOO was 94%, while the negative predictive value was
79%. IPP was an independent predictor of BOO. Its sensitivity and specificity for BOO were 76% and 92% for grade 3, 17% and 53% for grade 2, and 7% and 56% for grade 1 respectively. High grade IPP seems also to be a good predictor of failure of catheter trial in patients with acute urinary retention. [Tan and Foo, 2003]

Intravesical prostate protrusion is a new method being developed to predict BOO/BPO. It appears promising but the level of evidence is not yet sufficient to justify a recommendation for its routine use.

c) Other ultrasound based methods:

Post void residual

PVR is often used to assess patients presenting with LUTS, although the pathophysiology of elevated PVR is not generally well understood and its interaction with BOO and detrusor underactivity is complex. Elevated PVR (usually defined as PVR > 100ml) is commonly observed in patients with BOO [Ball et al 1981], although one third of BOO patients do not have significant residual urine [Turner-Warwick et al 1973]. Thus, in patients with BOO, PVR tends to decrease after surgery [Neal et al 1989]. Like other urodynamic parameters, PVR is quite variable in any given subject [Bruskewitz et al 1982]. In one study however [Chia et al 2003] PVR > 100 ml showed values of sensitivity and specificity (75% and 91% respectively) that approach the limit set by intrinsic variability of obstruction.

Elevated PVR may also reflect detrusor underactivity [van Mastrigt and Rollema 1992; Zang at al 2003]. The interaction of BOO, (impaired) detrusor contractility and PVR was recently investigated in 131 patients. This showed that there was only a weak correlation between BOO and PVR. This result is not surprising since elevated PVR is a consequence of BOO, and therefore not all patients with BOO will have developed an elevated PVR. By combining measurements of detrusor contractility and BOO, PVR mat be reasonably accurately predicted [Kranse and van Mastrigt 2003]. PVR is most useful clinically in conjunction with other measurements, such as uroflowmetry [Abrams et al 2001].

Bladder Wall Thickness / Weight

An additional problem is the effect of the volume in the bladder on BWT. As the bladder is filled the bladder wall is stretched, thus reducing BWT [Kaefer et al 1997]. To overcome this, a bladder thickness index can be calculated, which standardizes BWT with respect to bladder volume. Alternatively BWT can be measured at a fixed bladder volume (150ml) [Manieri et al 1998]. The mean BWT measured in this way at 3 sites was moderately strongly correlated with obstruction as measured by the A – G number (r = 0.6724, p<0.0001). In 58 patients with a
BWT greater than 5mm, 88% were obstructed on pressure-flow studies. The specificity for BOO of a value of BWT>5mm was 92%; however, the sensitivity was only 54%.

A similar way to eliminate the effect of variable bladder filling volume is to calculate the ultrasound-estimated bladder weight (UEBW, Kojima et al 1996), which has a standard deviation of ± 5 grams (12%) in repeated studies. In a group of 65 patients there was a significant correlation of UEBW with urodynamic parameters of obstruction (r = 0.478, p<0.0001 for AG number; r = 0.543, p<0.0001 for Schäfer grade) [Kojima et al 1997]. With a cut-off value UEBW >35 g, the sensitivity of the test for obstruction was 85% with a specificity of 87%. These values are as good as those of pressure-flow studies themselves, suggesting that this is an excellent method. In the group of 33 patients undergoing prostatectomy the UEBW changed from a mean of 53 g, pre-surgery, to less than 35 g, 12 weeks after surgery [Kojima et al 1997]. Nevertheless, there are patients with substantially increased UEBW who are not obstructed [Kojima et al 1997] because, like BTW, UEBW defines bladder wall thickening but not the cause, which may not necessarily be prostatic obstruction.

Thus these ultrasound-based methods appear quite promising (level of evidence 3), but they have not been thoroughly tested and will always have the disadvantage that they provide only an indirect assessment of obstruction. It should be noted, however, that these methods may measure the sequelae of possible obstruction, indicating that the obstruction, if present, is clinically severe. No recommendation is possible for their routine use in LUTS patients.

4. UROFLOWMETRY

a) Conventional uroflowmetry

Uroflow measurement is the least invasive urodynamic assessment. It gives an objective and quantitative indication of voiding dysfunction. Its limitation is that it does not distinguish a low flow rate due to prostatic obstruction from low flow due to poor detrusor contractility [Chancellor et al 1991]. Furthermore, obstructed patients with high detrusor pressures can maintain a normal flow rate. Uroflowmetry results show a considerable variation in the maximum flow rate (Q_{max}) measured on either the same or different days. [Feneley et al 1996]

The specificity of maximum flow rate for BOO depends on a number of factors, for example the volume voided and the value of Q_{max} used. In a large study the specificity and sensitivity for BOO of Q_{max} of less than 15 ml/s were 38% and 82% respectively. [Reynard et al 1998] Thus this value of Q_{max} is too non-specific to be useful. For Q_{max} < 10 ml/s the sensitivity and specificity were 70% and 45% respectively. The limitation of this approach remains therefore the poor sensitivity of this value of Q_{max}(10 ml/s).

In general, the sensitivity and specificity of Q_{max} do not approach the limits set by the intrinsic variability of BOO. Single centre smaller studies have suggested a higher specificity of up to 90 % for Q_{max} of < 10 ml in particular with multiple flows. [Nielsen et al, 1994; Poulsen et al., 1994; Reynard et al, 1996]. Therefore, for uroflowmetry to play a part in the diagnosis of BOO/BPO, the measurements need to be multiple. In this circumstance, the level of evidence 2 allows a recommendation, Grade B, for the reliable diagnosis of BOO, but only when Q_{max} is less than 10ml/s (Table 9).

<table>
<thead>
<tr>
<th>Q_{max} (ml/s)</th>
<th>&lt;10</th>
<th>&lt;15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>70</td>
<td>38</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>47</td>
<td>82</td>
</tr>
<tr>
<td>PPV</td>
<td>70</td>
<td>67</td>
</tr>
</tbody>
</table>

b) Penile compression release index.

Interruption of flow by manual pinching of the penis, followed by release, leads to a surge in flow followed by a steady state, just as in the cuff technique, described below [Sullivan and Yalla, 2000]. The penile compression release (PCR) index is defined as (Q_{surge} – Q_{steadystate})/Q_{steadystate} X 100. The PCR index differed in obstructed, non obstructed, detrusor underactivity and detrusor overactivity groups and a cut-off value of 100% could diagnose BOO with a sensitivity and specificity of 91% and 70% respectively [Sullivan and Yalla, 2000].

If a penile cuff (see below) was used to calculate the PCR, a cut-off value of 160% gave a sensitivity and specificity of 78% and 84% for BOO. [Harding et al., 2004] These values approach the limit set by the intrinsic variability of BOO.

5. NON-INVASIVE URODYNAMIC PRESSURE MEASUREMENT

Over the past decade a number of ingenious ways
have been described for measuring the bladder pressure associated with voiding in a non-invasive way. The principle underlying these techniques is the measurement of isovolumetric bladder pressure; this allows a low free flow rate, due to obstruction, to be distinguished from a low flow rate due to detrusor underactivity. The penile cuff and the modified condom method are the 2 principal methods. Both rely on the assumption that there is a continuous column of fluid from the bladder through the urethra to the point where flow is interrupted, so that the fluid pressure at the point of measurement is the same as the pressure within the bladder, thereby recording its isovolumetric value.

**a) Condom catheter method**

For the external condom method [Schäfer et al, 1994; van Masttrigt and Pel, 1999] the patient voids through a condom catheter (see Figure 25 below). At maximum flow, the catheter is blocked and the isovolumetric pressure is measured. In a study of 75 patients, who underwent both pressure-flow studies and the condom method, there was a 25% technical failure rate. Several strategies for analysing the data were used and the best method (using Qmax also) showed a sensitivity for BOO of 64% with a specificity of 79%. [Pel et al., 2002]. These are rather disappointing values, markedly inferior to the limits set by the variability of real pressure-flow studies.

In initial trials the isovolumetric pressure was not always attained, especially in obstructed patients, or those with low flow rates (< about 5 ml/s). [Gommer et al., 1999; Pel and van Masttrigt, 1999]. Recent improvements [Pel and van Masttrigt, 2001] have led to better reproducibility [Huang et al., 2004; van Masttrigt et al 2004] so that this method now has an overall accuracy of 90% in diagnosing obstruction, although only when the obstructed and equivocal groups on ICS nomogram were combined. However, the accuracy of agreement is only 67% for ICS obstructed group alone, [Pel et al., 2002] a value that should be compared with accuracies of 82 to 83% for pressure-flow studies themselves. Van Masttrigt’s group has shown that this method can usefully be applied in epidemiological studies of large populations to gain information about bladder and urethral function that would otherwise be inaccessible [Chung et al 2005].

**b) Penile cuff**

The penile cuff is a flexible inflatable cuff that is placed around the shaft of the penis (Figure 26 below). [McRae et al 1995]. Two methods of use have been suggested: the deflation and the interruption technique. For the deflation technique [Gleason et al, 1997] the penile cuff is used to occlude the urethra before voiding. The patient is instructed to void into a flowmeter and the cuff is deflated slowly by the patient (by pressing a button) when the urine is felt in the urethra. Once a flow rate of greater than 1ml/s is detected by the flowmeter, the cuff is deflated rapidly.

For the interruption technique, an automatically inflated penile cuff *(modified paediatric blood pressure cuff)* is used to interrupt the flow after voiding has commenced. [Griffiths et al 2002] The cuff pressure when the flow stops is presumed to be equal to
the bladder pressure. Once the flow has stopped, the cuff is rapidly deflated and there is a surge of urine after which the inflation cycle can be repeated. Simultaneous invasive urodynamics showed that the isovolumetric detrusor pressure was reliably estimated by this method, although the mean cuff pressure over-estimated the bladder pressure by 14.5 +/- 14 cm H2O [Griffiths et al., 2002]. The test/retest variability was 0 (SD 20.3 cm H2O) in patients with a voided volume of at least 150 ml. [McIntosh et al., 2004]. The interobserver agreement in the analysis of the results was good. [Drinnan et al., 2003] The majority of patients (80%) preferred the cuff to invasive urodynamics.

In order to diagnose BOO with this technique a modification of the ICS nomogram has been suggested. Alternatively a diagnostic parameter N (= pcuff – 6.4 * Qmax + 0.35 PCR) can be used (PCR is defined above); N > 100 indicates obstruction. A further study of the outcome of TURP using the modified ICS nomogram is in progress. Preliminary results show that preoperative assessment using the nomogram improves the outcome.

In conclusion, in spite of technical pitfalls [Blake and Abrams, 2004] and the fact that it measures intravesical and not detrusor pressure, non-invasive urodynamical pressure measurement, especially if combined with the PCR index and maximum free flow rate, promises to provide a reasonably reliable method of diagnosing BOO (Level 3 evidence). However it remains unclear whether the extra complications required are worth the relatively small improvement in diagnostic accuracy over uroflowmetry (no recommendation possible, as yet).

c) Doppler techniques

- DOPPLER ULTRASOUND TECHNIQUES

Doppler ultrasound, developed for measuring blood flow velocity, can be used to measure urine flow rates greater than 3 ml/s. [Ozawa et al., 1998] The technique measures urine flow velocity (V1) in the prostatic urethra, the site of the flow-controlling zone. The patient takes up a sitting position and the probe is positioned perineally by a robotic arm. In a small group of patients with and without BOO, the functional cross-sectional area (calculated by dividing maximum flow rate by maximum flow velocity, as determined by Doppler), was lower in the group with BOO (mean 0.31 cm2 SD+/-0.16) than the control group (0.78 cm2 +/-0.23) (p = 0.006). [Ozawa et al., 1998] Subsequently the flow velocity (V2) in the membranous urethra was added to the measurements and the velocity ratio V1/V2 was calculated. A velocity ratio greater than 1.6 showed a sensitivity of 60% and a specificity of 100% for the diagnosis of obstruction as shown by pressure-flow studies. [Ozawa et al., 2000] A further small study showed that the velocity ratio decreased after alpha blocker therapy, although V2 was more strongly associated with the change in symptom IPSS after treatment (r=0.584). [Watanabe et al., 2004]

- DOPPLER RESISTIVE INDEX

In animal models, detrusor blood flow has been shown to be reduced in obstruction. [Lin et al, 1995] In a pilot study, average detrusor arterial blood flow was measured with color Doppler at 3 sites in the bladder and the resistive index, an index of change in blood flow was calculated (RI = Vmax - Vmin/ Vmax). There was a significant difference between the values of RI in obstructed and unobstructed patients. The overall accuracy for predicting BOO was 86% but the predictive value was low (57%). [Belenky et al., 2003] Presumably because other factors also affect the change in blood flow. In men with LUTS, RI measured transrectally showed only a weak correlation with the Abrams-Griffiths number (BOOI; r=0.330, p<0.05).

In conclusion, the reliability of the Doppler urodynamical test appears reasonable, but there is large inter-rater variability in the calculation of the velocity ratio. [Ding et al., 2000] Moreover, Doppler urodynamics requires expensive and specialised equipment and a cooperative patient who is able to void in the sitting position. The Doppler Resistance Index is an interesting technique but there is insufficient evidence to reach any conclusion at present.

6. COMBINATIONS OF SINGLE MEASURES

Because of the shortcomings of individual non-invasive parameters for diagnosing BOO, many different combinations have been investigated.

Qmax and total prostate volume (PV) can be used to estimate bladder outlet obstruction index. [Ockrim et al., 2001] Data from 384 men suggest that estimated bladder outlet obstruction index = antilog10 (2.21 - 0.5 log Qmax + 0.18 log PV). In 42% of the population, an estimated BOOI index of greater than 40 showed a sensitivity of 92 % for obstruction or equivocal obstruction. Using Qmax alone provided a sensitivity of 86% of predicting BOO, but could be used in only a minority of the study population (17%) [Note: this is NOT the BOOI described in the ICS report 2002 (Abrams et al)].
The combinations of AUA symptom score and $Q_{\text{max}}$ with the highest specificity for BOO were determined in 134 patients. [Schacterle et al, 1996] With $Q_{\text{max}} < 10$ ml/s and AUA score > 20, specificity and sensitivity for obstruction were 98% and 38%. Conversely, with $Q_{\text{max}} > 15$ ml/s and AUA score < 10, specificity for no obstruction was 98% but sensitivity was only 22%. Only 20% of the population studied were categorised as obstructed or unobstructed using this approach. If prostate volume ($> 40$ grams) was added to the algorithm, [Steele et al, 2000] specificity increased to 100% but sensitivity remained only 26%, and the population diagnosed remained low at 20%.

$Q_{\text{max}}$, PV and relative residual volume (post-void residual volume as a percentage of pre-void bladder volume) can be used to calculate a bladder outlet obstruction number (BOON) as follows: [van Venrooij and Boon, 1996]

$$\text{BOON} = \text{prostate volume (from TRUS, in ml)} - 3 \times Q_{\text{max}} + (0.25 \times \text{relative residual volume}).$$

In a population of men with LUTS, the majority obstructed on urodynamics, a value of BOON $> -2$ diagnosed 50% of men with BOO (Schä fer grade ≥ 2), with a sensitivity of 96%. However for Schä fer ≥ 3 (equivalent to obstructed on ICS nomogram) the discrimination between obstruction and no obstruction disappeared. The equation was later refined [van Venrooij et al, 2004] to use voided volume instead of relative residual volume.

$Q_{\text{max}}$, prostate volume and PVR have been combined in a simple categorical nomogram to determine the probability of obstruction. [Madersbacher et al., 1997] The method has not been validated in an independent set of patients.

$Q_{\text{max}}$, prostate volume, PVR and voided volume [Rosier et al., 1996] were measured in 871 elderly patients and used to obtain a ‘clinical score’ (in which $Q_{\text{max}}$ was the most strongly weighted) to help in the diagnosis of BOO. A score of greater than 11 gave a sensitivity of 80% but a specificity of only 53% for BOO.

$Q_{\text{max}}$, flow pattern, PVR, prostate volume, voided volume, TZ index and median lobe enlargement, as measured in 324 Taiwanese men, were used to construct a clinical prostate score to diagnose BOO. [Kuo, 1999] A score of 3 or greater had a sensitivity of 87% and a specificity of 61% for BOO. However in the population studied, the majority (54%) would still require urodynamics to determine the presence of BOO. The generalisability of the results to non-Asian populations is uncertain.

Intravesical prostatic protrusion (IPP) and Doppler ultrasound appear to offer high sensitivity and specificity for obstruction. Intravesical prostatic protrusion (IPP) and Doppler ultrasound were recently compared with pressure-flow studies in 30 patients. [Nose et al., 2005] Combination of these parameters, with the same cut-off values, gave a sensitivity of 100%/5/5 with a specificity of 91%/10/11. [Nose et al., 2005] These impressive values are obtained by post hoc selection of the cut points in a small population and appear to exceed the limits set by the limited reproducibility of pressure-flow studies themselves (see above). Taken separately, the sensitivities of IPP (grade 3) and velocity ratio ($> 1.6$) for diagnosing BOO were 90%/9/10 and 100%/11/11 respectively. They require independent testing and confirmation in a larger population.

### IV. CLINICAL UTILITY OF NON-INVASIVE MEASUREMENTS

Of the many non-invasive parameters available currently for assessing obstruction in patients with LUTS, which are the most useful clinically? Only a few of them achieve both a high specificity and sensitivity for BOO (Table 10). The best in this respect seem to be ultrasound-estimated bladder weight; intravesical prostatic protrusion (grade 3); penile cuff test + PCR index; cuff test + PCR index + $Q_{\text{max}}$; and intravesical prostatic protrusion + velocity ratio. Many however have not been widely tested outside the centres where they were developed. A problem with all of them is that the majority of patients presenting with LUTS are not ascribed with certainty to any diagnostic group (e.g. patients with a mid-range flow rate, moderately sized prostate and/or moderate symptoms). In contrast the extremes of the population are generally easy to categorize (e.g., patients with large prostate, low $Q_{\text{max}}$ and severe symptoms), but for these such methods represent no improvement over clinical experience.

To address this problem it has been proposed that a 3-way classification system based on ultrasound findings (e.g., IPP), bothersomeness of symptoms, and flowrate/residual urine should be used [Chia and Foo, 1999]. This enables patients’ status to be classified as mild (no bothersome symptoms and no significant obstruction), moderate (bothersome symptoms but no significant obstruction) or severe (significant obstruction, irrespective of symptoms). Treatment can be tailored accordingly.
Table 10. Non-invasive methods for diagnosing bladder outlet obstruction.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Number of patients</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Likelihood ratio</th>
<th>Pre-test probability</th>
<th>Post-test probability =Positive predictive values</th>
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<tr>
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<td>94</td>
<td>8</td>
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<td>1.32</td>
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<td>78</td>
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<td>10.11</td>
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<td>[Ozawa et al, 2000]</td>
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<td>Penile cuff test Modified manogram</td>
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<td>[Griffiths et al, 2005]</td>
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<tr>
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<td>91</td>
<td>70</td>
<td>3.04</td>
<td>48</td>
<td>74</td>
</tr>
<tr>
<td>[Sullivan et al]</td>
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<tr>
<td>PCR index &gt; 160%</td>
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<td>[Harding et al]</td>
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117
Table 10. Non-invasive methods for diagnosing bladder outlet obstruction.

<table>
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<tr>
<th>Parameters</th>
<th>Number of patients</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Likelihood ratio</th>
<th>Pre-test probability</th>
<th>Post-test probability =Positive predictive values</th>
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<td>RI &gt; 0.7 [Kojima et al., 2000]</td>
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</tr>
<tr>
<td>BWT &gt;5 mm [Manicri et al, 1997]</td>
<td>174</td>
<td>54</td>
<td>92</td>
<td>6.367</td>
<td>56</td>
<td>89.7</td>
</tr>
<tr>
<td>BWT &gt;2mm [Oelke et al, 2002]</td>
<td>70</td>
<td>64</td>
<td>97</td>
<td>23.55</td>
<td>47.1</td>
<td>95.5</td>
</tr>
<tr>
<td>U/E:BW &gt;35g [Kojima et al, 1997]</td>
<td>65</td>
<td>85</td>
<td>87</td>
<td>6.61</td>
<td>52.3</td>
<td>87.9</td>
</tr>
<tr>
<td>Cuff, PCR and Qmax [Drinnan et al, 2004]</td>
<td>116</td>
<td>86</td>
<td>87</td>
<td>6.62</td>
<td>42</td>
<td>83</td>
</tr>
<tr>
<td>Qmax, PV, PVR, VV [Rosier et al, 1996]</td>
<td>871</td>
<td>80</td>
<td>53</td>
<td>1.70</td>
<td>61.5</td>
<td>73.1</td>
</tr>
<tr>
<td>Seven measures [Kuo et al, 1999]</td>
<td>324</td>
<td>87</td>
<td>61</td>
<td>2.23</td>
<td>65</td>
<td>81</td>
</tr>
<tr>
<td>Neural networks and IPSS [Wadie et al, 2001]</td>
<td>155</td>
<td>87</td>
<td>44</td>
<td>1.55</td>
<td>61</td>
<td>71</td>
</tr>
</tbody>
</table>
Further research is required to provide evidence that these methods will reduce the need for pressure-flow studies. Moreover, to be clinically useful, the parameter must not only accurately predict obstruction, but it must also be easy to measure. It is always more difficult to do a functional measurement than a static measurement, but uroflowmetry is a non-invasive functional measurement with 90% accuracy in the diagnosis of BPO when properly performed and if Qmax is less than 10ml/s [Abrams et al, 1995]. It is also more physiological and less invasive than other “non-invasive” methods such as the condom catheter, the penile cuff and Doppler ultrasound, which, although slightly less invasive than conventional urodynamics, may require the attendance of the investigator. Moreover, the current “non-invasive” urodynamic methods are no more accurate than free uroflowmetry in assessing BPO. It is more important to rule out BPO in equivocal patients than to prove its presence, as surgical intervention in patients without BPO has relatively poor results. Currently only conventional urodynamic studies can rule out obstruction with confidence.

The situation may be different for the ultrasound-based methods of assessing obstruction, provided that their sensitivity and specificity is maintained in wider practice. With ultrasound readily available in the clinics, enabling tests such as those listed above to be performed, the need for urodynamics before surgical intervention may be reduced to those with obstruction that remains equivocal after non-invasive (ultrasound) assessment.

V. PATHOPHYSIOLOGY OF DETRUSOR OVERACTIVE AND BLADDER OUTLET OBSTRUCTION

It has long been argued that urethral obstruction is responsible for the relatively high prevalence of detrusor overactivity found in men with LUTS, and in particular for its post-operative decrease, and there is some animal evidence to support this. Nevertheless the pathophysiological link between obstruction and detrusor overactivity is still not entirely clear, and a number of recent papers have examined this problem.

Knutson et al [2001] studied a cohort of 162 men with LUTS suggestive of BPO, without other diseases that might affect bladder function. All were assumed to have bladder outlet obstruction (BOO), but it was classified as ‘mild’ in 15%. They showed that 55% had pure BOO (judged from the obstruction parameter DAMP[Schäfer, 1995]), while the remainder had DO+BOO. Those with DO+BOO were older, had higher s-PSA, voided smaller volumes and were more severely obstructed, although there was no significant difference in Qmax or post-void residual urine. There was a strong association between DO and BOO (P= 0.008). They suggested that this indicates that BOO is a progressive disease that may contribute to the development of DO.

Eckhardt et al [2001] examined 565 men with LUTS suggestive of BPO. 53% had obstruction with Schaefer grade III or higher, equivalent to obstruction on the ICS nomogram. 465 (82%) showed detrusor overactivity. Detrusor overactivity (especially if present both supine and standing) showed a significant positive association with grade of obstruction.

Wadie et al [2002] studied 459 men with LUTS. 24% showed detrusor overactivity (with amplitude >15 cm H2O). Detrusor overactivity was positively associated with severity of obstruction: Schaefer grade [mean ± SD] was 3.4 ± 1.5 and 2.9 ± 1.5 in those with and without detrusor overactivity, respectively. This association, although statistically significant (P= 0.004), still implies that there is a great deal of overlap in obstruction grade between those with and without detrusor overactivity.

All the above suggest that detrusor overactivity is associated with bladder outlet obstruction. In apparent contrast, Eckhardt et al [2001] compared 14 older (≥50 y) male volunteers without LUTS with 465 older patients with LUTS. They found that 6 of the 14 volunteers (43%) showed detrusor overactivity, while 259/565 patients with LUTS (46%) showed it. Thus the incidence of detrusor overactivity was similar in volunteers and patients. In spite of the difference in LUTS, however, there was only a modest difference in obstruction: 5/14 volunteers (36%) and 301/565 patients (53%) were obstructed. These observations therefore remain consistent with the hypothesis that detrusor overactivity and bladder outlet obstruction are associated.

Hirayama et al [2003] investigated the etiology of detrusor overactivity in LUTS. They performed an ice water test in 2 groups of patients: 127 men with LUTS, without neurological disease, age > 50 y, IPSS ≥ 8, QOL index ≥ 2; and 20 neurological patients as controls. In an ice water or bladder cooling test, cold water is rapidly infused into the bladder. [Fall, et al 1995] A positive result (provocation of involuntary detrusor contraction) is believed to
indicate pathological involvement of C-fibre afferents in the voiding reflex. In this study 14/20 neurological patients (70%) showed a positive ice water test, suggesting (as expected) that C-fibre afferents were involved in the abnormal voiding reflex. However, 35/127 LUTS patients (27%) also showed a positive ice water test, and all 35 showed detrusor overactivity during regular cystometry also. They also had more severe bladder outlet obstruction and smaller volume at strong desire to void than those with a negative ice water test. These observations seem to suggest abnormal involvement of C-fibre afferents in LUTS patients with severe obstruction.

Dinis et al [Dinis, Silva, Ribeiro et al., 2004] were able to check the involvement of C-fibres directly. They examined the effect of C-fibre desensitization with a single intravesical administration of resinfectoritoxin (50nM solution). 12 patients with storage LUTS were treated. The IPSS decreased from 20 to 10 at 3 months and more. Urge incontinence was abolished in 4/6 patients with this symptom. Bladder volume at first desire to void and maximum cystometric capacity both increased. Voiding itself, as reflected in uroflow and PVR, was not altered. Thus this observation is not only consistent with the involvement of C-fibres in detrusor overactivity, but it also suggests a potentially useful treatment.

To summarize, detrusor overactivity in LUTS patients is associated with severity of obstruction, and it appears to have a neurological component, as shown by the involvement of C-fibre afferents in the voiding reflex.

VI. WHEN IS OBSTRUCTION SIGNIFICANT CLINICALLY?

In this section we have focused on the non-invasive diagnosis of obstruction defined ultimately in urodynamic terms. In practice however it would be more satisfying to determine whether such methods can diagnose obstruction of clinically relevant severity.

In assessing severity, it can be argued that actual obstruction is more important than symptoms. Although symptoms affect quality of life, obstruction, if not relieved in time, may lead to progression of the disease and affect organ function. In less developed parts of the world, obstruction still limits lifetimes.

Until recently, attention was paid only to the back-pressure effects of obstruction on the kidneys. More recent studies have suggested that bladder outlet obstruction affects bladder function, leading to structural changes also. Because the changes may eventually become irreversible, some would argue that management should be directed towards early relief of significant obstruction. [Flanigan et al., 1998; Lu et al., 2000; Brierly et al., 2003]

When is the level of obstruction clinically significant? Is the ICS definition of obstruction, based on pressure-flow studies, clinically significant? If the BOOI > 40, does the patient need more aggressive treatment such as surgical relief of obstruction? If not, at what level of obstruction would surgical relief be indicated? There are no evidence-based studies to suggest when surgical relief is indicated. However many papers have shown that, if there is no evidence of obstruction on pressure-flow studies, the results of surgical relief are not as good. [Porru et al., 2002; Thomas, 2004].

In clinical practice, it is important to know when surgical intervention is indicated in the management of BPO. Obstruction can vary from mild to severe, and not all patients with a urodynamic diagnosis of obstruction require surgery, especially in this era of 5-alpha reductase inhibitors. Going back to the basic principles of clinical practice, if obstruction is affecting the function of the organ, then more aggressive treatment such as surgical relief is indicated. Analogously, for the eye, in glaucoma, if the intra-ocular pressure is affecting vision, then it is clinically significant and requires more aggressive treatment. Similarly, in clinical shock, the exact level of the blood pressure is not as important as the hourly urine output, which reflects the effect of the low blood pressure on perfusion of the kidneys. If the hourly urine output is poor then shock is clinically significant. Clinical shock is not defined by the exact level of the blood pressure. Thus in real life practice, it is more important to assess the effects of prostatic obstruction than the exact degree of obstruction, whether using conventional urodynamic studies or the non-invasive methods described in this section.

This argument suggests that tests could be selected for their ability to assess potential changes in bladder function and structure. The two basic functions of the bladder are storage and emptying. If the storage function is affected by BPO, there will be inability to store urine, manifested clinically by frequency and urgency and voiding of small volumes. If the emptying function is affected then there will be persistent residual urine. Suitable tests (some but not all discussed above) are:
a. Measurement of voided volume
This can be done easily and non-invasively by asking patients to keep a voiding diary.

b. Measurement of residual urine
c. Measurement of bladder weight
This can be done with transabdominal ultrasound. Increased weight signifies a structural change.
d. Measurement of bladder blood flow (detrusor resistive index)
Can be measured with Doppler ultrasound. Unrelieved obstruction may lead to decreased bladder tissue perfusion and may eventually cause irreversible harm to the structure and function of the bladder.
e. Ultrasound of kidneys for hydronephrosis
Patients with minimal symptoms despite pronounced obstruction may rarely have bilateral hydronephrosis, as they seek treatment late. Measurement of serum creatinine is not sensitive enough to detect this complication until the kidneys have lost significant function. As surgeons we need to detect this complication early and the best clinical tool is transabdominal ultrasound. In less developed countries of the world, chronic retention of urine with bilateral hydronephrosis, and impaired renal function in about 6%, is still a common urological problem. Lim et al., 1999. However, this argument would logically demand the screening of the whole older male population, which is likely to remain impractical.

CONCLUSION
Many of the newer non-invasive methods that have been suggested are not very sensitive or specific for detecting BOO, and uroflowmetry – an old method – remains surprisingly good (Grade B recommendation). The non-invasive methods of measuring bladder pressure, although ingenious, have yet to prove their usefulness in the clinic. They may be useful for evaluating bladder function in epidemiological studies.
Ultrasound-based methods provide quantitative and objective measurements that are promising for making therapeutic decisions in clinical practice, although their reliability and applicability need to be independently tested in centres outside those involved in their development.

VII. URODYNAMICS IN PROSTATE CANCER
The following will be reviewed: the urodynamic situation in men with a diagnosis of prostate cancer, prior to any treatment; the changes after treatment, judged prospectively; whether pre-operative urodynamics can predict outcome (e.g. continence or incontinence); the mechanism of post-treatment incontinence; and the clinical utility of urodynamics in prostate cancer.

1. URODYNAMICS IN UNTREATED PROSTATE CANCER
Understandably, only limited urodynamic studies have been reported prior to treatment in men with a diagnosis of prostate cancer. Because such men may be identified either by screening or by symptomatic presentation, the prevalence of urodynamic abnormalities such as obstruction may be quite variable in different centers with different patient populations. It is usually suggested that the possible abnormalities are similar to those in benign prostatic obstruction: urethral obstruction and detrusor overactivity. The age ranges of the patients are usually similar (though quite wide).

a) Urethral obstruction
Urethral obstruction implies that the urethral resistance to flow is abnormally elevated, as revealed during voiding by a relatively low flow rate at a relatively high detrusor pressure (see Figure 18). Obstruction may be due to urethral overactivity (failure to relax during voiding) or to structural abnormalities (e.g. a stricture, or perhaps prostatic enlargement). A number of methods of assessing obstruction have been developed, all giving somewhat similar results except in borderline cases. The International Continence Society [Griffiths et al., 1997] recommends that the maximum flow rate (Qmax) and the detrusor pressure at maximum flow (Pdet.Qmax) should be recorded in ml/s and cm H2O respectively. A classification of obstruction can then be derived from the ICS obstruction nomogram or the bladder outlet obstruction index (BOOI).
In a study of urine flow rates [Masters and Rice, 2003], among 125 men examined prior to radical retropubic prostatectomy for prostate cancer, 38% had a maximum flow rate of 10 ml/s or less. Comparison with flow rates in benign disease (Table 9) suggests that the majority of these 38% had bladder...
outlet obstruction caused by an enlarged prostate. Presumably most of the remaining 62% had relatively slight prostatic obstruction, or none.

Direct assessment of obstruction by invasive urodynamic measurements prior to surgery is rare. Perhaps developments in non-invasive urodynamics will allow this gap to be filled in the future.

b) Detrusor overactivity and bladder compliance

Detrusor overactivity is a urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked. Characteristically it is associated with symptoms such as urgency and frequency of micturition and urgency incontinence. It is not a diagnosis but a urodynamic observation, the cause of which is sometimes clear (e.g. a neurological disease such as multiple sclerosis) but often is obscure. For example, it has been argued that detrusor overactivity may be caused by urethral obstruction, and this is discussed further below. In other cases there is no obvious cause at all and the detrusor overactivity is called idiopathic. Sometimes it may even be a normal variant.

The incidence of detrusor overactivity during filling cystometry has been noted in 5 studies. Constantinou and Freiha [1992] examined 29 patients with a mean age of 63 years, prior to surgery for prostate cancer. 16/29 patients (55%) demonstrated detrusor overactivity, with quite high maximum detrusor pressures (59 ± 28 cm H2O [mean ± SD]). Golomb et al [1999] reported on 20 patients with a diagnosis of prostate cancer. Detrusor overactivity with detrusor pressures exceeding 15 cm H2O was demonstrated in 12/20 patients (60%). Kleinhans et al [1999] studied 66 patients in the week before surgery for prostate cancer. Detrusor overactivity was observed in 21/66 (32%). Aboseif et al [1994] evaluated 92 men (mean age 64 years) prior to prostate cancer surgery. 19/92 showed detrusor overactivity (21%). Hammerer et al [1997] examined 82 prostate cancer patients pre-operatively, found that the mean maximum urethral pressure was 90 cm H2O : within the normal range. John et al, [2000] in 34 prostate cancer patients examined pre-operatively, found a maximal urethral closure pressure of 49 ± 10 cm H2O, perhaps a little lower than normal.

2. Urodynamics after treatment of prostate cancer: prospective studies

There are relatively few systematic prospective studies of the urodynamic situation after cancer treatment. The majority of studies have focused mainly on the changes produced by surgery, or on the risk and mechanism of incontinence. Consequently surprisingly little is known of the situation in the majority of patients – those who do not become incontinent or who quickly regain continence after surgery. Such knowledge is essential to provide the basis for informed medicine. Ideally systematic study of the effect of each treatment option is required, including radical prostatectomy and radiation treatments. The following references provide the only available knowledge.

a) Detrusor overactivity

As seen above, detrusor overactivity is moderately common preoperatively, although it does not usually lead to incontinence. An important question is
whether it is equally, more, or less common after treatment for prostate cancer, since a weakened sphincter mechanism may not be able to control urine loss if the detrusor is overactive. The reports are not entirely consistent; furthermore, the numbers in each study are small.

Golomb et al. [1999] showed that among 12/20 patients who demonstrated detrusor overactivity preoperatively, only 2 manifested urgency incontinence after prostate surgery. The postoperative incidence of detrusor overactivity was not reported, but would appear to be lower than preoperatively. Hammerer et al. [1997] examined 82 patients pre- and post-operatively. Detrusor overactivity increased to 41% after surgery, from 17% pre-operatively. Do et al. [2002] and Choo et al. [2002] performed urodynamics pre- and post-radiotherapy in 15 patients. There were no significant changes in detrusor overactivity. In fact the amplitude of detrusor overactivity can remain quite high postoperatively (mean 49 cm H\textsubscript{2}O) [Constantinou and Freiha, 1992]

b) Urethral obstruction

The urodynamics of urethral obstruction are discussed above.

Radical prostatectomy would be expected to remove any bladder outlet obstruction caused by a malignantly enlarged prostate, unless a urethral stricture or stenosis were to develop. Radiation therapy may increase obstruction in the short term, if swelling and inflammation develop.

Kumar et al. [2004] suggested that, in a group of 50 men with prostate cancer and moderate or severe LUTS preoperatively, there were significant improvements postoperatively in maximum flow rate (11.3 ml/s to 27.3 ml/s at 3 months) and PVR (63 ml to 24 ml), as well as in symptoms. In 8 men with mild LUTS (16% of the group) the symptomatic improvement was much less. This suggests that some men who are not highly obstructed preoperatively remain so and receive less symptomatic benefit than those who are highly obstructed to start with.

Constantinou and Freiha [1992] found that, in 13 post-operative patients, the maximum flow rate was 13 ± 2 ml/s and maximum voiding detrusor pressure was 39 ± 4 cm H\textsubscript{2}O. These values are within normal ranges, suggesting that the most severe outlet obstruction has been removed by surgery. Montorsi et al. [1993] found that, in 150 patients after radical prostatectomy, mean maximum uroflow was 16.9 ± 1.3 ml/s and PVR was 11 ± 2 ml. 22% were still obstructed post-operatively, by a stricture in 12% and because of ‘denervation’ in 10%. According to Masters and Rice, [2003] in 125 men, mean maximum flow rate post-operatively was 17 ml/s, rising to 24 ml/s at 20 months. This high value suggests that urethral obstruction has been removed by the surgery. Strictures or stenoses developed in 20% and were treated, partly explaining the gradual improvement in flow post-treatment, although improvement occurred even in men with no stenoses.

Taken together, these studies suggest that the majority of pre-operative outlet obstruction (presumably prostatic in origin) is removed by radical prostatectomy, but that a certain amount of obstruction remains or develops de novo (stenosis or stricture), and gradually resolves either spontaneously or with treatment over the following year or so.

Do et al. [2002] performed urodynamics pre- and 3 months post-treatment by external beam radiotherapy in 15 patients. This therapy caused no significant change in bladder outlet obstruction, although there was a significant decrease in PVR. Henderson et al. [2002] found that 27/100 patients had to use a catheter after prostate brachytherapy treatment or suffered acute urinary retention. This seems to have been due mainly to urethral obstruction (new or pre-existing) post-treatment.

c) Urethral pressure and other parameters

Because of anatomical propinquity, radical prostatectomy is likely to produce significant weakening of the striated urethral sphincter, by damage directly to the muscle or through damage to its innervation. Presumably the damage is more serious in those who suffer from post-surgery incontinence, but an important question is, how serious is it in those who have no problem with incontinence? In other words, is radical surgery always accompanied by sphincter damage, or is it possible to avoid damage, at least in some patients?

Hammerer et al. [1997] examined 82 patients. Preoperative mean maximum urethral pressure was 90 cm H\textsubscript{2}O, decreasing to 65 cm H\textsubscript{2}O post-operatively.

John et al. [2000] measured a number of urodynamic parameters in 34 patients pre- and post-operatively. Maximal urethral closure pressure was 49 ± 10 cm H\textsubscript{2}O preoperatively and became significantly lower postoperatively. At 6 weeks it was significantly lower in incontinent (11 ± 9 cm H\textsubscript{2}O) than in continent patients (35 ± 6 cm H\textsubscript{2}O and 42 ± 9 cm H\textsubscript{2}O, respectively. Posterior urethral electrosen-
sation also was reduced after surgery (i.e. the threshold for sensation was higher), more so in incontinent patients than continent.

These observations suggest that damage to the urethral striated sphincter and its innervation is extensive even in patients who are continent post-radical prostatectomy. Thus initially there is intrinsic sphincter deficiency (section 2.4.1), which seems to recover slowly in the months following surgery.

Choo et al [2002] studied urodynamic changes after radiotherapy for prostate cancer in 15 patients. They found that, in the supine position, bladder capacity had decreased by 100 ml. The bladder volumes at first sensation of filling and at normal desire to void also decreased. These observations suggest that, after radiation therapy, sensations referable to the bladder became stronger.

d) Incontinence after radical prostatectomy

Urinary incontinence is the complaint of any involuntary leakage of urine. For a full definition in a given context, factors such as frequency and severity need to be specified. Incontinence is both common and troublesome after surgery for prostate cancer. The reported incidence after radical prostatectomy varies greatly, from 5% to over 60% [Hunskaar et al., 2002]. It depends on the surgical technique, the definition of incontinence and how it is quantified, [Grise and Thurman, 2001; Peyromaure et al, 2002] who performs the evaluation of the incontinence (physician or patient) [Donnellan et al, 1997; McCammon et al, 1999] and (because of spontaneous regression) the time between the surgery and the evaluation. However, at 12 months post-surgery the prevalence of incontinence is probably about 15-20%. [Hunter et al, 2004]

e) Incontinence after radiation treatment

Henderson et al [2002] report no incontinence after radiation/brachytherapy treatment, in a total of 100 patients. Choo et al [2002] report that 4 of 17 patients suffered from urgency incontinence before radiotherapy for prostate cancer and were still incontinent afterwards. Three patients developed de novo urgency incontinence after treatment.

3. Can pre-operative urodynamics predict post-operative problems?

Kleinhans et al [1999] examined 44 patients eight months after radical prostatectomy, out of 66 examined preoperatively. 16% were continent at 6 months, and 98% after a year. Detrusor overactivity seen pre-operatively was not responsible for any case of incontinence post-operatively. No preoperative bladder function parameters predicted post-operative incontinence.

Golomb et al [1999] observed detrusor overactivity (amplitude > 15 cm H2O) pre-operatively in 12/20 patients. Only 5 of these 12 complained of urgency incontinence post-surgery. 5 of the original 20 had mild stress incontinence. There was no significant association between pre-operative detrusor overactivity and post-operative incontinence.

In an earlier but larger study, Aboseif et al [1994] came to a different conclusion. 92 men were divided into 2 groups on the basis of pre-operative urodynamics – with and without detrusor overactivity. After 1 year, the incidence of incontinence was 3% in the group without detrusor overactivity versus 39% in the other group. This result suggests that pre-operative abnormalities in bladder function can affect the post-operative situation.

John et al [2000] measured different variables and found that, in 34 patients, preoperative urethral sensory threshold (determined electrically) was not related to the severity of post-operative incontinence. Thus these reports are not entirely consistent, leaving it open as to whether post-operative incontinence can be predicted preoperatively. However, the predictive value of any urodynamic measurement does not appear to be high.

4. Mechanism of post-operative incontinence

a) Types of incontinence

The 2 principal types of urinary incontinence are stress and urgency incontinence. Stress urinary incontinence (the symptom) is the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing. The corresponding urodynamic observation, noted during filling cystometry, is urodynamic stress incontinence. It is defined as the involuntary leakage of urine during increased abdominal pressure, in the absence of a detrusor contraction. In women, stress incontinence is common and is believed to reflect a mechanical defect which may be either weakness of the pelvic floor, allowing the bladder base to become hypermobile, or weakness (deficiency) of the intrinsic urethral sphincter mechanism. In men, hypermobility is
almost unknown and stress incontinence is relatively rare. If stress incontinence is observed it almost inevitably implies intrinsic sphincter deficiency.

Urgency urinary incontinence (the symptom) is the complaint of involuntary leakage accompanied by or immediately preceded by urgency. The corresponding urodynamic observation is detrusor overactivity incontinence, which is incontinence due to an involuntary detrusor contraction. In a patient with normal sensation, urgency is likely to be experienced just before the leakage episode. Thus the observation of involuntary detrusor contraction (detrusor overactivity) suggests the possibility of urgency incontinence, which is proven if detrusor overactivity incontinence occurs during urodynamics.

In principle, the incontinence encountered after treatment of prostate cancer might be of either the stress or the urge type. One of the objectives of clinical research in this area has been to establish the relative importance of these two types, with a view to prevention and to selection of optimum treatment.

b) Radical prostatectomy

Many papers have been published on this topic. The better ones compare urodynamic parameters in continent and incontinent patients post-radical prostatectomy; that is, they seek variables whose changes mediate continence or incontinence. The majority however merely look for abnormalities in incontinent patients that appear to account for the incontinence.

Presti et al [1990] compared urodynamics in 24 incontinent and 13 continent patients after radical prostatectomy. They found differences in: functional profile length (2.1 vs 3.6 cm, P<0.001); maximum urethral closure pressure (39 vs 74 cm H₂O, P < 0.001); and maximum urethral closure pressure during voluntary sphincter contraction (107 vs 172 cm H₂O, P < 0.002). Detrusor overactivity was only weakly associated with incontinence. On fluoroscopy, ‘tubularization’ of the proximal urethra above the striated sphincter was seen in continent patients only.

John et al [2000] examined 34 patients, of whom 82% were continent at 6 months. The urethral sensory threshold was not only raised post-operatively, as reported above, but was worse in those with incontinence. So-called ‘pressure transmission’ (probably the ratio of pressure changes near the striated sphincter to those in the bladder, on straining) was diminished after surgery, and more so in incontinent than continent patients. Maximal urethral closure pressure became significantly lower postoperatively and was significantly lower in incontinent than in continent patients.

Bamshad et al [1999] measured retrograde perfusion pressure in patients after prostatectomy. Although not a standard measurement, retrograde perfusion pressure (the fluid pressure needed to slowly perfuse the urethra retrogradely from external meatus to bladder) should be equal to the maximum urethral pressure if carefully performed. There were 3 groups of subjects. Group 1 (n = 14) had received no operation; group 2 (n = 11) were continent post-radical prostatectomy; group 3 (n = 18) were incontinent post-radical prostatectomy with a normal filling cystometrogram. Perfusion pressure was 101 ± 16 cm H₂O [SD] in group 1, 78 ± 17 cm H₂O in group 2, and 37 ± 12 cm H₂O in group 3. Perfusion pressure in group 3 was thus much smaller than in the other 2 groups, and significantly so (P <0.0001 and P <0.001, respectively). The mean ages in the 3 groups were 60, 68 and 72 y respectively, and appear unlikely to account for the differences in perfusion pressure.

Taken together, the above comparisons of incontinent and continent patients suggest that intrinsic sphincter deficiency (due to sphincter damage and/or denervation) is an important contributor to post-prostatectomy incontinence and that it may have, at least in part, a neurogenic basis. This seems to imply that (urodynamic) stress incontinence is predominant and detrusor overactivity is somewhat less important, although if present it will certainly contribute to the incontinence.

The following papers deal with observations in incontinent patients only. Some are difficult to classify as they use terms that are non-standard or use them in non-standard ways. For example, does ‘urgency incontinence’ mean the symptom urgency incontinence (so not a urodynamic observation), or does it mean that the authors observed leakage on urodynamics associated with involuntary detrusor contraction (that is, detrusor overactivity incontinence)?

Chao and Mayo [1995] examined 74 men incontinent after radical prostatectomy eight years post-surgery. 42 (57%) showed sphincter weakness; in 29 (39%) either detrusor overactivity or decreased bladder compliance was observed in addition to sphincter weakness; in only 3 (4%) was detrusor overactivity seen alone.

Desautel et al [1997] examined 39 male patients
incontinent after prostatectomy, which was a radical prostatectomy in 35. Sphincter damage was the sole cause of incontinence that could be found in 23 (59%) and it was a major contributor in 14 (36%). Detrusor overactivity and low bladder compliance were observed in 15 patients (39%). They concluded that intrinsic sphincter damage (deficiency) accounted for the vast majority of post-radical prostatectomy incontinence, but bladder dysfunction needed to be identified and treated as well.

Winters et al [1998] examined 65 patients incontinent after radical prostatectomy and 27 after TURP. The predominant finding was sphincter incompetence (intrinsic sphincter deficiency as shown by leakage during Valsalva at pressures from 12 -120 cm H2O) in 85 pts (92%). Detrusor overactivity (said to be either phasic or ‘tonic’) was observed in 34 pts (37%) but was the sole observable cause of incontinence in only 3/92 pts (3%). They concluded that sphincter deficiency was the most common cause of incontinence, but bladder dysfunction could coexist with it and might occasionally be the only observable cause.

Ficazzola and Nitti [1998] examined 60 patients with post-radical prostatectomy incontinence at least 6 months post-surgery. Intrinsic sphincter deficiency, as shown by leakage on elevated abdominal pressure during Valsalva, was seen in 54 patients (90%). Detrusor overactivity was observed in 24 and reduced compliance in 3 (27 total = 45%). In spite of this bladder dysfunction, intrinsic sphincter deficiency was observed to be the sole cause of incontinence in 40 patients (67%); intrinsic sphincter deficiency and bladder dysfunction were the joint cause in 14 (23%); and bladder dysfunction alone was the cause in only 2 (3%).

Groutz et al [2000] examined 83 men incontinent after radical prostatectomy. They found sphincter weakness in 73 (88%), Detrusor overactivity was observed in 28 (34%) but it was found to be the main cause of incontinence in only 6 (7%). They encountered occasional bladder outlet obstruction or detrusor underactivity on voiding (2% together), which may have contributed to incontinence in unknown ways.

McCallum et al [2001] reported on 16 patients with longstanding incontinence (14 to 33 months, median 22 months) after radical prostatectomy. Half of the subjects showing urodynamic stress incontinence also showed either detrusor overactivity or low compliance, which presumably contributed to the severity of the incontinence.

Gomha and Boone [2003] examined 61 patients with incontinence after prostatectomy (radical prostatectomy in 58 cases). Urodynamic stress incontinence was present in all patients. There was concomitant urgency/urgency incontinence (detrusor overactivity?) in 48%.

Pfister et al [2002] measured urethral pressures in 20 patients with incontinence after radical prostatectomy. They divided sphincter function into 3 components (baseline, adrenergic, and voluntary), measured separately, that, in principle, might be differently affected by surgery. The most striking effect of surgery was on the component sensitive to alpha-adrenergic blockade, while the voluntary component (the increase on voluntary sphincter contraction) was hardly affected, if at all. This seems to confirm that damage to some aspects of sphincter innervation makes an important component to post-prostatectomy incontinence.

The above papers suggest that sphincter weakness (intrinsic sphincter deficiency or sphincter damage, possibly due to neuropathy) is the predominant cause of post-radical prostatectomy incontinence, and that detrusor dysfunction (detrusor overactivity or low bladder compliance) is rarely the sole cause but can exacerbate its severity. There is no clear evidence either that pre-existing detrusor overactivity, or low compliance persisting after surgery, predisposes to more severe or more probable incontinence, or that these abnormalities arise de novo after surgery. Presumably, however, one or both of these scenarios must be the case.

5. CLINICAL UTILITY OF URODYNAMICS IN PROSTATE CANCER

Consistent with the observations reported above, there is no evidence that performing urodynamics pretreatment will improve outcomes of surgery. Post-operatively, incontinence improves spontaneously in most men, so that conservative management (perhaps supplemented by pelvic muscle exercises) while awaiting return of continence is adequate for several months. In fact, nursing support and education without actual therapy may be the best management [McGlynn et al., 2004]. Regular monitoring of flow rates is advisable, as diminishing flow may signal stricture or stenosis that should be treated. This is equally important after radiation treatment. In those with persistent incontinence, say at one year, impaired sphincter function is the most common cause but there is still no evidence that performing urodynamics will hasten the return of continence. However, it appears logical to try to
understand the causes of incontinence at this stage, by urodynamic investigation, and in particular to establish whether detrusor dysfunction (overactivity or low compliance) is contributory, as in this case pharmacological treatment might be tried. Level of evidence = 4 (expert opinion), grade of recommendation C.

1. URODYNAMICS IN PATIENTS WITH LUTS SUGGESTIVE OF BENIGN PROSTATIC OBSTRUCTION

1. Pressure/flow studies remain the only means of establishing or ruling out the presence of BOO
2. Non-invasive methods of assessing obstruction are not yet able to fill that role, although some may ultimately be able to do so
3. The filling phase of micturition should also be assessed, as symptomatic detrusor overactivity may have a bearing on the outcome of treatment (Grade of recommendation C).
4. Patients being submitted to TURP, with its attendant risks, should have a definitive diagnosis of outlet obstruction (Grade of recommendation B).
5. If pressure-flow studies are not planned prior to invasive treatment, then the patient should be made aware of the diagnostic limitations of uroflowmetry (Grade of recommendation B).
6. In the research setting, pressure-flow studies of possible obstruction in men with LUTS are essential to reveal biological mechanisms, increase statistical power and reduce the number of men “at risk” from novel treatments for BOO.

2. URODYNAMICS IN PATIENTS WITH PROSTATE CANCER (PRE- AND POST-TREATMENT)

1. Comprehensive urodynamics should be performed if there is urinary incontinence that persists for >6 months after surgical treatment of prostate cancer and does not respond to conservative management / treatment. The aim should be to determine the type of incontinence (eg urodynamic stress incontinence) and any exacerbating factors (eg detrusor overactivity) (Grade of recommendation C).
2. Periodic monitoring of urine flow during the recovery period post-surgery may help in early detection of stricture (Grade of recommendation D).

E. PREDICTING OUTCOME AFTER THERAPY

Benign prostatic enlargement (BPE) is a common condition among older men and may lead to benign prostatic obstruction [Hong et al 2003]. Clinical manifestation of benign prostatic obstruction (BPO) includes lower urinary tract symptoms (LUTS), and impairment of urinary flow with a negative impact on Quality of Life (QoL). European and International “Benign Prostatic Hyperplasia” treatment guidelines have stated that watchful waiting is recommended for patients with mild symptoms, medical treatment for patients with mild to moderate symptoms, and BPO-related invasive therapy for those with moderate to severe symptoms [Mochtar et al 2005]. Many authors are researching parameters that could accurately predict the results of these three treatment modalities, and thereby reduce the numbers of men who experience a negative outcome from BPO treatment.

I. WATCHFUL WAITING

One of the treatment alternatives for LUTS secondary to BPO is watchful waiting (WW). Mochtar et al [2005] investigated the prognostic role of prostate-specific antigen (PSA) level and prostate volume (PV) for the need for benign prostatic obstruction (BPO)-related invasive therapy among patients treated with WW. Increasing PSA levels produced an increase in the 5-year cumulative risk of invasive treatment: 8%, 9%, and 15% for a PSA level of less than 1.5, 1.5 to less than 3.0, and 3.0 to 10.0 ng/mL, respectively. The hazard ratio for the highest compared with the lowest PSA strata was 2.7. An increasing PV also increased the 5-year cumulative risk from 8% to 11%, a hazard ratio of 1.0. These results suggest that PSA is a significant prognostic factor for invasive therapy among patients on watchful waiting but not prostate volume [Mochtar et al 2005]. Knutson et al [2001] studied 37 men with LUTS and suspected BOO with urodynamics and transrectal ultrasound and followed the patients for 4 years. They found that the prevalence of detrusor overactivity increased with BOO, and the failure rate of WW was higher in the more obstructed patients and significantly higher in those with more severe obstruction. Thus, by including urodynamics when investigating patients with BOO, it seems possible to predict the failure rate according to the patients’ obstruction grade [Knutson et al 2001].

There is level 3 evidence that higher PSA and BOO levels predict failure from WW.
Treatment with alpha-blockers and 5 alpha-reductase inhibitor provides an improvement in symptoms, uroflowmetric parameters and QoL indices in patients suffering from BPO [Hong et al 2003]. Currently, alpha-blockers are first-line drug therapy for BPO [Mimata et al 2002].

Hong et al [2003] evaluated 437 men over 50 years of age with LUTS, treated with alpha-blocker and/or 5 alpha-reductase inhibitor. After three months of medical treatment, failure was considered if a decrease of less than 30% in IPSS and QoL index was observed; Qmax increased less than 2mL/s from the initial visit; the post void residual urine volume was greater than 100 mL; or when patients were not happy to continue with medical treatment [Hong et al 2003]. These are not validated criteria, but some authors have used these measures to identify treatment failure. Medical treatment failure occurs in 22.9% of patients and the causes are: insufficient efficacy (44%), development of acute urinary retention (33%) and adverse events associated with medication (27%) [Hong et al 2003].

Failure was associated with older age, higher IPSS score and larger prostate volume. According to statistical analysis the best cutoff values for predicting medical treatment failure are an IPSS of over 21 and a prostate volume over 32 cm³.

The probability of medical treatment failure in patients with symptom scores above 21 is 27% (12 months), 38% (24 months) and 40% (36 months). In those with scores below 21 is 15% (12 months), 16% (24 months) and 16% (36 months). If the prostate volume is over 32 cm³ the probability of medical treatment failure is 24% (12 months), 33% (24 months) and 34% (36 months) and in those with volumes below 32 cm³ is 12% (12 months), 15% (24 months) and 16% (36 months) [Hong et al 2003]. Mochtar et al [2005] treated 389 patients with alpha-blocker and observed that higher PSA values (4-10 ng/mL) and larger PV (greater than 30 cm³) resulted in a greater risk of invasive therapy.

There is level 3 evidence that prostate volumes, and higher levels of IPSS, can predict the risk of invasive therapy in patients on medical treatment for BPO.

It is now widely accepted that giving an alpha adrenergic antagonist increases the success rate of a trial without catheter (TWOC) in men with BPO after a first episode of acute urinary retention (AUR), and up to 62% of patients will have a successful TWOC after receiving alpha blocker [McNeill et al 2003]. In other, somewhat older, studies, after 5 to 7 years follow-up, 80 to 84% of the patients who had previously experienced AUR ultimately needed surgery [Craigen et al 1969, Breum et al 1982]. Klarskov et al [1987] reported that the factors that predicted preserved voiding ability after a successful TWOC are a retention volume of less than 500 mL and a Qmax over 5mL/s. McNeill et al [1999], in a prospective trial, randomized 81 patients with a first episode of AUR related to benign prostatic obstruction, to receive either sustained-release alfuzosin or placebo for 48 hours. Thirty four patients had a successful TWOC (22 on alfuzosin, 12 placebo, p= 0.03). Twenty six had a further episode of AUR or surgery during the 6-year follow-up. Size of the prostate assessed by digital rectal examination was the only factor with a significant effect on the long-term outcome [McNeill et al 2004].

Historically, the standard management of a man with acute urinary retention (AUR) caused by benign prostatic obstruction was early prostatectomy. Recent data suggest that these patients can be managed with alpha-blockers and that prostate size can predict those who will subsequently require invasive therapy.

There is level 3 evidence that prostate size influences the success of TWOC.

Transurethral resection of the prostate is the gold standard treatment modality for BOO [Madersbacher 2004]. Although effective, TURP has considerable morbidity and also its overall cost per year is significant [Rodrigues et al 2001]. Therefore, to minimize unnecessary operations, predicting the outcome after TURP is important. It has been shown that one third of the men with LUTS do not have bladder outlet obstruction and 5 to 35% of the patients with LUTS do not have symptoms improvement after TURP [Kanik et al 2004].
Javle et al [1998] studied 53 patients who were suitable candidates for TURP, assessed by IPSS, uroflowmetry, ultrasonography (prostatic size and residual urine volume) and pressure flow study before and 3 months after surgery. TURP outcome was significantly better in patients with unequivocal obstruction and normal detrusor contractility. Treatment failure occurred in 80% of patients with equivocal obstruction and impaired detrusor contractility, and 100% of the unobstructed group. Urodynamic grading of obstruction and detrusor contractility predicted treatment outcome with a sensitivity of 87%, specificity 93% and positive predictive value of 95% [Javle et al 1998]. Accordingly, Rodrigues et al [2001] evaluated the TURP outcome in 253 patients and observed that the entire obstructed group demonstrated marked improvement compared to the nonobstructed group (p = 0.018). In addition, the more severely obstructed cases had greater clinical benefit compared to those with little or no obstruction. Furthermore, the nonobstructed subjects did not show any clinical or subjective improvement after transurethral prostatic resection (p = 0.24). Other studies also show that performing urodynamics pre-operatively helps to predict the degree of symptom relief, decreasing bother and increasing well-being after transurethral prostate resection [van Venrooij et al 2002].

Van Venrooij et al [2002] re-evaluated 93 patients, 59 obstructed and 34 unobstructed or equivocal, 6 months after TURP and observed that reductions in symptoms and bother in the unobstructed and equivocal men were about 70% of those reductions in the obstructed men, thus indicating that equivocal and unobstructed man also benefit from TURP [van Venrooij et al 2003]. In a prospective study, 95 men scheduled for TURP were assessed using the IPSS and pressure-flow studies. It was observed that the flow rate and degree of obstruction influenced the improvement in flow rate but not in symptoms after TURP. Symptom improvement was only related to the initial level of symptoms. In a multivariate analysis, only age was an independent predictor of the outcome variables of flow rate and symptoms [Hakenberg et al 2003].

The relationship among urodynamic parameters, treatment outcome, symptom relief and patient satisfaction are still the subject of controversy. The International Prostate Consultation 2001 recommends pressure-flow studies to evaluate patients, not only before invasive therapy, but also when a precise diagnosis of bladder outlet obstruction is important.

Detrusor underactivity (DUA) is a cause of lower urinary tract symptoms in a significant minority of men. Thomas et al [2004] followed 22 patients with DUA who had a TURP with a mean follow-up after surgery of 11.3 years and observed no significantly sustained reductions in any symptoms. Comparison with 58 age-matched patients with DUA who remained untreated showed no significant advantage of surgical intervention in the long-term evaluation. On the contrary, there was more chronic retention in those who had had surgery. Some authors have investigated noninvasive methods for predicting bladder outlet obstruction (BOO). Netto et al [1996] compared IPSS with pressure-flow studies in 227 patients. Of the patients with a severe symptom score 92 (82.9%) had bladder outlet obstruction, compared to 62 (53.4%) with a moderate symptom score. The authors concluded that when the total IPSS is greater than 28 or the “obstructive” symptom score is greater than 15, a pressure-flow study can be avoided. Steele et al [2000] demonstrated that the association of IPSS, flow rate and prostate volume reliably predicted BOO in patients with maximum urine flow rates of 10 or less mL per second, prostate volumes of 40 g or larger and IPSS greater than 20. Conversely, the combination of IPSS, flow rate and residual urinary volume could not predict BOO in the study of Porru et al [2002].

In summary, obstructed patients fare better after surgery than non obstructed ones. Non invasive methods are been evaluated and may have a role in identifying BOO, avoiding the need for a full urodynamic evaluation. These results strengthen the argument for a routine preoperative urodynamic assessment (Level of evidence 3, grade of recommendation B).

V. DETRUSOR OVERACTIVITY AND BLADDER OUTLET OBSTRUCTION

The clinical presentation (OAB) of detrusor overactivity (DO) is often similar to BOO. The prevalence of OAB and DO increases significantly with age, in a similar fashion to BOO. The rate of DO also increases with increasing grade of obstruction, but has no impact on other LUTS [Vesely et al 2003]. To distinguish between BOO and DO, cystometry and pressure flow study are necessary. In 162 patients with LUTS and suspected BOO the urodynamic evaluation demonstrated DO in 45% of the cases and 55% normal storage phase [Knutson et al 2001].
this study, patients with BOO and DO were older, had a higher PSA, voided smaller volumes, and were more obstructed. Prostate volume (measured by transurethral ultrasound), Qmax, IPSS, and PVR did not predict whether the patients had combined BOO + DO or not. Another study also observed that patients with BOO and DO were older (p < 0.05) and had a higher IPSS [Lee et al. 2004].

After 3 months of treatment with doxazosin, 35% of the patients with BOO and DO reported a symptomatic improvement ([Lee et al. 2004]. In those patients with no response to alpha blockers, 73% improved after adding tolterodine. Acute urinary retention developed in 3.3% treated with the alpha blocker and anticholinergic drugs. Combination treatment with an alpha-blocker (tamsulosin) plus an anticholinergic (tolterodine) improves quality of life in patients with bladder outlet obstruction and concomitant detrusor overactivity [Athanasopoulos et al. 2003].

Detrusor overactivity (DO) in men with evidence of bladder outlet obstruction due to benign prostatic enlargement typically resolves in about two thirds of patients after TURP. Twelve males (mean age 80 years,) with symptoms of OAB, were studied by 24-hour monitoring of incontinence and videourodynamic examination, before and after TURP [Gormley et al. 1993]. Preoperatively, all patients showed detrusor overactivity, which resolved postoperatively in only one patient, a significantly smaller proportion than that consistently reported in younger patients. In the geriatric population, detrusor overactivity and urgency incontinence may be the result of age-associated changes and not secondary to obstruction [Gormley et al. 1993].

Detrusor overactivity can be classified in three patterns: I - continual sporadic detrusor contractions; II – a single episode of detrusor contraction occurring at volume of < 160 mL with saline leaking around the urethral catheter; III – a single episode of contraction at bladder volume > 160 mL [Kageyama et al. 2000]. Cystometric patterns can predict the postoperative course. Twenty patients with BOO and DO underwent TURP and cystometry was carried out between 3 and 6 months after operation. Most pattern I patients had persisting DO, whereas DO disappeared after surgery in pattern III patients, and pattern II patients had an intermediate outcome.

For patients with the combination of severe BOO and severe DO, no straightforward and safe treatment exists due to the risk of persistent urgency incontinence after TURP [Knutson et al. 2002]. To predict the outcome after TURP for persistent urgency incontinence a biodegradable polyglycolic acid stent can be used [Knutson et al. 2002]. After this stent was inserted into the prostatic urethra, 68% of the patients noticed minor or no leakage and they later had a TURP with good results. A biodegradable polyglycolic acid stent may be a new tool to test the risk for post-TURP urgency incontinence in patients with combined BOO and severe OAB [Knutson et al. 2002].

There is considerable level 3 evidence for the advantages of performing urodynamics (UDS) prior to surgical treatment in men presenting with LUTS. UDS can predict failure by demonstrating detrusor underactivity, the absence of obstruction and the presence of DO as a cause of LUTS.

VI. ACUTE URINARY RETENTION AND SURGERY

In patients with acute urinary retention, pressure-flow studies are useful in predicting the surgical outcome. Old age, absence of detrusor overactivity, inability to void during the pressure-flow study and a maximum detrusor pressure < 20 cmH2O are associated with a poor outcome after prostatectomy [Dubey et al. 2001].

There is level of evidence 3, evidence for UDS predicting the outcome of TURP after AUR.

VII. PREDICTIVE/PROGNOSTIC VALUE OF URODYNAMICS

A potentially important application for urodynamics is prognosis and prediction of the outcome of treatment or of no treatment. Adequate predictive power might guide choice of the best treatment or might help in counselling patients about the likelihood of success of any given treatment (see Table 10). Since the last consultation on “BPH” [Abrams et al. 2001], where it was suggested that urodynamics has some but not strong predictive value for the outcome of treatment, there has been considerable activity in this field. Two recent reviews by Homma [2001] and Clemens [2003] reinforce the view of the last consultation. A third review [Bhargava et al. 2004] concluded that conventional urodynamic studies are useful in providing preoperative information about
detrusor function, and to exclude patients less likely to benefit from prostate surgery. Despite this, some regard the need for performing urodynamic evaluation routinely, before transurethral resection of the prostate, as still controversial (Table 11). However, the risk of operating on patients who will not benefit has to be balanced against the risk of not operating on patients who will benefit, although there may well be treatment methods as beneficial but less risky than TURP in unobstructed patients, such as drugs.

There has been considerable work on a variety of “non-invasive” methods of diagnosing BOO; however, these require further work before one or more can be recommended as routine tests. Level 3 evidence exists for tests that will predict the outcome of watchful waiting, drugs and a trial of catheter after a retention episode (see Table 12). However, the weight of evidence and the safe nature of these treatments means that we will not yet give a recommendation for UDS in these groups.

Although almost all evidence for the advantages of UDS prior to invasive therapy for BPO is Level 3, the quantity of evidence allows a Grade B recommendation.

### F. RESEARCH QUESTIONS

1. What components of filling/storage symptomology are susceptible to intervention?
2. Do all interventions act on all components of filling/storage (ie desire to void, urgency, warning time, urgency-free interval) in the same way?
3. Do successful treatments for overactive bladder prolong deferment time, or simply prolong the refractory period (ie decrease the number of episodes of urgency) or can they eliminate urgency altogether?
4. Are there subsets of patients with overactive bladder, and do the subsets give any insight into pathophysiology or response to treatment (ie presence or absence of DO; if DO, phasic or terminal)?
5. From what structure or structures does the sensation of urgency emanate?
6. Are there differences in the symptom of urgency and its clinical features in men as contrasted to women?

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### Table 11. Studies evaluating whether urodynamic studies (pressure flow) are necessary to predict the outcome of transurethral resection of the prostate

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients</th>
<th>Are UDS necessary?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ignjatovic I.</td>
<td>1997</td>
<td>48</td>
<td>“Only in inconclusive cases”</td>
</tr>
<tr>
<td>Javle P.</td>
<td>1998</td>
<td>53</td>
<td>Yes</td>
</tr>
<tr>
<td>Pannek J.</td>
<td>1998</td>
<td>25</td>
<td>No</td>
</tr>
<tr>
<td>Rodrigues P.</td>
<td>2001</td>
<td>253</td>
<td>Yes</td>
</tr>
<tr>
<td>van Venrooij G.E.</td>
<td>2002</td>
<td>93</td>
<td>Yes</td>
</tr>
<tr>
<td>Porru D.</td>
<td>2002</td>
<td>45</td>
<td>Yes</td>
</tr>
<tr>
<td>Kanik E.A.</td>
<td>2004</td>
<td>54</td>
<td>No</td>
</tr>
<tr>
<td>Thomas A.W.</td>
<td>2004</td>
<td>22</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### Table 12. An overview of predicting outcome after therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Parameters</th>
<th>Predictive Ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watchful Waiting</td>
<td>Urodynamics</td>
<td>PSA</td>
</tr>
<tr>
<td>Medical Treatment</td>
<td>Prostate volume</td>
<td>Severe obstruction and higher PSA predict treatment failure</td>
</tr>
<tr>
<td>Medical Treatment after Acute Urinary Retention</td>
<td>Prostate size volume Retained Qmax</td>
<td>Higher volume predicts treatment failure</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>Urodynamics</td>
<td>Obstruction predicts better results</td>
</tr>
<tr>
<td>Surgical treatment after Acute Urinary Retention</td>
<td>Urodynamics Age</td>
<td>Old age, inability to void and Pdet &lt; 20 cmH2O predict a poor outcome</td>
</tr>
<tr>
<td>OAB + BOO</td>
<td>Urodynamics</td>
<td>Severe OAB predicts urinary incontinence after TURP for BOO</td>
</tr>
</tbody>
</table>
7. Are there differences in the sensation of urgency due to a known neurologic cause, as opposed to those with so-called idiopathic detrusor overactivity?

8. Is there any correlation between prostate size, pressure-flow indices of obstruction and prostate configuration and any filling/storage or voiding/emptying symptoms?

9. Does the symptom of urgency always imply detrusor overactivity? In other words, we need investigations to look at what the pathophysiology of urgency is. In some cases, when it is associated with urgency incontinence, it is obviously related to an involuntary detrusor contraction. In other cases, it is clearly related to an involuntary detrusor contraction which can be aborted by inhibition of the contraction exerted by various manoeuvres at various levels, anywhere from the supraspinal area to the local inhibitory reflex arch initiated by pelvic floor musculature contraction. In some instances, however, it does not seem related to DO.

10. Can urgency exist as a discrete symptom during filling/storage with no detrusor overactivity?

11. Can urgency really be initiated from receptors in the urothelium? If so, what are these receptors and what are the possible pharmacologic avenues of inhibition?

12. Once urgency is established, does neuroplasticity occur; in some patients, do these changes persist even after the initial stimulus has been removed? If so, are there any methods to reduce or remove these abnormal pathways covered under the term “plasticity” that leads to persistence of the inappropriate sensation during filling/storage? The few experimental models which exist are interesting but far from proof that these occur clinically.

13. Can non-invasive methods of urodynamics predict outcome from treatment?
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Committee 6

New Medical Developments in the Management of LUTS in Adult Men

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Lower urinary tract symptoms (LUTS) suggestive of benign prostatic obstruction (BPO) — previously referred to as “symptomatic benign prostatic hyperplasia (BPH)” — are common in the ageing male. The term LUTS/BPO will be used in this review to refer to the symptomatic man with LUTS presumed to be associated with BPO. Approximately 25% of men over 40 suffer from LUTS, and the prevalence of this condition rises with age [1] (Figures 1-2).

No LUTS [2] are disease specific and hence diagnostic of BPO. Therefore appropriate evaluation of the symptomatic patient relies upon comprehensive evaluation. This begins with a careful clinical history augmented by the use of a validated symptom score such as the International Prostate Symptom Score (IPSS), combined with a physical examination including a digital rectal examination and the subsequent appropriate use of a serum PSA and transrectal ultrasonography, in appropriate patients to exclude malignancy. The quantification of BPO relies on the judicious use of urodynamics, incorporating a flow rate, transabdominal ultrasound (for post micturition residual volumes) and pressure flow studies in selected patients; i.e. where the flow rate is inadequate or equivocal or there is a large residual (suggesting possible detrusor underactivity); or in those with other features in the history suggestive of a more complex clinical situation (young age, previous neurological history, failed surgery). A major problem in the contemporaneous literature is the absence of an adequate internationally accepted and applied definition for ‘BPH’; in the remainder of this review since this is a review relating to clinical practice and hence symptomatic patients presumed to have histological BPH which has resulted in bladder outlet obstruction, hence the term LUTS/BPO will be used.

No more than ten years ago, surgery and watchful waiting were the only widely accepted management options for LUTS suggestive of benign prostatic obstruction (LUTS/BPO). There has been an enormous decline in the popularity of surgery and it is now clearly apparent that medication is the most frequently used treatment modality for LUTS/BPO. Arguably, this has therefore been the most major change in urological clinical practice in the last decade. Operative intervention is increasingly considered rather radical from the patient’s perspective,
and not surprisingly many patients feel reluctant to undergo surgery, and prefer a less invasive intervention such as medical therapy, before contemplating surgery. Indeed whilst few absolute indications for surgery still exist, the number of patients undergoing operations for BPO has decreased by around 60% in the USA over the last decade [3] and similar trends are evident across Europe. This trend has been encouraged not only by increased patient awareness of the availability of effective contemporary pharmacotherapy, but has also been encouraged by an increased awareness of the complications of surgery, in particular, that it can be associated with significant morbidity such as irreversible incontinence and loss of sexual function with subsequent impairment of a patient’s quality of life.

**Medical therapies to treat LUTS/BPO** include $\alpha_1$-adrenoceptor antagonists (which relax the smooth muscle in the prostate), 5α reductase inhibitors (RIs) (which shrink the glandular component) and phytotherapeutic agents which may have multiple mechanisms of action – often poorly defined.

Today, $\alpha_1$-adrenoceptor (AR) antagonists are the most widely used medical therapy and are thought directly and indirectly affect smooth muscle tone – the neural or so called ‘dynamic’ component of BPO. 5α–RIs (finasteride, dutasteride) are another medical treatment option for LUTS/BPO which reduce prostatic mass and therefore the mechanical or ‘static’ component of BPO. In the last ten years four direct comparative studies between $\alpha_1$–AR antagonists and finasteride including their combination have been published, the results of these and their implications for therapy are discussed. Another group of compounds, the phytotherapeutic agents act via various mechanisms – many as yet poorly defined. This review critically assesses the existing literature relating to the medical management of LUTS/BPO. We will principally emphasise the literature based on randomized controlled trials with rigidly enforced selection criteria and acknowledge that this introduces potential bias which may not reflect real life clinical practice.

With any pharmacotherapy for LUTS/BPO there are a number of general points which need to be considered:

1. **Data on the long-term safety and efficacy** of therapy, patient compliance and therefore willingness to continue with therapy is important. There is a little literature base on placebo controlled studies extending out beyond 3 months. Little prospective long-term epidemiological work has been carried out to date. Ultimately it is the perceived long-term ‘clinical effectiveness’ of therapy (representing the synthesis between efficacy, safety and tolerability), which underlies the usefulness and cost-effectiveness of any therapy. Adequate prospectively acquired comparative epidemiological data on the long term efficacy, tolerability and compliance with pharmacotherapy for LUTS/BPO does not at present exist.

2. **Outcome measures** and measures of disease progression (considered in detail by the Roehrborn committee). Contemporary literature relating to the evaluation of LUTS/BPO relates principally to both the objective and subjective quantification of voiding dysfunction, with limited reference to storage disorders. Consequently, the evidence based literature is anchored on objective assessments utilizing flow rates, with a limited amount of synchronous pressure/flow data, and subjective assessment utilizing the International Prostate Symptom Score (IPSS). The IPSS has 4 questions relating to voiding symptoms and 3 to storage symptoms. Review of the literature clearly reveals that storage symptoms are those that are the most troublesome to patients, although the IPSS does not include the important symptom of urgency incontinence. Clearly assessment of the impact of therapy on both storage and voiding symptoms must be addressed in future studies. This review will consider the literature base on the use of pharmacotherapy for both storage and voiding symptoms seen in the ageing male traditionally considered under the term LUTS/BPO.

3. Surprisingly, there is little robust information in the existing literature base on the subject of cost effectiveness and cost benefit. With the ageing of the population world wide, it is essential that adequate data on cost effectiveness and cost benefit are accrued in the future. The results of such analyses are likely to differ by country due to the different cost structure in various health care systems.

4. The subject of targeting of therapy based on morphology has been raised in the past (See Figure 3).

5. **The interpretation of data** derived from studies is not standardized:-
   a. With reference to the criteria relating to baseline values
   b. Relating to the change from baseline values that occurs during the placebo run in phase, prior to starting “active” therapy
c. In interpreting data, in particular it is important to consider the ‘size of the treatment effect’ and relate this to its clinical importance and relevance.

6. It is important prior to considering the potential role of pharmacotherapy to note that the placebo response in LUTS/BPO is notoriously high. For example, the AHCPR report estimated a mean probability of symptomatic improvement in 98, 88, 80, 57, 67, 74, 42 and 45% for open prostatectomy, TUR-P, TUIP, balloon dilatation, finasteride, α1-AR-blockade, watchful waiting and placebo [4]. Placebo effects have been reported out to 5 years and post-treatment.

7. It must be remembered that untreated LUTS/BPO does not necessarily progress, even to 13 years. Indeed, Isaacs has reviewed the contemporary literature and provided a metanalysis of existing studies to show that that 16% of those with LUTS/BPO had no changes in symptoms and 38% were better with a follow up ranging 2.6 - 5 years [5]. A policy of watchful waiting is therefore a very appropriate choice in patients with mild or moderate symptoms. Whilst the probability of disease progression in these patients remains uncertain, nevertheless we know from studies to date that the progression is slow[6]. It is (maybe) prudent for patients to be periodically monitored to check that there is no significant deterioration.

8. Since the efficacy of surgery is superior to pharmacotherapy in the treatment of LUTS/BPO it is often used as the ‘standard’ against which to compare other therapies. The 6th International Consultation on “BPH” [7] has recommended that the absolute indications for surgical intervention in LUTS/BPO patients should be urinary reten-

9. The existing literature base suggests that pharmacotherapy doesn’t lead to relief of obstruction as assessed on pressure flow assessment.

**RECOMMENDATIONS**

There is a lack of:-

- Data on the long-term safety and efficacy of therapy, patient compliance and therefore willingness to continue with therapy is important.
- Long-term data from real life practice
- Information on cost effectiveness and cost benefit.

The interpretation of data derived from studies is not standardized:-

- With reference the criteria defining baseline values
- Relating to the change from baseline values that occurs during the placebo run in phase prior to starting active therapy
- In interpreting data:-
  - it is important to consider the size of the ‘treatment effect’ and relate this to its clinical importance and relevance.
  - remember that there is a high placebo response in BPH/LUTS.
  - untreated BPO does not necessarily progress

Level 1 Grade A
B. HORMONAL APPROACHES TO THE TREATMENT OF BENIGN PROSTATIC OBSTRUCTION

I. INTRODUCTION

Clearly histological BPH is of heterogeneous aetiology (hormones, ageing, growth factors and stromal-epithelial interactions), in pathology (epithelium and smooth muscle) and in pathophysiology (mechanical obstruction, dynamic smooth muscle contraction and detrusor function); still it is an androgen-dependent process in which oestrogens may play a synergistic role. Many treatment strategies to inhibit androgen production/action in the prostate have been devised and tested. Oestrogen inhibition is less well studied. Of particular interest has been the possibility of hormonal approaches being able to reverse or even prevent the hyperplastic process itself.

II. THE ROLE OF STEROID HORMONES

The development of the BPH clearly requires a combination of testicular androgens and ageing [8-10]. Although the role of androgens as the causative factor for BPH is debated, they undoubtedly have at least a permissive role. Men castrated before puberty do not develop BPH. Furthermore, patients with a variety of genetic diseases that inhibit androgen production, or androgen action, have impaired if not absent prostatic growth. In addition, clinical studies using a variety of androgen withdrawal therapies have clearly shown that regression of established BPE can occur. However, even castration (medical or surgical) fails to restore the enlarged hyperplastic gland to a normal volume. Once BPE is established, androgen withdrawal alone may be insufficient to return the number of prostate cells - especially stromal cells - to normal. Partial involution may be insufficient to relieve urodynamic obstruction.

The principal prostatic androgen is dihydrotestosterone (DHT). Although not elevated in BPE, DHT levels in the prostate remain at a normal level with ageing, despite a decrease in the plasma testosterone [11]. DHT binds to specific receptors in the cytoplasm which translocate to the nucleus, where they are critical to the role of androgens in stimulating both normal and hyperplastic prostatic growth [10]. In other androgen-dependent tissues, for example in penis, androgen receptor levels are down-regulated after puberty, thus limiting further androgen-dependent growth. This maintenance of androgen receptors in the prostate permits androgen-dependent growth even in the face of the age-related declines in plasma testosterone [3]. Androgen receptor levels may not be elevated in BPH or BPE [12,13] but they are maintained at normal levels.

The rationale for androgen withdrawal in the treatment of BPO is based upon two hypotheses. First, a critical level of prostatic androgen is required to maintain the enlarged hyperplastic state. Second, androgen withdrawal will result in significant involution in prostatic size, thus reducing outflow resistance. However, androgen withdrawal in humans does not appear to return the hyperplastic prostate to a normal state. This observation does not necessarily invalidate the androgen hypothesis, but rather shows that the pathophysiology of BPH/BPE is multifactorial.

Oestrogens may play a role in the pathogenesis of BPH/BPE. In the dog, where oestrogens act synergistically with androgens to produce experimental BPH/BPE [14,15], oestrogen is involved in induction of the androgen receptor [16]. Oestrogen may, in fact, “sensitise” the ageing dog prostate to the effects of androgen [14]. The canine prostate contains an abundance of high affinity oestrogen receptors. In the dog, oestrogen treatment stimulates the stroma causing an increase in the total amount of collagen [17,18]. It was shown that the patterns of oestradiol-17ß or DHT, plus oestradiol-17ß (E2) - induced increases in activities of catechol oestrogen synthase, and of other drug metabolising enzymes, were consistent with the postulated free radical generation by redox cycling of catechol oestrogen specifically in the prostate [19].

The proposed role of oestrogens in the development of human LUTS/BPO has been reviewed in detail [20-22]. Serum oestrogen levels increase in men with age, absolutely or relative to testosterone levels.

III. ENDOCRINE CONTROL OF PROSTATE GROWTH

Testosterone is the principal circulating androgen. In men, it is secreted primarily by the testes, with the adrenal glands providing a minor contribution. To be
maximally active in the prostate, testosterone must first be converted to DHT by the enzyme 5α-reductase. Studies in rats have demonstrated that at equivalent androgen concentrations in the prostate, DHT is about twice as potent as testosterone [23]. However, DHT also has a greater affinity for the androgen receptor than testosterone [24], permitting it to accumulate in the prostate when circulating testosterone levels are low [25]. This dual action of 5α-reductase in androgen physiology explains the critical importance of this enzyme in stimulating prostate growth. It also explains why DHT concentrations in the prostate remain high in elderly men, in spite of the fact that serum testosterone concentrations decrease with age.

The concentration of testosterone in blood is about 10 times higher than that of DHT. From animal data, it is clear that circulating testosterone and DHT enter equally well into the prostate, and both can serve as precursors for intraprostatic DHT [25]. However, because of its low concentration in blood, DHT is unlikely to have a major role as a circulating androgen or as a precursor to intraprostatic DHT. In the prostate, nearly all testosterone is converted to DHT by 5α-reductase. Because testosterone is more abundant in blood, DHT has a minor role in normal prostate physiology. This is best demonstrated in men with 5α-reductase deficiency, who have near normal circulating levels of DHT, but small prostate glands throughout life [26].

### 1. 5α-REDUCTASE INHIBITORS

The mechanism of androgen action varies in different tissues, but in the majority of androgen target tissues either testosterone or DHT binds to a specific androgen receptor to form a complex that can regulate gene expression. DHT is essential for prostate development and growth, the development of the external genitalia and male patterns of facial and body hair growth or male-pattern baldness. DHT is synthesized from testosterone via the enzyme 5α-reductase [27-29].

Two isoenzymes of 5α-reductase have been discovered [30] (Table 1). Type 1 is present in most tissues of the body where 5α-reductase is expressed, and is the dominant form in sebaceous glands. The overall functional role of type 1 5α-reductase is unclear, because no one with a genetic deficiency of this enzyme has been discovered. Its predominance in sebaceous glands suggests that it has a role in the development of acne. Female type 1 knock-out mice have delayed parturition, indicating that this isoenzyme is critical for normal initiation of labour in mice [31,32]. However, the relevance of this observation for humans is unknown, and such mice appear otherwise normal. Type 2 5α-reductase is the dominant isoenzyme in genital tissues, including the prostate.

<table>
<thead>
<tr>
<th>Type</th>
<th>Chromosome</th>
<th>KM (μM)</th>
<th>pH optimum</th>
<th>Tissue Distribution</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>5</td>
<td>10</td>
<td>6.5-9.0</td>
<td>Skin, sebaceous glands, liver, lower level in the prostate</td>
<td>not known</td>
</tr>
<tr>
<td>Type 2</td>
<td>2</td>
<td>0.4</td>
<td>5.5</td>
<td>Prostate and genital organs; lower levels in other organs</td>
<td>Male pseudohermaphroditism</td>
</tr>
</tbody>
</table>

The notion that 5α-RIs could be useful in the treatment of androgen related disease emerged in the early 1970’s as the genetic phenotype of 5α-reductase type 2 deficiency was described and the role of DHT as the primary mediator of androgen action in many tissues was demonstrated. The clinical phenotype of 5α-reductase deficiency was first described in the 1960s when it was termed “pseudovaginal perineoscrotal hypospadias”. Affected subjects were noted to have a 46 XY karyotype, normally differentiated testes, male internal ducts, and ambiguous genitalia. These patients have non-palpable prostates as adults, despite otherwise normal virilisation at puberty. Two patient cohorts with this inherited form of male pseudohermaphroditism caused by deficient DHT production were described by Walsh et al. [33] and Imperato-McGinley et al. [34].

The structural features of steroids which are important for inhibition of human foreskin 5α-reductase activity were first investigated by Hsai and Voight 25 years ago and their conclusions still form the basis for understanding the structure-activity-relationships in this class: a 3-oxo-∆4,5 structure is preferred as well as a 17β but not a 17α substituent [5,36]. A number of compounds have been identified as inhibitors of 5α-reductase, including both steroidal inhibitors, MK-906, finasteride [37], SKF 105687, epristeride [38], dutasteride (a dual 5α-RIs) [39]. Only finasteride and dutasteride have reached clinical practice.
a) Pharmacology and mechanism of action

Boths finasteride and dutasteride lead to a reduction of DHT in serum and prostate tissue due to the inhibition of the 5α-reductase enzymes [40-45]. Finasteride solely inhibits type 2 whereas dutasteride inhibits both type 1 and type 2 enzymes [46].

The type 2 isoenzyme is the predominant form in genital tissue it is clear that the majority of DHT synthesized in the prostate derives from this enzyme. The same is known for serum DHT. About 80% of serum DHT synthesized derives from testosterone conversion through type 2, only 20% are synthesized by type 1 [47]. Reduction of serum DHT-concentration provided by dutasteride (90-93%) exceeds that of finasteride (70%) [48]. However, 5mg daily administration of finasteride reduces DHT-concentration in the prostate by 85-90% [49,50]. The intraprostatic DHT-concentration at the therapeutic 0.5mg dose of dutasteride is unknown.

Finasteride and dutasteride are both 4-azasteroids. The chemical name of finasteride is N-tert-Butyl-3-oxo-4-aza-5α-androst-1-en-17ß-carboxamid with dutasteride being an analogue thereof with a substitution of the tert-Butyl-group of finasteride through a 2,5-bis(trifluormethyl)phenyl-group in dutasteride (Figure 4), making dutasteride a more lipophilic agent with loss of type 2 enzyme specificity. Oral bioavailability (finasteride: 63 %; dutasteride: 60 %) and time to reach maximum plasma concentrations are equal (finasteride: Tmax = 1-2 hours; dutasteride: Tmax = 2-3 hours). Mostly due to the greater lipophily of dutasteride the two drugs differ in their plasma elimination time. Dutasteride has a long plasma elenmination half life for 5 (1-7) weeks under steady state conditions [51] compared to 6-8 hours of finasteride [41,45]. This leads to the recommendation that men receiving dutasteride therapy should not donate blood within 6 months of their last medication to avoid dutasteride contaminated blood being donated to pregnant women.

As 5α-RIs inhibitors reduce DHT concentration in the prostate, they also alter PSA concentration in serum of treated patient. It is now well established from multiple clinical trials, that dutasteride and finasteride both lower PSA-values by 50% in mid term [42,52]. However, after long term treatment, the PSA lowering effect may slightly exceed that of 50% as shown from the prostate cancer prevention trial.

In men treated with finasteride, multiplying PSA by 2 and using normal ranges for untreated men preserves the usefulness of PSA for prostate cancer detection. Use of an upper limit of normal for last PSA of 2.0 ng/ml for finasteride and 4.0 ng/ml for placebo yielded similar sensitivity (66% versus 70%, P=0.6), higher specificity (82% versus 74%, P<0.0001), and a higher likelihood ratio (3.6 versus 2.7, P < 0.05) for finasteride than for placebo (53). In addition it appears from data derived from PCPT that due to volume reduction, treatment with 5α-RIs may enhance cancer detection.

To interpret an isolated PSA value in a man treated with either agent for 6 months or more, the PSA value should be doubled for comparison with normal values in untreated men.

b) Treatment for symptomatic LUTS suggestive of BPO with 5α-RIs, evidence from clinical trials:

1. FINASTERIDE

The efficacy and safety of finasteride in men with LUTS/BPO has been demonstrated in several large-scale, randomised, placebo-controlled Phase III studies consisting of a double blind duration between 1 and 5 years (Table 2) [54-65] and has been summarised in numerous meta-analysis [66-84]. Additional evidence comes from a large scale double blind trial over 7 years comparing finasteride versus placebo and its ability to prevent prostate cancer [85].
Table 2. Randomized clinical phase III trials (with more than 100 pt. in each study arm) conducted with finasteride versus placebo for the treatment of symptomatic LUTS/BPH. Studies comparing finasteride either to other drugs or their combination, or trials conducted with less than 100 individuals randomized in each treatment arm, or study duration below 1 year, are not listed. (pla.=placebo, fin.=finasteride, PV: prostate volume, Qmax: maximum urinary flow rate, pt.=score points).

<table>
<thead>
<tr>
<th>Design of phase III trials</th>
<th>Study duration (y=Years, m=months, w=Weeks)</th>
<th>Treatment arms</th>
<th>N randomized / study arm</th>
<th>Primary outcome at</th>
<th>Secondary outcome at</th>
<th>Level of evidence</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>randomized, double-blind, placebo-controlled, dose finding study</td>
<td>1 y double blind + 2 y open extension</td>
<td>finasteride 1mg or 5mg/day, placebo</td>
<td>291 finasteride 5mg, 305 finasteride 1mg, 299 placebo, 192 patients entered open extension all of whom received 5mg finasteride</td>
<td>Year 1: mod. Boyarcsy score placebo: -1 pt. [-2%] 1mg: -1.8 pt. <a href="n.s.">-9%</a> 5mg: -2.7 pt. <a href="p%3C0.05">-21%</a> Year 3: mod. Boyarcsy score PV/Qmax 5mg: -2.6 pt. <a href="p%3C0.001">-21%</a></td>
<td>Year 1: change from baseline prostate volume (pla.): -1.3 cc (-3%) 1mg: -11.8 cc (-18%) (p&lt;0.001) 5mg: -11.3 cc (-19%) (p&lt;0.001) Qmax pla.: +0.2 ml/s (+8%) (p&lt;0.001) 1mg: +1.4 ml/s (+23%) (p&lt;0.001) 5mg: +1.6 ml/s (+22%) (p&lt;0.001)</td>
<td>1b</td>
<td>2.3</td>
</tr>
<tr>
<td>randomized, double-blind, placebo-controlled, dose finding study</td>
<td>1 y double blind + 2 y open extension</td>
<td>finasteride 1mg or 5mg/day, placebo</td>
<td>246 finasteride 5mg, 249 finasteride 1mg, 255 placebo, 155 patients entered open extension all of whom received 5mg finasteride</td>
<td>Year 1: % men with change from baseline flow at least 3 ml/s pla.: 21% 1mg: 33% 5mg: 31% Year 3: mod. Boyarcsy score PV/Qmax change from baseline placebo: -2.6 pt. 1mg: -3.9 pt. (p&lt;0.001) 5mg: -3.6 pt. (p&lt;0.001) 5mg: -27.1% (p&lt;0.001) 5mg: +2.3 ml/s (p&lt;0.001)</td>
<td>Year 1: change from baseline prostate volume (pla.): -2.6 pt. 1mg: -2.9 pt. (n.s.) 5mg: -3.9 pt. (p&lt;0.001) pla.: -5% 1mg: -23.6% (p&lt;0.001) 5mg: -22.4% (p&lt;0.001) Qmax pla.: +0.4 ml/s 1mg: +1.3 ml/s (p&lt;0.001)</td>
<td>1b</td>
<td>2.3</td>
</tr>
<tr>
<td>randomized, double-blind, placebo-controlled, multicenter study</td>
<td>2 y double blind</td>
<td>finasteride 5mg/day, placebo</td>
<td>347 finasteride, 346 placebo</td>
<td>Year 2: mod. Boyarcsy score pla.: +0.2 pt. fin.: -2.0 pt. (p&lt;0.01)</td>
<td>Year 2: change from baseline pla.: +11.6 cc (CBS 4.8.161) fin.: -9.2 cc (CBS -23.4.165) (p&lt;0.01) pla.: +0.3 ml/s (CBS 0.7.0) fin.: +1.5 ml/s (CBS 1.1.1) (p&lt;0.01)</td>
<td>1b</td>
<td>4</td>
</tr>
<tr>
<td>randomized, double-blind, placebo controlled, multicenter study</td>
<td>2 y double blind</td>
<td>finasteride 5mg/day, placebo</td>
<td>307 finasteride, 306 placebo</td>
<td>Year 2: mod. Boyarcsy score pla.: -0.7 pt. fin.: -2.1 pt. (p&lt;0.01)</td>
<td>Year 2: change from baseline pla.: +8.4% fin.: -21% (p&lt;0.01) pla.: +0.3 ml/s fin.: +1.4 ml/s (p&lt;0.01)</td>
<td>1b</td>
<td>5</td>
</tr>
</tbody>
</table>
Table 2. Randomized clinical phase III trials (with more than 100 pt. in each study arm) conducted with finasteride versus placebo for the treatment of symptomatic LUTS/BPH.
Studies comparing finasteride either to other drugs or their combination, or trials conducted with less than 100 individuals randomized in each treatment arm, or study duration below 1 year, are not listed. (pla.=placebo, fin.=finasteride, PV: prostate volume, Qmax, maximum urinary flow rate, pt.=score points).

<table>
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<th>Treatment arms</th>
<th>N randomized / study arm</th>
<th>Primary outcome at</th>
<th>Secondary outcome at</th>
<th>Level of evidence</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 y double blind</td>
<td>finasteride 5mg/day, placebo</td>
<td>1450 finasteride, 1452 placebo</td>
<td>Year 2: mod. Boyarsky score</td>
<td>change from baseline: pla.: -1.5 pt, fin.: -3.2 pt (p&lt;0.001)</td>
<td></td>
<td>1b</td>
</tr>
<tr>
<td>4 y double blind +2 years open extension</td>
<td>finasteride 5mg/day, placebo</td>
<td>1524 finasteride, 1516 placebo</td>
<td>Year 2:</td>
<td>change from baseline: pla.: +8.9%, fin.: -15.3% (p&lt;0.001), pla.: +0.7mls, fin.: +1.5mls (p&lt;0.002)</td>
<td></td>
<td>1b</td>
</tr>
</tbody>
</table>

$ p<0.001$ compared to placebo. * cohort originally randomized to placebo and switched to finasteride in open extension. § cohort originally randomized to finasteride and continued with finasteride in open extension.

These studies demonstrated that treatment with finasteride induced a significant decrease in symptom score compared to placebo after one year of treatment (-21% vs. -2% respectively [56,61,62], which was confirmed in 2-year double-blind studies (mean 17%, range 13-22% [58,63,64] and long-term placebo-controlled trials over a study period of 4 years [86]. Three and 5 year open-label studies also showed a reduction in symptom severity [83,87,88]. A meta-analysis of six RCTs demonstrated that the effect of finasteride treatment on symptom improvement depends on baseline prostate volume. Finasteride treatment is most effective in men with large prostates ≥40gms [84].

Several RCTs have demonstrated that finasteride reduces prostate volume by 20% (range 15-23%). All placebo-controlled studies that lasted more than 1 year indicate that the prostate volume decreased during the first year, with no further decrease thereafter [56-58, 61-63, 86, 89]. In the open-label studies the largest reductions in prostate volume were also noted during the first year of finasteride therapy, leading to a decrease of around 27% after 3 and 5 years [83,87,88].

Several placebo controlled trials demonstrated that finasteride induces an increase in Qmax varying between 1.8 and 2ml [56-58, 62-64, 86, 89]. A five-year open extension of an initial double-blind period showed a mean improvement of approximately 13% in Qmax in patients treated with finasteride 5mg/day [88]. Similar to symptom improvement, the effect of finasteride on Qmax also depends on prostate volume with finasteride being most effective in men with large prostates [84].

Long-term placebo-controlled studies with finasteride in large number of patients have demonstrated that finasteride reduces the occurrence of AUR from 2.7% to 1.1% in 4000 patients within 2 years [90], from 2.5 to 1.0% in 2900 patients within 2 years [64] and from 6.6% to 2.8% in 3040 patients within 4 years [59,86]. However, the frequency of AUR was comparable to placebo (1%) in a one-year finasteride trial in 750 patients [62]. Both in a community-based and primary care study, the incidence of AUR was similar between finasteride (0.6 and 0.2%) and placebo (0.7 and 0.4%) [61,91]. In addition to that, placebo-controlled clinical trials have shown that finasteride reduces the risk for surgery from 6.5% (in 2109 placebo patients) to 4.2% in 2113 finasteride patients treated for 2 years [90] and from 5.9% to 3.5% in 2900 patients treated for 2 years [64]. In the 4-year placebo-controlled Prostate longitudinal efficacy and safety study (PLESS) study the risk for surgery with finasteride was reduced from 10% to 5% [59,60].

Several studies have investigated the effect of finasteride on obstructive parameters in pressure flow studies. In a 12 months placebo controlled trial, Finasteride caused a moderate but significant decrease (~8.1 cm. water) in detrusor pressure at maximum flow (p <0.05 versus placebo) [89] Of the finasteride treated cases 75% were obstructed and 25% equivocal at baseline compared to 67% and 33% respectively at month 12. These results were confirmed by others where the percentage of patients obstructed by the Abrams-Griffiths classification decreased from 76.2% at baseline to 66.7% after 1-year finasteride treatment and to 59.6% after 2 years[92]. In general, the urodynamic effects of finasteride are only small or moderate in amplitude.

2. DUTASTERIDE:

The efficacy and safety of dutasteride in men with symptomatic BPO has been demonstrated in an analysis of three, large-scale, randomised, placebo-controlled Phase III studies each consisting of a double blind phase of two years and an open extension of additional 2 years (ARIA3001, ARIA3002 and ARIB3003, Table 3). Date from these trials have been summarized in 2 meta-analysis [93,94].

These studies have shown a significant but moderate decrease in AUA-SI symptom score, a reduction in prostate volume of about 25 %, and a marginal improvement of maximum flow rate of 1 ml/s, respectively, during the double blind phases of 12 months [28,39,79-81]. At 24 months, to calculate the primary outcome parameter “incidence of acute urinary retention” results from these 3 trials were pooled and a relative risk reduction of 0.43 over placebo was demonstrated[95,96, 97-99].

The effect of dutasteride on symptom improvement was the largest in patients with a large transition zone index TZI [100]. also, men with prostates in the 2 upper TZI-tertiles had statistically significantly fewer incidences regarding AUR and surgery. However, dutasteride did not have a differential effect on transition zone volume (TZV) or peripheral prostate volume (PV). Total PV, TZV and peripheral PV were reduced by approximately 26% after 2 years of dutasteride treatment [101].

In these trials, the effect of dutasteride on the emotional consequences of LUTS/BPO was assessed using a new questionnaire, the BPH-Psychological
Table 3. Randomized clinical phase III trials conducted with dutasteride for the treatment of symptomatic LUTS/BPH.

<table>
<thead>
<tr>
<th>Name of Study</th>
<th>Design of phase III trials</th>
<th>Study duration (y/years, m/months, w/weeks)</th>
<th>Treatment arms</th>
<th>N randomized / study arm</th>
<th>Primary outcome (adjusted mean difference)</th>
<th>Secondary outcome (adjusted mean difference)</th>
<th>Level of evidence</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIA3001</td>
<td>randomized, double-blind, placebo-controlled, parallel-group</td>
<td>2 y double blind + 2 y open label</td>
<td>Dutasteride Placebo</td>
<td>720 (Dutasteride) 720 (Placebo) 290 former dutasteride patients completed open label, 255 former placebo-pt. completed open label</td>
<td>Year 1: AUA-SI improvement -1.1 over placebo; (CI95 -1.7,-0.5, P &lt;0.001)</td>
<td>Year 1: PV -21.1% over placebo; (CI95 -23.4,-18.9) Qmax +0.7mI/s over placebo; (CI95 0.3,1.1)</td>
<td>1b</td>
<td>1,2,3</td>
</tr>
<tr>
<td>ARIA3002</td>
<td>randomized, double-blind, placebo-controlled, parallel-group</td>
<td>2 y double blind + 2 y open label</td>
<td>Dutasteride Placebo</td>
<td>677 (Dutasteride) 685 (Placebo) 287 former dutasteride patients completed open label, 266 former placebo-pt. completed open label</td>
<td>Year 1: AUA-SI improvement -1.5 over placebo; (CI95 -2.1,-0.9, P &lt;0.001) Year 2: incidence of AUR s.a.</td>
<td>Year 2: incidence of surgery relative risk 0.52 (CI95 0.37-0.74, P &lt;0.001) Year 4: AUA-SI PV -6.6<em>dut/d, -6.1</em>pla/dut Qmax 2.7<em>mI/s dut/d, 1.6</em>mI/s</td>
<td>1b</td>
<td>1,3</td>
</tr>
<tr>
<td>ARI83003</td>
<td>randomized, double-blind, placebo-controlled, parallel-group</td>
<td>2 y double blind + 2 y open label</td>
<td>Dutasteride Placebo</td>
<td>799 (Dutasteride) 753 (Placebo) 396 former dutasteride patients completed open label, 374 former placebo-</td>
<td>Year 1: AUA-SI improvement -1.2 over placebo; (CI95 -1.8,-0.6, P &lt;0.001) Year 2: incidence of</td>
<td>Year 1: PV -21.5% over placebo; (CI95 -23.9,-19.2) Qmax +1.1*mI/s over placebo; (CI95 0.7,1.5)</td>
<td>1b</td>
<td>1,4</td>
</tr>
</tbody>
</table>
**Table 3. Randomized clinical phase III trials conducted with dutasteride for the treatment of symptomatic LUTS/BPH.**

<table>
<thead>
<tr>
<th>Name of Study</th>
<th>Design of phase III trials</th>
<th>Study duration (yr</th>
<th>Randomized study arm</th>
<th>Treatment</th>
<th>Primary outcome</th>
<th>Secondary outcome</th>
<th>Level of evidence</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARI3004</td>
<td>Randomized, double-blind, placebo-controlled, parallel-group</td>
<td>6</td>
<td>dutasteride Placebo</td>
<td>56 (placebo)</td>
<td>436.3g-4.5g placebo, p&lt;0.001</td>
<td>0.6% difference in prostate volume from baseline</td>
<td>Year 4: Safety, tolerability</td>
<td>1b</td>
</tr>
<tr>
<td>ARI3001</td>
<td>Multicentre, randomised, double-blind, double-dummy, parallel-group</td>
<td>96</td>
<td>dutasteride Tamsulosin</td>
<td>156 (tamsulosin)</td>
<td>0.4% over tamsulosin, CI 0.8, 0.005</td>
<td>No difference in proportion of men with an increase in prostate specific antigen</td>
<td>Year 1: Safety, tolerability</td>
<td>2a</td>
</tr>
<tr>
<td>ARI3002</td>
<td>Multicentre, randomised, double-blind, double-dummy, parallel-group</td>
<td>96</td>
<td>dutasteride Tamsulosin</td>
<td>156 (tamsulosin)</td>
<td>0.0% over tamsulosin, CI 0.8, 0.005</td>
<td>No difference in proportion of men with an increase in prostate specific antigen</td>
<td>Year 1: Safety, tolerability</td>
<td>2a</td>
</tr>
</tbody>
</table>

5. Data made publicly available at [www.gsk.com](http://www.gsk.com)
Well-being (BPWB) questionnaire (5 questions on embarrassment, frustration, feeling down, worry and the desire that symptoms would improve). Compared to placebo, 2-year dutasteride treatment statistically significantly improved psychological well-being. Improvements were significant from 12 months of treatment onwards [102].

Of the 4,325 LUTS/BPO patients a total of 2,340 continued with open-label dutasteride treatment for another 2 years. In the 1,188 patients who had already received dutasteride in the placebo-controlled study, the total AUA-SI further improved in the open-label study. In the 1,152 patients who had previously received placebo, there was also a further improvement in total AUA-SI score when they were switched to dutasteride in the open-label study. However at 4 years, the improvements in the original placebo groups were, smaller than in the original dutasteride group [99].

In addition to these published trials, one randomized direct comparison trial of 12 months dutasteride versus finasteride including an additional 12 months open extention phase has been conducted (ARI 40001, table 3), of which only safety data have been published so far in peer reviewed journals [95], the outcome data have been made public however on the investigators web site and as abstract in one scientific conference [103]. In this trial, none of the outcome parameters (change of prostate volume, Qmax and AUA-SI) were statistically different in each treatment group [104].

Furthermore, one small randomized, double blind, placebo controlled trial of 6 months duration directly assessed obstructive parameters derived from pressure flow studies. Neither the primary outcome parameter pDet(Qmax) nor any of the other secondary outcome parameters have been statistically significant compared to placebo. Again, data from this trial were made public only on the investigators web site [104].

c) Effect of 5α-reductase treatment on overall disease progression

The Medical Therapy Of Prostatic Symptoms (MTOPS) study looked into the progression of 3047 LUTS/BPO patients who were treated for an average of 4.5 years with placebo, the α1- AR antagonist doxazosin, the 5α-RI finasteride and their combination [105]. The primary parameter in the MTOPS study was the effect of treatment on overall clinical progression defined as symptomatic progression (defined as total I-PSS ≥ 4 points), or the development of AUR, urinary incontinence, urinary tract infections or urosepsis or renal insufficiency. Finasteride reduced the risk of overall clinical progression from 16.6% (placebo) to 10.2% [105].

d) Side effects during treatment with 5 α-reductase inhibitors

Finasteride and dutasteride are generally well tolerated with the most prevalent adverse events being sexual function related, the highest incidence being reported in the first year of therapy. 5α-IRIs such as finasteride and dutasteride induce adverse events related to sexual dysfunction such as impotence, decreased libido and abnormal ejaculation. However, these side effects are rare compared to traditional anti-androgen treatment and mostly appear in the first year of treatment in up to 5% of patients (Tables 4 and 5).

However, the question has been raised about the advantages of dutasteride over finasteride, especially with regard to the risk of breast cancer induction and of prostate cancer prevention or induction of high grade prostate cancer.

There were 3 cases of breast cancer reported during the ARIA3001/2 and ARIB3003 clinical trials, one with placebo and two with dutasteride (after 10 weeks and 11 months of treatment) [119]. In the MTOPS study there were 4 cases of breast cancer with finasteride. In contrary, in the PLESS study there were no cases of breast cancer with finasteride and 2 with placebo, while in the Prostate Cancer Prevention Trial there was 1 case of breast cancer with finasteride and one with placebo [106,107]. Taken together these data do not point to a major effect on the risk of breast cancer induction with either drug.

The EPICS (Enlarged Prostate International Comparator Study) was a randomized double-blind active-controlled trial that compared 12 months of dutasteride and finasteride therapy in 27 European countries.

The study was conducted to fulfill European registration requirements. The primary objective of the study was the change in baseline prostate volume at 1 year. Safety and tolerability data were also obtained. Patients with BPE or BPO (N=1630) were randomized to receive either dutasteride 0.5 mg once daily (n=813) or finasteride 5.0 mg once daily (n=817) for 12 months. Of the patients randomized, 1454 completed the 12-month double-blind phase (719 dutasteride and 735 finasteride) [104].


Although fewer drug-related sexual adverse events occurred in patients receiving dutasteride than finasteride, there were no significant differences between the two drugs (17% in the dutasteride group compared with 20% in finasteride-treated patients). The most frequent drug-related adverse events were sexual in nature and are listed in Table 6.

Few adverse events led to patient withdrawal from the study (5% of dutasteride patients and 4% of finasteride-treated patients) [104]. Thus, dutasteride appeared to be as safe as finasteride for patients with BPO.

e) Effect of 5 alpha-reductase inhibitors on BPE-related haematuria and reduction of blood loss after TUR-P

Several studies have confirmed the benefit of finasteride in limiting hematuria arising from benign prostatic enlargement [108-119]. The role of vascular endothelial growth factor (VEGF), a potent stimulator of angiogenesis, and microvessel density have been independently evaluated in trying to establish the mechanisms of the decreased bleeding observed in patients treated with finasteride [120].

Haemorrhage is a significant complication of TUR-P which may result in blood transfusions and increased morbidity. The potential of finasteride to reduce blood loss after TUR-P was evaluated in several small randomised, placebo-controlled trials [121-124]. In total 160 patients have been treated prior to TUR-P. Some of these studies reached statistical significance, mainly with the parameter Hb loss/g resected tissue. Administration of finasteride prior to TUR-P might be useful to reduce blood loss and related complications, especially for high-risk patients. Similar data were shown when finasteride was administered prior to open prostatectomy. (Fig.1) [57].
f) 5 alpha-reductase inhibitors and Prostate cancer

The normal range for serum PSA concentrations applicable to men with BPO treated for 12 months with a 5-mg daily dose of finasteride is shifted downward by 50%. The range 0.0 to 4.0 ng/ml for untreated men with BPO corresponds to the range 0.0 to 2.0 ng/ml for finasteride-treated men. Hence, to interpret serum PSA in a man who has been taking finasteride for at least 12 months, the clinician can multiply the serum PSA concentration by two and consider it as in an untreated man with BPO. A serum PSA increase of 1.0 ng/ml over a 6- to 12-month period in placebo-treated men with BPO, corresponds to a 0.5 ng/ml increase from months 6 to month 12 among finasteride treated men with BPO [125].

In men treated with finasteride, multiplying PSA by 2 and using normal ranges for untreated men preserves the usefulness of PSA for prostate cancer detection. Use of an upper limit of normal for last PSA of 2.0 ng/ml for finasteride and 4.0 ng/ml for placebo yielded similar sensitivity (66% versus 70%, \( P=0.6 \)), higher specificity (82% versus 74%, \( P<0.0001 \)), and a higher likelihood ratio (3.6 versus 2.7, \( P<0.05 \)) for finasteride than for placebo [126]. Both agents reduce serum PSA values to similar extents. Dutasteride reduces total serum PSA concentration by approximately 40% following 3 months of treatment and approximately 50% following 6,12, and 24 months of treatment. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. However, since the ratio of free to total PSA is not significantly altered, PSA may still be used as a screening tool for the detection of prostate cancer. To interpret an isolated PSA value in a man treated with either agent for 6 months or more, the PSA value should be doubled for comparison with normal values in untreated men.

Prostate cancer was diagnosed in 4.7% of men on finasteride and 5.1% on placebo (\( P=0.7 \)). Elevated PSA prompted diagnosis in 35% of cases on finasteride and 34% on placebo. The area under the receiver operating characteristic curve for last PSA was 0.84 on finasteride and 0.79 on placebo (\( p=0.07 \)). Use of an upper limit of normal for last PSA of 2.0 ng/ml for finasteride than for placebo [126].

However, finasteride also reduces serum PSA in men with known prostate cancer [127,128]. In some patients, ultimately diagnosed with prostate cancer, the serum PSA did not increase in longitudinal follow-up [129]. Little is known about the effect of finasteride on unbound or free serum levels of PSA. Such information would be important since percentage free PSA may substantially improve the cancer specificity of PSA testing. The mean percent free PSA (13 to 17% at baseline) was not altered significantly by finasteride or placebo [130]. Certainly, finasteride-induced suppression of the serum total PSA does not appear to be a useful test to discriminate cancer from benign disease [127].

Since it has been suggested that, as DHT may be implicated in the development and progression of prostate cancer, then the use of a 5 α-RI might help. The Prostate Cancer Prevention trial has randomised 18,882 men 55 years or older with a normal digital rectal examination and a PSA <3.0 ng/ml to finasteride 5 mg/day or placebo treatment for 7 years and compared the prevalence and grade of histologically-proven prostate cancer. [106]. Prostate cancer was detected in 803 of the 4368 men (18.4%) in the finasteride group and 1147 of the 4692 men (24.4%) in the placebo group – a 24.8% reduction in prevalence. In contrast, tumours of Gleason grades 7-10 were more common in the finasteride group, 6.4% of the 4368, men as compared to 5.1% of the 4692 men on placebo. They concluded that finasteride prevents or delays the appearance of prostate cancer but this benefit and the improvement in urinary symptoms must be weighed against sexual side effects. The apparent increase in prevalence of prostate cancer in the finasteride treated group appeared to be related to an over detection of high grade cancers due to prostate volume reduction in the finasteride treated group. Nevertheless, at present, the results of this study remain the subject of continuing controversy.

g) Finasteride and alpha-blocker combination therapy

The initial experience with combining alpha-blocker and 5-alpha-reductase therapy was not promising. The effects of finasteride and alpha-blockers have been compared in the Veterans Affairs Co-operative Studies “Benign Prostatic Hyperplasia” Study Group [131]. Terazosin (10 mg daily), finasteride (5 mg daily) and the combination of both drugs in 1229 men with LUTS/BPO was assessed. The mean changes from baseline in the symptom scores in the placebo, finasteride, terazosin, and combination therapy groups at one year were decreases of 2.6, 3.2, 6.1 and 6.2 points, respectively (\( P > 0.001 \) for the comparisons of both terazosin and combination therapy with finasteride and...
with placebo). The mean changes at one year in the peak urinary-flow rates were increases of 1.4, 1.6, 2.7 and 3.2 ml per sec., respectively (P <0.001 for the comparisons of both terazosin and combination therapy with finasteride and with placebo). Finasteride had no more effects on either measure than placebo. In the placebo group, 1.6 percent of the men discontinued the study because of adverse effects, as did 4.8 to 7.8 percent of the men in the other three groups. The authors concluded that in men with BPH, terazosin was an effective therapy, whereas finasteride was not effective and that combination with terazosin was no more effective than terazosin alone [131].

From this Veterans Affairs Cooperative Group study, it could be concluded that one year of combination therapy was no more effective than monotherapy with an alpha-blocker in improving symptoms or flow rates and substantially increased the cost of treatment.

In a European study (randomized, double-blind, multicenter trial involving 1051 patients with LUTS/BPO, alfuzosin given at a dose of 5 mg twice daily and finasteride 5mg once daily were compared with both drugs combined for 6 months. Primary efficacy criteria were symptomatic improvement (International Prostate Symptom Score: IPSS) and maximum flow rate (Qmax). Safety was assessed by monitoring adverse events. In this 6-month trial, alfuzosin was more effective than finasteride, with no additional benefit in combining both drugs [132].

The PREDICT study randomized 1,089 patients to placebo, finasteride, doxazosin, or the combination for 1 year [133]. The results show that α1-AR antagonists are more effective than finasteride in reducing symptom score. In the studies which involved a placebo, finasteride did not perform better than placebo, and the combination of finasteride and an α1-AR antagonist was no more effective than the α1-AR antagonist alone. Data from the PREDICT study also suggested that finasteride was no more efficacious than placebo when adjusting data for prostate size using surrogate measures such as prostate specific antigen and digital rectal examination [133].

The recently published Medical Therapy of Prostatic Symptoms (MTOPS) study has changed our thinking regarding combination therapy [105]. More than 3000 men were randomized to receive either placebo, doxazosin (alpha-blocker), finasteride (5α-R1), or both. The principal outcome was clinical progression - defined as either an increase of at least 4 points in AUA symptom score, or urinary retention, incontinence, renal insufficiency, or recurrent UTI. Other dependent variables included maximum urinary flow rate, serum PSA, and incidence of invasive therapy. After a median 4.5 years of follow-up, the median change in AUA symptom score was -4 for placebo, -6 for doxazosin, -5 for finasteride, and -7 for combination therapy. All differences were statistically significant. Clinical progression, which was mostly due to increasing AUA symptom score, occurred in 4.5 per 100 patients per year in the placebo group. Doxazosin and finasteride reduced the risk of progression by 39% and 34% respectively, and while significantly different from placebo, the difference between the two agents was not. Combination therapy caused a 66% risk reduction of clinical progression compared to placebo, and this was significantly different from the other three arms.

Secondary analysis showed that prostate volumes greater than 40cc and serum PSA >4.0 ng/ml predicted a better response to combination therapy. Looking specifically at AUR, the risk reduction for doxazosin, finasteride, and combination therapy was 31%, 67%, and 79% respectively.

Finasteride and combination therapy also reduced the risk of invasive procedures by 64% and 67% respectively, but there was no significant effect of doxazosin compared to placebo. We must of course weigh against these findings the additive side effect profile accruing from combination therapy.

The following conclusions can be drawn from the MTOPS data:

1. Combination therapy is the most effective medical treatment to produce symptomatic improvement and to slow disease progression. Although this conclusion is different from previous trials of combination therapy, the data is actually consistent. Similar to the Veterans Affairs Cooperative Group study, at one year follow-up in the MTOPS trial there was no difference in symptoms between finasteride and placebo or between combination therapy and doxazosin alone. However, with longer follow-up to four years we see the effect of finasteride compared to placebo, and the overall benefit of combination therapy.

2. An alpha-blocker alone can reduce clinical progression, as defined by symptom deterioration. Although it delayed the time to acute urinary retention, doxazosin did not significantly decrease
its cumulative incidence as compared to placebo, nor did it have any effect on the incidence of surgical procedures.

3 With a clinical progression rate of 4.5 per 100 patients per year in the placebo group, we can accurately counsel patients with LUTS that over 5 years their risk of progression is approximately 20 percent without treatment.

4 Finally, although doxazosin and finasteride are the best tested agents in combination therapy and, in the absence of any head-to-head trials comparing different agents used in combination, we can conclude that all alpha-blockers and 5α-RIs should be equally effective in combination [134].

5 Preliminary evidence suggests that histological examination of prostatic biopsies taken in this study have shown the presence of chronic inflammatory changes within the prostate which may have a significant impact on clinical outcome, (Roehrborn CG personal communication)

Comments

Overall, the results of 5α-reductase therapy have fallen somewhat short of initial expectations, probably because the following obstacles will be faced by any inhibitor of 5α-reductase:

• heterogeneity of the disease;
• coincidental concurrence of human BPO and symptoms unrelated to prostatic obstruction;
• the role of residual, or rising testosterone levels in maintenance of prostate size;
• the possibility that the essential developmental role of DHT in the prostate is not mirrored by regression of the enlarged, hyperplastic gland on removal of DHT support.

Randomised, placebo-controlled trials have demonstrated the benefit of both finasteride and dutasteride over placebo in men with clinically enlarged prostates secondary to BPH. In the overall study population, the magnitude of benefit is modest; however, approximately one-third of patients have clinically significant improvement. The drug is less effective in men with LUTS/BPO without significantly enlarged prostates.

Given their minimal side-effects, both finasteride and dutasteride should be considered to be an acceptable treatment option in men with clinically enlarged prostates. Studies have suggested durability of initial treatment response out to nearly six years. Available data show that finasteride has a preventative influence on the progression of the disease over time. It significantly reduces clinically significant endpoints such as acute urinary retention and surgery. To date, there are no data to suggest that finasteride masks the detection of prostate cancer but it may affect its incidence. The combined blockade of both type 1 and 2 5α-reductase has not shown additional clinical benefits in the pathophysiology of benign prostatic hyperplasia relative to the inhibition of only one type of the enzyme.

**RECOMMENDATIONS:**

- Randomised, placebo-controlled trials have demonstrated the benefit of 5α-RIs over placebo in men with clinically enlarged prostates above 30-40cc secondary to BPH. (Level 1 Grade A)
- Randomised, placebo-controlled trials have demonstrated the benefit of 5α-RIs over placebo in men treated for LUTS/BPO. (Level 1 Grade B)
- Placebo controlled data for finasteride out to over 5 years and for dutasteride out to 2 years have confirmed the durability of the treatment response. (Level 1 Grade A)
- The efficacy and tolerability of both finasteride and dutasteride is identical. (Level 1 Grade B)
- The magnitude of systematic benefit is greater than placebo but consistently smaller than seen with α1-AR antagonists. (Level 1 Grade A)
- Other aspects of therapy relating to prevention of progression in volume increase, reduction of the risk of retention and the development of cancer, are considered by other committees.
- The efficacy of combination therapy with 5α-RIs and α1-AR antagonists is greater than either agent alone. (Level 1 Grade B)
- The clinical utility of this combination therapy should take account of the balance between cost efficacy and additional side effects. (Level 1 Grade B)
2. ANDROGEN WITHDRAWAL

True antiandrogens, which block the action of testosterone and DHT in the prostate, should be distinguished from agents that impair androgen production. Classification of treatment by mechanism of action is of some value in predicting relative side-effects: interventions that impair Testosterone production are usually associated with sexual dysfunction. Certain hormonally-active compounds used for the treatment of BPO exhibit both anti-androgen and androgen ablation activities.

a) Surgical Castration

**Recommendation:** Surgical castration may be effective for the treatment of BPO, but the invasiveness and risk of the procedure preclude its use.

b) Medical Castration: GnRH analogues

**Recommendation:** GnRH therapy has shown benefit in the treatment of BPO. However, cost, sexual dysfunction, decreased bone density and hot flashes preclude the use of these drugs in routine cases.

c) Progestational Agents

**Recommendation:** Progestational agents have evidence of efficacy for the treatment of BPO. One clinical trial shows that one agent in this class (CMA) has an efficacy similar to finasteride. However, undesirable androgen withdrawal side effects (e.g. impotence, decrease of bone density) limit the widespread use of progestational agents.

d) Androgen Receptor Antagonists

**Recommendation:** Data strongly suggest that the side-effects of current androgen receptor antagonists (gynaecomastia, hepatotoxicity, diarrhoea) outweigh any potential benefit in the treatment of BPO.

3. OESTROGEN WITHDRAWAL

There is evidence which suggests that oestrogens play some role in the development of BPH. The relative importance of oestrogens compared to androgens or other growth stimulatory factors in the prostate is uncertain. A variety of preliminary clinical studies have been conducted to determine whether anti-oestrogen-like approaches have clinical utility in the treatment of BPO. Only aromatase inhibition, however, has been studied in detail.

**RECOMMENDATION:**

The rationale for aromatase inhibitor therapy in the treatment of BPO is based solely on animal studies. Randomised clinical trials have failed to show benefit. Therefore, aromatase inhibitor therapy is currently not a recommended treatment option.

C. ADRENOCEPTOR ANTAGONISTS

I. INTRODUCTION

The effect on smooth muscle tone is dependent on the release of noradrenaline (NA) from adrenergic nerves, the amine stimulating $\alpha_1$-ARs on smooth muscle of the prostatic stroma, bladder neck and urethra. Storage symptoms, on the other hand, have been associated with bladder dysfunction secondary to outlet obstruction. However, there is no convincing evidence for direct links between the size of the prostate, BOO, and LUTS; [135].

$\alpha_1$-AR antagonists improve both LUTS and flow rate in BPH patients [136]. Since prostatic and urethral $\alpha_1$-ARs are considered to mediate the dynamic component of obstruction, and since a direct relationship between the amount of prostatic smooth muscle and dynamic obstruction (as assessed by the response to $\alpha_1$-AR blockade) has been demonstrated [137], it is logical to assume that these receptors mediate at least part of the symptoms.

On the other hand, many patients who have undergone prostatectomy, which should relieve obstruction, still experience persistent storage symptoms [138]. Since $\alpha_1$--AR antagonists can have beneficial effects on the LUTS even in the absence of outlet obstruction [136], mechanisms outside the prostate involving $\alpha_1$--ARs may be involved in the pathogenesis of, particularly storage symptoms. LUTS can be caused by a number of factors (Table 7) and beside the prostate, there are several possible sites of action of $\alpha$-AR antagonists (Table 8).
Meanwhile, however, it has become clear that the effects of alpha-blockers on BOO are moderate at best, [139] and are insufficient to explain the improvement in symptoms, particularly storage symptoms. Therefore, newer concepts highlight a possible involvement of $\alpha_1$-ARs in the bladder and/or spinal cord as possible mediators of alpha-blocker-induced symptom relief [140, 141] but the specific mechanisms of such effects need to be defined. Moreover, it is clear that the alpha-blocker effects on BOO are mediated predominantly, if not exclusively, by $\alpha_{1A}$-ARs; while it has been speculated that clinical effects on the bladder and spinal cord could involve $\alpha_{1D}$-ARs: this needs to be verified.

Further information relating to the recent evidence relating to pharmacological mechanisms are reviewed in the specific committee dealing with pharmacology

### II. UROSELECTIVITY

Drugs which decrease outlet resistance, without affecting blood pressure, would obviously be of therapeutic interest. There have been several reports of the effects of $\alpha_1$-AR antagonists decreasing urethral resistance in animals [142]. Indeed, such animal models can be used to determine the potency and selectivity of $\alpha_1$-AR antagonists for the prostate over other parameters such as blood pressure. In several such models, the potency order of effects of various $\alpha_1$-AR antagonists on the pressures in the urethra has been defined. This has then been related to blood pressure changes in the same animal [142]. Although such models may predict effects on, for example, flow rate in humans, they also have limitations, and the results may be both species and assay-dependent [143]. Thus, results obtained in one animal species may differ from those obtained in another, and it has not been established which animal model is the most relevant for effects in humans. Since side effects, that may be dose-limiting clinically, are not always cardiovascular, but may be from the central nervous system, e.g., drowsiness and dizziness, and since such effects cannot always be studied in animals, animal models may not adequately predict clinical usefulness.

Considering this, a clinically relevant definition of uroselectivity can only be made in man. Such a definition of uroselectivity is the one previously suggested by the 3rd International Consultation on Benign Prostatic Hyperplasia [144]: "desired effects on obstruction and LUTS related to adverse effects".

### III. $\alpha_1$-AR SUBTYPES AND $\alpha_1$-AR ANTAGONISTS IN THE TREATMENT OF BPH

The efficacy of $\alpha_1$-AR antagonists for improving flow rate and for treatment of LUTS in BPH patients has been well documented [136]. Among the $\alpha_1$-AR antagonists currently in common clinical use for treatment of BPH, only tamsulosin has some selectivity for the $\alpha_{1A}$-AR subtype [142]. Whether this pharmacological selectivity has clinical relevance, remains to be determined, in particular, if the prostate, bladder, and spinal cord are important sites for $\alpha_1$-AR antagonists, it seems that $\alpha_{1A}$- and/or $\alpha_{1D}$-ARs should be more important than $\alpha_{1B}$-ARs. This may give a therapeutic advantage for drugs with relatively low affinity for $\alpha_{1B}$-ARs, since these receptors seem to be important for regulation of blood pressure. Whether an $\alpha_1$-AR antagonist should have a preference for $\alpha_{1A}$- or $\alpha_{1D}$-ARs, or both, is still a matter of speculation. Since it appears that $\alpha_{1A}$-AR antagonism is more important for flow rate increase than for symptom relief (see above), and the role for $\alpha_{1D}$-AR antagonism for symptom relief has not been defined, the most advantageous subtype selectivity profile for an $\alpha_1$-AR antagonist is yet to be established.
The pharmacokinetic characteristics (absorption, distribution, metabolism, excretion) of the different α₁-AR antagonists may contribute to differences in effects and side effects. However, this is a field that has been incompletely explored. The rationale for introducing controlled (slow) release preparations is to change the absorption characteristics to obtain a sustained plasma concentration over 24 h, which can reduce dosing to once daily and/or improve tolerability (avoiding high peaks in plasma concentration).

In recent years, new formulation of alfuzosin (alfuzosin XL) [145], doxazosin (doxazosin GITS) [146] and tamsulosin (tamsulosin OCAS) [147] have been introduced. Although the new formulations tended to have maintained efficacy but a somewhat better tolerability, the clinical relevance of such improvements remains unclear. Differences in distribution between the α₁-AR antagonists may be of importance. If effects on the CNS are responsible for some of the adverse effects, e.g., asthenia and dizziness, these effects should be more frequent with drugs which have good penetration into the CNS. However, this has not been established. Drugs which seem to have a high diffusion into prostatic tissue [148, 149] should be expected to have better effect on flow rate than other α₁-AR antagonists; this does not seem to be the case.

New formulations, allowing agents to be prescribed once a day, have been developed. It has been suggested that some of these formulations have provided a better side-effect profile because of a more controlled release of agents within the gastrointestinal tract. For several of the above drugs, new formulations with smoother pharmacokinetic profiles have been introduced in recent years. Alfuzosin was originally marketed in a thrice daily immediate release formulation, since then twice daily sustained release (alfuzosin SR) [155] and once daily extended release (alfuzosin XL) [154] formulations have been introduced. In addition to the original once daily immediate release formulation of doxazosin, a once daily gastrointestinal therapeutic system (GITS) formulation with slower release (doxazosin GITS) has been introduced [146]. While the originally marketed once daily modified release tamsulosin version already represented a modified release formulation, a once daily oral controlled absorption system formulation with even slower release (tamsulosin OCAS) for hypertension in several countries. However, this should not influence treatment of BPO. In patients with BPO and hypertension, α₁-AR antagonists remain a first-line treatment for BPH. However, associated hypertension and cardiovascular diseases should be treated independently according to established guidelines.

Blood pressure reductions, particularly orthostatic hypotension, dizziness and asthenia are typical side effects in the use of alpha-blockers. They involve predominantly α₁-ARs in blood vessels and in the central nervous system. Both tissues express all three α₁-AR subtypes. Hence, selectivity for one or more of them may contribute somewhat to tolerability of some alpha-blockers, but pharmacokinetic aspects also appear to play an important role. These include drug enrichment in urogenital tissues [149, 152] as well as smooth pharmacokinetic profiles (long time to reach maximal plasma concentrations, small ratio between maximal and trough plasma concentrations, long half lives) seen with modified/extended/slow release formulations [146,153, 154].

The present review focuses on the four alpha-blockers which are globally available for the treatment of BPO, i.e. alfuzosin, doxazosin, tamsulosin and terazosin. Other alpha-blockers, which are available only in few countries (e.g. indoramin or naftopidil), have only been tested on a limited scale (e.g. prazosin) and/or those that are still in clinical development (e.g. sidolosin), will not be discussed in detail.

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has been introduced [147]. The new formulation of alfuzosin has involved an increase in the total recommended daily dose (from 7.5 to 10 mg), whereas the recommended total daily dose of doxazosin (4-8 mg) and tamsulosin (0.4 mg) has not changed. Randomized, double-blind studies directly comparing the old and the new formulations have demonstrated that they did not alter the overall efficacy of alfuzosin [45], doxazosin [146] and tamsulosin [147]. The extent of improvement, even where it reached statistical significance, was only small and may not be noticeable clinically in the majority of patients.

The efficacy of alpha-blockers in relieving LUTS has primarily been assessed by their ability to reduce validated symptoms scores (most often the International Prostatic Symptom Score, IPSS) and by their ability to increase the maximum free urine flow rate ($Q_{\text{max}}$). Multiple placebo-controlled, randomized, double-blind studies directly comparing the old and the new formulations have demonstrated that they did not alter the overall efficacy of alfuzosin [45], doxazosin [146] and tamsulosin [147]. The extent of improvement, even where it reached statistical significance, was only small and may not be noticeable clinically in the majority of patients.

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The aggregate of the data yields level 1 evidence to support the efficacy of alpha-blockers as a class in relieving both storage and voiding symptoms associated with BPO. A comparison of the results from placebo-controlled RCT’s and open-label studies suggests that the RCT’s may somewhat underestimate the true efficacy of the alpha-blockers, possibly due to the symptom improvement occurring during the single-blind placebo run-in phase, preceding randomisation, in most studies [160]. Indirect comparisons of placebo-controlled studies for the individual alpha-blockers had already indicated that they have similar efficacy when adequately dosed [156,157]. In this context, adequate dose refers to 2.5 mg thrice daily for the immediate release formulation of alfuzosin, 5 mg twice daily for the sustained release formulation of alfuzosin, 10 mg once daily for the extended release formulation of alfuzosin, 4-8 mg once daily for both the immediate release and the GITS formulation of doxazosin, 0.4 mg once daily for both the modified release and the OCAS formulation of tamsulosin and 5-10 mg once daily for terazosin. Somewhat smaller doses are used for some of these drugs in several Asian countries, but little published information supports the ratio-

nale for lower dosing in specific ethnic groups. Multiple direct comparative studies have confirmed the similar efficacy of the various alpha-blockers. Thus, direct comparative studies have been reported for alfuzosin vs. doxazosin [161], alfuzosin vs. tamsulosin [162, 163], alfuzosin vs. terazosin, [163] doxazosin vs. tamsulosin [164], doxazosin vs. terazosin[165] and tamsulosin vs. terazosin [166, 167, 168, 163]. While some studies, often involving small patient numbers, have reported greater efficacy of one drug compared to another [161, 164, 167], the majority of studies confirms similar efficacy for all of the alpha-blockers in relievingLUTS.

Several direct comparative clinical studies have demonstrated similar tolerability of various formulations of alfuzosin and the modified release formulation of tamsulosin [162,163], and this was supported by clinical pharmacology studies into their vascular effects [169]. In contrast, several direct comparative clinical studies have demonstrated greater tolerability with tamsulosin than with terazosin [166, 167, 168]; a direct comparative study between tamsulosin and doxazosin did not report such differences but may have had insufficient sensitivity due to small patient numbers [164]. The differences in tolerability between tamsulosin and terazosin appear to relate to a differential effect on the vasculature. This is supported by several clinical pharmacology studies demonstrating a greater vascular antagonism and/or greater orthostatic reactions with terazosin than with tamsulosin [170, 171, 172]; similar differences were also reported for the comparison of doxazosin with tamsulosin [173]. A recent systematic review of cardiovascular side effects of alpha-blockers in high-risk patients (i.e. those with cardiovascular comorbidities, anti-hypertensive comediations or concomitant use of phosphodiesterase inhibitors) also indicates greater tolerability of tamsulosin as compared to doxazosin and terazosin [174]. A notable exception from the above is the phenomenon of abnormal ejaculation. RCT’s have repeatedly reported this more frequent with tamsulosin than with placebo; its incidence is considerably less than 10% at 0.4 mg tamsulosin but may increase with 0.8 mg tamsulosin [175,176, 177]. On the other hand, no such differences have been seen in the placebo-controlled studies with other alpha-blockers. Nevertheless, two direct comparative studies between tamsulosin and alfuzosin involving more than 100 patients per group each have failed to detect significant differences in abnormal ejaculations between the two drugs [162]. While it had originally been assumed that the abnormal ejaculation seen with tamsulosin
Table 9. Placebo-controlled studies with $\alpha_1$-AR antagonists

<table>
<thead>
<tr>
<th>$\alpha_1$-Adrenoceptor antagonist</th>
<th>Study No.</th>
<th>First author</th>
<th>Total patients $^\circ$</th>
<th>Treatment duration (months)</th>
<th>Formulation, dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alfuzosin</strong></td>
<td>1</td>
<td>Jardin $^{182}$</td>
<td>518</td>
<td>6 $^\circ$</td>
<td>IR $^&amp;$, 2.5 mg t.i.d.-q.i.d.</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Hansen $^{183}$</td>
<td>195</td>
<td>3</td>
<td>IR, 2.5 mg t.i.d.</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Buzelin $^{155}$</td>
<td>390</td>
<td>3</td>
<td>SR $^&amp;$, 5 mg b.i.d.</td>
</tr>
<tr>
<td></td>
<td>4a</td>
<td>Van Kerrebroeck $^{145}$</td>
<td>447</td>
<td>3</td>
<td>IR, 2.5 mg t.i.d.</td>
</tr>
<tr>
<td></td>
<td>4b</td>
<td>Van Kerrebroeck $^{145}$</td>
<td>447</td>
<td>3</td>
<td>XL $^&amp;$, 10 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Roehrborn $^{184}$</td>
<td>355</td>
<td>3</td>
<td>XL, 10 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Roehrborn $^{154}$</td>
<td>955</td>
<td>3</td>
<td>XL, 10 mg o.d.</td>
</tr>
<tr>
<td><strong>Terazosin</strong></td>
<td>7a</td>
<td>Lepor $^{185}$</td>
<td>211</td>
<td>3</td>
<td>5 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>7b</td>
<td>Lepor $^{185}$</td>
<td>211</td>
<td>3</td>
<td>10 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>8a</td>
<td>Di Silverio $^{186}$</td>
<td>103</td>
<td>2</td>
<td>5 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>8b</td>
<td>Di Silverio $^{186}$</td>
<td>103</td>
<td>2</td>
<td>10 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>9a</td>
<td>Lloyd $^{187}$</td>
<td>61</td>
<td>2</td>
<td>5 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>9b</td>
<td>Lloyd $^{187}$</td>
<td>61</td>
<td>2</td>
<td>10 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Brawer $^{188}$</td>
<td>160</td>
<td>6</td>
<td>1-10 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>Roehrborn $^{189}$</td>
<td>2,084</td>
<td>12</td>
<td>2-10 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>Lepor $^{131, 190}$</td>
<td>610</td>
<td>12</td>
<td>10 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>Elhilali $^{191}$</td>
<td>164</td>
<td>6</td>
<td>2-10 mg o.d.</td>
</tr>
<tr>
<td><strong>Doxazosin</strong></td>
<td>14</td>
<td>Christensen $^{192}$</td>
<td>100</td>
<td>3</td>
<td>IR $^&amp;$, 4 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Fawzy $^{193}$</td>
<td>100</td>
<td>3</td>
<td>IR, 2-8 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>16a</td>
<td>Gillenwater $^{194}$</td>
<td>151</td>
<td>3</td>
<td>IR, 4 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>16b</td>
<td>Gillenwater $^{194}$</td>
<td>151</td>
<td>3</td>
<td>IR, 8 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>Mobley $^{195}$</td>
<td>97</td>
<td>3</td>
<td>IR, 4 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>Roehrborn $^{196}$</td>
<td>337</td>
<td>3</td>
<td>IR, 4-8 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>Janknegt $^{197}$</td>
<td>456</td>
<td>3</td>
<td>IR, 1-16 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Kirby</td>
<td>545</td>
<td>12</td>
<td>IR, 1-8 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>McConnell $^{105}$</td>
<td>1,493</td>
<td>54</td>
<td>IR, 4-8 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>22a</td>
<td>Andersen $^{198}$</td>
<td>795</td>
<td>3</td>
<td>IR, 1-8 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>22b</td>
<td>Andersen $^{198}$</td>
<td>795</td>
<td>3</td>
<td>GITS $^&amp;$, 4-8 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>23a</td>
<td>Kirby $^{146}$</td>
<td>1,475</td>
<td>3</td>
<td>IR, 1-8 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>23b</td>
<td>Kirby $^{146}$</td>
<td>1,475</td>
<td>3</td>
<td>GITS, 4-8 mg</td>
</tr>
<tr>
<td><strong>Tamsulosin</strong></td>
<td>24</td>
<td>Abrams $^{199}$</td>
<td>296</td>
<td>3</td>
<td>0.4 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>Chapple $^{175}$</td>
<td>575</td>
<td>3</td>
<td>0.4 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>26a</td>
<td>Lepor $^{176}$</td>
<td>756</td>
<td>3</td>
<td>0.4 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>26b</td>
<td>Lepor $^{176}$</td>
<td>756</td>
<td>3</td>
<td>0.8 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>27a</td>
<td>Lepor $^{200}$</td>
<td>418</td>
<td>12</td>
<td>0.4 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>27b</td>
<td>Lepor $^{200}$</td>
<td>418</td>
<td>12</td>
<td>0.8 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>28a</td>
<td>Narayan $^{177}$</td>
<td>735</td>
<td>3</td>
<td>0.4 mg o.d.</td>
</tr>
<tr>
<td></td>
<td>28b</td>
<td>Narayan $^{177}$</td>
<td>735</td>
<td>3</td>
<td>0.8 mg o.d.</td>
</tr>
</tbody>
</table>

$^\circ$: number of randomized patients in the placebo and presented dosage groups
#$^\circ$: for Qmax after 12 weeks
$^\&\&$: pooled analysis
Figure 4. Effect of $\alpha_1$-AR antagonists on total symptom score (a,b) and $Q_{\text{max}}$ (c,d) in placebo-controlled studies. Total number of patients in all studies included for total symptom score: alfuzosin $n=2,208$; terazosin $n=3,229$; doxazosin $n=3,947$; tamsulosin $n=1,331$; $Q_{\text{max}}$: alfuzosin $n=2,208$; terazosin $n=3,393$; doxazosin $n=1,777$; tamsulosin $n=2,066$.

Figure 5. Percentage of patients that discontinued due to AEs (4a,b) in placebo-controlled studies
represents retrograde ejaculation, recent studies demonstrate that it rather represents a reduced ejaculatory volume [178, 179]; the functional mechanism underlying this, i.e. whether it is $\alpha_1$-AR-mediated, remains unclear.

The present data indicate that the general tolerability of $\alpha$-blockers is good but somewhat better for those used solely in the treatment of LUTS/BPO (i.e. alfuzosin and tamsulosin) than for those primarily developed for hypertension treatment (i.e. doxazosin and terazosin), primarily due to reduced cardiovascular side effects (level 2 evidence). Abnormal ejaculation may occur more frequently with tamsulosin than with other alpha-blockers.

Due to the high prevalence of erectile dysfunction in LUTS/BPO patients, comedication with $\alpha_1$-AR antagonists combined with phosphodiesterase (PDE V) inhibitors such as sildenafil, tadalafil or vardenafil is likely to occur. Since both drug classes have vasodilating properties, such combinations can lead to enhanced blood pressure reductions, and a recent systematic review of corresponding studies confirms this [174]. Hence, the FDA-approved prescribing information states that sildenafil should not be used in doses exceeding 25 mg within 4 h of taking an $\alpha_1$-AR antagonist, and advises caution in the combination of tadalafil or vardenafil with $\alpha_1$-AR antagonists.

### RECOMMENDATION

There is insufficient evidence to recommend that the combination of phosphodiesterase inhibitors and an $\alpha$ AR antagonist has any advantage over monotherapy with $\alpha$-blocker therapy alone.

Level 4 Grade C

The average patient being diagnosed with BPO has a remaining life expectancy of 15-20 years. Therefore, an ideal treatment should have demonstrated durability over such a time span. To date, the efficacy of $\alpha$-blockers has been studied for time spans of up to 4-6 years. Most such studies were open-label extensions of earlier RCT’s. Such studies have demonstrated sustained symptom relief over at least 4 years for doxazosin [180] and tamsulosin [181]. More importantly, 4-year randomized, placebo-controlled data for doxazosin have recently been obtained as part of the MTOPS study [105]. This study demon-

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**Table 10. Direct-comparative studies between $\alpha_1$-AR antagonists**

<table>
<thead>
<tr>
<th>$\alpha_1$-Adrenoceptor antagonists</th>
<th>First author</th>
<th>Total patients</th>
<th>Treatment duration</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamsulosin vs. alfuzosin*</td>
<td>Buzelin</td>
<td>256</td>
<td>3 months</td>
<td>0.4 mg o.d. vs. 2.5 mg t.i.d.</td>
</tr>
<tr>
<td>Tamsulosin vs. alfuzosin</td>
<td>Anonymous</td>
<td>466</td>
<td>3 months</td>
<td>0.4 mg o.d. vs. 10 mg o.d.</td>
</tr>
<tr>
<td>Tamsulosin vs. terazosin**</td>
<td>Lowe</td>
<td>1,983</td>
<td>2 months</td>
<td>0.4 mg o.d. vs. 5 mg o.d.</td>
</tr>
<tr>
<td>Tamsulosin vs. terazosin#</td>
<td>De Mey</td>
<td>73</td>
<td>1 week</td>
<td>0.4 mg o.d. vs. 5 mg b.i.d.</td>
</tr>
</tbody>
</table>

*: The dose for alfuzosin was titrated from 2.5 mg b.i.d. during the first 2 weeks to 2.5 mg t.i.d. during the last 10 weeks whereas the 0.4 mg dose of tamsulosin was used throughout the whole study without dose titration.

**: The dose for terazosin was titrated from 1 mg for the first week, 2 mg for the second week and 5 mg from the third week onwards.

#: Administration according to prescribing information in most European countries: terazosin was administered in the evening after dinner and titrated from 1 mg for the first week, 2 mg for the second week and 5 mg for 1 day whereas tamsulosin was administered after breakfast and the 0.4 mg dose was used throughout the whole study without dose titration.

##: The dose for alfuzosin was titrated from alfuzosin 2.5 mg b.i.d to alfuzosin 5 mg b.i.d. for the remainder of the study. Tamsulosin was administered at 0.4 mg o.d. throughout the study without dose titration.

@: placebo-controlled
strated sustained symptom improvement relative to placebo over the entire observation period. While doxazosin prevented the overall LUTS/BPO progression as defined in this study, it had no statistically significant effect on the occurrence of AUR or progression to surgery at study end.

In conclusion, taken together, the available data provide level 1 evidence that alpha-blockers as a class are significantly more effective than placebo in the treatment of LUTS, and such efficacy is maintained for more than 4 years.

It is clear that there appears to be a discrepancy between the ability for \( \alpha_1 \)-AR antagonists to relieve symptoms when compared to the relief of BOO and consequent improvement in urodynamic parameters such as flow rate. Whilst an improvement in flow rate may be to some extent counteracted as a consequence of lowering the voiding pressure resultant from a significant improvement in outlet resistance, nevertheless the improvements of flow rate which are recorded in the literature appear to be substantially less than those to be expected from the degree of concomitant symptomatic relief. It is clear that other pathophysiological mechanisms do need to be identified to explain the observed drug effects.

The epidemiological data relating to the use of these agents in clinical practice is as yet scanty and this is also an area which needs to be urgently addressed in future studies. There is no convincing evidence that new formulations of existing alpha-blockers result in clinically relevant improvements of efficacy or that any drug within this class is more effective than another member of this group.

**RECOMMENDATIONS**

The efficacy of \( \alpha \)-AR antagonists on symptoms has been demonstrated in placebo controlled studies out to 5 years.  
*(Level 1 Grade B)*

The benefit of \( \alpha_1 \)-AR antagonists is not related to prostate size.  
*(Level 1 Grade A)*

The efficacy of all \( \alpha_1 \)-AR antagonists is similar.  
*(Level 1 Grade A)*

The tolerability of alfuzosin and tamsulosin is similar and better than the other agents.  
*(Level 1 Grade A)*

**D. PHYTOTHERAPY**

**I. INTRODUCTION**

There is interest in phytotherapy of BPO/LUTS, particularly within the framework of complementary medicine. The fundamental question, however, is to critically assess the evidence-base supporting the use of phytotherapy.

Plant extracts are complex mixtures of various agents and are in a sense unique, as the extraction procedures differ from company to company and the exact compositions of the preparations vary and are only partially chemically defined. Therefore, the product of one company may be different from that of another with regard to specific formulations and their potentially active effective components, even if the preparations originate from the same plant. In addition, an extract from one plant, for example saw palmetto, could have different mechanisms of action, efficacy, bioavailability and pharmacodynamics, compared to an extract made from stinging nettles, the African plum tree, pollen extract, pumpkin seeds or cactus flower extracts.

Therefore, the different preparations from the various producers with their recommended doses each have to be submitted to separate evaluation, as the results of basic research and clinical trials cannot automatically be transferred from one product to another. It is therefore essential that each individual manufacturer of plant extracts should perform separate scientific studies and placebo-controlled clinical trials, to allow an adequate assessment and evaluation of their individual product(s) in comparison to placebo with adequate long term follow up.

Comparative, placebo-controlled studies with other phyotherapeutic preparations as well as with 5\( \alpha \) RIs
and alpha AR blockers, in addition to a placebo arm, are essential.

Although more than 30 different plant species can be identified as components of the these products, most of the phytotherapeutic agents used are extracted from the roots, seeds, bark or fruits of the plants listed in Table 11. Some products stem from a single plant only (monopreparations); others are combination preparations of two or more plants.

The number of identified components in plant extracts is increasing (Table 12). For many of the agents the suggested mechanisms of action are purely hypothetical, lacking scientific proof and evidence in man. For others, there are conflicting data in the literature, for example relating to the inhibitory effect on 5α-reductase activity.

A major problem of many in vitro and experimental studies is that supraphysiologic doses were used which were many times higher than the doses recommended for clinical use. There is little data on the pharmacodynamics and bioavailability of most preparations. Some of the ingredients of plant extracts are probably not absorbed at all and others only minimally. Much of the existing literature base with phytotherapy is based on parameters such as nocturia and frequency with less reference to other objective measures such as flow rates and post voiding residuals.

Table 11. Origin of phytotherapeutic agents used for the treatment of LUTS secondary to BPH

- American dwarf palm/ (fruits of Serenoa repens/Sabal)
- Saw palmetto serrulata
- African plum tree (bark of Pygeum africanum)
- South African star grass (roots of Hypoxis rooperi)
- Pine, Spruce (Pinus, Picea)
- Stinging nettle (roots of Urtica dioica)
- Rye (pollen of Secale cereale)
- Pumpkin (seeds of Cucurbita pepo)
- Cactus flower extracts (Opinia)

Table 12. Main Components of plant extracts suggested to be active

- Phytosterols (α-sitosterol)
- Phytoestrogens
- Fatty acids (lauric and myristic acid)
- Lectins
- Flavonoids
- Plant oils
- Polysaccharides

II. SERENOAA REPENS EXTRACTS

1. INTRODUCTION

The most widely used plant extract is from the American dwarf palm, (Serenoa repens), formerly known by the botanical name Sabal serrulata and colloquially as saw palmetto. The different extracts are mainly comprised of free and esterified fatty acids, phytosterols, long chain alcohols, cycloartenol, lupeol, upenone and methylcycloartenol. However, since the extraction procedures differ and the origin of the plant differs, individual extracts differ in their final composition.

A study was performed aiming at fully quantifying the variations in commercially available Serenoa repens extracts [204]To this end, 14 brands of Serenoa repens were compared in terms of concentrations of free fatty acids, methyl and ethyl esters, long-chain esters and glycerides. The analysis revealed marked differences between brands despite their common origin. The mean proportion of free fatty acids ranged from 80.7% in one product to 40.7% in another analysed product. Methyl and ethyl ester content ranged from 16.7% to 1.5%, while long chain ester content ranged from 1.36% to 0.7%. The disparity between the extracts indicates that any clinical benefits derived may vary between products.

The most rigorously investigated plant extract to date is a lipido-sterolic extract of Serenoa repens composed of various compounds and commercialized worldwide under the trademark Permixon.

2. MECHANISM OF ACTION

The possible mechanisms of action attributed to the extract of Serenoa repens have been suggested to fall into three main categories [205].

- Anti-androgenic activity
- Anti-proliferative activity
- Anti-inflammatory activity
2. CLINICAL STUDIES

a) Placebo controlled trials

Clinical studies performed with Permixon have suggested clinical efficacy for the lipido-sterolic extract of Serenoa repens, with improvements in symptoms and urinary flow rate[206]. Overall, in placebo-controlled trials, mean reduction from baseline in urinary frequency at night ranged from 33 to 74% with the extracts of Serenoa repens compared to 13 to 39% with placebo; corresponding day-time reductions ranged from 11 to 43% and from 1 to 29%. Mean increase from baseline in maximum urinary flow rate ranged from 26 to 50% with Serenoa repens extracts versus 2 to 35% with placebo. Six of the seven studies performed between 1983 and 1995 with a Serenoa repens extract show superiority over placebo[207, 208, 209,210, 211, 212].

On the other hand in a trial published by Reece Smith, no significant difference in any parameter between a group of patients (n=33) who had taken a Serenoa repens extract for three months and a placebo group (n=37) was found. However the number of patients included in both arm was very small[208].

Most of these studies were carried out some time ago and were often not performed in accordance with modern guidelines.

b) Meta Analyses of clinical trials

Boyle undertook a meta-analysis [213]of thirteen studies of Permixon: 7 placebo-controlled studies, 4 comparator studies and 2 large, open label studies, involving 2857 men. No uniform symptom assessment was used in those studies, so only data on Qmax and nocturia were assessable. In all these trials, the average placebo effect was associated with an increase in maximum urinary flow rate of 0.5 ml/s. The estimated effect of the Serenoa repens extract was a further increase of 2.2 ml/s. The placebo effect was associated with a reduction in the mean number of night time urinations of 0.69 and the effect of the product, a further 0.5 urinations over and above this.

In addition to these 13 studies, another 4 trials were recently available for an update of the meta-analysis, including 4,820 men[214].The additional data allowed the examination of the effect of Permixon on I-PSS and revealed that, in addition to improving maximum flow rate (2.28 ml/s above placebo) and nocturia (1.0 above placebo), the drug caused a significant fall in I-PSS (-4.7). Permixon in this analysis produced similar effects to those described in equivalent meta-analyses for terazosin[215]and finasteride[216]. Those results have been confirmed in a recent meta-analysis published by the Cochrane Library including a total of 21 randomized controlled trials lasting 4 to 48 weeks and involving 3139 patients [217]. 18 trials were double-blinded and treatment allocation concealment was adequate in 11 studies. Compared with placebo, Serenoa repens improved urinary symptom scores, symptoms and flow measures. The weighted mean difference (WMD) for the urinary symptom score was −1.41 points. The WMD for nocturia was −0.76 times per night and 1.86 ml/s for maximum urinary flow rate. The authors suggested that Serenoa repens provides mild to moderate improvement in urinary symptoms and flow measures. However, this meta-analysis is of limited value since Saw Palmetto products from 11 different manufacturers were used in these trials and some included mixtures of various phytotherapeutic preperations.

c) Comparative Studies

In a comparative 6-month double-blind study conducted on 1,098 men, Serenoa repens (Permixon) 160mg twice daily showed equivalent efficacy to finasteride 5 mg once daily in the treatment of men with mild or moderate LUTS [218]. At the end of the study mean total I-PSS had decreased by 37% in the Permixon group and 39% in the finasteride group. In addition to improvement in symptom scores, patient self-rated Quality of Life score improved in 69% of Permixon recipients and 73% of finasteride recipients. Both treatments were associated with an improved maximum urinary flow rate. Results of a questionnaire on sexual function demonstrated that it was modestly improved among men receiving Permixon compared to deterioration in those treated with finasteride.

A recent one year double-blind, randomized study compared the efficacy and tolerability of Permixon 320mg/day and tamsulosin 0.4mg/day (the PERMAL study) [219]. Conducted in 11 European countries this. 704 patients were randomized to treatment : 350 to Permixon and 354 to tamsulosin.

After one year of treatment, analysis of the primary efficacy variable, the mean change from baseline in I-PSS total score, showed no statistically significant difference between the two groups : a decrease of −4.4 points. At week 6, the decrease in symptoms was slightly greater in the tamsulosin group than in the Permixon group but this difference was not statistically significant (p=0.09). Full activity was
achieved for tamsulosin at 3 months and maintained until the final visit. For Permixon, continuous improvements were observed throughout the duration of the study. No differences were observed between the treatment groups at 12 months in terms of storage symptoms, -1.7 and -1.5 and voiding symptoms, -2.8 and -2.9 for Permixon and tamsulosin respectively.

d) Tolerability
Data from clinical trials in men with BPO receiving Permixon 320mg / day indicate that this drug is well tolerated by most patients [206]. Overall, 3% and 2% of patients, respectively reported adverse events in two large non-comparative trials of 592 and 500 men receiving the drug for 3 months [220,221]. All complaints, which were spontaneously reported, were minor gastrointestinal problems such as nausea, and resolved when Permixon was taken with meals. None of the patients had to discontinue therapy because of adverse events. Similar results were demonstrated in a 1-month placebo controlled study of 176 patients [212].

e) Conclusion
The Permixon extract of Serenoa repens, which has been extensively studied in the field of BPO, has been suggested to have superior efficacy against placebo and equal efficacy to finasteride and tamsulosin.

Unfortunately there is a lack of modern well powered placebo controlled studies and its principal mode of action still remains to be established. Since not all brands of Serenoa repens are equal, the differences, in terms of final composition and activity, prevent a direct comparison of the various phytotherapeutic preparations even though they originate from the same plant.

III. PYGEUM AFRICANUM

1. ORIGIN, SUGGESTED MECHANISMS OF ACTION
An extract of the african plum tree, Pygeum africanum, is mainly used in France (Tadenan®), but also in the US where it is sold as a dietary supplement. The chloroform extract contains phytosterols, short- (lauric and myristic) and unsaturated long chain (oleic and linoleic) fatty acids. In vitro data suggest that the extract with the trade name Tadenan® is thought to exert an inhibitory effect on b-FGF and EGF-induced prostate fibroblastic proliferation and displays anti-inflammatory activities by inhibition of the production of chemotactic leucotries and other 5-lipoxygenase metabolites and may have a protective effect on the cellular membrane: also suggested to be one of the main potential mechanisms of action for Pygeum africanum. [222], Experimental studies by Choo [223,224] and Constantinou [225,226] described that the plant extract selectively reduces DHT-stimulated prostate growth.

2. CLINICAL STUDIES
The clinical effects of the Pygeum africanum extract (Tadenan®), suggesting efficacy, were demonstrated in placebo-controlled [227-231] and in open studies [232, 233] using both subjective and objective assessment criteria.

However, these studies were performed years ago and do not meet the strict guidelines recommended by the International Consultation Conferences. A review has been presented by this committee during the previous conference in 1997 [222]. No placebo-controlled studies with Tadenan® have been published since the last Consultation Conference. Some new data from uncontrolled studies are available [234-238]. The recent trials lack a placebo group and thus do not meet the strict guidelines recommended by the International Consultation Conferences.

3. COMPARATIVE TRIALS
In 1996, Abbou [239] reported the results of a randomized trial comparing Alfuzosin to an extract from Pygeum africanum: 331 patients completed the 8 week study. Alfuzosin was more effective than Pygeum africanum with regard to maximum flow rate, decrease of residual urine and improvement of storage symptom score .

4. META-ANALYSIS
A systematic review and quantitative meta-analysis has been performed on the studies of the therapeutic efficacy and tolerability of Pygeum africanum in men with symptomatic BPO; where it was used either alone or in combination with other phytotherapeutic agents, with a control group who received placebo or other pharmacological therapy, and where the treatment duration was at least 30 days.

Compared with placebo in 6 studies, P. africanum provided a moderate improvement in urological symptoms and flow rate. Nocturia was reduced by
19% and residual urine volume by 24%; maximum urine flow was increased by 23%. Adverse effects due to P. africanum were mild and similar to placebo. The overall dropout rate was 12% and was similar for P. africanum (13%), placebo (11%), and other controls (8%; P = 0.4 versus placebo and P = 0.5 versus other controls) [240].

However, the literature on P. africanum for the treatment of BPO is limited by the short duration of studies and the variability in study design, the type of phytotherapeutic preparation, and the nature of reported outcomes. Further research is needed using standardized preparations of P. africanum to determine its long-term effectiveness and ability to prevent complications associated with BPO.

1. ORIGIN, SUGGESTED MECHANISM OF ACTION

Although β-sitosterol and other phytosterols are contained in most plant extracts used for the treatment of LUTS/BPO, some manufacturers suggest that β-sitosterol is the major active component and therefore specify their preparation by a high (main) content of the β-sitosterol fraction. Most of these preparations derive from the species Hypoxis rooperi (South African Star Grass), Pinus (pine) or Picea (spruce).

β-sitosterol has been suggested to have an inhibitory effect on cyclo-oxygenase and lipoxygenase, interfering with prostaglandin metabolism and thereby exerting anti-inflammatory effects. A stimulating effect on transforming growth factor (TGF-β) as an apoptosis inducer is also reported [241-246]. However, whether these effects play a relevant role in BPO remains uncertain.

2. CLINICAL STUDIES

Most of the earlier studies were open or retrospective [247].

A study, with a phytosterol preparation (Harzol® that contains mainly beta-sitosterol and smaller amounts of sitosterol, campesterol, stigmasterol and several other sterols) extracted from the plants Hypoxis rooperi, Pinus or Picea showed a positive effect which was, superior to placebo [242,248]. The improvement observed in the treatment group, compared to the placebo group, was statistically significant for the modified Boyarski Score, IPSS, QoL score, flow maximum rate and residual urine. Berges et al recently published the results of an 18-month follow-up of that study [243] and reported that the patients who continued taking Harzol® maintained "their benefit".

The beneficial effect of another preparation (Azuprostat®), which also mainly contains β-sitosterol has been evaluated in another study [249-251]. The origin of the product is not mentioned by the company. After 6 months of therapy with Azuprostat® (65 mg phytosterol bid), there was a significantly greater improvement detected in the treatment group compared to the placebo group for IPSS (5.4 points), QoL Score (0.9 points) maximum flow rate (4.5 ml/sec) and decrease of residual urine (33.5 ml). Side effects were minimal in both studies. The results of both studies with phytosterols, as the suggested main active component, are interesting but await confirmation by other authors.

3. METAANALYSIS

In 1999, Wilt T et al, reported a review on four double blind trials comprising a total of 519 men. Three studies used nonglucosidic beta-sitosterols and one used a preparation that contained only beta-sitosterol-beta-d-glucoside. He concluded that these trials were limited by short treatment duration and lack of standardized beta-sitosterol preparations. Their long-term effectiveness, safety and ability to prevent the complications of BPO are unknown [252].

V. URTICA DIOICA
(STINGING NETTLE)

1. ORIGIN, SUGGESTED MECHANISM OF ACTION

Extracts from the roots of the stinging nettle (Urtica dioica) have been widely used in Germany. There are 16 different preparations.

The roots of the stinging nettle contain a complex mixture of water- and alcohol-soluble compounds including lectins, phenols, sterols and lignans. Extraction procedures vary from company to company using methanol, ethanol or exhaustive percolation with hot water. Numerous potential pharmacological mechanisms have been suggested [253-257]. Hirano et al. [253] suggested suppression of prostatic cell metabolism and growth by inhibition of membrane Na+,K+ -ATPase and Hryb [254] postulated that the binding of SHGB to its receptor on prostatic membranes might be modulated.
2. CLINICAL STUDIES
The data of two double blind placebo-controlled studies performed more than 10 years ago are inconclusive because of low patient numbers and only 8 and 9 weeks trial duration [258,259].

VI. POLLEN EXTRACT

1. ORIGIN, SUGGESTED MECHANISM OF ACTION
The pollen extract “Cernilton®” is prepared from a few plants growing in Southern Sweden and is available as a registered pharmaceutical in some European countries (Switzerland, Austria, Germany, Spain, Greece), Japan, Korea and Argentina. [260,261]

The preparation is obtained by microbial digestion of pollen followed by extraction with water and an organic solvent. The total extract consists of a water-soluble and a fat –soluble fraction. Studies to discover the mechanisms of action suggested several possible effects.

2. CLINICAL STUDIES
No additional randomized placebo-controlled studies have been reported since the last International Consultation when the conclusion reached was that the Cernilton® trials analyzed were limited by short duration, limited number of enrollees, gaps in reported outcomes, and unknown quality of the preparations.

VII. PUMPKIN SEEDS (CUCURBITAE PEPONIS SEMEN)
The seeds of pumpkin contain a sweet tasting oily substance, mainly composed of linolic acid, delta-5 – and delta-7-sterols, tocopherol, selen, magnesium and carotinoids. The extract is suggested to have an antiandrogenic and antiphlogistic mechanism of action [262].

A published randomized, placebo-controlled double-blind trial of 476 patients, of 12 months duration showed a significantly greater reduction of IPSS (6.8) compared to the placebo group (-5.6) while the other parameters (Qmax,QoL,Pvol,PVR) did not change in either of the groups [263].

VIII. CACTUS FLOWER EXTRACTS (OPUNTIA)
Aqueous and organic solvent extracts of dried cactus flower powder have been described to have a broad spectrum of activity, including inhibition of both Type I (foreskin fibroblast) and Type II (human prostate hyperplastic cells) 5α-reductase activity, inhibition of aromatase and antioxidant activity. The authors postulate that, as cactus flower has simultaneous 5α-reductase and aromatase inhibitory activity, [264].

There are no reports of any controlled clinical trials with cactus flower products.

E. SYNTHETIC POLYENES

I. MEPARTRICIN

1. SOURCE AND SUGGESTED MECHANISMS OF ACTION
Mepartricin, marketed in several countries under the trade name Ipertrofan or Iperplasin, is not a plant extract but a semisynthetic polyene substance isolated from a streptomyces strain. The final preparation is a mixture of closely related identified polyenic structures. In the doses used, it is not absorbed after oral administration and is well tolerated. Mepartricin reportedly acts by interrupting the enterohepatic circulation of oestrogens. Mepartricin binds to oestrogens in the intestine, inhibits their re-absorption, thus decreases the blood oestrogen concentration and thereby diminishes oestrogen-induced growth stimulation of the prostate [265-268]. Mepartricin, dose dependently, inhibited the estradiol-induced increase of prostate weight, of hydroxyproline content and of the activity of growth factors in its soluble fraction [269-271]. The androgen receptors, too, were significantly reduced, although with a non linear dose-response relationship.

In a controlled study in LUT/BPO-patients, treated for 30 days, a highly significant decrease of serum concentration of estrone, estradiol and estriol has been reported [272].

2. CLINICAL STUDIES
Short term open label studies have suggested clinical efficacy for mepartricin. The results of a multicentre
double-blind randomized, placebo-controlled trial were published by Denis et al.[273-275]. 98 patients were included in each group, follow-up was 6 months. There was evidence of a more rapid and significant (p=0.006) decline in the mean IPSS of patients treated with Mepartricin than in controls. The mean increase in maximum flow rate (ml/sec) of treated patients relative to controls and determined at 6-months, showed a significantly different (p=0.053) linear trend between the groups.

Whilst a review of the results of 23 clinical studies performed with mepartricin was published by Boehm et al. [276], suggesting clinical efficacy and good tolerability for mepartricins; this needs to be confirmed by adequately powered, longer term placebo controlled studies.

F. NEW MEDICAL DEVELOPMENTS IN THE MANAGEMENT OF LUTS IN ADULT MEN

LUTS and in particular, those of OAB, increase in prevalence with increasing age amongst both men and women. (Figures 6-10).

Weak stream, incomplete emptying, show an age-related increase in prevalence among men, but not among women. LUTS occur with high prevalence in the background population, but they do not always cause trouble.

I. OVERACTIVE BLADDER

1. INTRODUCTION AND ASSESSMENT OF PATIENTS

BPO is one of the most common diseases of aging men, interfering with normal daily activities and sleep patterns [277]. Voiding symptoms (such as slow stream, intermittency, hesitancy, straining or terminal dribbling) and post-micturition symptoms (feeling of incomplete emptying and post-micturition dribble) are classically related to BPO, although are not associated with obstruction [278,279]. A percentage of patients as high as 50% can experience however, storage symptoms [280] which significantly bother patients, their quality of life.

There is clearly detrusor dysfunction manifest as storage symptoms are seen in patients with BOO. There is clearly a disparity between the accepted norms for the appropriate assessment of patients with voiding and storage symptoms. The existing literature base in the field of LUTS/BPO has relied on the use of the IPSS and flow rates and post-void residuals. In contrast in the assessment of OAB, other measures such as frequency volume charts are commonly used. Clearly the appropriate assessment of patients must incorporate a combination of both sets of measures.

RECOMMENDATIONS

• Lower urinary tract symptoms relating to voiding (LUTS) are not disease specific and hence diagnostic of BPO or BOO.

• Appropriate assessment of the symptomatic patient relies upon comprehensive evaluation.

• A major problem in the contemporaneous literature is the absence of an adequate internationally accepted and applied definition for ‘BPH’

• When evaluating therapy we need to:-
  • Identify and standardise robust outcome measures pertinent to the condition - LUTS, OAB, BPO, BOO....
  • With reference to what is most bothersome to patients

Level 1 Grade A

• The management of OAB component of LUTS in men is of potential interest.

• We would recommend that specific measures developed for the assessment of OAB should be applied to this disease area.

• The IPSS has only 3/7 questions dealing with storage symptoms – one documents nocturia

Level 1 Grade B

2. MATERIALS AND METHODS

Our aim was to review the available evidence concerning the use of anticholinergic drugs, alone or in combination with alpha-blockers, in the patients with LUTS due to BPH/BPE/BPO and concomitant overactive bladder syndrome (OABS). The review of the literature was performed using MEDLINE through a
Figures 6-10
complex search strategy including both “free text” and “MeSH” (Medical Subject Heading) protocols. Specifically, the MeSH search was conducted with the use of the following terms retrieved from the MeSH browser provided by MEDLINE at www.pubmed.org: “Prostatic Hyperplasia”, “Adrenergic alpha-Antagonists”, “Cholinergic Antagonists”. Multiple “free text” searches were performed applying singularly the following terms through all the fields of the records: “Antimus*”, “Oxybutynin”, “Tolterodine”, “Propiverine”, “Trospium”, “Emepronium”, “Propantheline”, “Darifenacin”, and “Solifenacin”. Subsequently, the following search limits were employed: Humans, gender (Male).

Nineteen records were selected from the MEDLINE search and the authors reviewed their abstracts. They agreed on the selection of six papers concerning the topic of the review. Moreover, the Cochrane database of systematic review was browsed for records regarding BPH and the abstract books of both AUA and EAU annual meetings from 2000 to 2004 were hand-searched for studies concerning the topic of the review. In addition, other significant studies cited in the reference lists of the selected papers were considered.

All the papers were defined according to the grade of evidence as stated by Phillips and Sackett [281]. Meta-analyses of randomized clinical trials (RCTs) constitutes the highest evidence (level 1), followed by an adequately sampled single randomized clinical trial (level 1) and observational studies (level 2). Lower grade of evidence was provided by surgical series (level 4). Among the selected papers, there was only one published RCT. All the other studies were prospective series, reviews or congress abstracts.

3. RESULTS

Two-hundred twenty-one patients were randomized (2 to 1) to tolterodine 2 mg twice daily for 3 months (149 patients) or placebo (72 patients) [282, 283]. There were no significantly differences in the changes of both Qmax (-0.7 ml/sec) and PdetQmax (-7 cm H2O) due to tolterodine but the antimuscarinic drug caused a statistically significant increase in the post-void residual urine volume (+25 ml), compared to placebo. However, this finding had limited clinical significance. Similarly, only two patients (one in each arm) experienced acute urinary retention [282,283]. This study, although underpowered might suggest that anticholinergic drugs can be safely used in patients with BOO without causing urinary retention. This study did not suggest any significant beneficial clinical effect on patients’ symptoms, although it was designed only as a safety study.

In another randomized clinical trial performed by Athanasopoulos et al [284], after a seven-day run-in period with tamsulosin therapy, the authors randomized 50 patients with urodynamically proven mild to moderate BOO (according to Schafer’s nomogram) and concomitant detrusor overactivity to either single drug therapy with tamsulosin (0.4 mg once a day) or a combination of tamsulosin (same dosage) and tolterodine (2 mg twice a day). After 3 months of therapy, the patients were evaluated through a quality of life score (the Greek version of the Urolife “BPH” quality of life 9 questionnaire) and a urodynamic study. The clinical characteristics of the patients in the two arms were overlapping. In both groups, similar improvements in the maximum flow rate and volume at the first detrusor contraction were shown. Only the combination therapy arm demonstrated a statistically significant reduction in maximum detrusor pressure during micturition and maximum pressure of the detrusor contraction during the filling phase of the pressure-flow study. No data, however, was reported on the effect on storage symptoms, but, quality of life scores in 6 out of 9 domains were significantly better in the combination therapy group. Tolterodine did not appear to increase the post-void residual urine. and no acute urinary retention was reported, however, two patients stopped anticholinergic because of xerostomia and two other ones (one in each arm) stopped alpha-blockers because of orthostatic hypotension [284].

In 2004 Lee et al [285] published a prospective study where a combination therapy with doxazosin and tolterodine was used in 60 patients with LUTS who had not improved after doxazosin monotherapy [285]. All the patients had undergone a pressure-flow study, which had shown the presence of detrusor overactivity in 44 of them. Six of the 16 (37.5%) patients without detrusor overactivity and 24 out 68 (35%) of those with detrusor overactivity showed significant improvement in the IPSS after combination therapy. On the other hand, the use of tolterodine was associated with xerostomia in 16 patients (27%) but only in 2 of them this side-effect was so severe to discontinue the drug. Similarly, tolterodine therapy was stopped in 2 patients because of acute urinary retention (3.3%) [285].

A cohort of 43 men who had previously failed alpha blocker therapy and where subsequently treated with tolterodine extended-release (4 mg once a day) for 6 months has been reported [286]. Comparing baseline and 6-month data, the authors found statistically sig-
nificant reductions in daytime (from 9.8 to 6.3 per
day) and nighttime frequency (from 4.9 to 2.9 per
night), with AUA symptom index decreasing from
17.3 to 11.2. Moreover, Qmax increased from 9.8 to
11.7 ml/sec, while post-void residual urine decreased
from 97 to 75 ml.

In a multicentre study, Okada et al [287] assessed the
impact of propiverine on both storage and voiding
symptoms in 35 patients non-responsive to alpha
blockade. The authors showed significant decreases
in IPSS values (from 20.4 to 15.8, p<0.05), due to
better scores to the IPSS questions 2, 4, and 7 (those
assessing storage symptoms). Furthermore a higher
Qmax and voided volume resulted as did a more
favourable quality of life score [287].

Table summarizes the figures from the retrieved
studies (Table 13).

4. DISCUSSION

Although the presence of storage symptoms is
extremely common in patients with BOO only a few
published papers specifically addressed this issue.
Only a single randomized controlled trial has been
published [284], while the other retrieved studies
were prospective series [285], reviews, or congress
abstracts [282,283,286,287].

The randomised study published by Athanasopoulos
et al. [284] although underpowered suggest that
anticholinergic therapy can be safely used in the
patients with BOO and detrusor overactivity. How-
ever, the study has to be criticised on a number of
counts; small sample size with only 25 patients treat-
ed in each arm; short study follow-up period and lim-
ited follow-up data. The randomization criteria were
not described and it was unblinded; also there was a
lack of a third arm with tolterodine mono-therapy.
Although a statistically significant advantage was
demonstrated in the combination therapy arm, it was
clearly shown that allocation bias and the absence of
blinding could overestimate the efficacy of a treat-
ment by up to 40% [288]. Hence, according to Jadad,
who reported a score to assess the quality of RCTs
based on their methodological design, that RCT has
to be considered a low quality study (score=0) [289].

According to the Evidence-based Medicine criteria,
a low-quality RCT provided only a level 2b of evi-
dence and grades “B” of recommendation [281].
Furthermore, the studies reported by Lee, Kaplan,
and Okada [285-287] are all prospective case-series
(level 4 of evidence and grades “C” of recommenda-
tion) [281].

It has been postulated that the safe use of antimus-
carinic drugs is due to these drugs mainly acting by
decreasing urgency and increasing bladder capacity
during the storage phase, when there is no activity in
the efferent parasimpatic nerves. Hence, it has been
hypothesized that these drugs act on the afferent
nerves which initiate the micturition reflex, by the
slow tonic release of acetylcholine from afferent
nerves or, maybe, from the urothelium [290]. More-
ever, being competitive antagonists, the action of
these drugs may be reduced during the voiding
phase, when there is a massive release of acetyl-
choline [291].

To date, both AUA and EAU guidelines on “BPH”
[277,292] do not consider this category of drugs in

Table 13. Summary of the data on the effect of the antimuscarinic drugs in male patients with LUTS/ BPO.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Cases</th>
<th>Study design</th>
<th>Duration (months)</th>
<th>IPSS</th>
<th>Qmax (ml/sec)</th>
<th>Pdet(Qmax) (cmH₂O)</th>
<th>PVR (ml)</th>
<th>Inc. AUR</th>
<th>Q of L score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrams [282,283]</td>
<td>221</td>
<td>To vs P</td>
<td>3</td>
<td>NA</td>
<td>-0.7</td>
<td>-7</td>
<td>+25</td>
<td>0.6%</td>
<td>NA</td>
</tr>
<tr>
<td>Athanasopoulos  [284]</td>
<td>50</td>
<td>Ta vs Tα+To</td>
<td>3</td>
<td>NA</td>
<td>+1.2</td>
<td>-8</td>
<td>-4.2</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Lee [285]</td>
<td>60</td>
<td>Do + Tα</td>
<td>3</td>
<td>-23 points in 63%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3.3%</td>
<td>NA</td>
</tr>
<tr>
<td>Kaplan [286]</td>
<td>43</td>
<td>Pro + Tα-block</td>
<td>6</td>
<td>-6</td>
<td>+1.9</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Okada [287]</td>
<td>35</td>
<td>To</td>
<td>3</td>
<td>-4.6</td>
<td>+0.8</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

To: Tolterodine; Ta: Tamsulosin; Do: Doxazosin; Pro: Propiverine; P: Placebo; α-block.: α-blockers; PVR: post-void residual urine; Inc. AUR: Incidence of acute urine retention increased; Q of L score: quality of life score; NA : not assessed; NS : not statistically significant.
the management of the patients with LUTS due to BPO. The NHMRC guidelines on the management of uncomplicated lower urinary tract symptoms in men [293,294] suggest that men with predominantly storage symptoms who request pharmacological intervention could be offered a trial of an anticholinergic agent. However, this suggestion is based solely on expert opinion.

The limited data available highlights the need to plan larger and better designed RCTs with the intent to appropriately assess long-term safety and efficacy of either monotherapy with antimuscarinics or combination therapy with alpha blockers.

5. RECOMMENDATIONS

BPO is one of the most common diseases of aging men, interfering both directly on normal activities of daily living and indirectly via an effect on sleep patterns. Although voiding and post-micturition symptoms are classically associated with BPO; it must be remembered that as many as 50% of patients experience significant storage symptoms and these are often the most bothersome to them, producing significant impairment of quality of life.

We recommend further evaluation of the potential for an empirical approach to the initial treatment of male OAB symptoms. This approach would rely on careful assessment of storage symptoms, a physical examination, and urinalysis.

- If BPO is suspected based on symptom assessment or uroflowmetry, an α1-receptor antagonist would be prescribed as first line therapy.
- In men with enlarged prostates, use of a 5α-reductase inhibitor may also be appropriate.
- Addition of an antimuscarinic would be considered for patients with a normal urinalysis and no PVR of note whose symptoms do not respond sufficiently to either therapy.
- Preliminary data suggests that when used alone or in combination with α1-receptor antagonists, antimuscarinic agents relieve male storage symptoms without increasing the risk for urinary retention in patients with comorbid BPO.

- At present, it must be concluded that the existing literature is based on pilot studies using urodynamic criteria for patient selection that do not necessarily represent real life practice. On the whole these studies are not placebo-controlled and/or not adequately powered.

Combination therapy with an anticholinergic and an α1-receptor antagonist in men with OAB and with suspected BPO is an interesting potential direction in pharmacotherapy that requires testing in well-designed clinical trials before it can be recommended for routine clinical use.

- OAB symptoms are more bothersome than voiding LUTS in men and may occur in the presence or absence of BPO.
- The treatment of OAB in the absence of BPO should be as suggested by the 3rd ICI Level 1 Grade A
- The management of OAB occurring in the presence of BPO is the subject of ongoing research
- Antimuscarinic therapy as solo therapy can not be recommended for routine use Level 2 Grade B
- Combination therapy of an antimuscarinic and alpha blocker may be efficacious Level 2 Grade B

II. NOCTURIA

1. INTRODUCTION

Nocturia is a very common problem among elderly men and often a reason for urological consultation [295]. Nocturia has been poorly studied and, has only recently been classified according to its aetiology and pathogenesis. Nocturia may be attributed to nocturnal polyuria (nocturnal urine overproduction), diminished nocturnal bladder capacity, or a combination of the two. Multiple factors may result in nocturia, among which are pathological conditions such as cardiovascular disease, diabetes mellitus, lower urinary tract obstruction, anxiety or primary sleep disorders, and behavioural and environmental factors.

Distinction between these conditions is made by a simple arithmetic analysis of the 24-hour voiding diary.
Based on a review of the current state of knowledge, this article presents a scheme for the classification and treatment of patients suffering from loss of sleep resulting from nocturnal micturition is presented [296].

With the increase in the mean age of the general population, the number of individuals with LUTS and in particular nocturia, is likely to increase and must be considered when resources are allocated for medical care [297,298].

2. DEFINITION, EPIDEMIOLOGY, AND QOL IN NOCTURIA

The storage symptom of nocturia is defined as the complaint that the individual has to wake at night one or more times to void, each void being preceded and followed by sleep [299]. Nocturia is a very common problem among elderly men and is often a reason for urological consultation [300,295]. The prevalence of nocturia is positively correlated with age, and is higher in men than in women in the age group of 60 years or older [301]. According to a health survey data of 1247 women (age 49.8 +/- 13.5 years) and 1221 men (age 48.5 +/- 11.9 years), the percentage of individuals with nocturia of two or more times increased constantly with age: less than 30 years, 3.1% of women and 3.4% of men; 30 to 59 years, 7.2% of women and 5.7% of men; and 60 years old or older, 26.7% of women and 32.4% of men. Nocturia is almost equally present in both sexes, and the incidence and severity increase constantly from early adolescence to senescence. Approximately 10% of the general population (older than 20 years) have nocturia of two or more times, which impairs the quality of life in two thirds [302].

Voiding symptoms were almost identical in both sexes until the 5th decade, thereafter they increase significantly in men but not in women. ‘Urgency’ and ‘frequency’ are more bothersome to older individuals, but ‘nocturia’ and voiding symptoms were almost equally bothersome to younger and older participants (303,304).

In an otherwise healthy and professionally active group of individuals, waking at night to void significantly diminishes their overall well-being, vitality and productivity, leading to a significant level of indirect and intangible costs [305]. Impairment of both somatic and mental health is associated with increased nocturnal voiding. Sick-leave is more common in association with more nocturnal voids [306].

3. THE MULTIFACTORIAL AETIOLOGY OF NOCTURIA (Figure 11)

There are several common causes of nocturia which may exist singly or in combination. The circadian pattern of urine production is maintained in healthy people until the age of 60 years, after which a greater proportion of 24-h urine production occurs at night [307]. This shift in the relative proportions of urine produced during the day and night-time does not affect the total volume of urine produced over a 24-h period [308,309]. Nocturia may be due to the 24 hour overproduction of urine (polyuria) or to the nocturnal overproduction of urine (nocturnal polyuria). Decreased nocturnal voided volumes have 2 common causes: the presence of residual urine, or a decrease in bladder capacity due to involuntary detrusor contractions characteristic of detrusor overactivity. There was no correlation between the number of nocturnal voids and known and treated hypertension, angina pectoris, congestive heart failure or diabetes mellitus. The number of nocturnal voids is highly correlated with both urgency and incontinence indicating detrusor overactivity as a causative factor [310]. Since nocturia is clearly associated with a number of factors; multiple approaches are needed to the treatment of patients with nocturia [311].

![Figure 11](image-url)

**Figure 11**

a) Polyuria

Polyuria is defined by the ICS as the measured production of more than 2.8 litres of urine in 24 hours in a 70-kg adult [299]. This is based on the upper limit of urine production being 40 ml per kg bodyweight.
per 24 hours. The commonest cause is habitual excessive fluid intake, rather than for any medical reason. However, an increased total urine production can be due to disease: a common cause of polyuria is diabetes mellitus, which may give rise to a glucose-induced osmotic diuresis [312]. In the much rarer disease, diabetes insipidus, the kidney either fails to respond to the presence of arginine vasopressin (AVP), or else the secretion of AVP may be impaired [25]; consequently large amounts of urine are secreted.

b) Nocturnal polyuria

Nocturnal polyuria has been defined as night-time production of urine that is either 33% of the total 24-h urine volume [314,315] or >0.9 ml/min, with an age dependant relationship [316].

The hormone AVP is responsible for regulating urine production. In healthy adults, the release of AVP into the circulation follows a diurnal pattern, with peak blood concentrations occurring during the hours of sleep [317,318]. The rhythm appears to be linked to the wake-sleep cycle rather than to the time of day [317] and is established during childhood. With advancing age, the nocturnal secretion of AVP becomes blunted, resulting in similar day-night time blood levels of AVP [319] and hence to an increase in night-time urine production. Another hormone that is likely to play a role in the altered renal sodium handling of elderly people is atrial natriuretic hormone (ANH).

The action of ANH on the kidney, leads to natriuresis and diuresis, (blood ANH levels increases with age [320].

It is evident that an increase in night-time urine excretion, causing individual to rise and void, is part of the normal ageing process. Nocturnal polyuria is believed to be account for at least 50-65% of cases of nocturia [307,309].

c) Reduced bladder capacity

In older men BPO commonly coexists with detrusor overactivity resulting in reduced voided volumes and increased micturition frequency due to a significant PVR [321]. An increase in the frequency of nocturnal micturition is also as well-established symptom of LUTS suggestive of BPO for the same reason [322]. Indeed, LUTS/BPO is considered as an independent risk factor for nocturia [323].

Homma et al. [324] suggested that not only BOO, but also independent age-related changes in the urinary tract may contribute to nocturia in older men [324]. However, nocturia correlates significantly with LUTS and BPO [325]. Indeed, Yoshimura et al. reported in their study that 71% of the men who were diagnosed with LUTS and BPO had at least two nocturnal voids, which is much higher than community-based studies where a much lower prevalence of nocturia (>=2) of 25-45% is reported in older men [325]. Other factors that may be involved in the pathology of detrusor overactivity include activation of muscarinic receptors, patchy denervation of the detrusor, and changes on the central nervous system [326]. A gradual deterioration in the function of the central nervous system may also contribute to bladder dysfunction, particularly bladder hypersensitivity or detrusor overactivity. Neurological disease (for example, Parkinson’s disease), may also cause an increase in urinary frequency and nocturia.

d) Sleep disorder

Nocturia is widely prevalent and increases with age, affecting men and women equally. Incremental increases in the number of voids/night have further negative effects on sleep, symptom bother, and HRQoL [327].

Adequate sleep is a basic requirement for good health. Adults generally require 7 to 8 hours of sleep per night. Sleep deprivation is associated with a decreased ability to perform tasks controlled by the frontal lobe, such as planning, concentration, motor performance, and high-level intellectual skills. Constant poor-quality sleep can also cause excessive daytime sleepiness, depression, and immune function compromise. In addition, continued sleep disruption has been associated with an increased risk for mortality [328].

Older adults with severe sleep-disordered breathing have a greater number of nocturia episodes. Sleep disordered breathing is an important differential diagnosis in the evaluation of older patients with nocturia [329]. Pathological nocturia is common in obstructive sleep apnea-hypopnea syndrome patients. The strongest predictors are age and selected polysomnographic variables reflecting obstructive sleep apnea-hypopnea syndrome severity [330].

Nasal continuous positive airway pressure reduces obstructive sleep apnea and nocturia and improves quality of life of elderly patients [331,332]. The apnea hypopnea index was calculated as the sum of apneas and hypopneas divided by hours of sleep. In subjects with elevated the apnea hypopnea index (>15), nighttime urine production and ANH excretion are elevated [333]. The measurements are usually performed in a sleep laboratory.
e) Depression

Major depression has previously been found to be associated with increased nocturnal micturition. Twice as many men and women treated with SSRIs as those not so treated had two or more nocturnal voids, after adjusting for major depression and age [334].

f) Serum factors, nutrients, smoking, and hypertension

Rohrmann and associates reported that the role of metabolic abnormalities in the aetiology of LUTS including nocturia [335]. They found that greater circulating concentrations of vitamin E, lycopene, and selenium, antioxidant micronutrients that are supported in published reports as protecting against prostate cancer, were observed also to be inversely associated with LUTS. The effect modification of the association with vitamin C by cigarette smoking warrants additional examination [336]. Dietary elements may also have an important role in the development of diseases causing LUTS. Direct effects of food components may likewise influence the occurrence of LUTS including nocturia [337]. Smoking increases the prevalence of LUTS. The similarity in the odds ratios of these symptoms between current and former smokers suggests that changes caused by smoking occur long term or the pathological process resulting in symptoms starts early in smokers. The decreased risk of LUTS after the cessation of smoking suggests that the process is reversible but recovery is a long-term process [338]. Elderly obese men with urgency at night should be questioned about snoring, and that micturition frequency and volume charts should be completed by such men, particularly before deciding to operate [339].

4. DIAGNOSING THE CAUSE OF NOCTURIA:

History-taking, physical examination, and laboratory tests are necessary to exclude polyuria and nocturia resulting from certain diseases, including those associated with oedema (i.e. congestive heart failure and renal disease), reduced renal concentration capacity (i.e. diabetes insipidus and renal insufficiency), and bladder storage symptoms resultant from bacterial cystitis, painful bladder syndrome, bladder calculi or bladder cancer. An accurate diagnosis of nocturia requires careful questioning of the patient, including details of bladder storage and voiding symptoms, which may suggest detrusor overactivity or BOO. Other factors, such as fluid intake, medications, neurological disorders and nocturnal apnoea, may make an accurate diagnosis difficult and must also be examined. The frequency of nocturia is reliably self-reported by patients [52] but in order to reveal the underlying cause, frequent volume charts have been found to be particularly useful in documenting clinical data. Poor agreement between subjectively estimated nocturnal frequency and chart-determined nocturnal frequency has been demonstrated.

Nocturia due to polyuria can be detected by using a FV chart. In these patients, a 3-day FV chart is sufficient to detect nocturia not a polyuric and seems therefore to be a valuable tool in evaluating patients with LUTS referred for potential BPO [314, 342-344].

Nocturia is a result of a mismatch between nocturnal urine volume and largest voided volume, rather than abnormal values of either. The treatment of nocturia should be directed at one or both of these factors, depending on the findings from the 3-day frequency-volume chart of the individual [345].

In a well-defined group of men with LUTS suggestive of BPO, filling cystometric capacities were strongly associated with maximal and mean voided volumes derived from frequency-volume charts. The presence of detrusor overactivity during filling cystometry did not significantly affect voided volumes, or nocturia [346].

Except for nocturia, older men had lower voiding scores on the IPSS. Prostate volume and obstruction grade were not, but low detrusor contractility and low capacities were, associated with the symptom index. The presence of an overactive bladder and/or residual volume was poorly correlated with the symptom index or quality-of-life score [347].

The ICSmaleSF represents a comprehensive, concise, valid and reliable instrument for evaluating men with LUTS. Unlike other questionnaires in the field it contains sub scores for the domains of voiding and incontinent symptoms as well as the separate consideration of frequency, nocturia and impact on daily life. It will become the tool of choice for the comprehensive evaluation of treatment of men with LUTS associated with benign prostatic disease [348].
5. RECOMMENDATIONS FOR TREATING NOCturIA POLYURIA

There are two main therapeutic options for treating nocturnal polyuria: antidiuretic agents (retention of water until a more appropriate time for voiding) and diuretic agents (preventing water accumulation by forcing water out of the system before the early sleeping hours). The 3rd ICI committee also evaluated publications on drugs affecting urine production (349).

LOOP DIURETICS

They found insufficient evidence to allow them to make any recommendations about the use of the loop diuretics, bumetanide and frusemide, in nocturia.

DESMOPRESSIN

Desmopressin is the only analogue of vasopressin (antidiuretic hormone) that is currently available. Desmopressin is an antidiuretic agent, but unlike vasopressin, it does not directly affect the cardiovascular system. The ICI committee highly recommended the use of desmopressin for treating nocturnal polyuria, because there was clear evidence for its efficacy in children with nocturnal enuresis, and in adults (349) with nocturia resulting from nocturnal polyuria. Desmopressin may be associated with an increased risk of developing hyponatraemia and water retention, so care should be taken when desmopressin is used in older patients (over 65 years).

Desmopressin, a synthetic antidiuretic hormone analogue, is the only drug currently approved for the treatment of nocturia associated with nocturnal polyuria or multiple sclerosis (MS). Compared with vasopressin, desmopressin has a longer lasting and more potent antidiuretic effect and is devoid of vasopressor and uterotonic effects. In two large, randomised, double-blind phase III trials in adults with nocturia associated with nocturnal polyuria, 3 weeks of oral desmopressin therapy was significantly more effective than placebo in reducing the mean number of nocturnal voids and in normalizing the rate of nocturnal urine production. Beneficial effects of desmopressin on nocturia were maintained or increased in patients completing 10 or 12 months of further treatment in a non-blind extension of short-term trials. In randomized, double-blind trials in MS patients with nocturia, nasal desmopressin reduced the mean number of nocturnal voiding episodes by 31-54%. In both patient populations, desmopressin increased the initial sleep period or mean maximum period of uninterrupted sleep by approximately 2 hours, an outcome significantly greater than that achieved with placebo. In trials of 6 weeks or less duration in adults with nocturia, desmopressin was generally well tolerated. Most desmopressin-related adverse events were transient and mild or moderate in severity. Clinically significant hyponatraemia was reported in approximately 5% and required withdrawal from studies in 3% or less of patients (350). A long-term study shows that desmopressin is a generally well tolerated and effective treatment for nocturia (351). Desmopressin was well tolerated in elderly patients with nocturia, but the results suggest that serum sodium should be measured before and after a few days of treatment (352). Orally administered desmopressin is an effective and well-tolerated treatment for nocturia in men. Desmopressin is also an effective treatment for nocturnal polyuria in some elderly men. However, it can cause fluid retention and should not be given to patients with cardiac failure. Those undergoing treatment must be closely monitored (353). Desmopressin was effective in reducing nocturnal diuresis and nocturnal voids in polyuric elderly subjects, with no significant adverse events or inconvenience to the patient. The length of uninterrupted sleep was also improved (354).

• New drugs for the treatment of nocturia in men (Table 14)

**Botulinum A toxin** injections into the detrusor have a significant and comparable, but temporally limited, effect in idiopathic and neurogenic detrusor overactivity resistant to anticholinergic treatment (355). Fourteen of 31 patients with refractory (OAB) and nocturia improved with oral gabapentin. Gabapentin was generally well tolerated and can be considered in selective patients when conventional modalities have failed although the evidence base is very limited (356).

**Melatonin** treatment is associated with a significant nocturia response rate, improvement in nocturia related bother, and a good adverse effect profile, in a single study. However, it is uncertain whether the observed changes in this study are clinically significant (357).

**Loxoprofen** can be an effective and useful treatment option for patients with BPO complaining of refractory nocturia. Further placebo-controlled studies are required (358).
Table 14. New drugs for the treatment of nocturia in men

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Patients (Indication)</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioural therapy</td>
<td>Polyuria</td>
<td>Level 3 Grade C</td>
</tr>
<tr>
<td>Phytotherapy (Permixon)</td>
<td>LUTS-related</td>
<td>Level 2 Grade B</td>
</tr>
<tr>
<td>Alpha1-blockers</td>
<td>BPO-related</td>
<td>Level 1 Grade B</td>
</tr>
<tr>
<td>5-alpha reductase inhibitors/combination: (Finasteride and doxazosin)</td>
<td>BPO-related</td>
<td>Level 2 Grade C</td>
</tr>
<tr>
<td>Anti-cholinergics</td>
<td>OAB-related</td>
<td>Level 3 Grade B</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>Nocturnal polyuria</td>
<td>Level 2 Grade A</td>
</tr>
<tr>
<td>Treatments</td>
<td>Patients</td>
<td>Grade of recommendation</td>
</tr>
<tr>
<td>Botulinum A- toxin injection into detrusor</td>
<td>Detrusor overactivity resistant to anti-cholinergics</td>
<td>Level 4 Grade D</td>
</tr>
</tbody>
</table>

Oral Gabapentin                      | Refractory OAB and nocturia | Level 4 Grade D         |
Oral Melatonin                       | LUTS with refractory nocturia | Level 4 Grade D         |
Oral Loxoprofen                      | LUTS with refractory nocturia | Level 4 Grade D         |

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I. Overactive Bladder


II. Nocturia

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Committee 7

New Minimally Invasive and Surgical Developments in the management of BPO

Chairman

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R. Muschter (Germany),
S. Naito (Japan),
N. R. Netto (Brazil)
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REFERENCES
Benign prostatic obstruction (BPO) and its related lower urinary tract symptoms (LUTS) are a common problem that has an impact on daily activity and quality of life. It may lead to serious outcomes, including urinary tract infection (UTI), hematuria, bladder stones, hydronephrosis, renal insufficiency and urinary retention [1]. Transurethral resection of the prostate (TURP) has been the reference standard for the treatment of BPO over the past 30 years, however, the intraoperative and postoperative morbidity of TURP has been the driving force behind the development of several minimally invasive treatments of symptomatic BPO [2-4].

Several minimal invasive treatments (MIT) have reached the surface in the arena of instrumental treatments for BPO. These therapies include the use of different modalities in the minimally invasive approach to overcome BPO. Although the use of electro resection has dominated the surgery of BPO, more recently, different energy sources have challenged TURP. On the one hand microwaves and laser techniques have matured during the past years, whereas needle ablation, stents and injectables are at present under evaluation. Within the coming years it will be decided whether they pass the test of time and are accepted both by the urological community and regulatory authorities.

Figure 1 illustrates that the number of publications on MIT is rapidly increasing, thus reflecting the increased interest and use of these new technologies. The numerous options available use different principles and result in different ablative abilities. In figure 2 the full spectrum of MIT for BPO is presented: an increased ablative power results in an increased relief of BPO. But besides improvement of objective and subjective parameters, a whole range of factors may influence the choice of MIT. The ‘perfect’ MIT option balances in a favourable way the different issues that need to be addressed (see Figure 3).
In this chapter we have reviewed the different instrumental techniques available to treat BPO and we have provided recommendations.

One should, however, keep in mind that ‘new’ by definition implies that there are limited long term data on some of the technologies considered by the committee. Moreover, the power of the data is limited by the number of patients included, as compared to drug studies. Also, durability may be an issue since the committee feels that for making any recommendation one needs at least 3-5 year data.

Together with Open Prostatectomy the by far most common surgical procedure for BPO is Transurethral (Electro-) Resection of the prostate (TURP). Historically this developed from lithotomy and lithotripsy of bladder calculi secondary to bladder outlet obstruction, which has been done since the sixteenth century without any knowledge of the etiology and pathophysiology of the condition, using instruments inserted into the urethra. Development of the early resectoscope depended on many scientific advances, such as the cystoscope, the incandescent lamp, and the vacuum tube which made possible the development of an electrosurgical unit for coagulation and cutting of tissue. Modern transurethral resection is based on improved materials and engineering, fiber optic light sources, rod lens systems, video cameras, and high-tech electro surgery generators. Open prostatectomy was also improved by developments in modern surgery, such as anesthesia, blood transfusion, and antibiotics. To date, open surgical techniques have used the retropubic, perineal and suprapubic transvesical approaches.

Certain complications of BPO are generally considered a definite requirement or absolute indication for surgical intervention. These complications are acute refractory urinary retention, recurrent urinary tract infection, recurrent hematuria, bladder stones, and renal insufficiency secondary to BPO.

Although TURP continues to be the operation most commonly done for benign disease of the prostate and the reference standard for treatments utilized in the management of BPO-related LUTS, the number of TURP’s performed declined by 52% between 1989 and 1995 (Holtgrewe, AUA Health Policy Brief). This decline, which is documented worldwide in several countries, represents the impact of newer medical treatments as well as the availability of less invasive interventional treatments. The morbidity and mortality of TURP, although considered acceptable, still exists. However, TURP achieves excellent clinical results with a low retreatment rate.

TURP is usually referred to as the “Gold Standard” or more recently ‘reference standard’. However, supporting this reputation by data isn’t easy, because most reports on major series of patients were pub-
lished decades ago. In spite of expected improvements because of recent technological and medical progress, there are few more recent publications. And hence little data can be found in the literature detailing minor and early side effects, such as postoperative storage symptoms, long-term results and retreatment rates of larger patient cohorts. It is equally surprising that the technique for TURP is not well standardized (see Figure 1). Several different techniques used to perform the procedure can be found in textbooks. Generally, all have in common that the adenomatous tissue needs to be resected completely down to the capsule. Whether this is always done in reality is a matter for discussion. Furthermore, no experimental or clinical data are available to give evidence that the complete resection of the adenoma is necessary and superior to a somehow standardized incomplete resection. Although it has been known for years that the presence of BPO, or the degree of prostate enlargement, does not correlate to the degree of bladder outlet obstruction and LUTS, it remains unknown why TURP with complete removal of the adenoma works in the majority of patients. Finally, in contrast to the subjective feeling of most urologists judging TURP, even the most recent publications demonstrate a constant relevant overall complication rate and in particular a requirement for blood transfusion in a high percentage, as well as a significant number of unsatisfied patients.

Most clinical data regarding symptom and quality of life improvement, improvement of urinary flow rates (Table 1) and residual urine volumes, and other parameters such as pressure-flow-studies, come from TURP groups in prospective randomized studies comparing so-called minimally-invasive procedure with TURP. Only few of such studies contain long-term results and retreatment rates for longer than 5 years.

Intraoperative complication rates of TURP can also be obtained from such studies, in addition some current publications investigating these complication specifically are also available.

In recent years, several modifications of TURP have been introduced, most of them trying to improve hemostasis (see Figure 2). In this context some studies were performed in which BPO patients were pretreated before TURP with finasteride. Data are available on a limited number of such patients, showing encouraging results.

Open prostatectomy certainly removes more completely all adenomatous tissue and achieves the best clinical results with the lowest retreatment rate; however, it is highly interventional and has a considerable morbidity and mortality. On the other hand TURP in patients with very large glands (i.e., 100 g or larger) can be associated with significant fluid absorption, intraoperative bleeding, and intraoperative and immediate postoperative complications. Therefore, the open procedure is usually reserved for patients with larger glands (i.e., >80 g). The decision whether to do a TURP or open prostatectomy depends on the urologist’s training and surgical skills in resecting larger glands. Open surgery has a proven good effect on obstruction and symptoms with 80% completely asymptomatic [24] and a reoperation rate of 2% within 5 years [25]; however, the transfusion rate is very variable (0.3-100%). Other complications include secondary bleeding in 4%, bladder neck stricture in 5-7%, and retrograde ejaculation in 75%.

Comparative studies of TURP and open adenectomy to prostate volumes >50g (resected weight) showed a shorter hospitalization and lower early complication rate for TURP, but with a higher rate of late complications. No significant differences regarding Qmax and residual urine volume were found [26]. In another study [27] it was reported that improvements in objective and subjective parameters were significantly better in open prostatectomy. In a prospective randomized study [28] 9% of patients of the open prostatectomy group and 15% of the TURP group were dissatisfied with their clinical outcome.

CONCLUSION:

• TURP is the reference instrumental treatment modality

BUT:

• Outcome data on TURP are outdated and scarce

• There is significant variability in clinical outcomes

• There is questionable standardization

• The development of bipolar is still inadequately studied
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Laser prostatectomy as described initially in 1986 was a novel way to treat patients with LUTS, and became popular after 1990 when the side-firing fiber was introduced [29]. Four types of laser have been used for treatment of LUTS secondary to BPO; Neodymium: Yttrium Aluminum Garnet (Nd: YAG), the Holmium: YAG (Ho: YAG), the Potassium Titanyl Phosphate: YAG (KTP: YAG) and the diode laser.

The ideal type of laser light for the treatment of LUTS secondary to BPO is the one that has a high degree of incisional and vaporizing properties allowing clean removal of prostatic tissues, has the ability to coagulate blood vessels in the prostatic fossa, and is not significantly absorbed by fluid. The laser techniques include coagulation, vaporization, resection and dissection depending on the wavelength, power, and type of emission (continuous or pulsed). Currently, many laser procedures use distinctly different surgical techniques and the broad term ‘laser prostatectomy’ is quite ambiguous if the exact technique is not elaborated upon [30].

1. TYPES OF LASER FIBERS

Several types of fiber systems are used in the treatment of BPO including: bare fibers; right-angle fibers, contact tip, and interstitial fibers [31]. A variety of right-angled delivery systems are used in non-contact laser procedures. The laser energy is passed along the laser fiber and then reflected or refracted. Reflective fibers utilize a 6 to 7.5 F gold or gold-plated alloy dish that is glued to the end of the fiber [32]. The Urolase fiber is composed of a bare fiber that ends in an open metal cavity with a prism. This system allows application of laser to certain areas of the prostate for a fixed period of time (30-60 sec). The air refraction fibers include a bare fiber ending in a plastic enclosed cavity in which the laser energy is bent by air refraction and exists through a small aperture in order to decrease the fiber damage by treated tissues. The advantages of this type include higher power density with narrower beam. Also the fiber can be dragged through the entire prostate and allows the choice of coagulation or vaporization treatment [39]. Contact fiber tips are composed of fused silica quartz or synthetic sapphire, which, when placed directly against the prostate, produce intense thermal energy and immediate removal of tissue. Contact fibers have been improved over the years to allow delivery of greater energy and the vaporization of larger amount of tissue. The interstitial fibers have a diffuser tip that is inserted directly into the prostatic tissue causing coagulative necrosis while sparing the urethra from injury.

2. TYPES OF LASERS AND SURGICAL TECHNIQUES

a) Visual laser ablation of the prostate (VLAP)

In 1992, Costello and associates were the first to report using Nd: YAG laser for the treatment of BPO [29]. This procedure utilized a side firing fiber in a non contact mode (see Figure 1). Tissue effects are largely based on the power setting (40 to 60 W in most studies), duration of the treatment (30 to 120 seconds), and the distance between the fiber tip and the prostate. In most series, four quadrant areas of laser treatment (2, 4, 8, and 10 o’clock) are used in patients with prostatic urethral lengths of 2.5 to 4 cm or less [32]. In larger prostates sextant spots were described. In an attempt to avoid retrograde ejaculation Nau et al [33] started the coagulation effect 1 cm distal to the bladder neck with a scanning motion radially or longitudinally. The advantages of the VLAP include simplicity of the procedure and a haemostatic effect, which means it can be used safely in anticoagulated patients [34]. It also carries no risk of dilutional hyponatremia or TUR syndrome [35]. A number of randomized trials comparing VLAP to TURP were reported. In a multicenter study, Cowles et al [36] (level 1 evidence) randomized 115 patients to TURP (n=59) or VLAP (n=56) and found that the operative and hospitalization times were shorter in the VLAP group. The improvement in symptom score was 48% and 64% in the VLAP and TURP arm, respectively. The Qmax

Figure 1. Example of side fire laser treatment
increased by 59.5% and 73.7% in the VLAP and TURP group, respectively. The long-term results were reported to be durable. McAllister et al. [37] reported on 5-year follow-up of patients who underwent VLAP and TURP. The authors found that 8 of 51 patients (16%) in the TURP group required reoperation, compared with 18 of 47 patients (38%) in VLAP. The subjective and objective outcome of VLAP was similar to that of TURP, with the results of both treatments maintained at 5 years. The other reported complications of VLAP include storage symptoms for 1 to 2 months, and urinary retention in up to 30.4% of patients requiring longer catheterization for up to several weeks [36]. Retrograde ejaculation rates varied from 27% to 33%, with loss of potency in 4.3% [36-38]. The EAU does not recommend VLAP as a first line surgical treatment for BPO patients, but indicate that it may have a role in the treatment of a high-risk patient group [39].

b) Contact Nd: YAG Laser Vaporization

In this approach the laser is applied in contact mode using a sapphire contact tip that converts the laser light into heat whereby the high temperature induces vaporization and immediate removal of some tissue. This results in immediate relief of obstruction, early catheter removal, rapid improvement of voiding symptoms and decreases the postoperative retention and storage symptoms. The disadvantages of this approach include the inability to ablate large glands and less effective hemostasis compared with the non-contact approach.

In a randomized trial Keoghane et al. [40] compared the symptom improvement and Qmax in 72 contact laser treated patients and 76 patients who underwent TURP. At 3 months the results were quite comparable (symptoms score decreased from 19.9 to 9.6 in the laser group and from 19.4 to 7.5 in the TURP group and maximum flow rate improved from 11.8 to 21.3 ml/sec in the laser group and from 11.4 to 21.8 ml/sec in the TURP group). They reported an update at 36 months in 43 and 44 patients showing a similar long-term outcome [41].

The reported 7-year follow up of the patients in this study confirmed the durable effect of the treatment in the two groups and the re-operation rate after TURP and laser treatments was 6% and 7%, respectively (Level 1) [41]. Keoghane et al. [42] reported on the long term results of Oxford Laser Prostatectomy Trial. The authors found that the voiding outcomes were equally maintained after TURP and contact laser prostatectomy and the re-operation rate were similar (18% in laser group and 14% of TURP patients) [41,42] (level 1).

c) Interstitial Laser Coagulation of the prostate (ILC)

In 1991 Hofstetter introduced ILC of the prostate [43]. In this technique, Nd: YAG, a diode or holmium laser fibers are placed directly into the prostatic adenoma (see Figure 2). The fiber is fitted with a special diffuser tip or used as a bare fiber placed percutaneously through the perineum or directly through a cystoscope. The Nd: YAG laser fiber is left in position for 10 minutes at 5 to 10 W. The diode laser requires a 3-minute treatment at each location starting at 20 W and decreasing to 7 W in the “turbo mode”. The aim of this technique is to preserve the urethra, thus preventing tissue sloughing with less storage symptoms than seen with other laser techniques.

Martenson and de la Rosette [415] reported a comparative study between ILC and TURP in 30 and 14 patients, respectively with 2 years follow up. The retreatment rate for the ILC group was 21% compared to 7% in the TURP group, no incontinence was documented in either group, with one patient in the TURP group developing a urethral stricture. The authors found that when using a temperature sensing system, the objective results of laser treatment improved and seem to be more durable. The storage symptoms are frequent and long post-operative catheterization is required for up to one month in some studies. To achieve immediate relief of obstruction, some authors perform a limited resection of the coagulated tissues immediately after ILC [46].
A multicenter randomized trial at six U.S hospitals comparing TURP (n=35) with ILC (n=37) was published by Kursh et al. [47]. At 2-years follow up, the Qmax improved by 81% in the TURP group (from 9.1 to 16.5 ml/sec) and by 51% in the ILC group (from 9.2 to 13.9 ml/sec). The improvement in AUA symptom index was 70% in the TURP group and 63% in the ILC group. The ILC group had a significantly shorter hospital stay and a better sexual function score. The urinary tract infection rate in ILC group was 20%, the retreatment rate was 16% and no decrease in PSA was noted at 2 years [23]. Floratos et al [48] reported on long-term follow up (34 to 53 months) after VLAP (n=107), contact laser (n=30), and ILC (n=53). The retreatment rate was higher in ILC group than other groups (41% vs 14%). Similar retreatment rate (35%) within 8 years after ILC was reported by Terada et al. [49].

The future of ILC technique in the treatment of BPO is debatable. The unacceptable re-operation rate, delayed improvement and longer catheterization time support the AUA guidelines which do not recommend ILC as a treatment option. The EUA guidelines suggest using the ILC only in the treatment of high-risk patients [39,44,50].

d) Photoselective Vaporization of the Prostate (PVP)

The potassium Titanyl phosphate-YAG (KTP) laser is based on the technique of passing Nd: YAG laser light through a KTP crystal. This halves the wavelength of the emitted laser to 532 nm and doubles its frequency. The emitted light is a visible green light, which is strongly absorbed by red tissues and hemoglobin; this means that a blood rich organ such as the prostate gland is an excellent target. Based on these qualities, its name (photoselective vaporization of the prostate) was coined [51].

In 1997 Malek et al [52] developed the technique of high power KTP laser vaporization using the 60 W setting at the Mayo clinic. This pilot study of 10 patients assessed the safety and efficacy of the procedure in the outpatient setting. (Level 3) At 24 hours the Qmax improved from 8 to 19.4 ml/sec, and none of the treated patients developed dysuria, hematuria or required re-catheterization. In 2000, Malek et al [53] reported a 2 years follow-up of 55 patients with pre-operative prostate volumes as large as 90 cc (mean prostate volume 43cc) who underwent 60 W KTP laser vaporization of the prostate. At 2 years follow-up there was an 82% improvement in the mean symptom score and a 278% mean improvement of Qmax, from 8 to 29.1 ml/sec. Recently an 80 W KTP laser generator was developed. Hai and Malek [54] reported the first pilot study of 10 patients who underwent 80 W KTP laser vaporization of the prostate. Te et al [55] reported the first multicenter study of 139 patients with a mean prostate volume of 54.6 cc who underwent 80 W KTP laser vaporization of the prostate with a 12-month follow-up. The mean operative time was 38.7 minutes, the mean catheterization time was 14 hours and 32% of patients required no post-operative catheterization, thus making PVP a cost-effective procedure. There was an 82% improvement in symptom score, 190% improvement in Qmax, and 37% reduction in prostate volume. The postoperative complications included dysuria (9.4%), transient hematuria (8.6%), transient urge incontinence (6.5%) recatheterization (5%), retrograde ejaculation (36%) bladder neck contracture (1.4%) and urethral stricture (0.7%). Sandhu et al [56] reported on 64 men with a mean prostate volume of 101 cc who underwent PVP. The mean operative time was 123 min and 62 out of 64 patients were discharged within 23 hours.

Long-term results demonstrated sustained improvement in voiding parameters. Of 84 patients who underwent PVP, Malek and Kuntsman [57] reported 80% improvement in symptom score and 170% to 250% improvement in the Qmax after 5 years follow-up, with no need for re-operation.

e) Holmium: YAG laser

Holmium: YAG (Ho: YAG) is a multifunction surgical laser that has multiple applications in urology such as incision of urethral and ureteral stricture [58], lithotripsy of urinary calculi [59], ablation of superficial urothelial tumours [60], bladder neck incision (BNI) [61] and ablation, resection and enucleation of the prostate [62]. The excellent haemostatic properties of holmium laser result in a mostly bloodless field and decrease or eliminate the need for bladder irrigation [63]. Holmium laser works through thermal energy that allows the use of physiologic irrigants such as normal saline which eliminate the risk of dilutional hyponatremia and TUR syndrome [64].

Initially, the Ho: YAG laser was used in combination with ND: YAG laser to vaporize and coagulate prostatic tissue in a technique known as Combination Endoscopic Laser Ablation of the Prostate (CELAP). [65]. However, the addition of Ho:YAG laser does not improve the longer catheterization time, storage
symptoms, delayed improvement and high recatheterization rate (26%) caused by the Nd: YAG laser [66].

Now, with more clinical experience, the high power Ho: YAG laser is used alone for ablation, resection and enucleation of the prostate due to its excellent incisional, ablative and haemostatic properties [67].

1. HOLMIUM LASER BLADDER NECK INCISION

This technique uses holmium laser energy to perform a single or bilateral incision of the bladder neck [66]. Cornford et al [61] reported the results of holmium laser incision of the bladder neck in 100 men with prostate glands less than 30 gm. IPSS decreased from 19.2 to 3.7 at 6 weeks and remained improved at 2 years. Qmax increased from a mean of 9.79 to 19.23 and 18.27 ml/sec at 6 weeks and 2 years, respectively. The authors confirmed that the holmium: YAG laser allows transurethral prostatic incision to be performed without the need for postoperative catheterization and without significant perioperative complications.

2. HOLMIUM LASER ABLATION OF THE PROSTATE (HoLAP)

Holmium Laser Ablation of the Prostate (HoLAP) is a simple procedure and suitable for small to moderate sized prostates but it is not efficient and is tedious for treating larger prostate glands and also generates no tissue specimen for histopathological analysis [68,69]. Currently, HoLAP is being revisited as an easy to learn procedure which is comparable to the KTP prostate ablation. Vaporization of the prostate usually starts at the bladder neck using the side firing laser fiber to make a BNI at 5 and 7 o’clock, then the laser fiber is gently moved over the surface of the lateral lobes towards the apex of the prostate, proximal to the verumontanum. Circumferential vaporization of the obstructive tissue at the bladder neck and both lobes creates a TURP-like defect.

Mottet et al [70] (level 1 evidence) reported a prospective Randomized Catheter Trial (RCT) comparing HoLAP and TURP in men with prostate size <60 ml. The subjective and objective improvement in the HoLAP group was similar to that obtained with TURP at 1-year follow up. The advantages of HoLAP over TURP included less bleeding, shorter hospital stay, and shorter catheter times without the need for any irrigation.

Tan et al [71] reported a 7-year follow-up of 34 patients who underwent HoLAP. There was an 83% improvement in Qmax and 47% decrease in AUA score with a re-operation rate of 15% and recatheterization in 9% of patients. At the McGill University Health center (MUHC) similar results were obtained in 80 patients who underwent HoLAP. They demonstrated a 64% improvement in Qmax, 51% decrease in IPSS and 67% decrease in PVR at 5 years compared to pre-operative values.

HoLAP is an easy technique with a short learning curve but the procedure is rather slow [68].

3. HOLMIUM LASER RESECTION OF THE PROSTATE (HoLRP):

This procedure is similar to the standard TURP. Resection of the prostate is achieved by using the end firing Ho: YAG laser fiber. The procedure is started with bilateral incisions to define the depth and amount of tissue to be removed. The two incisions are joined just in front of the verumontanum to undermine the median lobe and detach it back into the bladder. Incisions at the 1 and 11 o’clock position are needed to define the upper margin of the lateral lobes excision. The lobe is peeled off the surgical capsule until only a bridge of tissue remains at the bladder neck. Then the lobe is cut into small pieces to facilitate their removal with a modified resectoscope loop or Ellik evacuator [62, 72].

In 1996 Gilling et al [62] reported the results of the initial 84 patients who underwent HoLRP. The mean AUA symptom score improved from 21.3 pre-operatively to 4.1 at 3 months. The mean Qmax increased from 7.5 to 19.3 ml/sec at 3 months post-operatively. Only 2 patients’ required bladder irrigation for hematuria and 5% of patients’ required recatheterization. The authors concluded that, the HoLRP technique produces a cavity identical in appearance to TURP with a relatively bloodless procedure that results in a short catheter time, immediate symptom relief and minimal storage symptoms. Similar results were confirmed by other larger studies that demonstrated that HoLRP has equivalent or even better results than TURP [73].

Mackey et al [74] reported their results of HoLRP in 96 patients with mean prostate volume of 52 cc (10-200 cc). The mean operative time, the catheterization time and hospital stay was 43 min, 1.5 and 1.1 days, respectively. They suggested that the HoLRP technique is equivalent to TURP and can be performed as day case surgery and can be used safely in a fully anticoagulated patient with a large prostate. In 1999 Gilling et al [75] (level1) published the results of a prospective randomized trial with 1-year follow-up of patients assigned to HoLRP (n=61) and TURP...
(n=59). The improvement in flow rate and symptoms score was similar but the operating time was longer in the HoLRP group, however the nursing contact, catheter time (20 vs 37.2 hours) and hospital stay (26.2 vs 47.5 hours) were significantly shorter than the TURP group. At 12 months, 8.3% of the HoLRP group and 10.6% in the TURP group had deterioration in their level of potency compared to the pre-operative level. Retrograde ejaculation developed in 96% and 86% of the HoLRP and TURP groups, respectively. Re-operations included 1 bladder neck incision in the HoLRP group and 2 bladder neck incisions and 2 revisions in the TURP group. The reported stricture rate was similar in each group (9.9 and 9.8%). No perioperative blood transfusion was needed in the HoLRP group while 6.6% of patients in the TURP group required blood transfusion. The long-term results showed no significant difference between the two groups in terms of symptom score or flow rate at 2 years and 4 years follow up [76, 77, 78].

Fraundorfer et al [79] reported a comparison between HoLRP and TURP in terms of cost effectiveness. HoLRP offers a 24.5% cost saving over TURP and 93 procedures annually would cover the initial and maintenance cost of the laser machine.

The 2 major critiques of the HoLRP procedure are the longer operative time than TURP (average 16 minute) and the resulting difficulties with pathological interpretation of the resected small pieces of the adenoma that may have been affected by thermal damage [80].

These drawbacks have been overcome with the development of a transurethral morcellator that allows complete enucleation of the adenoma in a new technique known as Holmium Laser Enucleation of the Prostate (HoLEP).

4. Holmium Laser Enucleation of the Prostate (HoLEP):

Holmium Laser Enucleation of the prostate (HoLEP) is the most recent step in the evolution of holmium laser prostatectomy (see Figure 3).

Refinement of the holmium laser technique and development of an efficient tissue morcellator have led to the true anatomic enucleation of a prostatic adenoma of any size. Ho: YAG laser fiber acts like the index finger of the surgeon during an open prostatectomy peeling the median and lateral lobes off the surgical capsule. In contrast to TURP, HoLEP is equally suitable for small, medium sized and large prostate glands with a similar clinical outcome that is independent of the prostate size [81].

The steps of the technique has been described in detail elsewhere [82, 83]. Briefly, the two-lobe technique starts with a 5 or 7-o’clock incision with enucleation of one lateral lobe which is followed by the median and remaining lateral lobe enucleation as a single unit into the bladder. The three-lobe technique is suited for a large gland with a large median lobe.

In 1998 Fraundorfer and Gilling [84] reported the first 14 patients treated with HoLEP where, the mean ultrasound volume of the prostate was 98.6 cc (55-200 cc). The mean total operating room time was 98 min (64-190). At 1 month, the mean Qmax was 25.2 ml/sec and the mean AUA score was 7.2. Gillling et al [85] subsequently reported their preliminary experience with 64 patients who had undergone HoLEP combined with intravesical morcellation. The mean pre-operative prostate volume was 75.3 cc. The mean laser time and morcellator time was 46.9 and 10.5 minutes respectively.

In 2000 Gilling et al [86] reported on 43 patients with pre-operative prostate volume >100 g, the mean catheter time was 19.7 hours, and the mean hospital time was 28.4 hours. One patient required readmission for evacuation of tissue fragments. The authors concluded that the holmium: YAG laser can be used to enucleate the adenoma of a large prostate in more or less the same way the surgeon’s finger does during open prostatectomy.
Moody and Lingeman [64] reported the initial U.S experience with 61 patients who underwent HoLEP. The laser time was 77 minutes and morcellation efficacy was 2.3 g/min. The complications were stress incontinence observed in 13 patients, and bladder neck contracture in 2 patients. Prostatic capsule perforation and bladder mucosal injuries occurred in 1 and 5 patients, respectively.

The authors attributed these complications to the learning curve. Two patients were unable to void postoperatively and were placed on intermittent self-catheterization. Kou et al [87] reported on 108 patients with a mean prostate volume of 63 cc. All the outcomes parameters were decreased significantly with 91.7% and 85% decrease in PSA and prostate volume. The dramatic reduction of PSA after HoLEP confirms a nearly complete removal of adenoma. Vavassori et al [88] reported 2 years follow-up of 196 patients who underwent HoLEP.

The improvement of voiding outcome is durable for 2 years with a 2.5% reoperation rate, bladder neck contracture and urethral stricture developed in 0.5% each. The authors reported bladder mucosal injuries in 6.6%, perforation in two patients (1 capsular and 1 bladder perforation) storage symptoms in 23% and transient stress incontinence in 7.1%. Another study reported the morbidity of 206 patients undergoing HoLEP: whereby the transfusion rate was 1%, capsular perforation 1.5% and bladder mucosal injury rate 1.9%. The recatheterization rate was 7.8% and bladder neck contracture and urethral stricture occurred in 3.9% and 2.4%, respectively [89].

One of the advantages of HoLEP is that it has no size limitation, with significant improvement of the symptoms and flow rate regardless of the size of the prostate. The rate of blood transfusion, catheterization time and hospital stay did not depend on the prostate size either [90, 91]. The classical treatment of large prostates used to be limited to either staged TURP or open prostatectomy, both of which are associated with significant morbidity. Now, HoLEP allows the patients with large prostates who traditionally required open prostatectomy, to be treated endoscopically [86, 92].

Randomized comparative trials (level 1 evidence) have shown similar results for HoLEP and traditional surgery used to treat BPO. Tan et al [93] found that HoLEP is superior to TURP for relieving bladder outlet obstruction. HoLEP is also superior to TURP with less bleeding, amount of tissue removed, decreased catheter time and hospital stay [94, 95]. There was no blood transfusion needed in the HoLEP group in contrast to the TURP group where the transfusion rate was 3.3%. In another study Montorsi et al [96] found that HoLEP and TURP were equally effective with similar rate of complications at 1 year follow-up. The erectile function did not show a decrease from baseline in either group. There was no TUR syndrome in the HoLEP group, versus in 2.2% of patients in the TURP group.

Transient urge incontinence was reported in 44% and 38% of the HoLEP and TURP groups, respectively. This complication is usually short term and self-limiting. Urethral stricture occurred in 1.7% in HoLEP group and 7.4% in the TURP group. Kuntz et al [97] reported that the AUA symptom scores improved 13-fold in the HoLEP and more than 5 fold in the TURP group, however, the maximum flow rate improved about 5-fold in each group. Mean PVR decreased by 98% in the HoLEP and 88% in the TURP group. Of sexually active patients, 74% in the HoLEP group and 70.3% in the TURP group had retrograde ejaculation. The operative time of HoLEP was 25% longer than TURP, but this is because Kuntz used the electrocautery loop to fragment the tissue in most of the HoLEP cases at the beginning of their study, until the tissue morcellator became available.

The operative time was longer than TURP, which seems to be due to the significant learning curve of HoLEP, which is the main problem of the HoLEP procedure. It is difficult to compare operative time in HoLEP and conventional surgery, as the prostate size influences the mean operative time.

In the experience at the MUHC, HoLEP requires longer training than TURP and the operator became comfortable with the HoLEP technique after a mean of 20 to 30 cases with moderate size prostates [98]. Some authors suggest that learning HoLEP is equivalent to learning TURP because it is a mostly bloodless procedure with good visibility, however close supervision of an experienced urologist is a prerequisite for success [93].

A randomized study comparing HoLEP and transvesical prostatectomy (Kuntz et al [99, 100]) found that both procedures are equally effective with less perioperative morbidity in the HoLEP group. The blood transfusion rate was 13% in open prostatectomy group and zero in the HoLEP group (level 1 evidence).

Unlike HoLRP, there are no thermal tissue artifacts.
in the enucleated specimen in the HoLEP procedure which improves the histological assessment compared to TURP [101]. HoLEP has the advantage of safely treating (critically ill) patients and anticoagulated patients, with low perioperative morbidity regardless of the prostate size [102]. This justifies the suggestion that HoLEP is the modern gold standard alternative to TURP and open prostatectomy. It appears to be at least as effective as the traditional surgery of BPO in terms of its short and long-term efficacy and low perioperative complications [103].

**SUMMARY**

Over the last decade, several minimally invasive treatments have been introduced to challenge the standard TURP in the treatment of symptomatic BPO. Laser therapy is one of the most documented alternatives. The improvement in laser technology has led to the development of promising treatment options.

The long catheterization time and severe storage symptoms with delayed improvement, resulted in abandoning VLAP as a treatment option. Furthermore, contact laser and interstitial laser coagulation of the prostate are not considered as first line treatments of BPO and are only used in high-risk patients. KTP laser has produced promising results as a challenge to TURP but a randomized control trial with long-term follow-up is still needed.

Holmium laser provides several applications in urology and its use in the treatment of BPO is considered a true challenge for TURP, as well as to open prostatectomy. HoLEP has the same or even better results than the traditional surgery, with low morbidity, regardless of the prostate size and it is being promoted as the new gold standard for treatment of BPO.

**CONCLUSION:**

- HoLEP ≈ is equivalent to TURP/Adenomectomy
- HoLEP has the disadvantage of a long learning curve.
- Resurgence of vaporization techniques (green light and holmium side fire ablation) need to be better studied.

**MICROWAVE THERMOTHERAPY**

Therapy uses high temperatures to produce coagulation necrosis of prostatic tissue, attempting to achieve results with heat that are similar to those achieved by TURP but inducing a lower morbidity. Microwaves delivered via the transurethral route have been the dominant means used to heat prostatic tissue, but hot water (Water-Induced Thermotherapy) has also been used for the same goal.

1. **TRANSURETHRAL MICROWAVE THERMOTHERAPY (TUMT)**

TUMT uses a special transurethral catheter with a microwave antenna that transmits heat into the prostate with the eventual goal of destroying tissue by achieving temperatures that exceed the cytotoxic threshold and inducing cell death. More specifically, heating in excess of 45°C results in coagulation necrosis. In addition, apoptosis has been observed, at temperatures lower than those inducing necrosis [105] (see Figure 1).

**Figure 1. Example of TUMT principle**
It has also been proposed that induced necrosis disrupts periurethral alpha-adrenergic receptors, resulting in denervation of the smooth muscle cells [106]. These findings may be responsible for the increased urinary flow after TUMT. Recently, it was demonstrated that TUMT increased the sensory threshold (evoked by electrical stimulation) in the posterior urethra by 30%, resulting in the alleviation of storage symptoms [107]. During the last decade, numerous studies have been published presenting the clinical results from the application of TUMT for the treatment of LUTS associated with BPO. These studies have used different devices and energy protocols, have had different follow-up periods and response criteria, and have differed in patient selection. The steadily increasing number of publications on TUMT is suggestive of the method’s acceptance and the efforts made to optimize the treatment outcome. The identification of the deficiencies of the first-generation devices, mainly the limited and often interrupted energy delivery, contributed to their further evolution regarding heat distribution, treatment time, energy, and monitoring of the treatment effect. Many TUMT devices with different technical specifications and treatment protocols have been evaluated. Bolmsjo et al [108] reported substantial differences in heating profiles between devices with different microwave antenna designs.

However, at present time there is not enough critical data to support the hypothesis that TUMT challenges TURP. Further studies that provide high quality of evidence are needed.

\[ a)\] Clinical outcomes- efficacy

Hoffman et al [109] combined all evidence from randomized controlled trials evaluating the efficacy and safety of microwave thermotherapy in treating men with LUTS and BPO, in order to quantify the therapeutic efficacy. This excellent systematic review provides level 1 evidence and represents a cornerstone on which we can build our recommendation on the efficacy of TUMT in the management of BPO. Overall, 540 patients were randomized in the six eligible randomized studies, including 322 to TUMT and 218 to TURP. Patients included in the studies had moderate to severe LUTS, with decreased Qmax and moderately enlarged prostates. Studies generally excluded men with very large prostates (>100 g), prominent median lobes and in urinary retention. These exclusion criteria are similar to those used in other surgical studies of BPH treatment, suggesting that the present results are generalizable. Treatment was offered by different TUMT devices and software including Prostatron (Prostatsoft 2.0 and 2.5) and ProstaLund Feedback.

The mean (range) age was 67.8 (65-70) years, baseline symptom score 19.5 (15.7-21.3), baseline Qmax 8.6 (7.9-10.1) ml/sec and prostate volume 44.5 (33.9-52.7) ml, and did not differ by treatment group. Two studies followed patients for 6 months and 4 studies provided a 12-month follow-up. The proportion of patients who completed follow-up ranged from 85 to 100%. Five studies found significant decreases in urinary symptoms and significant increases in Qmax between baseline and follow-up for both TURP and TUMT, while Ahmed et al [110] found that TUMT did not improve Qmax.

TUMT was somewhat less effective than TURP in reducing LUTS. The pooled mean symptom score for men undergoing TUMT decreased 65% in 12 months (from 19.4 to 6.7), compared with 77% (19.6 to 4.5) in men undergoing TURP. Weighted Mean Differences (WMD) were calculated with 95%CI for the between treatment differences in pooled means. WMD for the symptom score at the follow-up for all six studies was 1.83 (0.39 to 0.58), favouring TURP. TURP led to greater improvement in Qmax than TUMT; the pooled mean Qmax for men undergoing TUMT increased by 70% (7.9 to 13.5 ml/sec), and by 119% (8.6 to 18.7 ml/sec) in men undergoing TURP. The WMD for Qmax at the follow-up was 5.37 (4.226.51) ml/sec, favouring TURP. The mean Qmax after TUMT was usually <15 ml/sec, since only two studies reported a mean post TUMT Qmax greater than 15 ml/sec. In contrast, five studies reported that TURP achieved a mean Qmax >15ml/sec. Three studies [111,112,113] evaluated the effect of treatment on QOL using the eight IPSS question. The pooled mean QOL score for men undergoing TUMT decreased by 58.5% (4.1 to 1.7) and by 63.4% (4.1 to 1.2) in men undergoing TURP. Although QOL significantly improved after both TUMT and TURP, there were no significant differences between treatments.

The urinary symptom scores (WMD 1.83) and Qmax (WMD 5.37 ml/sec) significantly favoured TURP at the follow-up. However, the mean urinary symptom scores for TUMT patients almost always decreased from the moderate-to-severe symptom range to the mildly symptomatic range. Analytical results are listed in Table 1 [114, 115, 116, 117, 118, 119].

Gravas et al performed a pooled analysis of 3 studies of ProstaLund Feedback TUMT with 12-month follow-up [120]. They combined 2 randomized studies.
comparing PLFT to TURP and an open label study with no comparative group. It should be noticed that the study by Wargell et al [113] has also been included in the systematic review by Hoffman et al. The authors underlined that inclusion and exclusion criteria of the 3 studies were identical and this fact reduced any selection bias. They tested noninferiority of PLFT (183 patients) compared to TURP (65 patients) using a Confidence Interval (CI) approach. The responder rate was 85.3% and 85.9% in the PLFT and TURP group, respectively. One-sided 95% CI analysis showed noninferiority of PLFT as compared to TURP. A responder was defined as a patient that following treatment had an IPSS of 7 or less, and/or 50% or greater improvement in IPSS from baseline, and/or Qmax of 15ml/sec or more, and/or 50% or greater improvement in Qmax from baseline. In the PLFT group there was a marked decrease from a mean IPSS of 20.9 at baseline to 6.4 at the 12-month visit (69% decrease). Mean IPSS was decreased from 20.7 at baseline to 7.1 at the 12-month visit after TURP. The 1-sided CI (95%) for the ratio of IPSS between the PLFT and TURP group (1.06) suggested noninferiority of PLFT compared to TURP. In the PLFT group the mean Qmax value improved from 7.7 ml/sec at baseline to 16.1ml/sec at the 12-month follow-up visit, corresponding to a 109% increase. In the TURP group, Qmax increased significantly from baseline in both groups by 6 months and remained stable thereafter; it was 19.8% higher after TURP than with terazosin. The percentage of TUMT patients having a ≥50% increase in Qmax at 6 months (64.7%) markedly exceeded that in the terazosin group (9.6%). The mean QOL declined significantly in both groups at 6 months, with scores 38% lower after TUMT than with terazosin. Furthermore in an update of the previous study, patients have been followed-up for 18 months [122]. The significant between-group differences observed at 6 months in the mean IPSS, Qmax, and QOL score were maintained at 18 months, at which time the improvements in these three outcome measures were significantly greater (p <0.0005), by 35%, 22%, and 43%, respectively, in the microwave group compared to the terazosin group. Patients were judged to have failed TUMT if they required further

| Table 1. Clinical outcome of randomized controlled trials (RCT), Hoffman’s systematic review and pooled data of PLFT Treatment |
|---|---|---|---|---|---|---|---|---|---|---|
| STUDY | TUMT | | | TURP | | | | | | |
| | IPSS | Qmax(ml/s) | | | Baseline | Post | Baseline | Post | Baseline | Post |
| Ref 86 | 18.5 | 5.3 | 18.4 | 5.2 | 10.1 | 9.1 | 9.5 | 14.6 |
| Ref 90-92 | 11.2 | 2.7 | 13.3 | 0.9 | 8.0 | 12.3 | 7.9 | 17.7 |
| Ref 93,94 | 18.3 | 5.0 | 16.7 | 3.4 | 9.3 | 17.1 | 9.3 | 19.3 |
| Ref 87, 95 | 20.1 | 7.6 | 20.8 | 3.2 | 9.6 | 15.2 | 7.9 | 23.5 |
| Ref 88 | 20.5 | 9.5 | 21.3 | 6.8 | 9.1 | 13.2 | 9.6 | 20.6 |
| Ref 89 | 21.0 | 7.2 | 20.4 | 7.1 | 7.6 | 13.3 | 7.9 | 15.2 |
| Review of RCT | 19.4 | 6.7 | 19.6 | 4.5 | 7.9 | 13.5 | 8.6 | 18.7 |
| Pooled PLFT | 20.9 | 6.4 | 20.7 | 7.1 | 7.7 | 16.1 | 7.5 | 18.6 |
therapy, e.g. TURP. Patients on terazosin were classified as treatment failures if they discontinued their medication because of either ineffectiveness or side effects. By 18 months, 21 patients had failed terazosin therapy, in 13 because it was ineffective and in 8 because of side effects. Subsequent to terazosin failure, 19 of these patients underwent TUMT and 2 TURP. Three patients failed TUMT by 18 months and proceeded to surgery. The rate of treatment failure at 18 months in the terazosin group (41%) significantly exceeded that of the TUMT group (5.9%).

b) Durability – The test of time

The burning question for thermal-based treatment is how good the results remain in a long-term perspective. Stated differently, how durable are the achieved clinical outcomes?

It will be attempted to give a reply to these questions using evidence of varying levels of quality. There is a lack of any systematic review or meta-analysis of randomized controlled studies, therefore the preponderance of data presented in this section consists of level 2 and 3 evidence. No randomized or other studies with a follow-up >2 years have been published. In most studies the attrition rate was significant, thus less than half of the initial group of patients treated is analyzed at 4-5 years. In addition, the analyses are done in those patients who remain in the study and are likely to represent the best data (responders). Despite these flaws, these types of studies remain the best data available. Retreatment rate, defined as the percentage of any additional therapy given for the primary treatment failure, may serve as a measure of durability.

Historically the Low-Energy TUMT has been abandoned due to the disappointing durability of its effects. At 5 years after TUMT with the Prostasoft 2.0, 41% of the patients had received instrumental retreatment, and 17% were being retreated with medication [123]. More recent studies confirm the limited durability of clinical outcome obtained by lower-energy programs, with a retreatment rate as high as 84.4% after 5-year follow-up [124,125,126].

In the randomized study with the longest available follow-up by Floratos et al [111], the results of 36 month follow-up were presented. One hundred and fifty-five patients were randomized to receive either high-energy TUMT with software version 2.5 or undergo transurethral resection. Improvement in Qmax of the TUMT group from 9.2 ml/sec retreatment to 15.1 ml/sec, 14.5 ml/sec and 11.9 ml/sec at 1-, 2 and 3 years, respectively, was reported, whilst the IPSS symptom score improved from 20 to 8, 9 and 12, respectively. These data indicate that the level of improvement is durable up to 3 years. The retreatment rate for TUMT and TURP (including medication for primary treatment failure) was 19.8% and 12.9%, respectively. It is important to underline the different causes of retreatment. Retreatment was offered to the TUMT patients because of primary treatment failure, while in the TURP group, retreatment included reintervention mainly because of urethral strictures, bladder neck sclerosis, meatal stenosis, but rarely, treatment failure. Similarly, d’Ancona et al [117] found a retreatment rate of 26% and 4.7% for TUMT and TURP in their randomized study with a mean follow-up of 30 months. Improvement in terms of IPSS and Qmax was significant and remained stable during follow-up. The relatively longer-term outcomes still favoured TURP in both of these studies.

Recently, Wagrell et al [127] presented the 3-year results of a prospective randomized multicenter study comparing TUMT with ProstaLund Feedback Treatment (PLFT, the Core-Therm device) toTURP. At 36-month follow-up, the average value for the PLFT group was 8.2, 1.2, and 11.9 ml/sec for IPSS, QOL, and Qmax, respectively. The corresponding values for the TURP group were IPSS 5.0, QOL 1.0, and Qmax 13.5 mL. The degree of improvement was in the same range as that observed after 12 and 24 months for both groups. These data suggest that at 3 years clinical results obtained with PLFT and TUMT were comparable to those seen after TURP.

Trock et al [128] performed a pooled analysis of 6 multicenter studies of cooled thermotherapy with comparable baseline measures. In total 541 patients were pooled and data showed an improvement of 55%, 53% and 51% in AUA symptom score, QOL and Qmax after TUMT, respectively. A slight decrease was observed at 48 months since subjective and objective improvement remained durable (43%, 50% and 35%, respectively).

However, given the low morbidity of TUMT, a higher risk of retreatment may be a reasonable trade-off for patients with LUTS attributable to BPO. In Table 2 retreatment rates of long-term studies are presented [129,130,131].

c) Morbidity (side effects-complications)

Morbidity of treatment remains one of the main considerations for both clinicians and patients. One of the commonly used arguments for the application of TUMT as an alternative to TURP for BPO is its low
morbidity. Pooled data of the available randomized studies comparing TUMT and TURP regarding morbidity have been published recently. Hoffman et al systematically reviewed the adverse events of TUMT and TURP that were reported in randomized controlled trials. Morbidity variables are presented as the percentage of adverse events (ratio of events to pooled subjects). The authors also estimated the rate of retreatment due to treatment failure or strictures during the follow-up.

These data were reported as the number of events per person per year of follow-up. De la Rosette et al [132] and Walmsley and Kaplan [133] pooled data from available randomized studies of the two invasive treatments for the management of BPO. In these studies values of each morbidity variable are expressed as estimated mean value of the pooled analysis. The range of mean values of the studies is also provided. This solid body of high quality evidence is presented in Table 3 and 4.

Catheterisation time, incidence of dysuria/urgency and urinary retention were in favour of TURP. The incidence of hematuria, clot retention, transfusions, TUR syndrome, erectile dysfunction, retrograde ejaculation and urethral strictures is reported to be significantly less for TUMT than for TURP.

Having pooled data of 3 studies (2 randomized and 1 open label without a control arm) of PLFT TUMT, Gravas et al [120] reported that serious adverse events (SAE) probably or possibly related to the treatment occurred in 6.0% of the patients (11/183) in the PLFT group, including post-operative hemorrhage, urethral disorder (perforation with hematuria occurred prior to treatment during the catheterization and TUMT was not performed), fever, urinary incontinence, thrombosed hemorrhoids, urethral stricture, urinary retention (2 cases), vertigo, sepsis, and epididymitis. This SAE rate was higher in the TURP-group, where 15.4% of the patients (10/65) presented SAEs probably or possibly related to the treatment including gout, delirium, sepsis, post-operative hemorrhage (2 cases), hematuria (3 cases), urinary tract infection, orchitis and urethral stricture. The difference between groups was significant (p=0.035).

In the same study the mean post-treatment catheter time was on average 16.0 (±10.9) days for the PLFT group, while for the TURP groups the mean catheterization time was markedly shorter (3.1 ±3.7 days), a finding that was expected due to the two different types of intervention (coagulation vs. resection of prostate).

One important complication that was not reported in clinical trial reports was thermal injury. Although USA Food and Drug Administration has recognized that TUMT is safe and effective, it issued a warning regarding unexpected procedure-related complications, due to 16 reported severe thermal injuries, including 10 resulting in fistula formation and 6 resulting in tissue damage to the penis or urethra [134].

Among the factors that may have contributed to the occurrence of these complications, the FDA included improper placement of the microwave catheter and inadequate monitoring of the patient during treatment.

The reported low morbidity and the absence of any need for spinal or general anesthesia make TUMT a true outpatient procedure, representing an excellent option for patients at high operative risk (American Society of Anesthiologists class 3 or 4) who are unsuitable for an invasive treatment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>FU (months)</th>
<th>Retreatment Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Ancona [117]</td>
<td>31</td>
<td>30</td>
<td>26.0</td>
</tr>
<tr>
<td>Floratos [111]</td>
<td>78</td>
<td>36</td>
<td>19.8</td>
</tr>
<tr>
<td>Thalmann [130]</td>
<td>200</td>
<td>42</td>
<td>21.5</td>
</tr>
<tr>
<td>Miller [129]</td>
<td>150</td>
<td>60</td>
<td>29.3</td>
</tr>
<tr>
<td>Gravas [131]</td>
<td>213</td>
<td>48</td>
<td>29.1</td>
</tr>
</tbody>
</table>
WIT was developed as a minimally invasive treatment option for the interventional management of LUTS due to BPO. The concept is to produce heat-induced coagulative necrosis and secondary ablation of the obstructing hyperplastic tissue. The source of thermal energy is heated water circulated in a proprietary device.

### Table 3. Morbidity following TUMT and TURP (pooled data of randomized controlled studies)

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<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>TUMT</td>
<td>TURP</td>
<td>TUMT</td>
</tr>
<tr>
<td>Hospitalization time (days)</td>
<td>0</td>
<td>4</td>
<td>0</td>
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<tr>
<td>Catheterization time (days)</td>
<td>13.7</td>
<td>3.6</td>
<td>-</td>
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<tr>
<td>Urinary Tract Infections (%)</td>
<td>14.6</td>
<td>13.1</td>
<td>9</td>
</tr>
<tr>
<td>Dysuria (%)</td>
<td>-</td>
<td>-</td>
<td>51</td>
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<td>Hematuria (%)</td>
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<td>Retention (%)</td>
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<tr>
<td>Clot retention (%)</td>
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<tr>
<td>Transfusions (%)</td>
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<td>-</td>
<td>1.5</td>
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<tr>
<td>TUR syndrom (%)</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Erectile Dysfunction (%)</td>
<td>4.4</td>
<td>9.3</td>
<td>8.7</td>
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<tr>
<td>Retrograde ejaculation (%)</td>
<td>19.8</td>
<td>63</td>
<td>20</td>
</tr>
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</table>

### Table 4. Reintervention/Retreatment following TUMT and TURP (pooled data of randomized controlled studies)

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<tbody>
<tr>
<td></td>
<td>TUMT</td>
<td>TURP</td>
<td>TUMT</td>
</tr>
<tr>
<td>Reintervention &lt;30 days %</td>
<td>0</td>
<td>7.4</td>
<td>-</td>
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<tr>
<td>Retreatment &gt;30 days %</td>
<td>18.7</td>
<td>12.2</td>
<td>-</td>
</tr>
<tr>
<td>a) Strictures-meatal /bladder neck stenosis</td>
<td>0.7</td>
<td>9.6</td>
<td>2</td>
</tr>
<tr>
<td>b) Treatment failure</td>
<td>18</td>
<td>2.6</td>
<td>18</td>
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### RECOMMENDATIONS-FUTURE PERSPECTIVE:

The best available clinical data suggest that TUMT is an effective treatment for BPH that can be delivered to outpatients and has fewer adverse events than TURP. However, TURP offers greater improvements in symptom scores and Qmax resulting in a smaller number of patients requiring retreatment for BPO. Further research is needed to evaluate the long-term effectiveness and safety of TUMT and to determine which devices and energy settings are most effective. Our future efforts should be focused on the development of new protocols and direct comparator trials to investigate differences between similar therapeutic interventions, development of standard definitions of treatment failure and retreatment rates, determination of cost-effectiveness through randomized clinical studies, and incorporation of numerical findings into daily clinical practice.

### CONCLUSION:

TUMT:
- Has good clinical outcomes that seem durable
- Has low morbidity
- Is outpatient based and under local algesia
- Is an option when instrumental treatment is indicated (except when absolute indication for surgery exists)

2. Water-Induced Thermotherapy, (WIT™)

WIT was developed as a minimally invasive treatment option for the interventional management of LUTS due to BPO. The concept is to produce heat-induced coagulative necrosis and secondary ablation of the obstructing hyperplastic tissue. The source of thermal energy is heated water circulated in a proprietary device.
etary closed-loop system, which includes a specially designed catheter. During WIT, the conductive heat is distributed evenly around the cigar-shaped treatment balloon (see Figure 2).

Currently limited data are available for the evaluation of WIT in the management of LUTS and BPO. Evidence comes mainly from a single international, uncontrolled, multicenter trial demonstrating symptom reduction and safety. In this prospective international study [135] and its subsequent updates [136,137], 125 patients were enrolled at 8 study centers and evaluated both short term (3, 6, and 12 months) and long-term (24 and 36 months) follow-up. In addition a single-center experience has been published [138]. Breda and Isgro treated patients with and without retention using two different protocols including a “standard” with a temperature setting of 60°C and balloon inflation to 50F and an “enhanced” with balloon inflation to 60F and a treatment temperature of 62°C. The overall failure rate was 23% with a mean follow-up of 10 months. The remaining available data have only been reported in abstract form. [139,140]. Clinical efficacy of WIT in terms of IPSS, QOL and Qmax are presented in detail. (see Table 5).

Published studies have not reported significant morbidity. The duration of indwelling catheterization was as follows: 45.5% of patients were catheter free after 1 week (the minimum required by the protocol), 30.5% after 2 weeks, and the remaining 24.0% after 3 to 5 weeks. Adverse events included prolonged (>1 month) or excessive dysuria (11.2%); epididymitis (3.2%); prolonged (>1 month) or excessive hematuria (22.4%); transient impotence (1.6%); transient urinary urge incontinence (2.4%); culture-confirmed bacteriuria or urinary tract infection (32.8%); urethral pain (4.8%); proctitis (0.8%); and urinary retention subsequent to the post-treatment catheterization period (12.0%) [132]. The effect of WIT on sexual function has been studied by Muschter et al. [141] No patient suffered from newly occurring permanent erectile dysfunction or retrograde ejaculation. Interest in sex, sexual activity, and other measures were not affected or were slightly improved by WIT. In general during follow-up, no serious morbidity has been reported. Breda and Isgro preferred a more general description of the adverse events reporting minor storage symptoms. None of the patients complained of urinary incontinence, retrograde ejaculation or erectile dysfunction. One case of acute prostatitis was reported [138].

Data regarding durability are also preliminary. In the only long-term series by Muschter et al [135-137], it was reported that the treatment failure rate of WIT,

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<thead>
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<th>Table 5. Clinical outcome of WIT studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Muschter [139]</td>
</tr>
<tr>
<td>Minardi [140]</td>
</tr>
<tr>
<td>Muschter [135, 136, 137]</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Breda [138] 60° / 50F</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Breda [138] 62° / 60F</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

b: baseline  
p: postWIT  
R: retention  
*  8 patients catheter-free  
**  11 patients catheter-free
requiring subsequent TURP was 5.6%, 9.6% and 11.2% after 12, 24 and 36 months, respectively. On an intention-to-treat basis, which counts all patients lost to follow-up and unrelated deaths as treatment failures, the percentages are higher: 10.4% after 12 months, 23.2% after 24 months and 36% after 36 months.

It seems that WIT acts as an improved transurethral incision of the prostate with some degree of cavity formation, since the procedure has also been associated with statistically significant post-treatment prostate shrinkage (median 3.2 cc) at 12 months compared with baseline [135].

For the evidence-based approach to a critical evaluation of WIT, it is obvious that randomized studies against one of the reference standards (including medical therapy or TURP) are required.

CONCLUSION:

• Remains investigational

In patients who are unwilling to remain on medication, in whom medical therapy has failed or who are unsuitable candidates for surgery, several minimally invasive therapies have been developed, including transurethral microwave therapy [142], interstitial laser therapy [143], water induced thermotherapy [144], and transurethral needle ablation of the prostate (TUNA) [145,146,147].

1. TUNA THERAPY

TUNA therapy uses low-level radiofrequency (RF) energy that is delivered by needles into the prostate and that produces localized necrotic lesions in the hyperplastic tissue. The inner region of the prostate is selectively ablated with temperatures approaching 90-100°C while the prostatic urothelium is preserved [145,148].

The TUNA system (Vidamed, Menlo Park, Calif) consists of a special catheter attached to a generator. At the end of the catheter there are two needles that are withdrawn into two adjustable shields made from Teflon. (See Figure 1) The needles are advanced into the prostatic tissue and can be placed accurately into the required position. The generator produces a monopolar RF signal of 490 kHz, which allows excellent heat penetration and uniform tissue distribution of heat [145,148].

The procedure is performed with the patient in the lithotomy position under topical anesthesia with 2% introuthral lidocaine. The best result is achieved by applying a penile clamp for 10 minutes and giving intravenous sedation if required [145].

The TUNA catheter is advanced under vision with the 0-degree fiberoptic telescope. The exact position of the needle tip within the prostate can be visualized by transrectal ultrasound. The thermal lesion may extend up to 5 to 6 mm beyond the position of needle deployment with lesions measuring up to 20 x 10 mm [148].

At the end of the procedure, either a urethral catheter may be left in overnight or the patients can go home after they have voided and feel that they are emptying their bladder, without a catheter.

In general, improvement in symptoms is seen fairly early (within 2 weeks) and is usually complete within 6 weeks following TUNA treatment [149].
The advantage of TUNA is that it can be delivered under topical anesthesia to patients with symptomatic BPO and is an attempt to minimize operative risk and reduce postoperative sequela and the need for a long recovery period, while optimizing the therapeutic benefit.

**a) Clinical Results**

The initial clinical evaluation of TUNA therapy was conducted in the early 1990s in Europe [150,151] and in the USA in 1994 [152]. Results from a multi-center, randomized trial comparing TUNA and TURP led to the approval of the procedure by the Food and Drug Administration in 1996 [145]. Subsequently there have been several clinical studies of TUNA therapy reported, showing significant improvement in the symptom score (Table 1). There is a wide variety in the number of patients in each series and in the length of follow-up. It can be noted that most are open series, with a minority of randomized studies. The size of studies varies from 10 to 188 patients, and, in many cases, the number of patients, followed up for a long period of time is less than 50% of the original sample, which makes it difficult to draw definitive conclusions [148].

The overall average improvement in symptom score is 58% at 1 year (546 patients in 10 series), 60% at 2 years, and 66% at 3 years. The improvement in the maximum flow rate ($Q_{\text{max}}$) reported improved flow rates in the range of 60% to 80% (77% at 1 year, 82% at 2 years and 92% at 3 years). These results were significant when compared with baseline and surpass the expected placebo effect of 30% [149].

**b) Trials comparing TUNA to TURP (Table 2 and 3)**

In a non-randomized prospective study the standard TURP was compared with other minimally invasive treatments in 212 patients, including TUNA therapy. TURP achieved the highest decrease of prostate volume (48.8%), the best increase of maximum flow rate (75.3%) and the largest decrease of residual volume (89.8%) in comparison to other methods [165].

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Preop</th>
<th>Postop</th>
<th>% change</th>
<th>Preop</th>
<th>Postop</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zlotka et al [153]</td>
<td>188</td>
<td>20,9</td>
<td>8,7</td>
<td>58%</td>
<td>8,6</td>
<td>12,1</td>
<td>40%</td>
</tr>
<tr>
<td>Daehlin et al [154]</td>
<td>26</td>
<td>21,2</td>
<td>10,5</td>
<td>50%</td>
<td>10,9</td>
<td>13,7</td>
<td>25%</td>
</tr>
<tr>
<td>Namiiki et al [155]</td>
<td>33</td>
<td>20,7</td>
<td>11,2</td>
<td>46%</td>
<td>8,0</td>
<td>11,0</td>
<td>37%</td>
</tr>
<tr>
<td>Roehrborn et al [146]</td>
<td>130</td>
<td>23,7</td>
<td>11,9</td>
<td>50%</td>
<td>7,8</td>
<td>14,6</td>
<td>68%</td>
</tr>
<tr>
<td>Bruskewitz et al [145]</td>
<td>65</td>
<td>24,7</td>
<td>11,1</td>
<td>55%</td>
<td>8,7</td>
<td>15,0</td>
<td>72%</td>
</tr>
<tr>
<td>Kahn et al [156]</td>
<td>45</td>
<td>20,9</td>
<td>9,9</td>
<td>52%</td>
<td>8,3</td>
<td>14,9</td>
<td>79%</td>
</tr>
<tr>
<td>Campo et al [157]</td>
<td>72</td>
<td>20,8</td>
<td>6,2</td>
<td>67%</td>
<td>8,2</td>
<td>15,9</td>
<td>71%</td>
</tr>
<tr>
<td>Ramon et al [158]</td>
<td>68</td>
<td>22,0</td>
<td>7,5</td>
<td>66%</td>
<td>8,4</td>
<td>11,6</td>
<td>33%</td>
</tr>
<tr>
<td>Steele and Sleep [159]</td>
<td>41</td>
<td>22,4</td>
<td>7,0</td>
<td>68%</td>
<td>6,6</td>
<td>10,2</td>
<td>54%</td>
</tr>
<tr>
<td>Millard et al[60]</td>
<td>20</td>
<td>19,0</td>
<td>8,2</td>
<td>56%</td>
<td>3,0</td>
<td>11,4</td>
<td>280%</td>
</tr>
<tr>
<td>Schultman et al [161]</td>
<td>36</td>
<td>21,6</td>
<td>7,8</td>
<td>64%</td>
<td>9,9</td>
<td>16,8</td>
<td>69%</td>
</tr>
<tr>
<td>Virdi et al [162]</td>
<td>71</td>
<td>22,3</td>
<td>7,4</td>
<td>67%</td>
<td>7,0</td>
<td>14,2</td>
<td>103%</td>
</tr>
<tr>
<td>Chapple et al [163]</td>
<td>58</td>
<td>22,0</td>
<td>10,0</td>
<td>54%</td>
<td>8,8</td>
<td>11,5</td>
<td>30%</td>
</tr>
<tr>
<td>Gicunakopoulos et al [164]</td>
<td>50</td>
<td>22,4</td>
<td>9,1</td>
<td>59%</td>
<td>7,6</td>
<td>16,8</td>
<td>121%</td>
</tr>
</tbody>
</table>

TOTAL 903

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Figure 1. Example of TUNA treatment

Table 1. Worldwide results of Transurethral Needle Ablation (TUNA) of the Prostate with 12-month follow-up
In another prospective study comparing TURP to minimally invasive treatments, the TURP group achieved the best results according to IPSS and Qmax. In up to a quarter of the patients, a secondary TURP was performed within the first 2 years after “less invasive” procedures, including TUNA therapy [166].

In the United States a randomized clinical trial with a 1 year follow up compared TUNA to TURP [145]. A total of 65 patients were treated by TUNA and 56 by TURP. The symptom score improved from 24.7 to 11.1 (13.6 symptom units) in the TUNA group against 23.3 to 8.3 (15.0 symptom units) in the TURP group. The maximum urinary flow rate improved from 8.7 to 15.0 ml/sec (6.3 ml/sec) in the TUNA group and from 8.4 to 20.8 ml/sec (12.4 ml/sec) in the TURP group. The treatment was found to be effective and safe. The complication rate of TUNA was low in both the short and the long term. The most commonly reported adverse events were bleeding (32.3%), urinary tract infection (7.7%), and urethral stricture (1.5%). There was no reported change in the sexual function in patients treated by TUNA. In the TURP group there was a high incidence of retrograde ejaculation.

In conclusion, compared to TURP, TUNA is an efficacious minimally invasive treatment for symptomatic BPO with few side effects [145]. The results of 5 year follow-up of the United States randomized clinical trial were presented [167]. Following treatment, significant improvement from baseline occurred in symptom score, higher for TURP than for TUNA (statistically significant in the first 4 years). The two groups demonstrated a significant improvement in maximum urinary flow rate (greater for TURP patients). TUNA showed significantly fewer adverse events than TURP. The TURP group reported 41% retrograde ejaculation, while the TUNA group reported none. However, in the TUNA group 14% required further intervention with additional treatment (TURP), against only 2% in the TURP cohort. The results of this study demonstrate stable treatment outcomes after 5 years of follow up and suggest that TUNA is an attractive treatment option for men with LUTS due to BPO. While the TURP improvement was superior, TUNA showed lower adverse events [167].

Another randomized clinical trial comparing TUNA with TURP analyzed 59 patients [168]. Improvements in Qmax, post voiding residual volume (PVR),

Table 2. Trials comparing transurethral needle ablation with transurethral resection of prostate

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruskewitz et al [145]</td>
<td>TUNA</td>
<td>65</td>
<td>24.7</td>
<td>11.1</td>
<td>8.7</td>
<td>15.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TURP</td>
<td>56</td>
<td>23.3</td>
<td>8.3</td>
<td>8.4</td>
<td>20.8</td>
<td></td>
</tr>
<tr>
<td>Hill B et al [167]</td>
<td>TUNA</td>
<td>65</td>
<td>24.0</td>
<td>10.7</td>
<td>8.8</td>
<td>11.4</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>TURP</td>
<td>56</td>
<td>24.1</td>
<td>10.8</td>
<td>8.8</td>
<td>18.6</td>
<td>14%</td>
</tr>
<tr>
<td>Schatzl et al [166]</td>
<td>TUNA</td>
<td>15</td>
<td>Decreased 9.8</td>
<td>Increased 2.3%</td>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TURP</td>
<td>28</td>
<td>Decreased 13.9</td>
<td>Increased 11.5%</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Detrusor pressures following Transurethral Needle Ablation (TUNA) of the prostate

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Months of follow-up</th>
<th>Baseline</th>
<th>Post-TUNA</th>
<th>% change</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Issa et al [152]</td>
<td>12</td>
<td>6</td>
<td>91.8</td>
<td>70.9</td>
<td>22.7%</td>
<td>p=0.094</td>
</tr>
<tr>
<td>Millard et al [160]</td>
<td>20</td>
<td>6</td>
<td>70.7</td>
<td>59.9</td>
<td>15.8%</td>
<td>p=0.90</td>
</tr>
<tr>
<td>Campo et al [157]</td>
<td>72</td>
<td>12</td>
<td>85.3</td>
<td>63.7</td>
<td>25.3%</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Steele and Stemple [159]</td>
<td>29</td>
<td>12</td>
<td>92.4</td>
<td>72.9</td>
<td>21.1%</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Chapple et al [163]</td>
<td>39</td>
<td>12</td>
<td>97.0</td>
<td>84.0</td>
<td>13.4%</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>
IPSS and the QOL score were statistically significant for both groups at 3 and 18 months of follow-up. The increase in the mean \( Q_{\text{max}} \) of the TURP group was higher than that in the TUNA group, whereas no significant differences were found between the two groups regarding improvements in IPSS and QOL scores. There were no complications associated with the TUNA procedure, while after TURP 16 patients suffered from retrograde ejaculation, 4 from erectile impairment, 2 from urethral stenosis and 1 from urinary incontinence [168].

c) Meta-analysis

A recent meta-analysis [169] analyzed the data from two randomized trials [167,170], two non-randomized protocols [159,166] and 10 single-arm studies conducted on TUNA [153,155,156,159,171,172,173,174,175]. The meta-analysis was based on the difference in the mean score at the end of the study from baseline. In almost all studies the patients recruited had severe lower urinary tract symptoms and a mean IPSS of more than 20 before treatment. The effect of TUNA was a decrease of the mean IPSS by 50% from baseline at 1 year after treatment. This effect maintained up to 5 years. The \( Q_{\text{max}} \) increased by 70% from baseline after 1 year in virtually all studies and approached or exceeded 15 ml/sec. Although there was a tendency for the \( Q_{\text{max}} \) to decline slightly over time, the mean \( Q_{\text{max}} \) 5 years after treatment was more than 50% improved compared to baseline.

When only the two randomized trials are considered, the mean decline in IPSS was 11.6 after TUNA and 15.7 after TURP (difference statistically significant). The effect of TUNA therapy on \( Q_{\text{max}} \) (+7.0 ml/sec) was smaller than that of TURP (+11.6 ml/sec= statistically significant) [169].

This meta-analysis shows that TUNA is an effective and minimally invasive treatment for men, even with severe symptoms. There is a significant improvement in symptoms and flow rate after 1 year which persists for at least 5 years. TUNA therapy would appear to be an alternative to surgery and an attractive option for men who do not wish to undergo long-term medical therapy, for men who are poor candidates for surgery or those concerned about the side-effects of TURP [169].

d) Adverse effects

The most common post-treatment complication reported after TUNA is urinary retention, ranging from 13.3% to 41.6%. The retention is transient (12-48 hours) in the majority of patients [148,149]. A mild degree of transient macroscopic hematuria is noted in most patients for a period of 24 hours and does not require specific treatment [149].

Other common adverse event reported are storage symptoms, occurring in about 40% of patients in the early post treatment period. These are mild and transient in nature, usually lasting 1 to 7 days and rarely more than 2 to 4 weeks [148,149].

Postoperative urinary infection and epididymitis occur rarely (0% to 3.1%). The risk of infection is minimized by maintaining urine sterile preoperatively by the use of antibiotics [149].

Urethral strictures may occur in 0% to 1.5% of patients and are related to instrumention of the urethra. The risk of urethral stricture is smaller than after standard TURP [149].

Sexual dysfunction is rare after TUNA and urinary incontinence was not reported in any series [148,149].

e) Re-Operation

Although a 14% requirement for re-operation due to the lack of efficacy of the primary treatment with TUNA may seem low, it occurred within 2 years [161,167]. In addition, the 12.7% incidence reported by other authors also occurred within a 2 year period [159].

f) Indications

The patient most likely to benefit from TUNA would be the one who has lateral lobe enlargement and a prostate of 60g or less [171]. Patients with larger prostates, purely bladder neck hypertrophy, or median lobe enlargement are not ideal patients to receive this kind of treatment. However, they can be treated by rotating the TUNA catheter so that the needles will point posteriorly, with special care being taken in assessing the depth of their penetration into the prostate [148].

CONCLUSIONS

TUNA:
- Has good clinical outcomes that seem durable
- Has reported low morbidity
- Is outpatient based and performed under analgesia/anesthesia
- Is an option when instrumental treatment is indicated (except when absolute indication for surgery exists)
Ethanol and Botox have been described as possible agents for injection into the prostate. No data have been published yet on the latter.

Transurethral Ethanol Ablation of the Prostate (TEAP) is defined as a minimally invasive transurethral procedure to effectively treat patients with symptomatic BPO, by injecting anhydrous ethanol into the periurethral prostatic nodule under continuous urethroscopic irrigation. (see Figure 1)

Microscopically, the ethanol injection created a uniformly demarcated line of tissue necrosis, which did not extend to the capsule of the prostate or to the sphincter [176]. The integrity of the prostate capsule is said to act as a relative barrier to ethanol diffusion, and systemic absorption of ethanol is apparently minimal.

Several articles on intra prostatic ethanol injection have been published [177,178,179,180].

1. Efficacy of TEAP

After TEAP, IPSS and QOL score decreased significantly at 1 month and these improvements were sustained for 12 months (Table 1, 2). However, Goya et al [195] followed 17 patients for longer than 3 years (median follow-up for 4.3 years), and reported durable improvements in only 59%.

With regard to the maximum flow rate, an increase of 35% was seen 3 months after TEAP (Table 3) and the effect was mostly sustained through 12 months. The post-void residual volume seems to be decreased by TEAP [180,184,195], but this change has not been remarkable in some studies [182].

2. Complications

Plante et al [192] reviewed the complications of TEAP among 200 patients from 15 countries. Most patients do well with catheter removal 3 days after the procedure. Overall more than 90% of patients were able to void 96 hours after TEAP [192]. The most common reported adverse events were storage symptoms (21.5%), urinary retention (17.5%) and hematuria (13%), most of which resolved without intervention by one month post TEAP. Urinary incontinence, erectile dysfunction and retrograde ejaculation occurred in less than 5% of the time overall. Bladder necrosis was reported in three cases including one case requiring urinary diversion.

3. Re-intervention Rate

The reported re-intervention rate ranged from 7% after one year [194] to 26% after 3 years after TEAP [195]. TEAP conversion to TURP within 6 months was reported in 10% of the deep injection group and 15% in superficial injection group [186]. If the reported case series are continuously observed for another 4 years, the re-treatment rate may increase further.
Urinary drainage catheters function by passive bladder drainage whereas urethral stents, whether temporary or permanent, work on the principle of active drainage requiring a detrusor contraction. Urethral stents may act as substitutes for indwelling catheters, ideally replacing them and thus reducing the risks seen with catheters, such as infection, hematuria and overall discomfort. The ideal stent can be placed or removed atraumatically, has a high radial force, and can be used as a bridge before more permanent therapy in those not presently medically stable or at high surgical risk, or after procedures after which urinary retention can occur in the short term, such as microwave thermotherapy or brachytherapy. Stents can be temporary or permanent. Permanent stents are biocompatible allowing epithelialization and are therefore subject to less complications, whereas temporary stents do not epithelialize. Temporary stents can be either biostable or biodegradable. A stent must not extend beyond the bladder neck into the bladder, should cause no local tissue reaction, must be easy to place and remove, and should allow

### SUMMARY

One year follow up data from 5 case-series reports (evidence level 3) demonstrate similar success rates regarding improvements in IPSS, Qmax and QOL score. TEAP is effective, at least for one year, and might be a suitable option in patients with co-morbidities who are unfit to undergo TURP. With regard to durability, one year data only have limited value. A longer term result suggests a continued decline in success rate by 26%. Further follow-up for another 3-5 years is required before this procedure is considered to be a reasonable alternative treatment for BPO.

The local toxicity in the form of spreading necrosis warrants further research in establishing the safe injection site before it can be recommended and it can be put to regular clinical use.

### CONCLUSION

Remains investigational.

### VI. PROSTATIC STENTS

Urinary drainage catheters function by passive bladder drainage whereas urethral stents, whether temporary or permanent, work on the principle of active drainage requiring a detrusor contraction. Urethral stents may act as substitutes for indwelling catheters, ideally replacing them and thus reducing the risks seen with catheters, such as infection, hematuria and overall discomfort. The ideal stent can be placed or removed atraumatically, has a high radial force, and can be used as a bridge before more permanent therapy in those not presently medically stable or at high surgical risk, or after procedures after which urinary retention can occur in the short term, such as microwave thermotherapy or brachytherapy. Stents can be temporary or permanent. Permanent stents are biocompatible allowing epithelialization and are therefore subject to less complications, whereas temporary stents do not epithelialize. Temporary stents can be either biostable or biodegradable. A stent must not extend beyond the bladder neck into the bladder, should cause no local tissue reaction, must be easy to place and remove, and should allow
endoscopy through it. However, in reality both types are subject to misplacement, migration, poor tolerability due to the exacerbation of lower urinary tract symptom (LUTS) and encrustation.

1. PERMANENT STENTS

The following permanent stents will be discussed: the Urolume, the Memotherm, the Titan.

The original justification for permanent stents for BOO secondary to BPO was in men at high surgical risk. Several early reports outline short-term success (18 months) in these men [198,199] with success both in men with severe voiding symptoms and in those in frank retention. A result of these reports was the development of multicenter trials evaluating the use of permanent stents in men with BPO who were otherwise healthy. These included the North American UroLume Study Group [200], and the European Multicenter Study [201]. Two-year follow-up in these studies revealed significant and durable changes in the following: decrease in symptom score, post void residual volume and increase in maximum flow rate in men with and without urinary retention. Voiding symptoms were alleviated best, whereas men with storage symptoms had the most difficulty tolerating the stents. Sexual activity and spontaneous voiding returned to normal in most of those previously in retention. Complete epithelialization was noted in the majority at 12 months. Stent removal was performed in 17 (13%) and 21 (15.5%) patients at two years in both trials, mainly due to intractable detrusor overactivity, stent encrustation, stent migration, recurrent outlet obstruction, perineal pain and urinary incontinence. Common complications that did not necessitate stent removal and were managed conservatively included hematuria, hematospermia, UTI, urgency, retention, and stricture.

The stent with the longest follow-up is the UroLume endourethral prosthesis (American Medical Systems, Minnesota, USA). It is a woven tubular mesh composed of a nonmagnetic stainless steel alloy that is biocompatible and inert. Initial long-term follow up in the multicenter North American trial for BPO included 126 patients who underwent stent placement in 1990-92 [200]. A post approval study [203] of 32 patients had further follow-up beyond the closure of the original study date of July 1997. Maximum flow at baseline compared to 10 years showed a return to baseline 10.0/10.1 (n=9), however Madsen-Iverson scores remained above baseline, 13.8/5.8 (n=16). Tissue reaction remained unchanged in 14 appearing with no/mild changes, while 1 had moderate change. Six patients had stent explantation between 7 to 10 years, due to worsening of voiding symptoms, tissue overgrowth, prostate enlargement outside the stent, encrustation, and hematuria [203]. Four additional patients died, all from non-stent related events.

The Memotherm stent (Bard, Covington, GA, USA) is a permanent stent, and unlike the UroLume, is made from a nitinol alloy that is thermosensitive, biocompatible and flexible. Between 1993 and 1996, 123 patients considered poor operative candidates but necessitating TURP received the stent [205]. Mean prostate volume was 40 ml. Only 77 (62.6%) patients were able to void pre-operatively, with the remainder in retention and 27 (22%) demonstrating a weak/absent detrusor contraction. Mean age was 77.6 years. One, two, and four year follow up was achieved in 52, 26 and 4 patients respectively. Forty-four patients (36%) died during follow-up unrelated to stent placement. Eleven patients became immobilized from other morbidity and required catheterization. Average follow up was only 12.2 months, and therefore no generalizations could be made about long term follow up. Baseline characteristics for IPSS, QOL, Qmax and PVR were 24, 4.5, 7.4 ml/sec, and 154 ml respectively. At 1, 2, and 4 years, IPSS, QOL, maximum flow rate, and residual urine were: 8.8/7.6/5.7, 1.9/1.5/1.4, 13.0/16.4/14.8 ml/sec and 31/14.8/5.0 ml, respectively.

The authors observed that their complication rate and retreatment rate exceeded that experienced at equal time points from early UroLume data where voiding symptoms were transient (2-3 weeks) [200], and obstruction was absent or mild [199].

The TITAN Intra-prostatic Stent (Boston Scientific, Watertown, MA, USA) is a pure titanium mesh tubing with an internal diameter of 33 French, and is deployed under direct cystoscopic vision. Kaplan [206] reported on 144 patients with moderate to severe symptoms enrolled between 1991 and 1993 with mean follow up of 17.6 months, and mean age of 73.5 years. At 24 months, Madsen-Iverson symptom score improved from 16.3 to 6.2 (p<0.001) (n=19) and Qmax increased from 5 to 12 ml/sec (p<0.01). Cystoscopy revealed “varying degrees of epithelial covering and no evidence of encrustation” at intervals of 1 and 12 months. Eight patients required removal and redeployment due to poor positioning, 28 (19%) had the stent explanted for migra-
tion or treatment failures, 15 died, and 4 withdrew or were lost to follow up. Anticipated adverse reactions, most commonly storage symptoms (4%) resolved by 4 weeks. No comments were given on the number of stents requiring tissue resection secondary to tissue reaction.

2. Biodegradable and Temporary Stents

In this section data on the biodegradable stents, and non biodegradable stents, the Spanner, the Conticath and the Prostacoil will be presented.

Biodegradable stents are composed of poly-lactic acid and glycolic acid, and have a presumed advantage for temporary management of BOO in high surgical risk patients, where the stent would not need to be removed a later date [187]. They are self-expanding, promote little encrustation, and have an outer diameter between 21-24 French. They have been used in conjunction with minimally invasive therapies such as interstitial laser coagulation and microwave. However, strength retention time may be short, degradation is inconsistent, and the stents may cause worsening flow from obstructing fragments and are expensive [183]. At this time none are currently commercially available.

A number of small case studies involving a variety of temporary non biodegradable stents exist. Earlier generation stents were coils that were subject to a high rate of migration and encrustation. In addition, they would frequently worsen the voiding symptoms they were meant to alleviate. Herein we report the devices with the largest and latest series.

The Spanner (AbbeyMoor Medical, Minnesota, USA) is a temporary stent that resembles the proximal 4-6 cm of a Foley catheter and is designed to relieve BOO, improve voiding efficacy and maintain the bladder as a reservoir. The proximal end has a balloon similar to a Foley preventing distal migration, a urine port to allow drainage and a distal anchor that sits in the bulbar urethra attached by a suture spanning the external sphincter. A retrieval suture extends distally and is cut just proximal to the fossa for later removal. It is inserted with an inser-tion device. When pulling on the retrieval string the proximal balloon deflates allowing the stent to be removed. In the largest case series, thirty men with mean age of 68 years, of which 5 were in retention, had the Spanner inserted under local anesthesia [208]. Position was confirmed with a radiograph. Maximum flow rate, voided volume, residual volume and IPSS were measured. Mild urgency, stress and/or urge incontinence, and perineal discomfort developed in approximately 1/3 of cases, but resolved within two weeks. No patients dropped out of evaluation which was performed after placement, at 24 hours, 4 days, and every seven days thereafter. Significant changes were seen with maximum flow increasing from 8.2 to 11.6 ml/sec (p<0.001), PVR from 312 to 112 ml (p=0.004), and IPSS 22.3 to 7.1 (p<0.001). Voided volume only demonstrated a 1% improvement. Upon removal no significant encrustation was noted.

A group of 5 patients with severe LUTS after [I-125] brachytherapy for prostate cancer underwent Spanner placement an average of 40 days after implant. [189]. All patients had previously failed medical therapy. Mean age was 64 years, mean IPSS before and after brachytherapy were 5.4 and 25.2 respectively. Post-Spanner IPSS at 5 days decreased to 14.6 (p<0.03). Two patients requested stent removal at 1 week due to discomfort, while the other three had symptoms treated with tolterodine and continued with the stent for 30 days until planned removal. The two patients who had stent removal then developed acute urinary retention and were then managed with intermittent catheterization until voiding resumed at 7 and 10 days. The best Qmax improved from a mean of 13.9 ml/sec before brachytherapy to 23.2 ml/sec after the Spanner was inserted (p<0.03). The three who completed the course of treatment found that their urinary symptoms reverted to pre-stent levels after removal. Despite improvement in IPSS and flow rate, all had dysuria/pain from the stent that the authors attributed to radiation urethritis in the immediate post-treatment period.

A multicenter pilot study enrolled 64 patients with post-operative or temporary urinary retention who were treated with ContiCath (ContiMed Minneapolis, MN, USA), a temporary stent similar in concept to the Spanner [210]. A 20 French prostatic segment is anchored in the bladder with a proximal curl inserted with a trochar. The narrowed segment that passes the external sphincter ends with a long suture taped to the meatus that is used for later removal. The stent is not hollow but has 3 deep grooves that allow urine passage along side the stent. Sixty-one patients with stents placed were divided into three groups: group 1 (37) included those with non-neuropathic retention and retention less than 1 week; group 2 (19) included those with non-neuropathic retention with retention longer than 1 week; group 3 (5) included neuropathic retention with retention longer than 1 week. After insertion, the onset of
spontaneous voiding was recorded, and then patients were reassessed at 24 hours, and then every week until it was removed at 28 days. Within 3 hours, 34 (89%) in group 1 resumed spontaneous voiding regardless of the reason for retention (microwave, brachytherapy, general anesthesia). Eight (24%) experienced symptoms requiring removal including urgency, leaking, migration and pain. Of the 24 patients in both groups 2 and 3, only 3 (12.5%) resumed voiding within 3 hours of placement. Flow rates and residual urine were not recorded. The authors concluded it to be useful in only those with non-neuropathic causes of retention less than one week.

The Prostacoil (Instent, Eden Prairie, MN, USA) is a newer generation temporary prostatic coil stent made of nitinol and was designed to overcome the short-coming of frequent migrations (up to 75%) seen with earlier prostatic coils [192]. Prior to insertion the Prostacoil has a diameter of 17 French that expands up to 30 French once in situ. Wound on a delivery catheter it is composed of 3 parts: a prostatic urethral body, a trans-sphincteric head, and a bulb anchor head. In addition it allows endoscopy through it into the bladder. 65 patients with moderate to severe BOO treated by Prostacoil insertion have been reported [209]. Of these, 37 patients had the stent removed between 3-12 months when fit for TURP, while 27 continued to void “without difficulty” through the stent. One required removal for urgency, 5 required repositioning, and 14 had temporary dysuria and perineal pain. Advantages included ease of placement and removal and instrumentation if necessary.

Another example of a spiral prostatic stent is the Horizon prostatic stent. Two designs of this stent, differing in shape, have been the subject of study: the hourglass-shaped [216] and the bell-shaped [217] prostatic stent. Both designs are made of nitinol coiled wires with a temperature based memory for the shape and can be inserted in an outpatient setting, under local anesthesia, using a gun-shaped delivery system.

The hourglass-shaped stent has an increasing diameter towards both ends of the stent. The stent was tested in 35 patients with LUTS due to BPO [196]. In 5 patients, insertion of the stent failed, mainly because of anatomical limitations. After all placement procedures minimal temporary haematuria was observed. Spontaneous voiding was achieved in all patients, with immediate significant improvements in voiding parameters and symptom scores. At 14 days and at 3, 6, and 12 months, the stent was still in situ in 73%, 40%, 33% and 23% of the patients, respectively. The main reason for removal of the stent was migration (93%), in most cases towards the bladder. Due to the high migration rate, the hourglass-shaped stent was not suitable for clinical practice. An explanation for this was sought in the design of the stent. Therefore, the successor of the hourglass-shaped stent was designed with an increasing diameter towards the distal end only (bell shape) with the aim of preventing migration.

The efficacy, safety and durability of the bell-shaped nitinol stent were assessed in 108 patients with LUTS due to BPO [227]. Stents were successfully inserted in 97% of the cases. Spontaneous voiding was achieved in all patients, with significant improvements in voiding parameters and symptom scores. Significant improvements, however, are only maintained for a period of 1-3 months. The main complications were haematuria (19%), urge incontinence (22%) and migration into the bladder (15%). At 1, 3, 6, 12, 18, 24 and 30 months after insertion, the stent was still in situ in 85%, 54%, 36%, 31%, 26%, 22%, and 18% of the patients. The primary reason for removal of stents was worsening of symptoms. Upon removal, many stents appeared to have tilted within the prostatic urethra. This phenomenon could have been a contributory factor with respect to the worsening of symptoms after 1-3 months. Although the bell-shaped prostatic stent showed improved migration rates compared to the hourglass-shaped stent, for widespread clinical application improvements in stent design are essential.

3. UROLUME REMOVAL

Once epithelialized, for intact endoscopic removal, the overlying urothelium must be resected. The most common method [214] of resection is performed with a low monopolar cutting current using a standard resectoscope. Pure cut is used and resection is performed in smooth sweeping strokes. Small gullies are created on either side of the UroLume in the soft tissue. Longitudinal compression is performed to free it from the prostatic base, and forceps can then grasp and pull out the stent. As reported above, most explantations are performed within the first one or two years for incorrect stent positioning and/or migration, when the learning curve for stent placement is the steepest. A secondary method [215] for stent removal once all tissue has been resected is placement of a 0.038 inch guide wire through the stent into the bladder, removing and replacing the endoscope sheath next to the wire, then advancing
the stent into the bladder. The other end of the wire is retrieved and both wire ends are pulled to pull the stent into the sheath and out of the patient.

4. COMPLICATIONS OF PERMANENT STENTS

Hematuria and urgency can occur during stent placement and may persist until epithelialization is complete, however they are frequently mild and self-lmiting. Catheterization should be avoided before 4-8 weeks to allow for epithelialization to occur, so that if drainage is required, a suprapubic tube may be placed.

Urinary retention can occur from clots, but often is secondary to chronic retention from detrusor failure, or from obstructing apical tissue that may necessitate a second overlapping stent. This can be assessed by transrectal ultrasound.

Stress urinary incontinence will clearly occur if the stent overlaps the external striated sphincter, also, it appears that the stent can promote urge incontinence due to prostatic irritation. Stent repositioning may be necessary. Anti-cholinergic medication can address detrusor overactivity which is usually self-limiting.

Urothelial obstruction is benign in nature and occurs as a reaction to foreign body placement, yet tends to subside after 6-12 months. Although uncommon, if tissue ingrowth is severe, resection is necessary.

Perineal pain is usually self-limiting but has lead to stent explantation. Irradiated prostatic urothelium is expected to be more sensitive and may not tolerate the stent despite apparent successful voiding.

The critical moment for permanent stent placement is its release from the delivery mechanism. Precise evaluation of the contour and length of the urethra is necessary to properly select the appropriate stent size, but also permits proper stent expansion without too much shortening. Stent placement just distal to the bladder neck will allow epithelialization and avoid encrustation while still providing its intended relief of obstruction. Overlap of the bladder neck into the bladder is more apt to occur at the 12 o’clock position due to the oblique angle the prostatic urethra forms with the bladder.

5. DISCUSSION

The high rate of early removal of the UroLume, caused initial apprehension about the usefulness of the device. Many urologists avoided placement in order to avoid the potential need for manipulation and removal. Explantation rates were clearly higher within the first 2 years of placement, reflecting the learning curve. Adoption of stent placement in urologic practice should begin with live proctoring and careful patient selection, as well as appropriate informed consent.

Proper initial positioning is important to minimize later difficulties, however, the cylindrical stent will often not uniformly conform to the asymmetric prostatic urethra. This may lead to poor epithelialization and/or migration. Delayed epithelialization can lead to stent encrustation although only mild encrustation was often noted when exposed. Tissue reaction was more prominent in trial patients treated for BPO, with adenomatous obstruction within the stent, yet the retreatment rate for those patients at 10 and 12 years was minimal. Dropout rates were high, often due to patient death, as expected in an elderly population with comorbidities, and from explantation, so that only a fraction of those originally enrolled in the

Table 1. Summary of long-term evidence in the literature on urethral stents for BPO. M: Multicenter, P: Prospective, C: case series

<table>
<thead>
<tr>
<th>Author</th>
<th>Stent</th>
<th>Type</th>
<th>Follow-up</th>
<th>Study type</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osterling</td>
<td>Urolume</td>
<td>Permanent</td>
<td>7 yrs</td>
<td>M, P, C</td>
<td>3</td>
</tr>
<tr>
<td>AMS</td>
<td>Urolume</td>
<td>Permanent</td>
<td>10 yrs</td>
<td>M, P, C</td>
<td>4</td>
</tr>
<tr>
<td>Masood</td>
<td>Urolume</td>
<td>Permanent</td>
<td>12 yrs</td>
<td>P, C</td>
<td>3</td>
</tr>
<tr>
<td>Gesenberg</td>
<td>Memotherm</td>
<td>Permanent</td>
<td>4 yrs</td>
<td>P, C</td>
<td>3</td>
</tr>
<tr>
<td>Kaplan</td>
<td>TITAN</td>
<td>Permanent</td>
<td>2 yrs</td>
<td>M, P, C</td>
<td>3</td>
</tr>
<tr>
<td>Corica</td>
<td>Spanner</td>
<td>Temporary</td>
<td>57 days</td>
<td>P, C</td>
<td>3</td>
</tr>
<tr>
<td>Henderson</td>
<td>Spanner</td>
<td>Temporary</td>
<td>30 days</td>
<td>P, C</td>
<td>3</td>
</tr>
<tr>
<td>Corujo</td>
<td>ContiCath</td>
<td>Temporary</td>
<td>28 days</td>
<td>M, P, C</td>
<td>3</td>
</tr>
<tr>
<td>Yachia</td>
<td>Prostacoil</td>
<td>Temporary</td>
<td>365 days</td>
<td>P, C</td>
<td>3</td>
</tr>
</tbody>
</table>
post-approval study of the North American trial [203] and Masood et al. [204] were available for follow-up. It appears that those that survived the treatment had few adverse events, yet with a shrinking denominator, definitive conclusions can not be made. For optimal outcomes patient selection must include accurate urethral measurement, exclusions of patients who had radiation or TURP, and patients with inadequate detrusor function on preoperative studies. Permanent urethral stents are a suitable alternative for patients who are at too high a risk for TURP as the stent can be placed in less than 1/2 hour and under local or regional anesthesia, yet its use should be avoided in healthy men who can tolerate TURP or minimally invasive heat therapy. Moreover, with the rise in popularity of heat therapies for BPO in men who are high surgical risks and in men with BPO in general, the pool of available patients for permanent stents is likely to diminish. Stenting of the prostate is reasonable and effective but it does not seem likely that randomized trials of permanent stents versus TURP or heat therapies will be the most efficient use of time or resources. The Memotherm does offer the unique opportunity to become a hybrid stent that can act as a permanent stent where indicated, yet can be removed in a technically unchallenging manner similar to a temporary stent, if necessary. Further investigations in patients with the definitive indications for BOO treatment and for relief of temporary retention would be useful. Complication and retreatment rates were higher than with UroLume, but possible device modifications may address these discrepancies. The TITAN offers no advantage over the UroLume and requires the extra step of balloon inflation to maximally expand the stent, and leaves the impression of inferior epithelialization compared to UroLume. The available studies do indicate a place for temporary stents in relieving short-term obstruction from non-neurogenic causes such as after minimally invasive heat therapies for BPO, and brachytherapy. Their ease of placement and removal warrants further investigation in those with larger glands that undergo these procedures in order to predict which patients would prospectively benefit from prophylactic stent placement. In addition, the added cost of the device must be proven to decrease ultimate costs of out-patient or emergency room patient visits from post-procedure acute retention episodes in order to justify usage.

An inexpensive biodegradable stent that does not obstruct during degradation and whose degradation is predictable would be the ideal solution for relief of temporary obstruction.

A systematic review of the literature was conducted to evaluate the efficacy and safety of a range of MIT for BPO. The MEDLINE and Cochrane Library from 1992 through 2002 was searched to identify studies of 3 months or greater in duration and with at least 10 subjects in each treatment arm. The data were also extracted on study design, subject and treatment characteristics, adverse events, urinary symptoms and urinary flow. The following treatments were reviewed in table 1 and table 2. Details of the number of studies included as well as number of patients, clinical data and data on follow up duration are presented. We can observe that the baseline data of the patients treated with the different MIT are within the same range regarding age, prostate volume, IPSS symptom score, QOL parameter and uroflow parameters.

In Figure 1, 2 and 3 the follow up of the symptom scores, QOL scores and uroflow parameters are presented. It is interesting to observe that at first glance the symptomatic improvements and the QOL improvements more or less follow the same pattern, with a more pronounced improvement in the more ablative techniques. The durability, however, seems to be similar for the different therapies. A similar trend is observed for the flowmetry changes. The improvements for most therapies seem to be durable whereas significant better outcomes are achieved with more ablative technologies.

In table 3 and 4, the morbidity of the different therapies is presented. Urinary retention is more often seen following heat therapies and consequently, in these patients, a higher level of urinary infections is observed. Macroscopic hematuria is observed in most therapies but it is obvious that TURP has the highest transfusion rate. The highest rate of adverse events is also found for TURP in respect to urethral strictures, urinary incontinence and sexual dysfunction. Last but not least, the urological community is

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**CONCLUSION**

- Long term data (multicenter) for safety and efficacy for permanent stents exist, but the clinical use of permanent stents is limited.
- There is clinical use for temporary stents, which have potential, but they have not yet been adequately evaluated.

**VII. OVERALL CONCLUSIONS**

A systematic review of the literature was conducted to evaluate the efficacy and safety of a range of MIT for BPO. The MEDLINE and Cochrane Library from 1992 through 2002 was searched to identify studies of 3 months or greater in duration and with at least 10 subjects in each treatment arm. The data were also extracted on study design, subject and treatment characteristics, adverse events, urinary symptoms and urinary flow. The following treatments were reviewed in table 1 and table 2. Details of the number of studies included as well as number of patients, clinical data and data on follow up duration are presented. We can observe that the baseline data of the patients treated with the different MIT are within the same range regarding age, prostate volume, IPSS symptom score, QOL parameter and uroflow parameters.

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Figure 1. Baseline and follow-up QOL score (IPSS)

Figure 2. Baseline and follow-up maximum urinary flow (ml/s)

Figure 3. Baseline and follow-up post void residual (ml)
facing challenges regarding morbidity and costs reflected in catheter duration and hospital stay. The balance here is in favour of less ablative technologies with respect of hospital stay but less favourable for catheter duration.

The key issue that needs to be addressed is: which is the best choice of instrumental therapy? We feel that there is not one straightforward answer to that question. One needs to balance on the one hand the clinical outcomes, morbidity and technical improvement of these technologies. On the other hand there are obvious patients’ preferences as well as doctors preferences that may guide the eventual choice of therapy.

**IN SUMMARY WE CAN CONCLUDE THAT:**

- The efficacy of TURP is greater than the efficacy of MIT. However: HOLEP is equal to TURP
- The morbidity of TURP is higher than the morbidity of MIT
- The durability of TURP is longer than the durability of MIT
Table 3. Outline of different treatments versus side effects

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Retention</th>
<th>Transfusions</th>
<th>Hematuria</th>
<th>Urinary tract infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIFU</td>
<td>29.4%</td>
<td>0.2%</td>
<td>11.2%</td>
<td>2.5%</td>
</tr>
<tr>
<td>ILCP</td>
<td>18.3%</td>
<td>0.0%</td>
<td>7.6%</td>
<td>14.0%</td>
</tr>
<tr>
<td>TUMT</td>
<td>7.1%</td>
<td>0.0%</td>
<td>11.5%</td>
<td>4.0%</td>
</tr>
<tr>
<td>TUNA</td>
<td>27.4%</td>
<td>0.2%</td>
<td>14.1%</td>
<td>7.4%</td>
</tr>
<tr>
<td>TURP</td>
<td>2.5%</td>
<td>3.9%</td>
<td>4.6%</td>
<td>2.4%</td>
</tr>
<tr>
<td>TUVP</td>
<td>4.0%</td>
<td>0.2%</td>
<td>2.5%</td>
<td>1.8%</td>
</tr>
<tr>
<td>VLAP</td>
<td>14.7%</td>
<td>0.4%</td>
<td>2.3%</td>
<td>4.6%</td>
</tr>
<tr>
<td>HoLEP</td>
<td>3.4%</td>
<td>0.1%</td>
<td>3.1%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Table 4. Outline of different treatments versus adverse events

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Stricture</th>
<th>Incontinence</th>
<th>Erectile dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIFU</td>
<td>0.6%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>ILCP</td>
<td>0.3%</td>
<td>0.1%</td>
<td>0.7%</td>
</tr>
<tr>
<td>TUMT</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.2%</td>
</tr>
<tr>
<td>TUNA</td>
<td>0.6%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>TURP</td>
<td>3.4%</td>
<td>1.4%</td>
<td>1.1%</td>
</tr>
<tr>
<td>TUVP</td>
<td>1.7%</td>
<td>0.9%</td>
<td>1.5%</td>
</tr>
<tr>
<td>VLAP</td>
<td>0.9%</td>
<td>0.2%</td>
<td>0.4%</td>
</tr>
<tr>
<td>HoLEP</td>
<td>4.3%</td>
<td>1.2%</td>
<td>0.0%</td>
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CHAPTER 7

Committee 8

Prevention of Progression and Adverse Outcomes in BPH/BPE/BPO

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C. ROEHRBORN (USA)

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R. ROSEN (USA)
The concept of lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH) as a chronic progressive disease is relatively new. Historically, the emphasis of medical care for BPH on the part of both physicians and health care providers has been solely on the improvement of symptoms and acute treatment of outcomes, such as urinary retention with the subsequent need for surgery. This should not be surprising as urology as a specialty concerns itself principally with the treatment and management of acute illnesses, rather than disease prevention and chronic disease management or modification. In contrast, other medical specialties have long embraced the concept of disease prevention and disease modification, possibly leading to earlier and more successful long-term management. Examples of such programs in other therapeutic areas are the effort to prevent coronary artery disease, myocardial infarctions, and strokes by long-term management of serum cholesterol, or the disease management programs for diabetes mellitus. The actual events prevented in many of these examples are obviously more significant and potential lethal compared to the potential outcomes in LUTS and BPH, limiting the relevance of such comparisons.

Two developments in particular have led to a reconceptualization of the progression and management of BPH in this regard. For one, long-term follow-up data from population-based studies became available suggesting that in fact, both symptom severity and other signs and markers of BPH show evidence of progression over time. Secondly, long-term, randomized, placebo-controlled trials were conducted to study the effect of 5alpha-reductase inhibitors on LUTS, which revealed additionally that this class of drug may also be capable of preventing clinically relevant outcomes, such as acute urinary retention (AUR) and the need for subsequent prostate surgery.

For the purpose of this chapter we attempt to replace the often misused term “BPH” with the more appropriate terminology as outlined in the consensus document at the end of this volume which differentiates the following terms:

- **Benign Prostatic Hyperplasia (BPH)** is reserved for the histological pattern the phrase describes.
- **Benign Prostatic Enlargement (BPE)** is used when there is gland enlargement. It is usually a presumptive diagnosis based on the size of the prostate.
- **Benign Prostatic Obstruction (BPO)** is used when obstruction has been proven by pressure-flow studies or is highly suspected from flow rates, and if the gland is enlarged.

Prevention of progression, and disease management represent new concepts in BPE/BPO management from a urological perspective. Not surprisingly, there is a knowledge gap between specialists, i.e., urologists, and primary care providers as well as patients, and secondly, that the specific parameters as to when preventive therapy might be indicated are not, as yet, well defined. A recent survey suggested that most urologists are aware that alpha-adrenergic receptor blockers are effective in treating bothersome urinary symptoms, while 5alpha-reductase inhibitors are effective in arresting the progression of the disease and reducing prostate size. However, when primary care providers were asked the same question con-
cerning symptom alleviation versus progression of disease, they were far less able to distinguish effects of 5alpha-reductase inhibitors and alpha-blockers (Figure 1A and B). When patients were asked in the same survey, 72% of the patients stated that they were concerned about long-term outcomes, even more so than about acute symptom relief, and 73% of the queried men were willing to take at least one tablet daily to reduce the long-term risk of surgery, the amount of reduction, however, being not specified in the questionnaire (Roehrborn 2005).

Djavan et al., assessed 472 European urologists by means of a 15-item questionnaire regarding their views on BPH progression, etc. (Djavan, Nickel et al. 2002). On a scale from 0 to 10, with 10 being extremely important, improvement of the patient’s overall quality of life was rated at 9.0 with relief of LUTS at 8.5. Prevention of long-term complication was rated a little lower at 7.6, whereas reduction in prostate volume was only rated at 3.5. When asked about their concern with preventing BPO-related changes, deterioration of patients’ quality of life and urinary retention were both rated equally at 8.6. When asked about their confidence in certain risk factors as reliable predictors of progression, the highest rating was given to reduction in urinary flow rate being an important risk factor for progression. Seventy-seven and 79% of urologists believed in, and used evidence of a reduced flow rate as an important risk factor, and the overall rating for this variable was 7.2. Increases in post-void residual urine and LUTS severity was rated slightly lower, as was urodynamic evidence of obstruction. Two factors that were found to be significantly related to progression in randomized, control trials, namely increase in prostate volume and elevated serum PSA, were given ratings of importance of only 5.5 and 3.5, while an increase in age was rated in importance as 4.0, despite the fact that the Olmsted County Study of Urinary Symptoms in Men documented that progression of BPO is strongly related to age.

These observations suggest a need for a more precise definition of progression and outcomes in LUTS and BPH/BPE/BPO, increased awareness of the accumulating evidence for LUTS and BPE/BPO being a progressive condition with long-term outcomes, a deeper understanding of what baseline factors may be predictive of progression and outcomes, and ultimately, what the evidence and results are associated with efforts to prevent both progression and outcomes. Lastly, progression of LUTS has many causes which become more important with advancing age. Prior to initiation of treatment it is therefore important to attempt to identify these causes for the most targeted treatment.

II. DEFINITION OF PROGRESSION AND OUTCOMES

It is important first to have consensus on terminology and definitions. This is the nomenclature and definitions used throughout this chapter.

1. PROGRESSION

We refer to progression as a transition within the
same health state in the direction of a worsening or increase in severity, or to a higher level of threat for an outcome to occur. For example, consider a patient who during the course of observation, worsens from an IPSS score of 12 to an IPSS score of 17 points, or, whose urinary flow rate deteriorates from 15 to 9 ml/sec. This patient can be considered as having progressed in their symptoms or symptom score within the same specific health state.

2. OUTCOMES

Outcomes are defined as a transition from one health state to another. For example, consider a patient who urinates normally and develops AUR, i.e., inability to void at all. This patient has transitioned from the health state of ‘normal urination’ to the disease state of ‘urinary retention’. For the purpose of this chapter we will consider for the most part only adverse outcomes, ie changes from a more to a less desirable health state.

It is important to differentiate both theoretically and in practice, this progression in outcomes as both can be measured and analyzed in various ways. Classification into evidence-based categories of outcome is an important corollary of this definition.

3. TYPES OF PREVENTION

For purposes of the current chapter, we define prevention along the timeline of the progression of LUTS and BPH/BPE/BPO (Figure 2). As men age, histological benign prostatic hyperplasia develops in the prostate beginning approximately at the age of 40 and increasing relentlessly for each decade of life, ultimately reaching almost 100% prevalence by age 80 or 90. At the same time, the prostate begins a steady pattern of growth, also roughly beginning at about age 40, and continuing throughout a man’s adult life. LUTS although these may develop early in life, are likely not related to BPH, but possibly to issues such as bladder dysfunction, urethral stricture disease, infectious diseases, or other causes. LUTS secondary to BPH increases in severity, also, beginning at about age 40 and increasing steadily with advancing age.

a) Primary Prevention

Primary prevention is defined as the a priori prevention of histologic benign prostatic hyperplasia and associated LUTS. There is very little evidence available regarding the primary prevention of BPH. This evidence stems from two sources, namely a congenital abnormality characterized as a deficiency in the 5 alpha-reductase type II enzyme leading to a condition known as pseudovaginal perineoscrotal hypospadias, an under development of the prostate, and from our knowledge of men castrated prior to puberty to serve as eunuchs in the courts of the Ottoman empire and forbidden city of the Chinese empire (Wagenseil 1927; Walsh, Madden et al. 1974; Wilson, Harrod et al. 1974; Imperato-McGinley 1991; Imperato-McGinley, Gautier et al. 1992; Wilson and Roehrborn 1999). Results of these studies will be presented in detail in a later section.

b) Secondary Prevention

Far more common and in everyday practice are efforts at secondary prevention, implying that prevention of progression events after the condition has been diagnosed or treated; i.e., preventing further worsening of symptoms, flow rate, prostate growth increases, etc., in men already diagnosed with benign prostatic enlargement and obstruction. Late secondary or tertiary prevention can be referred to as the prevention of future progression or outcomes after an outcome has already taken place. An example for this would be a patient developing acute urinary retention, being given an alpha-adrenergic receptor blocker, and then a trial without catheter in hopes of re-establishing normal urination.

d) Direct Versus Indirect or Proxy Outcome Variables

There are several types of outcomes that can be categorized as direct health outcomes versus proxy or
**indirect** health outcomes. Direct health outcomes are those that can be immediately perceived by the patient and have a direct impact on his life or the quality of his life. Indirect or proxy health outcomes are those that cannot be immediately perceived by patients and do not have a direct impact on the patient. An example in the area of LUTS and BPO would be a patient who develops AUR. The inability to void and the pain associated with it are direct health outcomes. However, the slow growth of the prostate over years triggering the acute urinary retention event is an indirect outcome as it is not noted by the patient and has no immediate impact until the final event of AUR occurs.

**e) Efficacy or Outcome Variables**

It is further necessary to define different types of efficacy or outcome variables (Figure 3). **Continuous variables** are those that are measured along a continuous scale. Examples in the field of LUTS and BPO are the IPSS Score ranging from 0 to 35 points, the maximum urinary flow rate ranging from 0 theoretically to infinity, but more realistically to 50 ml/sec, a serum PSA ranging from 0 or undetectable to theoretically infinity, prostate size ranging from very small glands to glands over 200 grams, etc.

In contrast, categorical outcomes are outcomes that can be divided in certain categories. For example, scores on the IPSS scale of 7 or less points are defined as mildly symptomatic, while men scoring from 8 to 18 points are referred to as moderately symptomatic, and those above 19 points are defined as severely symptomatic. Categorical outcomes represent health states, and changes between the categories can be viewed as outcomes, while changes along a continuous variable can only be viewed and analyzed as a progression event. This minor conceptual difference can make a large difference in which outcomes are viewed as primary and what effect sizes will be needed to achieve significance in clinical trials.

A **dichotomous efficacy variable** is one variable for which there are only two states, yes or no, and an example for this would be the status of urinary retention being present or not present.

It is important to note that from an analytical point of view, categorical and dichotomous variables can be viewed as distinct health states, and analyzed as a probability of changing from one health state to another, while continuous variables can only be analyzed as changes along the dimension of the continuous variable, and are typically expressed as changes in means or medians.

![Continuous, Categorical and Dichotomous Outcome](Image)

**Figure 3.** The IPSS Score is a continuous variable running from 0 to 35 points. A division into mild, moderate, and severe symptoms converts this into a categorical outcome. A division into patients with mild symptoms as requiring no treatment versus those above 7 points requiring treatment converts the IPSS Score into a dichotomous outcome.
There is a need for better defined categorical outcomes in BPO/LUTS research, and it would be advantageous for future health care researchers to have clearer understanding of what constitutes optimal categorization of outcomes utilized. For example, it would be good to understand what constitutes a small, moderately, or markedly enlarged prostate, if and when these categories could be tied to significant probabilities of outcomes. If, for example, we would know that a prostate of 40 or more grams in size has a greater probability of creating AUR episodes, it would be important to quantify the probability of a patient moving from a small to moderately or markedly enlarged prostate in that risk group over time. Similar examples can be drawn for other continuous variables, such as IPSS score, Bother score, “BPH” Impact Index, Sexual Function questionnaires, flow rate parameters, prostate size, and serum PSA.

A final concept for consideration is the role of **static versus dynamic predictor variables**. For example, a patient who presents to a health care provider with a symptom score of 20 points and a quality of life score of 4 points (range 0 to 6) may be placed on medical therapy. The treatment decision is based on the observed static (baseline) variables at the time of presentation.

On the other hand, if this same patient after a temporary improvement eventually progresses, and is re-evaluated a year later with a symptom score of 22 points, and a quality of life score of 5 points, he may be referred for surgical treatment. In this case, however, the change in treatment plan is based on a **dynamic change** in variables. As it turns out, the majority of treatment decisions in daily practice are made based on changes and patterns of dynamic changes and variables, rather than on static baseline variables. In essence, a health care provider seeing patients with LUTS and BPH has only one chance to base recommendations and treatment decisions on static variables, namely when he sees the patient for the first time as a new encounter. At subsequent visits, she or he will make clinical decisions based not only on the baseline variables, but more likely on the dynamic changes taking place regarding the patient’s age, symptom severity, changes in prostate size, serum PSA and others. A pertinent example is the use of PSA velocity in the diagnosis of prostate cancer and the management of patients with PSA recurrences after curative treatment.

### III. EVIDENCE FOR PROGRESSION AND OUTCOMES (Table 3)

The evidence base for LUTS and BPH/BPE/BPO being a progressive condition associated with long-term outcomes stems from a variety of studies, each type of study having methodological advantages and disadvantages. Advantages and disadvantages of specific types of research designs are as follows:

1. **Population-Based Longitudinal Studies**
   - No predefined selection criteria.
   - Excellent ability to study the natural history of the condition.
   - Fewest biases of any study design.
   - Hawthorne effect which states that a population may behave differently when observed compared to when it is not observed.
   - No ability to study the effect of an intervention.

2. **Registries and Similar Databases**
   - Limited selection criteria are applied.
   - Good ability to study the natural history.
   - Ability to study the effect of an intervention.
   - Ability to study dynamic changes and variables as trigger points for treatment initiation and changes.
   - Limited biases.
   - Hawthorne effect.

3. **Clinical Practice Studies**
   - Some selection criteria apply as the study takes place in a physician’s or health care provider’s office.
   - Reduced ability to study the natural history.
   - Ability to study the effect of intervention.
   - Biases are common.

4. **Placebo/Sham Groups From Control Clinical Trials**
   - Strong selection criteria are applied.
   - Limited ability to use the placebo or sham groups of a proxy for the natural history of the disease.
   - Best ability to study the effect of an intervention.
   - Censoring of patients limits universally.
   - Lack of generalizability of the data.

5. **Effect of Selection Bias**

The effect of selection biases on the ability of the study design to answer questions regarding the natural history is worthy of a more detailed discussion.
Figure 4 A through D highlights the issue. Let’s assume that the possible universe of men with LUTS and BPO that can be studied ranges in age from 40 to 100 years. The possible range of symptom score ranges from 0 to 35, etc. (4 A). Figure 4 B would show a typical selection bias for a population-based study. For various reasons, patients above the age of 80 may not be included due to the fact that their life expectancy is not long enough to warrant their participation in a long-term study. For one reason or another, patients with a PSA of over 10 may also be excluded. A registry (4 C) may further restrict patients to those with a flow rate and symptom score within certain parameters, may not allow patients with excessively large prostate and may not allow patients who had already undergone a minimally invasive or surgical treatment for their condition. The most severe restrictions or selection biases are applied to patients participating in either medical or surgical interventions as shown in Figures 4 D and E. It is clear from this observation, that our ability to comprehend and predict the natural history of the disease is severely restricted based on these fundamental selection biases.

If we learn from the placebo-control group of a medical treatment trial that peak maximum urinary flow rate is a strong predictor of future episodes of urinary retention, this knowledge can be applied only to the specific patient population studied, i.e., patients who presented originally at the age of 50 to 80, with a symptom score from 10 to 30 points, a PSA of under 10 ng/ml, and most importantly, a maximum urinary flow rate between 5 and 15 ml/sec.

While this is an important aspect of selection bias, which narrows the observation spectrum and potential generalizability of findings, another important consequence is the ability to study correlations between parameters. It is an acknowledged truism in all areas of medicine that correlations are best studied in groups of patients with the fewest selection biases. For example, it is a well-established fact that blood pressure magnitude is a strong predictor of patients suffering a cerebrovascular accident (CVA). However, when focusing only on a very limited range of blood pressure scores, this correlation may lose its significance. Similarly, in LUTS and BPO studies, it is best to study correlations between age, symptom score, flow rates, prostate size, and PSA in relatively unrestricted populations, while in the severely restricted populations found in some arms of a clinical trial, there may not be a demonstrable correlation. Different study populations are likely to be found in population survey studies, registry studies and clinical trials, each with different selection biases as below.

IV. METHODOLOGICAL ISSUES AND DEFINITION OF PROGRESSION

There are several methodological issues relating to the definition of progression and the interpretation of progression measures, some of which are discussed in the following paragraphs.

1. THRESHOLDS OF IMPROVEMENT VERSUS GLOBAL SUBJECTIVE ASSESSMENT (GSA)

Other than for the most obvious dichotomous outcomes, such as urinary retention present - “yes”, or - “no”; there are surprisingly few established criteria and changes in defined variables that are accepted as validated measures of disease progression. One such example is a negative change in the IPSS score, for which there is at least limited evidence. However, the magnitude of the progression effect is not well established at this time. Hardly any evidence exists for the effects of progression on other continuous variables. Baseline values can effect or influence perception of outcomes. For example, Barry et al. demonstrated in 1995 that depending on baseline symptom severity (moderate versus severe), patients perceived an improvement of 7.4 versus 15.3 points from baseline IPSS values as “marked” improvement (Barry, Williford et al. 1995). A slight improvement was noted if the change was 1.9 versus 6.1 points. Patients perceived worsening of their condition if the symptom score increased by 3.3 versus 1.2 points in moderate and severe patients, respectively. Similar observations were made regarding the “BPH” Impact Index (range 0 to 13 points) (Table 1). There are other studies utilizing a similar approach to demonstrate the

Table 1. Mean absolute changes in IPSS Score and BPH Impact Index as they relate to levels of self-rated global subjective assessment in categories of marked, moderate, slight improvement versus no improvement versus symptom worsening. (Barry, Williford et al. 1995)
Figure 4 A – E. Demonstration of the selection bias. Patient population can be defined by age, IPSS, QMAX, TRUS volume, PSA, and treatments chosen. In the ideal setting, if no selection criteria are applied, no bias occurs. In population-based studies of LUTS and BPH, men are chosen over the age of 40, and oftentimes, other criteria are applied. In registries, again, age, but also symptom severity criteria are often applied limiting the generalizability. In controlled clinical trials, in addition, symptom score, flow rate, and prostate size criteria are applied limiting the generalizability similar to controlled medication trials in which again age, symptom score, flow rate, and other parameters are strictly controlled.
relationship between changes in the symptom score and the global subjective assessment or self-rating of symptom relief. One such example is the HYCAT trial (Roehrborn, Oesterling et al. 1996) as Figure 5 demonstrates, excellent relief of symptoms by self-rating is dependent on the change in the symptom score from baseline, but also depends on the absolute values of the baseline symptom score. For example, for patients at baseline with a score of 15 points, a 9-point improvement represents excellent improvement, but for those starting with a symptom score of 30 points, a 23-point improvement would represent an excellent improvement. Similarly, poor relief of symptoms is associated with a 1-point worsening versus a 3-point improvement for patients starting at 15 and 30 points, respectively.

Another example comes from the ALFUS study (Figure 6) (Roehrborn 2001). In this multi-center clinical trial, patients were asked to rate their satisfaction with treatment outcome following treatment with an alpha-blocker on a visual analogue scale (VAS) ranging from 0 to 100. Arbitrarily, the VAS scale was divided in five categories ranging from much better (80 to 100) to much worse (0 to 20). As shown in Figure 6, patients with a baseline symptom score of 10 points associated worsening with virtually no change in their symptom score, and a much worse condition of their illness with an increase in 2 to 3 points. Those starting with a baseline score of 20 perceived the same changes at –2 and +1 and 0 points, while those starting at 30 points, perceived worsening even if their symptom score improved by 4 points and perceived much worse outcomes than expected at a –2 point improvement. It is interesting to note that the same association between change scores from baseline and baseline values, and global subjective assessment measures cannot be shown for changes in the urinary flow rate. (Figure 7). As one can see, patients are not able to relate objectively measured changes in their urinary flow rate with perceived changes in the strength of their urinary stream. This is an important finding since it suggests that maximum urinary flow rate changes are not relevant to patients’ perception of change, at least not in the observed range of changes with current medical treatment modalities for BPO.

The relationship between patients’ self-rating of change and overall outcomes has been examined in the VA Coop study reported by Barry et al, the HYCAT study, and recently, the ALFUS study. Each of these studies have shown that patients can relate global assessment of relief of symptoms to numerical changes in symptom scales and other outcome scores. However, it must be noted that for patients beginning treatment at very different points on the symptom severity scale, different thresholds of response, and different amounts of changes are needed for patient’s to perceive an improvement versus no change, or a worsening in their symptoms. This introduces a second issue, with the definition of a single threshold as evidence for worsening. As Figure 8 clearly illustrates, the room for improvement is greater when patients start with a higher baseline symptom score, while the room for worsening is greater when the patients start with a lower baseline symptom score. In the MTOPS trial, a 4-point worsening was predefined as evidence for symptomatic worsening based on data published by Barry et al. Figure 8 would suggest, that a worsening in symptom score by 4 points or greater is likely to occur less often in patients starting out with high or very high levels of IPSS scores at baseline. The experimental evidence to prove this point comes from the MTOPS study. Paradoxically, the probability of a 4-point worsening in the symptom score is higher in all four treatment groups, particularly for patients starting at low-moderate levels of IPSS scores, versus those patients beginning the study with more severe symptoms. Clearly, this observation limits the applicability of a categorical threshold of IPSS score worsening as the definition of progression, if this is applied regardless of the baseline IPSS score. The degree of change is affected by the baseline level, The change required is not the same for all patients, i.e., patients along a spectrum of possible baseline symptom scores. In turn, it is very likely that this observation is also true for other continuous variables with a finite continuous measurement scale, i.e., not an open ended scale.

2. PLACEBO EFFECT VERSUS REGRESSION TO THE MEAN: INTERPRETATION AND EXTRAPOLATION

The last theoretical point to consider is the so-called “placebo effect” that is observed in nearly all placebo or sham control groups regarding both subjective, and objective measures, direct and indirect parameters of change. A significant component of the placebo effect consists of a unilateral regression to the mean induced by artificially imposed thresholds at screening or baseline assessment, and which are typically used as a component of the inclusion or exclusion criteria. This use of the measure as a component of the inclusion criteria for the study introduces a source of bias or artifact, and limits the informative
Figure 5. Relationship between baseline and mean change in symptom score with self-rating of symptom relief in the 12-month HYCAT trial. (Unpublished data from the HYCAT trial (Roehrborn, Oesterling et al. 1996; Roehrborn, Oesterling et al. 1996))

Figure 6. Baseline IPSS Score with a change in IPSS Score stratified in quintiles of visual analogue score question regarding the expectation of the treatment regarding from much better to much worse than expected.

Figure 7. Baseline maximum flow rate versus change in maximum flow rate stratified by response of the patients regarding the strength of their stream ranging from much stronger to much weaker stream. There is no discernible pattern of relationship identifiable.
value of placebo or sham control groups regarding the natural history, progression, and outcomes of the disease. In fact, the so called “placebo effect” may be one of the most inherently confounded effects in medical science, thus offering little if any meaningful information about the actual role of placebos.

In one typical study, for example, a group of 145 volunteers were asked to perform two flow rate recordings and fill in the IPSS, BPH Impact Index, and Quality of Life question twice within one month without any interim interventions. There were only very small differences in these parameters between the first and the second assessment, as anticipated. The mean IPSS score was 12.0 and 11.7 at assessment 1 and 2 (p=0.27) and the maximum flow rate 17.6 versus 17.5 (p=0.72). The correlation between the first and the second symptom score was r=0.892 (p<0.0001) (Sech, Montoya et al. 1998)

If this experiment had been a clinical trial, it is likely that flow rate or IPSS thresholds would have been applied to the population after the first flow rate measurement or symptom score assessment. When applying increasingly stringent enrollment criteria to the first assessment, a unilateral regression to the mean would be anticipated. For example, if at baseline, only patients with moderate levels of disease would be allowed to proceed into the study and ipso facto to the second measurement point (i.e., patients >7 points IPSS), the mean score at the first assessment was 17.8, but at the second assessment, it was 16.8 for a difference of nearly 1 point (p=0.035). The obvious explanation is that patients with a score of 7 or less points were excluded at the first observation, but not at the second observation. Thus, the natural variability of the symptom score resulted in more patients tending to have an “improvement” compared to a worsening in their symptom score from the first visit to the second, and thus, a unilateral regression to the mean takes place. (Figure 9). When applying the entry criteria more stringently, such as a symptom score of greater than 15 points, the difference between the means could be 22.0 versus 20.6 for an “improvement” of 1.4 points (p=0.026) (Table 2). Similar “improvements” can be induced for the BPH Impact Index and the Quality of Life score. Even the maximum urinary flow rate, perhaps the most objective measure of improvement, will show this effect when increasing threshold levels applied at baseline will induce an “improvement” of 1.5 to 1.7 ml/sec when the threshold applied is lowered from less than 15 ml/sec to less than 10 ml/sec at baseline.

In all controlled, clinical trials, the selection bias applies at baseline. This introduces a unilateral regression to the mean artifact, which makes it difficult to study the natural history and/or progression of continuous variables in placebo or sham groups of control clinical trials. This regression to the mean artifact adds to the true placebo effect, also referred to as a doctor, clinic, or “white coat” effect, while the quantitative contribution of each element can not under normal circumstances be assessed.

Figure 10 shows an example of regression to the mean occurring in the placebo group in the 4-year

Table 2. Regression to the mean artifact. Depending on the severity and restrictiveness of the criteria applied, an artificial “regression to the mean” improvement from 0.4 to 1.4 points can be produced without any active interventions. (Sech, Montoya et al. 1998)
Figure 9. Effect of regression to the mean. If only patients are chosen who score on the initial assessment more than 12 points, several of those patients will experience an artificial improvement in their symptoms even without any treatment at a second assessment point. Of all patients, many will experience either an increase or decrease in the symptom score, however, due to the artificial restriction, at assessment no. 1 the trend will be for a reduction, i.e., improvement in the score on the second assessment. (Sech, Montoya et al. 1998)

Figure 10 A – C. Regression to the mean artifact. Figure 10 A shows a unilateral regression to the mean plus the true placebo effect after which the symptom score slightly deteriorates back to baseline. In Figure 10 B, the initial regression to the mean artifact is eliminated showing just the slight worsening over time in the placebo group of the PLESS trial. Figure 10 C shows the actual data regarding prostate volume in the placebo group. As there is no threshold applied, there is no regression to the mean effect and the natural history is visible in terms of increase in prostate volume (original data adjusted from (McConnell, Bruskewitz et al. 1998))
PLESS trial. At approximately six months, patients in the placebo group seemingly improved by 1.5 points (Figure 10A). This likely represents a component of true placebo effect, but also a likely large degree of regression to the mean artifact. If one aimed to study the natural history or disease progression in the placebo group, one would need to begin the observation period at approximately six months after baseline. To eliminate the artifact, it would be necessary to alter the Y axis to reflect the true baseline as a starting point, or 0 point value for the symptom score. Figure 10B shows how this can lead to a different assessment of the natural history of LUTS symptoms in the placebo group of PLESS. It is important to note, however, that the regression to the mean artifact only applies to those parameters where a threshold is applied at baseline. In the PLESS study, no threshold was applied to the baseline prostate volume and prostates of all sizes were enrolled. Therefore, in the absence of a specific inclusion criterion for this measure, or an artificial threshold for inclusion, the prostate volume increases over time appear to reflect the true natural history at shown in Figure 10C.

V. EVIDENCE FOR PROGRESSION AND ADVERSE OUTCOMES IN BPH

The evidence for LUTS and BPH/BPE/BPO as a progressive disease and for long-term outcomes can also be divided into direct versus proxy/indirect health progression events as well as outcomes. Furthermore, the sources for the evidence can be divided into those derived from population-based studies versus placebo/sham-control groups with all the appropriate caveats mentioned in the previous sections.

When assessing the evidence for progression, i.e., the transition of a patient within a given health state, one can search for evidence that symptom severity and frequency, bother, BPH impact, disease-specific quality of life, sexual function, sleep disturbances, and many other subjective measurable direct health outcomes show evidence of worsening or deteriorate over time. Concerning indirect/proxy outcomes, we can consider evidence that urinary flow rate, post-void residual urine, urodynamic studies, and others deteriorate or worsen over time. In addition, growth of the prostate gland as well as changes of serum PSA over time might be considered as evidence for progression, although these measures should always be viewed as indirect/proxy outcomes.

Concerning outcomes, (i.e., transitions from one health state to another, as defined above), the evidence base is strongest for acute urinary retention (AUR), and the associated or subsequent need for invasive therapy by either minimally invasive surgical intervention (MIST) or direct surgical interventions. Other transitions between health states or categories within health states would be changes from one category of IPSS Score to another, development of urinary tract infections, renal failure, bladder stone occurrences, incontinence episodes, etc. One of the most common outcomes is that of health or health care-seeking behavior. With this, we mean to say that a patient may decide that his symptoms have worsened to a point that he is now prepared to seek medical care. Unfortunately, however, such health or health care-seeking behavior is not adequately documented in the current literature, and cannot be derived from placebo controlled or sham-control treatment groups. The only study designs that permit a true investigation of health or health care-seeking behavior are the longitudinal, population-based studies of which there are preciously few available for review.

The key studies supporting LUTS and BPH/BPE/BPO as a progressive condition are listed in Table 3). There are several population-based cohort studies that have longitudinal follow-up over variable periods of time, and in addition, there are a substantial number of placebo-control groups and practice studies that allow certain types of progres-

Table 3. Key study supporting key population based on placebo groups supporting BPH as a progressive condition.
sion events to be studied with the caveats listed in the above section.

1. Evidence for Progression of Direct Health Outcomes

While the most desirable way of measuring progression of direct health outcomes such as symptom severity and frequency would be an accounting of the proportion of men who over a stated period of time progressed from one health state to another, this evidence is less available. It is indeed more common for the outcomes analysis to be presented in a semi-quantitative way, indicating broadly whether or not symptoms have worsened over time. A good example for this is the Scottish prospective community-based study conducted in 217 men from Forth Valley, Scotland, and published by Lee et al (Garraway, Collins et al. 1991; Garraway, EB et al. 1993; Lee, Russell et al. 1996).

Figures 11 shows the changes in urinary symptom and bother status between baseline and three years of follow-up. From this report, it is evident that, by and large, significant increases occurred in mean symptom and bothersome levels for nocturia, urgency, dribbling, intermittency, and incomplete emptying. However, there was a high level of variability or fluctuation in the occurrence of the symptoms. At the same time, the bother associated with these symptoms in general increased, but again, there was a considerable degree of fluctuation associated with varying symptoms listed. An obvious shortcoming of this type of analysis is the fact that it does not allow us to quantify the worsening for a given patient, to assess the probability of a given patient to experience such worsening, and to assess the subjective correlates of symptom worsening over time.

The Olmsted County study provides a numerical estimate for the average annual increase in the IPSS Score in a cohort of community dwelling men in Olmsted County, Minnesota (Jacobsen, Girman et al. 2001). After 42 months of follow-up, the mean slope of the annual increase was 0.18 points/year, with a standard deviation of 1.22. The average annual change increased from 0.05 points/year among men in their 40s to 0.44/year among men in their 60s leveling off for men in their 70s. If one were to assume an approximately linear increase for a man starting out in his early 60s, this would translate into a 4.4-point increase spanning a decade in a given man’s life. Figure 12 (Jacobsen, Girman et al. 1996) depicts the progression of symptoms observed over four years stratified by decade of life suggesting the age dependency of the numerical increase or progression of symptoms in community dwelling men.

A slightly different picture emerges when examining men already diagnosed with LUTS. Djavan et al. (Djavan, 2004 #19807) followed a group of 397 men presenting to a urology clinic with mild symptoms defined as scoring less than 8 points on the IPSS Score. These men were followed for four years beginning with a watchful waiting protocol and were reevaluated every three months for 48 months total time. The authors assessed the cumulative incidence of clinical progression defined as worsening of the IPSS with migration from mild to moderate (IPSS 8 to 18 points) or severe symptoms (IPSS 19 to 35

![Figure 11. Changes in urinary symptoms and bother status between baseline and 3 years in Scottish community-based study. (Lee, Russell et al. 1996)](image1)

![Figure 12. Progression of IPSS Score stratified by age over four years in the Olmsted County study. (Jacobsen, Girman et al. 1996)](image2)
points). The likelihood of transitioning from one health state to another was 6, 13, 15, 24, 28, and 31% at 6, 12, 18, 24, 36, and 48 months, respectively. This is graphically shown in Figure 13.

Data from community-based longitudinal studies regarding changes in subjective parameters such as bother, BPH Impact Index, sexual function assessment, etc., are not readily available. Concerning progression in subjective parameters from placebo-control groups, the best study for evaluating these effects is the four-year randomized, placebo-controlled study comparing finasteride with placebo (PLESS study) (McConnell, Bruskewitz et al. 1998). However, due to the fact that patients were screened at study entry to have moderate LUTS, there is a noticeable “placebo” or regression to the mean effect observed during the first six months of this study. As discussed above, thereafter, the symptom score shows a trend towards worsening, however, any interpretation of such changes over time is based on an artificial resetting of the baseline to approximately a six month time point of follow-up and thus, is scientifically less valid. The limitations of using outcomes observed in a placebo arm of randomized, clinical trials of BPO in this regard was highlighted by the report of Roberts et al., who found substantially fewer outcomes in the placebo arm of the MTOPS study, compared to the Olmsted County community study cohort (Roberts, Lieber et al. 2005).

2. INDIRECT/PROXY HEALTH OUTCOMES

Indirect or proxy measures may provide additional data on the progression of disease. One of the most commonly used physiological or proxy measures of benign prostatic obstruction is the urinary flow rate. In the cross-sectional results of the Olmsted County study, a consistent decrease of approximately 2%/year across all age groups was seen. However, when analyzing these data by decade of life, men in their 40s had a 1.3%/year decrease, whereas those in their 70s had a 6.5%/year increase. The authors attribute this effect to the baseline selection factors that influence differences between the cross-sectional and longitudinal estimates (Roberts, Jacobsen et al. 2000). (Figure 14).

Virtually all BPO treatment studies utilized maximum urinary flow rates as an inclusion criterion, and thus, an inevitable regression to the mean artifact markedly diminishes our ability to learn much about the natural history or likely deterioration of the maximum flow rate in placebo-control groups.

Other indirect/proxy measures of interest for study-
of the clinic population in the Olmsted County, the average volume increase was in the order of 1.6%/year. This did not vary by age, but the trend was greater among men with larger prostates at baseline compared to those with smaller baseline prostates. The rate of increase was greater than estimated from the baseline cross-sectional data, but similar to the autopsy-based estimates (Berry, Coffey et al. 1984).

A sub-parameter or component of prostate volume, namely the transition zone or central zone volume was found to increase on average by 2.3%/year, and this increase does not appear to differ by age. In an earlier publication from the Olmsted County study, the mean overall annual growth rate was estimated at 0.6 cc/yr over the observation period of 3.5 years. The increase ranged from 0.4 cc in men aged 40 to 59 years, to 1.2 cc in men aged 60 to 79 years of age (Corica, Jacobsen et al. 1999).

In contrast, men participating in the PLESS trial and being treated with placebo experienced an annual growth of 1.8 cc/yr over four years with a range from 1.45 in men 50 or 60 to 2.4 cc in men 70 to 79 years of age. The patients in the PLESS trial had a larger baseline prostate volume and thus, these data are consistent with the observation from the Olmsted County study that baseline prostate volume is a reliable predictor of future prostate growth (McConnell, Bruskewitz et al. 1998).

3. THE TRANSITION BETWEEN HEALTH STATES OR OUTCOMES

a) Acute Urinary Retention (AUR) and Surgery

There are a variety of population-based studies available from which the overall prevalence and the annualized incidence rate of AUR episodes can be calculated. Similarly, data from several long-term placebo-controlled studies permits us to calculate the probability for an individual patient to experience urinary retention and the need for associated or subsequent surgery. Generally, the available literature on this topic approaches the subject using analyses by baseline risk factors, and a more detailed discussion of the predictors of progression can be found in the relevant section. Table 4 lists a number of watchful waiting studies, TURP versus watchful waiting studies, and other studies including the Olmsted County that allow for calculation of incidence rates. The incidence rate is expressed as AUR episodes/1000 patient years of follow-up, and ranges widely from 3.7 to 130. In the most carefully conducted study of this type – the Olmsted County study, the incidence rate is 6.8/1000 patient years, with a 95% confidence interval of 5.2 to 8.9 (Craigin, Hickling et al. 1969; Birkhoff, Wiederhorn et al. 1976; Ball, Feneley et al. 1981; Wasson, Reda et al. 1995; Barry, Fowler et al. 1997; Jacobsen, Jacobson et al. 1997; Meigs, Barry et al. 1999)

Figures 15 and 16 lists the cumulative incidence of AUR and surgery in the placebo arms of controlled BPO trials. While the incidence rates for each of these outcomes varies greatly from study to study, it is evident that these incidence rates are generally higher than those in the population-based studies or in the watchful waiting cohort shown in Table 4. The reasons for these differences are obvious, namely that the patient in the placebo arms of controlled tri-

Table 4. Acute urinary retention episodes in population-based studies.
als are typically diagnosed by a physician with BPE, thus, are more symptomatic, and likely to have an enlarged prostate gland at baseline. This affects the overall risk for both AUR and prostate surgery. (Andersen, Nickel et al. 1997; McConnell, Bruskewitz et al. 1998; Roehrborn, Boyle et al. 2002; McConnell, Roehrborn et al. 2003)

When assessing the overall risk of progression and adverse outcomes, it should be stressed that in most studies, the risk for AUR or surgery increased in a linear fashion over time. An example of this trend is shown in Figure 17 from the PLESS study (McConnell, Bruskewitz et al. 1998). The probability of either surgery or AUR as an outcome is shown to increase in a linear fashion in the placebo group, beginning at the start of the study to the end point at four years. Similar observations can be made from the dutasteride phase III trials (Roehrborn, Boyle et al. 2002; Debruyne, Barkin et al. 2004; Roehrborn, Marks et al. 2004).

Based on findings in the Olmsted County Community study, it does not appear that symptomatic worsening or prostate growth occurs in a linear fashion over time. However, certain conclusions regarding the likelihood of progression and developing certain clinical outcomes over time can be drawn.

Consider a 60-year-old man with no prior diagnosis of LUTS or BPE/BPO, who presents to a health care provider with a prostate size of 30 ml, a 10-point baseline score on the IPSS, an annual risk of progression of 1 ml volume increase of his prostate, and a 0.2-point increase in his symptom score. The annual risk of AUR for this individual is approximately 1%, with the annual risk of requiring any form of treatment of 3%, and the risk for surgery of 1%. Assuming a linear risk, this same patient at the age of 80 might have increased his prostate size by 20 ml to 50 ml, and have a symptom score from 10 to 14 points. The cumulative risk of AUR would be 20% with a cumulative risk for overall treatment to 60% and the risk for surgery 20%. (Figure 18 A). In contrast, a 60-year-old man already diagnosed with LUTS or BPH might be assumed to start out with an already enlarged prostate gland of 50 grams and a higher symptom score of 15 points.

The annual increase in the prostate size might be 2 ml for a total volume increase of 40 ml to an end volume of 90 ml at the age of 80. Similarly, the symptom score might worsen from 15 to 19 points, although the overall risk of AUR and surgery appears to be higher in patients diagnosed with BPE, leading to a cumulative risk of 40% for AUR, and 60% for surgery. (Figure 18 B).

Clearly, these predictions are based on generalized assumptions presupposing a linear risk of progression for all direct and indirect/proxy health outcomes, as well as for the risk of urinary retention and surgery. This assumption of linear progression has not been established for all risk factors; although by and large, it appears that linearity can be assumed at least for the risk of urinary retention or surgery.
Figure 17. The risk of AUR and surgery in placebo-treated patients in the four-year PLESS study is linear. (McConnell, Bruskewitz et al. 1998)

Figure 18 A-B. A and B demonstrate annual changes and changes over 20 years for 60-year-old men with no diagnosis of BPH or LUTS (A) and with diagnosed BPH and LUTS (Figure 18 B) based on annual changes in size, symptoms, risk of AUR, and surgery as reported in the literature.
While the previous section analyzed the evidence for progression and outcomes, in this section we will consider the evidence for potential baseline predictors of disease progression and outcomes. These predictors are in general factors that can be assessed at baseline, i.e., at the first encounter of the patient with the health care provider in either population-based studies or placebo-controlled trials. The analysis of outcome predictors has been extensive, and has focused on both direct as well as indirect or proxy health outcomes, subjective and objective outcome variables, health progression events, and clinical outcomes such as health care-seeking behavior, AUR, and the need for surgery.

1. Symptoms, Bother, Quality of Life and Sexual Function

One study assessing longitudinal changes and LUTS in African-American men is the Flint Men’s Health Study (Sarma, McLaughlin et al. 2004). The probability sample of 369 black men aged from 40 to 79 years residing in Genesee County, Michigan, without prior history of prostate cancer or surgery participated in prostate cancer screening. Of these men, 175 agreed to participate in a follow-up of over four years. The mean IPSS score at baseline and four years of follow-up were 7.1 and 7.0 points, respectively, i.e., no overall change was observed. However, men in their 40s had a decrease of –0.42 points, while men in their 70s, an increase of 2.1 points. Of those men reporting none or mild symptoms at baseline, 26.4% reported moderate to severe symptoms at follow-up. This is a clinically significant increase. Conversely, of those who had moderate to severe symptoms at baseline, 44.8% had none or mild symptoms at follow-up, while 55.2% remained in the moderate category or progressed to severe symptoms.

Figure 19 shows the percent of men experiencing either one or more-point increase versus three or more-point increase in IPSS scores, and corresponding decreases in scores by decade of life. It is evident that older men are more likely to experience a 1 or 3-point increase, compared to a decrease in IPSS scores, and vice versa in younger men. The authors examined predictors of progression versus regression in the IPSS Score, and in addition to age, prostate size at baseline was a significant predictor of progression. The odds ratio for a progression of the AUA Symptom Score over time for men with a baseline prostate volume of over 30 ml was 1.52, with a non-significant confidence interval from 0.69 to 3.38.

Figure 19. Longitudinal changes of LUTS severity and black Americans in the Flint study. (Sarma, McLaughlin et al. 2004)
The earlier study by Djavan et al (Djavan, Fong et al. 2004) also examined the risk of progression versus non-progression, stratified by pre-defined baseline parameters. In this study assessment, transition zone volume, “obstructive symptoms” sub-score, and serum PSA, were found to be significant predictors of progression from the mild category, to having moderate or severe symptoms. Higher baseline values of serum PSA, transition zone volume, and higher “obstructive symptoms” sub-scale scores were all seen in those men progressing, versus those not progressing. (Table 5). Interestingly enough, age was not a factor in the Vienna study (Djavan et al.) while it played a significant role in the Flint study, as well as in the well-known Olmsted County study, where symptom progression over time was more pronounced in men in their 60s, compared to men in their 40s and 50s, and flattened out almost completely for men in their 70s.

Table 5. Predictors of symptomatic progression of men with wide symptoms in a watchful waiting study. Serum PSA, transition zone volume, and obstructive symptom score are significant predictors of progression. (Djavan, Fong et al. 2004)

Despite the limitations in generalizing about progression effects from results of placebo groups in clinical trials, we have recently examined findings from the placebo group in the four-year PLESS study, which can be used to assess predictors of the natural history and progression of symptom severity, bother, interference of daily activities, as well as sexual function and general health perception (Bruskewitz, Girman et al. 1999; Roehrborn, Boyle et al. 1999). As shown in Figure 20 A and C, there is a consistent placebo/regression to the mean effect of similar magnitude and proportion regardless of PSA stratification. However, after this initial effect is taken into account, distinct differences emerge between those men in the lowest tertile of PSA, namely from 0 to 1.3 mg/ml, versus those in the intermediate (PSA 1.4 to 3.2 ng/ml) or in the higher PSA tertiles (PSA 3.3 to 12.0 ng/ml). The general trend seen is that men in the lowest PSA tertile maintained a placebo/regression to the mean effect, in terms of symptom severity, bother, and interference with activities. These men also experienced the least change over time in their sexual activity, sexual frequency, and general health perception. However, men in the intermediate to higher PSA category and intermediate to high PSA tertile, after the initial placebo/regression to the mean artifact phase, subjects showed a deterioration of symptoms, bother, interference with activity score, and a progressive decline in sexual activity, sexual frequency, and general health perception over the four years follow-up period. Despite the limitations of analyzing natural history phenomena in this placebo group, it is strikingly evident that higher PSA values at baseline predict an accelerated return of symptom severity, bother, and interference score compared to the baseline levels, i.e., an accelerated and worsened natural history of the disease, compared to those men starting out with lower PSA values.

The only controlled trial which truly assesses the risk of symptom progression, based on a priori definition, was the Medical Therapy of Prostatic Symptoms or MTOPS study (McConnell, Roehrborn et al. 2003). In this study, progression was defined as an increase in four or more IPSS points from baseline, as verified twice within a two-week window, or the development of urinary retention, recurrent urinary tract infections with an infection-free interval, development of socially unacceptable incontinence, or development of renal failure secondary to BPO. Progression to a surgical intervention for BPO was not defined as integral to the primary outcome. When stratifying the risk of symptomatic worsening by four or more points in the placebo group, Figure 21 demonstrates that the risk of symptomatic progression decreases significantly for men with baseline PSAs of less than 1.4 ng/ml compared to those with a PSA in the intermediate or higher range. Similarly, the risk of symptomatic progression nearly doubles for those men with baseline prostate volumes by transrectal ultrasound of > 40 ml, versus those with baseline values < 40 ml.
Figure 20 A - D. Stratification of the PLESS placebo group in PSA tertiles. It is evident, that the patients in the lowest PSA tertile experience a regression to the mean/placebo improvement and maintain that improvement in symptom score over the four years in terms of their symptom score (A), bother score (B), interference with activity score (C), and sexual function (D). The patients in the intermediate and higher PSA categories experience initial placebo/regression to the mean effect and then a worsening towards baseline. Figure D shows sexual activity, frequency, and general health stratified in PSA tertiles. Again, it is evident that the greatest decrease in these three parameters is experienced in the men with the highest PSA tertile at baseline.

Figure 21. Association of baseline PSA and prostate volume in convenience tertiles in the MTOPS trial and symptomatic progression, i.e., (greater than 4-point worsening). A significant difference exists between men with prostate volumes less than 40 and over 40 ml.
2. Urinary Flow Rate

Clear evidence for the rate of decline in urinary flow rate comes from the Olmsted County Study. This study established a consistent decrease in maximum flow rate of 2%/year across all age groups in the cross-sectional results. The annual change in this variable based on longitudinal follow-up ranged from 1.3%/year decrease for men in their 40s, to a rate of 6.5% decrease for men in their 70s.

Similar to the above-described results of the placebo group in the PLESS study, maximum urinary flow rate changes can also be stratified in that study by PSA tertiles (Roehrborn, McConnell et al. 1999), (Figure 22). As is evident, men in the lowest PSA tertile in the placebo group of PLESS experienced a mild improvement in the maximum maximum flow rate of about 1 ml/sec. Those in the middle tertile experienced an initial placebo (or regression) effect, but then a return to baseline, while those in the highest PSA tertile experienced initially no change and then a sustained deterioration of the maximum urinary flow rate by –1 ml/sec. The phase III dutasteride studies (Roehrborn, Boyle et al. 2002) found a similar relationship between baseline serum PSA scores, and changes in maximum urinary flow rate for the placebo group, (Figure 23). While in this study only patients with a PSA > 1.5 ng/ml were included, there is a trend towards decreasing placebo/regression to the mean effects over two years, with the subjects in the highest PSA quartile (i.e., > 6.0 ng/ml) showing no change in maximum flow rate over the course of the study.

3. Prostate Volume

Detailed analyses are available regarding changes in prostate volume and predictors thereof from a number of studies. In the Olmsted County study, a detailed analysis of annualized percent volume increases stratified by various baseline parameters was performed (Table 6) (Jacobsen, Jacobson et al. 1997). As is evident, the median percent volume increase is nearly identical for men in their 40s compared to men in their 70s, and independent of peak urinary flow rate, as well as mild versus moderate to severe baseline symptoms. However, greater increases in prostate volume are observed for men with larger prostate volumes, as well as for those with higher serum PSA values at baseline (Roberts, Jacobsen et al. 1997; Rhodes, Girman et al. 2000).

The placebo group of the four-year PLESS study also permitted an analysis of predictors of prostate growth over time, with the usual caveats to be considered (Roehrborn, McConnell et al. 2000). Figure 24 demonstrates the percent change of prostate volume stratified by PSA tertiles versus decade of life (men in their 50s, 60s, and 70s). As is evident, men in the lowest PSA tertile show a volume growth of 7.4% over four years for an annualized growth of 1.9%, compared to those in the intermediate PSA category of 16.2% (for an annualized growth of 4.1%), and those in the highest PSA category 22%, resulting in an annualized growth of 5.5 points in this group. Of note, the stratification by age in the placebo group yields considerably smaller differences, i.e., age does not play as much of a role in men...
already diagnosed with BPE in predicting future prostate volume increases, compared to the baseline PSA score. A striking example for this can also be seen in a quartile PSA analysis of the relationship between baseline PSA and the median percent of change in transition zone volume at two years in the placebo group of the dutasteride study. (Figure 25). The median percent change ranges from 0.8 for an annualized increase of 0.4%, to an increase of 10.4% (for an annualized increase of 5.2%). This occurs in the highest quartile of men with a PSA of > 6.0 ng/ml. Comparing results of the PLESS placebo group with those of the dutasteride placebo group, in the highest PSA stratum, the annualized volume increase is 5.5 versus 5.2%, a very similar and thus, seemingly reproducible rate. When considering this, it appears that over a 10-year period, a man starting out with LUTS and BPE and a PSA at 4 or above, may experience up to a 50% increase in prostate volume or, for an example, an increase from 40 to 60 or 60 to 90 ml.

Figure 26 shows the total prostate volume, the absolute and percent changes in prostate volume in the placebo group of the MTOPS study (McConnell, Roehrborn et al. 2003). The prostate volume at baseline increases substantially for all men in this age group. However, neither the absolute nor the percent change over the five-year observation period differed substantially for men in their 50s, 60s, or 70s. This data corroborates the findings from the PLESS study suggesting, that in placebo-control groups, prostate volume increases over time are more influenced by baseline PSA compared to baseline age. This may be related to the selection criteria applied at baseline and population selection biases, as discussed above. In contrast, baseline serum PSA again in the MTOPS study proves to be a powerful predictor of future prostate growth in regards to both the total volume and the transition zone volume. (Figure 27).
Figure 25. Relationship of baseline PSA with a median percentage of change in transition zone from two years in the Dutasteride phase III study.

Figure 26. Total prostate volume (yellow), percent change in prostate volume (green) and total prostate volume absolute change in red stratified by decade of life in MTOPS. Baseline prostate volume is higher in older men, however, neither percent nor absolute changes are different between men in their 50s, 60s, and 70s.

Figure 27. Change in total prostate volume and transition zone volume (yellow and red) stratified by baseline PSA quartiles in the MTOPS study placebo group. In the lowest quartile, the total prostate volume is either 5 ml or 1 ml/year, while in the highest quartile, it increases to 15 ml or 3 ml/year.
lowest PSA quartile, an overall increase in prostate volume of 5 ml (or an annualized increase of 1 ml) is observed, while in the highest PSA quartile, the overall increase is in the range of 15 ml, or 3 ml/year. Similar, although numerically smaller, changes in size are observed for the transition zone.

Barry et al. followed 500 potential candidates for elective prostatectomy who were treated medically in five North American urology practices over a period of four years. Complete data were obtained on 371 “survivors”. Over the follow-up period, 10, 24, and 39% of patients originally presenting with mild, moderate, and severe baseline symptoms had undergone surgery, while 27, 31, and 27% of those were receiving medical therapy. This resulted in 63%, 45%, and 33% of patients who had discontinued treatment at four years (Barry, Fowler et al. 1997) (Table 7).

Another investigation of health care-seeking behavior for men with urinary symptoms comes from the Olmsted County study (Jacobsen, Girman et al. 1995). In the clinic study of 475 men, this study found that men with moderate to severe symptoms were 3.4 times as likely to have sought medical care in the previous year compared to those with mild symptoms. Men with enlarged prostates of over 40 ml were 3.9 times as likely to have sought health care and men with maximum urinary flow rates of under 10 ml/sec were only slightly more likely to have sought health care. Seventy-six percent of men who sought medical care had prostate enlargement, reduced maximum flow rates, or moderate to severe symptoms, while only 55% of men who did not seek health care had mild symptoms, normal prostate volumes, and normal maximum flow rates. This suggests that clinical, physiological, and anatomical measures of LUTS and BPE/BPO did not adequately distinguish men who sought medical care for their urinary symptoms from those who do not. On the other hand, investigators in the Olmsted County study, (Roberts et al.,) reported that men who were significantly embarrassed or worried about their urinary function were more likely to have sought medical care for their symptoms compared to those who were not. . The association between health care-seeking behavior and embarrassment or concern was especially strong among men with little or no bother associated with their urinary symptoms (Roberts, Rhodes et al. 1994). The role of psychological predictors of health-care seeking or other outcomes warrants further investigation.

4. AUR AND SURGERY

In reviewing predictors for acute urinary retention (AUR) and surgical intervention for LUTS and presumed or proven BPO, significant and well-analyzed data are available from population-based studies, as well as cohort designs and placebo-controlled studies.

Arrighi et al. reported in an early study in 1990, that the need for surgery was strongly dependent on baseline factors such as change in size and force of stream, sensation of incomplete emptying, and prostate enlargement as noted on DRE (Arrighi, HA et al. 1990) (Figure 28). In population-based studies, it has been known for sometime that age is a strong predictor of the incidence of AUR (Meigs, Barry et al. 1999) (Figure 29), as data analyzed by Meigs et al. from the Physicians’ Health Study clearly demonstrates.

In the Olmsted County study, the relative risk of AUR and treated significantly for men in their 70s compared to younger men, for men with moderate to severe symptoms compared to those with mild symptoms, and for men with a reduced maximum urinary flow rate of less than 12 ml/sec (Jacobsen, Jacobson et al. 1999). (Figure 30).

The focus on psychological factors (e.g., worry/distress) as predictors of health care seeking behavior, observed in the Olmsted County study, was assessed further in the VA Cooperative Study comparing a cohort of moderately symptomatic men, and randomizing them to either immediate TURP or watchful waiting (Flanigan, Reda et al. 1998). Over time, it was observed that the patients with high baseline bother scores crossed over from watchful waiting to a TURP in a significantly higher proportion compared to those with low bother scores at baseline. (Figure 31).
Figure 28. Need for surgery by baseline risk factors and presence or absence of prostatic enlargement. (Arrighi, HA et al. 1990)

Figure 29. Incidence of acute urinary retention stratified by decade of life in population-based studies. (Meigs, Barry et al. 1999)

Figure 30. Relative risks of acute urinary retention stratified by baseline parameters (age, symptom severity, maximum urinary flow rate). (Jacobsen, Jacobson et al. 1997)

Figure 31. Risks of watchful waiting in patients crossing over to TURP stratified by bother. It is evident that patients with high bother more commonly cross over to surgery. (Flanigan, Reda et al. 1998)
An informative analysis of the role of baseline variables in predicting the risk of medical or surgical treatment overall, or for needing a TURP, can be seen again in findings from the well-known Olmsted County study. The risk for treatment in this study was increased for men in their 50s, 60s, and 70s compared to those in their 40s, and for those with moderate to severe symptoms, compared to those with mild symptoms. Furthermore, a reduced urinary flow rate, prostate volume over 30 grams, and a PSA of over 1.4 predict an increased risk for treatment compared to those with a normal flow rate, small prostate volume, and a low serum PSA. (Figure 32) (Jacobsen, Jacobson et al. 1999). Age plays a major role as seen in Figure 33, which shows the cumulative incidence of overall treatment and TURPs stratified by age. It is noteworthy, that the risk of overall treatment as well as the risk for surgical treatment appears to be linear, i.e., predictable over time.

Extensive information regarding baseline predictors of the risk of retention or surgery comes from three placebo-control arms of the dutasteride phase III studies, the PLESS study, and the MTOPS study. In dutasteride phase III studies, patients were enrolled who had a baseline prostate volume of over 30 ml and a baseline serum PSA of greater than 1.5 ng/ml. The relationship of baseline PSA with the proportion of patients experiencing AUR and/or requiring BPH-related surgery is shown in Figure 34 A and B. The incidence rate of AUR increases from 1.6 to 9%, while the proportion of subjects requiring BPH-related surgery from 2.9 to 7.5% stratified in quartiles of serum PSA (Roehrborn, Boyle et al. 2002; Debruyne, Barkin et al. 2004).

Figure 35 A and B shows the cumulative incidence of progression events in the placebo-control group of the four-year PLESS study (Roehrborn, Boyle et al. 1999). Of note, prostate volume was measured by MRI only in a subset of 10% of patients. The tertile analysis groups these patients according to prostate volume (40 to 41 grams, 42 to 57 grams, and 58 to 220 grams), while the PSA tertiles have been described above. As is evident from the figure, the risk of spontaneous retention, precipitated retention, or the combined spontaneous plus precipitated or total AUR rate, as well as the risk of surgery increases with both increasing prostate volume as well as increasing serum PSA tertiles. The overall risk of surgery or AUR reaches 22% in the highest prostate volume group, and 20% in the highest PSA tertile, while it is only 11% and 8% in the lowest volume and PSA tertile groups, respectively. Figure 36 shows that the risk of AUR or surgery is indeed increased in a linear fashion with increasing serum PSA. The higher the PSA threshold along the X axis, the greater is the risk for both urinary retention or surgery, suggesting again that this is a linear risk and that all thresholds chosen are artificial. In line with this interpretation, there is no obvious break point between patients at low versus high risk (See Figure 36).

Additional information regarding the risk of AUR stratified by baseline prostate volume and serum PSA comes from the MTOPS study (McConnell, Roehrborn et al. 2003) As Figure 37 shows, the risk of AUR increases with increasing serum PSA and specifically, doubles with a PSA of greater than 4.0 ng/ml compared to those with a lower PSA. The risk of AUR increases although much less noticeably with an increase in prostate volume from less than 20 to over 20 ml.

A comprehensive evaluation of clinical predictors of spontaneous urinary retention across pooled data of placebo-treated patients in clinical trials was reported by Roehrborn et al.(Roehrborn, Malice et al. 2001). More than 110 variables were considered individually and in combination as predictors of AUR using the logistical regression analysis and classification and regression tree method (CART) with a split-sample approach. Data from over 5000 patients were included in the analysis. A five-variable model including the baseline parameters of serum PSA, symptom problem index, maximum urinary flow rate, frequency of urination less or equal to two hours, and urinary hesitancy was found to perform best, however, it performed only slightly better than serum PSA alone as a predictor of spontaneous AUR. In the combined data set, the area under the curve for the receiver operating characteristics was 0.706 for the five-variable model and 0.709 for PSA alone. The overall algorithm including all parameters yielded an AUC value of 0.754. This study clearly demonstrates that PSA, at least in patients in clinical trials diagnosed with LUTS and BPE, is indeed the most powerful predictor of spontaneous AUR.

As discussed earlier, many decisions in clinical practice are made based on changes in variables or dynamics predictors during periods of observation. Data regarding dynamic variables or changes of variables during follow-up are extremely rare, although in clinical practice they probably constitute the most common reason for a change in therapeutic regimens. A recent analysis of a real life practice study suggested that, in addition to a previous episode of
Figure 32 – Part I and II. Baseline variables and risks for BPH treatment stratified by age, symptom severity, maximum urinary flow rate, prostate volume, and serum PSA. Men over the age of 50, those with more than moderate or severe symptoms, peak urinary flow rate under 12 ml, prostate size over 30 ml, and serum PSA greater than 1.4 experience greater risks for treatment in the Olmsted County study. (Jacobsen, Jacobson et al. 1999)

Figure 33. BPH treatment and TURP. BPH treatment (left) and TURP treatment (right) stratified by age in the Olmsted County study. Older men experience more treatment and are more commonly referred for TURP. (Jacobsen, Jacobson et al. 1999)
Figure 34 A - B. Relationship of baseline PSA with the proportion of subjects experiencing AUR and BPH-related surgery in the Dutasteride phase III studies placebo group.

Figure 35 A - B. Cumulative incidence of progression events in PLESS stratified by MRI volume tertiles in the placebo group and by PSA tertile (B). Patients with larger prostate volumes and higher serum PSA values have a greater likelihood of progression compared to patients with lower PSA and prostate volume. (data from PLESS study (Roehrborn, McConnell et al. 1999))
Figure 36. Cumulative incidence of AUR (left) and surgery (right) stratified by baseline PSA threshold in the placebo group of PLESS. The risk for AUR and surgery increases nearly linearly with increase in serum PSA. (data from PLESS study (Roehrborn, McConnell et al. 1999)

Figure 37. Association of baseline PSA and prostate volume and risk of acute urinary retention in the placebo group of MTOPS stratified by convenience tertiles. The risk of progression increases dramatically when the PSA is over 4, and for patients with prostate volumes over 20 grams.
AUR, a rise in the IPSS score or the bother score under treatment were the most powerful predictors of future episodes of AUR and BPO-related surgery, and in fact, more powerful than either age, baseline PSA, or baseline IPSS and bother score. (Figure 38) (Emberton et al. AUA and EAU abstract). This is an important observation, which warrants replication and further investigation.

Table 8 (Sections 1 and 2) lists the evidence for progression/outcomes in population studies and placebo-control groups in clinical trials, as well as the evidence for predictors of progression. The tables list the types of predictors studied across the top row, and the outcome variables or parameters of progression down the left-hand side of the table. In general, there is reasonably good concordance in the evidence for progression from population-based studies and placebo groups, although the evidence of progression from placebo-control groups is limited by the described regression to the mean artifact. Regarding predictors of progression, however, good to excellent evidence is available from both population studies, as well as placebo-control groups for many of the potential predictors and reported outcomes. Notably missing from this list is evidence for the role of urodynamic studies in predicting progression and outcomes. This is likely due to the invasive nature of urodynamic testing.

Considering evidence for prevention of progression and outcomes, we refer to the initial discussion regarding primary versus secondary prevention, and early secondary versus late-secondary or tertiary prevention.

1. PRIMARY PREVENTION

Primary prevention implies that the development of a disease and its complications is prevented entirely, while secondary prevention refers to the prevention of further symptomatic deterioration of worsening of the condition. Late secondary or tertiary prevention may refer to the prevention of an outcome after an initial event has already taken place (e.g. AUR). Obviously, in the area of LUTS and BPH, the literature on prevention is concerned mostly with secondary or tertiary prevention, although primary prevention in this condition is not only theoretically possible, but may also be practically achievable.

It is known that androgen action is required for the development of the prostate during androgenesis. Growth of the prostate and the development of BPH do not occur in men with mutations of the androgen V e
Table 8 – PART I - II. Evidence for progression/outcomes and predictors of progression/outcomes in population-based studies (Part I) and placebo groups (Part II). The evidence is rated for each of the parameters listed in the first column for both population-based studies and placebo group, and for the predictors in the various columns. (Jacobsen, Jacobson et al. 1999)
receptor with profoundly affected function. (Wilson and Roehrborn 1999) or in men with congenital deficiency of the 5alpha-reductase type II referred to as male pseudohermaphroditism.(Imperato-McGinley 1991) Ultrasonography was performed on male pseudohermaphrodites with a 5alpha-reductase type II deficiency and the results compared to age-matched controls. In addition, six of these patients underwent MRI studies of the prostate, as well as their heterozygote fathers. The prostates of the male pseudohermaphrodites appeared as a plate-like soft tissue structure posterior to the urethra on both imaging modalities. The prostate volume was significantly smaller (approximately .01% compared to the volume of age-matched controls). The biopsies performed on two of such affected individuals revealed stromal tissue only. These results correlate with undetectable serum PSA levels in affected subjects, suggesting an atrophic epithelium or lack of epithelial differentiation altogether. There was no difference, however, in the prostate size between the heterozygous fathers and age-matched controls.

The effect of pre-pubertal castration on the prostate has been examined in several populations. It has been shown, for example, that the prostate becomes atrophic in eunuchs serving in the Ottoman Court who were castrated prior to puberty. (Hikmet et al, New York Academy of Med, 1901). In addition, the prostate was found to be very small or non-palpable in a group of eunuchs serving at the Imperial Court in the Forbidden City in Beijing, China. Autopsy on a single 40-year-old eunuch castrated and emasculated prior to puberty revealed a 4-gram prostate size gland. Digital rectal examination on 26 eunuchs with a mean age of 72 and duration of castration of 54 years revealed a non-palpable prostate in 21 of 26 (81%) of affected individuals (Wu and GU, EORTC Genitourinary Group, 1991).

These observations indicate that primary prevention of BPH is indeed possible by either pre-pubertal castration, or by a congenital deficiency of the 5alpha-reductase type II enzyme leading to a significant deficiency of dihydrotestosterone at the pivotal time of the development of the prostate and later on, development of BPH. Incidentally, prostate cancer has also not been reported in either the eunuch group or in the individuals affected with the 5alpha-reductase type II deficiency syndrome.

2. Secondary Prevention

a) Symptoms, Bother, Quality of Life

In contrast to primary prevention, secondary prevention has been extensively studied and is a well-documented strategy in the field of LUTS and BPE/BPO. When looking at disease progression as a transition within one health state, it is evident that the prevention of progression of symptoms, bother, interference with daily activities, quality of life, sexual function, and other direct outcomes are difficult to quantify and analyze. The same is true for the indirect or proxy health outcomes, such as changes in maximum urinary flow rate, post-void residual urine, urodynamics, growth of the prostate, and PSA changes over time. The reason for this is a lack of evidence to suggest what margin of change should constitute clinical progression, with the exception of the aforementioned threshold of worsening in IPSS scores.

For the other progression events, a clearly defined margin of change is needed which would constitute true progression. This leaves only two choices for the interpretation of evidence related to progression, and the prevention thereof.

Progression could be defined as a worsening by any margin of change on any of the continuous scales, and conversely the absence of any worsening on these parameters could be defined as prevention of progression.

The definition could be limited to those instances where clear thresholds have been established, such as in the case of the IPSS Score.

The only trial in which the prevention of a predefined progression event is adequately addressed is the MTOPS trial. When faced with this difficulty, the vast majority of the urological literature has focused on symptom score, quality of life score, “BPH” impact indices, and maximum urinary flow rate.

These are typically reported an an improvement of these scores from baseline, rather than prevention of progression in these scores. The recently published guidelines of the American Urological Association offers a comprehensive overview of the improvement in the IPSS Score, the maximum urinary flow rate, and the quality of life score achieved with all medical therapies, minimally invasive therapies, and surgical interventions. (http://auanet.org/guidelines/bph.cfm). Figure 39 a-c shows the average improvement shown with various medical therapies at 3 to 9 months, 10 to 16 months, and >18 months duration, the average improvement maximum urinary flow rate and the average improvement in the quality of life score. Figure 40 A – C shows the range of observed symptom scores, quality of life scores, and maximum urinary flow rate improvement with medical therapy, minimally invasive therapies, and surgi-
Figure 39 A, B, C. Average improvement in symptom score for various medical therapies, peak urinary flow rate, and quality of life score according to the AUA Guidelines. (AUAPracticeGuidelinesCommittee 2003)
Figure 40 A, B, C. Range of observed improvements in symptom score (A), flow rate (B), and QOL (C) for medical therapy, minimally invasive therapy, and surgical therapy stratified by duration of follow-up from the AUA Guidelines. (AUAPracticeGuidelinesCommittee 2003)
b) Serum PSA

If one were to consider an increase in serum PSA over time as evidence of progression of BPE, then the reversal of such, namely a decrease in serum PSA could be considered a prevention of progression. Clearly, an increase in serum PSA can only be considered an indirect or proxy health outcome and thus, a decrease in the serum PSA cannot be construed as being directly beneficial to the patient. However, there is substantial evidence linking the decrease in serum PSA to a decrease in prostate volume, in turn, linking this change to clinically relevant outcomes such as the prevention of AUR and surgery (see later in this section). The class of drugs, 5alpha-reductase inhibitors contains two compounds, namely finasteride, which inhibits exclusively the type II of the 5alpha-reductase isoenzyme, and dutasteride, which inhibits both type I and type II of the 5 alpha-reductase isoenzymes. Both drugs prevent the conversion of testosterone to dihydrotestosterone and thereby reduce circulating serum dihydrotestosterone (DHT) by 70% (finasteride) and 90% (dutasteride). As a result of this, prostate volume decreases and serum PSA is reduced by a median of 50% over time.

This decrease in serum PSA has been shown for finasteride to be maintained over a period of observation of up to six years. *(Figure 41).* (Roehrborn, Bruskewitz et al. 2004). Dutasteride reduces total serum PSA to a similar degree at least over an observation period of 12 months. In addition, serum free PSA is reduced by approximately 50% as well, leaving the ratio of free to total PSA more or less unchanged. *(Figure 42).* (Roehrborn, Andriole et al. 2002). The effects of dutasteride and finasteride on serum PSA have been studied in a head-to-head comparison trial (EPIC) *(http://ctr.gsk.co.uk/Summary/dutasteride/studylist.asp).* In this study, finasteride and dutasteride reduced serum PSA by –45 and 46%, respectively, at 3 months, by –53 and 54%, respectively, at 12 months (median percent change from baseline). It has been shown that the reduction in serum PSA actually increases over time, i.e., there is a further reduction in serum PSA, at least with dutasteride over time. Whether or not this relates to any clinically meaningful changes or not is an unresolved question.

c) Prostate Volume

Another indirect/proxy outcome is an increase in prostate volume, as discussed in previous sections. Conversely, a reduction in the prostate volume could be considered a prevention of progression. The 5alpha-reductase inhibitors, finasteride and dutasteride, have again been shown to reduce prostate volume over a period of 3 to 6 months by approximate-
ly 15 to 30%. As Figure 43 A and B shows, the reduction does not change significantly from an observation period of 6 months to an observation period of 48 months. This has been verified for both finasteride and dutasteride in a multitude of placebo-controlled clinical trials.

The reduction in prostate volume has been sustained over a period of at least 6 years as published by Lowe et al., (Lowe, McConnell et al. 2003) for finasteride. It is reasonable to assume that a similar sustained decrease in prostate volume would apply to dutasteride. Until recently, it had been assumed that the effect on prostate volume induced by the 5alpha-reductase inhibitor drugs would be more pronounced on the transition zone as it is assumed to be the source of BPE. However, data recently presented by Marks et al., suggests that the effect on the transition zone is identical, as well as on the peripheral zone of the prostate (Marks 2005). (Figure 44 A and B). The dutasteride phase III trials allow an assessment of the changes in total prostate volume (PV), transition zone volume (TZV), and peripheral zone volume (PZV). Figure 44 A shows that there is a simultaneous decrease in transition zone and peripheral zone volume combining for a significant decrease in total prostate volume. Figure 44 B suggests that the transition zone index, which is the ratio of TZV over PV remains unchanged from baseline to 24 months at approximately 0.5. Overall, this suggests that the effect of 5alpha-reductase inhibitors is identical on peripheral and transition zone volume.

Another question of interest is whether or not baseline prostate volume or baseline serum PSA might predict changes in the opposing factor, namely whether baseline serum PSA would predict changes in prostate volume or whether prostate volume would predict changes in serum PSA. Figure 45 demonstrates that in fact, baseline serum PSA predicts the degree of volume increase in the placebo treated patients, with those patients in the higher PSA categories having greater increases in prostate volume over time (Figure 45). An analysis of several controlled studies performed with finasteride allows a definite answer to these questions. Figure 46 shows the two-year change in prostate volume by serum PSA categories. As is evident, prostate volume decrease remains steady at around 20%, whether or not the baseline serum PSA is in the 0 to 0.5 range, or in the 8 to 10 range. In the placebo-treated patients (open circles), there is an increase in prostate volume noted, which ranges from 5 to maximally 20% over the same time period. Figure 47 shows the change in serum PSA by baseline prostate volume in six categories. The decrease in total serum PSA is strictly volume dependent, i.e., patients with larger prostate volumes tend to have a higher serum PSA, and thus, do have a larger absolute decrease in serum PSA. The percent reduction in serum PSA, however, is not affected by prostate volume. This figure also illustrates that patients with larger prostate volumes have a greater increase in serum PSA when treated with placebo (open circle). Figure 48 shows the percent volume changes in control clinical trials for the placebo and alpha-blocker group (the latter one only referring to the doxazosin group in the MTOPS trial). Due to the regression to the mean artifact, there are no substantial changes noted in prostate volume at 6 months in both trials in which it was reported. At 12 months, either a decrease or an increase was noted. At 24 months, the majority of studies report an increase in prostate volume in the placebo groups, and all studies reporting data out to 48 months report an increase in prostate volume between 10 and 25%. Of note, an increase in prostate volume in the MTOPS study is identical for the placebo and the doxazosin group. The increase in transition zone volume in the phase III dutasteride studies is identical to the increase in the total prostate volume in the dutasteride studies at 24 months.

The issue of volume increases as evidence for progression and the reversal thereof as evidence for prevention of progression can therefore be summarized as follows:

• Alpha-blockers do not affect the natural growth history of the prostate as evidenced in the MTOPS and VA Cooperative trial.

• The 5alpha-reductase inhibitors, finasteride and dutasteride, reduce the prostate volume by 15 to 30% over a period of treatment of 24-48 months.

Figure 42. Dutasteride reduces total PSA by approximately 50% and, also, free PSA by approximately 55%. The ratio of free to total PSA is preserved.
Figure 43 A-B. Baseline and follow-up volumes in controlled clinical trials with 5\(^{-}\) -reductase inhibitors ranges from 3 to 48 months. Figure 43 B shows the percent volume reduction, which ranges from 15 to 30% across the various trials and various time points starting at six months.
Figure 44A. Dutasteride affects total prostate volume, transition zone volume, peripheral zone volume to the same degree. There is no differential effect on peripheral versus transition zone volume.

Figure 44B. Transition zone index, i.e., the ratio of transition zone volume to prostate volume remains unchanged over 24 months of treatment with dutasteride.
Figure 45. Change in prostate volume at year 4 in MTOPS for the four treatment groups (McConnell, Roehrborn et al. 2003)

Figure 46. Two-year changes in prostate volume stratified by serum PSA for patients treated with finasteride (closed circles) and placebo (open circles). There is no difference in prostate volume changes in finasteride-treated patients stratified by baseline serum PSA.

Figure 47. Two-year change in PSA by prostate volume (closed circles, finasteride) and (open circles, placebo). The absolute decrease in PSA increases with increase in prostate volume as those prostates have a higher baseline serum PSA.
Data from the EPIC study suggests that the reduction in prostate volume at 12 months is nearly identical, namely 26.3% versus 26.7% for finasteride, and dutasteride, respectively. The shrinkage of prostate volume affects both peripheral and transition zone volume to the same degree. The reduction in prostate volume is maintained to six years and likely longer. The percent reduction in prostate volume is not dependent on baseline size or baseline serum PSA.

**d) Relationship Between Baseline Parameters and Likelihood/Magnitude of Improvement Versus Progression**

There is some evidence that the improvement in symptoms and maximum urinary flow rate, and presumably other parameters such as bother score, interference with daily activity score, and quality of life, is dependent on baseline parameters such as prostate size or serum PSA, at least when treatment with 5alpha-reductase inhibitors are studied. An early observation by Boyle et al. suggested that finasteride is more effective than placebo in improving symptoms and urinary flow rate in men with larger glands at baseline. (Figure 49 A and B). As is evident from these figures, the placebo effect (in orange) decreases with increasing prostate size, both in terms of symptom score and in terms of urinary flow rate. Simultaneously, the effect of finasteride increases slightly leading to a greater net benefit of finasteride over placebo (Boyle, Gould et al. 1996). A similar analysis was performed for symptom score improvement and flow rate improvement, this time stratifying patients into six categories of PSA ranges. (Figure 50 A and B). Again, the placebo effect decreases with increasing serum PSA reflecting an accelerated natural history, while the finasteride effect increases slightly leading to a greater net drug benefit.

In a similar manner, the data from the MTOPS study support the notion that patients with larger glands at baseline respond more favorably to 5alpha-reductase inhibitors. Figure 51 shows the changes from baseline in terms of maximum urinary flow rate, IPSS score, BPH impact index, and quality of life score for patients treated in the MTOPS trial with placebo, doxazosin, finasteride, and combination therapy. Figure 51 A shows the improvements for patients with total prostate volume under 20 ml, transition zone volume under 10 ml, or a serum PSA of less than 1.4 ng/ml. As is evident, in this group of patients with small glands and low PSA, the alpha-blocker, doxazosin, is associated with greater improvement that placebo or finasteride alone, but is equal to combination therapy. Figure 51 B shows the same analysis repeated in patients with a total prostate volume of over 40 grams or a transition zone volume of over 20 grams, or a total serum PSA of greater than 4.0 ng/ml. In this instance, the alpha-blocker still is superior to placebo, but the margin is less pronounced. Surprisingly, finasteride performs as well or slightly superior to the alpha-blockers, but combination therapy performs superior to both single arm therapies. This analysis from the MTOPS study suggests the interpretation that, for patients with small glands and lower serum PSA values, alpha-blocker therapy alone is sufficient to treat symptoms, bother,
Figure 49 A, B. Meta-analysis of finasteride one-year study. This meta-analysis shows the average changes in peak flow rate and quasi-IPSS Score (A and B) with finasteride and placebo stratified by baseline prostate volume. It suggests that the placebo effect decreases with increasing prostate size, and that the finasteride effect slightly increases leading to a greater therapeutic benefit. (Boyle, Gould et al. 1996)

Figure 50 A, B. Finasteride one-year study meta-analysis for peak flow rate and quasi-IPSS Symptom Score. When stratified by serum PSA, the placebo-treated patients experience less improvement in peak flow rate and symptom score, while the finasteride-treated patients experience greater improvement with higher PSAs, thus, increasing the therapeutic benefit.
Figure 51 A, B. Changes from baseline to end-of-study for maximum flow rate, IPSS Score, BPH Impact Index, and Quality of Life Score for placebo, doxazosin, finasteride, and combination therapy-treated patients in the MTOP study. Figure 51 A shows the changes for patients with a prostate volume of under 20 grams, a transition zone volume of under 10 grams, and for a PSA under 1.4 ng/mL. The efficacy of doxazosin is superior to placebo and finasteride in comparison to combination therapy.

Figure 51 B. The data are shown for patients with prostate volumes over 40 grams, transition zone volumes of over 20 grams, and serum PSA of over 4.0. In this case, the efficacy of doxazosin and finasteride is virtually identical, and the combination therapy is superior in improving these longitudinal outcomes.
BPH impact, and improve the maximum urinary flow rate, while in patients with larger glands and higher PSA values, combination therapy is superior. The beneficial effect of the combination therapy must be weighed against the side effect, particularly the sexually related adverse event seen with several of the drugs used.

A strikingly similar observation concerning the relationship of improvement in symptoms, BPH impact, and maximum urinary flow rate to baseline prostate characteristics can be made in the dutasteride phase III trials. When stratifying the patients into those with a prostate volume less than 40 ml, a PSA less than 3.0 ng/ml, and a transition zone volume of less than 25 ml, and comparing them with those with a TRUS volume over 40 ml, PSA over 3.0 ng/ml, and a transition zone volume of over 25 ml, it is evident that the margin of improvement, i.e., the net drug benefit, is significantly greater for all three groups in all three outcome parameters. (Figure 52 A and B).

Table 9 shows the net improvement in IPSS Score at 24 months in the dutasteride phase III trials stratified by total prostate volume tertiles and by transition zone index tertiles. As shown, the greatest net improvement in AUA symptom index is achieved in patients with the highest PSA tertile and the highest prostate volume tertile. The least effect is achieved in patients in the lowest tertile of prostate volume, and the lowest PVI tertile. Taken together, these observations strongly suggest that when treating patients with 5alpha-reductase inhibitors, baseline prostate volume, and serum PSA is a powerful predictor of the expected net drug benefit. Similarly, the net drug benefit can be expected to increase with increasing prostate volume, transition zone volume, transition zone index, and serum PSA. Conversely, with alpha-blockers, the net drug benefit can be shown to decrease with increasing prostate volume and serum PSA.

The only study addressing prevention of symptom progression in an a priori fashion is the MTOPS trial. In this study, symptom progression was defined

Table 9. The net decrease in AUA Symptom Score at 24 months in the Dutasteride phase III trials is greatest in those patients in the higher prostate volume tertiles, and in the higher transition zone index tertiles. The benefit may be as low as 0.9 points between placebo and dutasteride, but may also be as high as 3.5 in those patients with a transition zone index of greater than 0.55.

Figure 52 A, B. Shows the difference between placebo and dutasteride for AUA Symptom Index, BPH Impact Index, and maximum urinary flow rate in the Dutasteride phase III studies for patients with a total prostate volume of less than 40 grams, serum PSA less than 3, and transition zone volume of less than 25 versus those with a total prostate volume of over 40 grams, PSA greater than 3.0, and transition zone volume greater than 25. The marginal benefit increases significantly in these larger prostates with higher baseline PSA.
as a worsening from baseline by 4 or more points on the IPSS score, and this worsening had to be verified within two to four weeks by repeat administration of the IPSS score. Overall, a 4-point symptom worsening was the most common progression event in the MTOPS trial. **(Figure 53)**. Symptomatic progression was prevented by both single arm therapies with finasteride and doxazosin. Although numerically different from one another, there were no statistical differences between the ability of finasteride or doxazosin to prevent symptomatic worsening. However, combination therapy was statistically superior to both single arm therapies and to placebo in terms of prevention of symptomatic worsening.

**Figure 54 A and B** provides a stratified analysis of the cumulative incidence of symptomatic worsening based on baseline volume (**Figure 54 A**) and serum PSA (**Figure 54 B**). The analysis provides evidence for the following conclusions. In the placebo group, the risk of symptomatic progression increases with increasing prostate volume, as well as increasing serum PSA. The alpha-blocker, doxazosin, prevents symptomatic progression for patients with small, intermediate, and large prostate volumes, as well as for patients with low, intermediate, and high serum PSA. Finasteride prevents symptom progression best in patients with prostate volume of over 40 grams, and in those with a serum PSA of greater than 1.4.

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**Figure 53. Cumulative incidence of symptomatic worsening defined as a greater than 4-point increase in the MTOPS study or before-treatment group.** (McConnell, Roehrborn et al. 2003)

**Figure 54 A, B. Symptom worsening in the MTOPS study stratified by prostate volume and convenience tertiles show the four treatment groups and stratified by serum PSA in figure 54 B.** (McConnell, Roehrborn et al. 2003)
ng/ml. Combination therapy is effective in preventing symptom progression in patients of all prostate sizes and all serum PSA levels. However, combination therapy is truly only superior to doxazosin in terms of symptom progression for a prostate volume $>40$ mL and a PSA of $>4.0$ ng/mL.

f) AUR and Surgery

Clearly, AUR and surgery are the most significant outcomes of LUTS and BPE/BPO due to their impact on the patient’s personal life, the potential for further complications, and the health care costs associated with the treatment thereof. The first report regarding the possible prevention of acute AUR or surgery was published in 1997, a meta-analysis of three studies comparing finasteride with placebo in men with BPE/BPO over 24 months (Andersen, Nickel et al. 1997). Figure 55 A and B shows the reduction in the risk of AUR and the need for surgery in these studies. Overall, a reduction of approximately 50% in the rate of retention and surgery was observed. Table 10 shows the three studies contributing to this analysis, namely the SCARP, PROSPECT, and PROWESS studies, as well as a combined analysis.

Table 10. Risk reduction of AUR and need of surgery in either/or in three two-year studies and the combined meta-analysis based on 4222 patients.

The next study published was the Proscar Long-Term Efficacy and Safety study or PLESS study, (McConnell, Bruskewitz et al. 1998) In the PLESS study, finasteride when compared to placebo induced a reduction in risk of AUR of 57% and a reduction in risk of surgery of 55%. Figure 56 shows that the risk of AUR and surgery is linear and that finasteride resulted in a statistically significant reduction in the risk over time. The MTOPS study allowed a comparison between single arm therapies with finasteride and doxazosin as well as combination therapy to placebo (McConnell, Roehrborn et al. 2003). Figure 57 A shows the cumulative incidence of AUR and Figure 57 B shows the cumulative incidence of BPE/BPO invasive therapy. As is evident from Figure 57 A, there is a steady increase in the risk of AUR in the placebo group. Finasteride reduces this risk significantly compared to placebo, but contributes markedly to the risk reduction with combination therapy. Treatment with the alpha-blocker, doxazosin, delayed the risk of urinary retention by about two years, but ultimately did not significantly reduce the risk. In fact, the slope of the two curves (doxazosin and placebo) parallel each other following a delay of about 2 to 2.5 years. Regarding invasive therapy, Figure 57 B demonstrates that the alpha-blocker, doxazosin, does not alter the risk of surgery at all, but finasteride reduces the risk significantly and contributes entirely to the risk reduction observed with combination therapy. Table 11 shows the actual reduction in risks for the combined two-year studies, the PLESS study, and the MTOPS finasteride, doxazosin, and combination therapy arm. As is evidenced, combination therapy reduced the risk of AUR by 81% and the risk of surgery by 67%, which is superior to monotherapy with finasteride. Doxazosin reduced the risk of AUR by 35%, but did not affect the risk of surgery.

Additional data are available from the phase III dutasteride studies (Roehrborn, Boyle et al. 2002). In this analysis, patients were included who at baseline had a serum PSA of greater than 1.5 ng/mL and a prostate volume of over 30 mL. This led to a study population with a relatively high serum PSA and relatively large prostate volumes. Figure 58 A and B shows the pooled data from the three phase III trials regarding the risk of AUR (Figure 58 A) and the risk of surgical intervention (Figure 58 B). Table 12 adds the risk for AUR and surgery observed in the dutasteride phase III trials, and the risk reduction, which is nearly identical to the risk reduction with finasteride, namely 57% for the risk of AUR and 48% for the risk of surgery, compared to the data shown in table 12, which only reflects finasteride vs placebo data.

Figure 59 A and B assesses the changing risk of AUR after the placebo-treated patients are converted to active drug in an open label extension of the dutasteride phase III trials (Figure 59 A) or the open label extension of the PLESS trial (Figure 59 B). As is evident, the placebo group, which up to the open label extension had more than twice the risk of AUR, after being converted to open label drug, adjusts to the ongoing baseline risk of the dutasteride and finasteride group, respectively. The same is true for
Figure 55, A, B. Reduction in the incidence of AUR (55 A) and surgery (55 B) in the meta-analysis of finasteride two-year study for finasteride versus placebo. (Andersen, Nickel et al. 1997)

Figure 56. Reduction in the risk of AUR and the need of surgery (left and right) in the four-year PLESS study. (McCon nell, Bruskewitz et al. 1998)
Figure 57 A, B. Cumulative incidence of AUR (A) and surgery (B) over four years in MTOPS for the four treatment groups. (McConnell, Roehrborn et al. 2003)
Figure 58 A, B. Pooled data from the three phase III trials with dutasteride showing the risk of AUR (Figure 58 A) and the risk of surgical intervention (Figure 58 b) in the placebo versus dutasteride arms (Roehrborn, Marks et al. 2004)
Table 11. Risk reduction of AUR and need of surgery in patients with BPH. Combined analysis of two-year data three-year finasteride study, four-year PLESS study, and four-year MTOPS study for finasteride, doxazosin, and combination therapy.

Figure 59 A, B. Acute urinary retention. Following conversion to open-label dutasteride, the placebo group assumes the baseline risk of the dutasteride group (59 A). Similarly, after conversion to open-label finasteride in the four-year PLESS study, the placebo group assumes the baseline risk of finasteride group (59 B). (Roehrborn, Marks et al. 2004) (Roehrborn, Bruskewitz et al. 2004)
BPO-related surgery where the risk in the placebo group after switching to open label drug is converted to the baseline risk of the active drug group. (Figure 60 A and B). This suggests that the risk reduction achieved with 5alpha-reductase inhibitors takes effect regardless of the time in a patient’s life in which the drug is introduced, i.e., independent of the disease progression or natural history of BPH/BPE/BPO for the individual patient.

While these data are all derived from randomized, placebo-controlled trials, there are other large datasets published in the literature supporting the reduction in the risk of AUR or surgery, particularly with the use of 5alpha-reductase inhibitors.

Boyle et al., published results of a two-year follow-up from a large cohort of patients observed in general practices in the United Kingdom and treated with either alpha-blocker or 5alpha-reductase inhibitors (Boyle, Roehrborn et al. 2004) Figure 61 shows the unadjusted Kaplan-Meier survival from first initiation of treatment to either surgery or AUR stratified by first treatment with either an alpha-blocker (blue) or a 5alpha-reductase inhibitor (red). The difference at two years was significantly in favor of a risk reduction with 5alpha-reductase inhibitors. When the Hazard ratio for 5alpha-reductase inhibitors was set at 1.0 as a reference, it was 1.89 (1.44 – 2.48 95% CI) for alpha-blockers. Souverein et al. performed a retrospective cohort study amongst 1430 men over the age of 45 who were registered with general practitioners in the Netherlands. They found that there was no difference in the risk of prostatic surgery between patients on medical treatment and watchful waiting. Patients using a 5alpha-reductase inhibitor at any stage had a statistically significant reduced risk of surgery compared to those using an alpha-blocker only with an adjusted Hazard ratio of 0.35 (0.13 – 0.96 95% CI) for alpha-blockers. Souverein et al. performed a retrospective cohort study amongst 1430 men over the age of 45 who were registered with general practitioners in the Netherlands. They found that there was no difference in the risk of prostatic surgery between patients on medical treatment and watchful waiting. Patients using a 5alpha-reductase inhibitor at any stage had a statistically significant reduced risk of surgery compared to those using an alpha-blocker only with an adjusted Hazard ratio of 0.35 (0.13 – 0.96 95% CI). (Figure 62). (Souverein, Erkens et al. 2003) There is a retrospective analysis of observational data from the general practice of the research database (UK GPRD). This cohort contains 4500 patients with LUTS suggestive of BPOaged over 50 years who were prescribed either a 5alpha-reductase inhibitor (finasteride) or an alpha-blocker as initial therapy for symptoms between 1996 and 1999. Patients prescribed an alpha-blocker were significantly more likely to experience AUR (Hazard ratio 2.32) or surgery (Hazard ratio 1.78) than patients prescribed 5ARI. These differences were sustained with sensitivity analysis.

Clifford et al. utilized also a population from the United Kingdom General Practice Research Database (GPRD) and analyzed a total of 61,364 men with LUTS suggestive of BPO without a record of prostate cancer of which 14,195 were treated with either an alpha-blocker or finasteride. They observed that the incidence of LUTS increased linearly from the age of 45 to 85, and the prevalence increased from 3.5 to 35% for men in their 40s and 80s. During the observation period, they observed a progressive increase in the interval between first diagnosis and prostatic surgery. This interval was found to be significantly longer for medically treated patients than those receiving no medical therapies. The intervals between the initiation and failure of medical therapy were shorter for patients receiving the older alpha-blockers, indoramin and prazosin, than those receiving specific medications for LUTS such as tamsulosin, alfuzosin, terazosin, doxazosin, and the 5ARI, finasteride, used as a reference (Figure 63). (Clifford, Logie et al. 2000).

**VIII. PREDICTORS OF EFFECTIVENESS OF PREVENTION OF PROGRESSION AND ADVERSE OUTCOMES**

Much effort has been devoted to analyzing baseline parameters that might predict whether or not a given patient would benefit from efforts to prevent either progression or adverse outcomes. Much of this attention has focused on the patient’s age, baseline prostate volume, and serum PSA, as it has been shown that prostate volume and serum PSA in treatment studies are powerful predictors of progression and outcome events. Mochtar et al. analyzed the prognostic role of serum PSA and prostate volume for the risk of invasive therapy for BPO in men treated with either watchful waiting or alpha-blockers (Mochtar, Kiemeney et al. 2005) He found that under watchful waiting, the Hazard ratio increased from 2.7 for men with a PSA of greater than 3.0 compared to those with a PSA of less than 1.5. For alpha-blockers, the Hazard ratio increased to 2.8 for the same threshold of PSA. TRUS volume was not a powerful predictor of invasive therapy in the watchful waiting group, but was so in the alpha-blocker group where the Hazard ratio was 1.8 if the prostate volume was greater than 30 grams compared to those men with a prostate volume of less than 30 grams. (Figure 64).

Analyses of serum PSA and prostate volume as predictors of progression, as well as their impact on the
After converting to open-label dutasteride, the previously placebo-treated patients assume the baseline risk of the dutasteride population (60 A) and, similarly, after converting to open-label finasteride, the previously treated placebo patients assume the baseline risk of the finasteride-treated patients in the PLESS study (60 B). (Roehrborn, Marks et al. 2004) (Roehrborn, Bruske-witz et al. 2004)

Figure 61. AUR or surgery in patients treated with 5ARI (red) and alpha-blocker (blue) in a general practitioner’s database. (Boyle, Roehrborn et al. 2004)
Figure 62. Hospital admission for BPH treatment for patients treated with 5ARI and alpha-blocker showing the proportion of patients remain free of prostate surgery. (Souverein, Erkens et al. 2003)

Figure 63. Survival from first BPH/LUTS therapy to treatment failure for various medical interventions.

Figure 64. Prognostic role of serum PSA and prostate volume for the risk of invasive therapy in men on alpha-blocker and watchful waiting stratified by PSA and prostate volume stratification, and by alpha-blocker versus watchful waiting. (Mochtar, Kiemeney et al. 2005)
effectiveness of treatment with finasteride on prevention of progression and adverse outcomes were reported in the PLESS study. (McConnell, Bruskewitz et al. 1998) (Figure 65 a-d). The adverse outcomes that were analyzed were spontaneous AUR, precipitated AUR, and BPO-related surgery. In the placebo group, the incidence of spontaneous AUR increased from 1.4 to 7.6% from the lowest to the highest PSA tertile, while the incidence of precipitated AUR increased from 1.5 to 4%, and the incidence of surgery from 6.2 to 14.6%. In the finasteride treatment group, the incidence changed from 1.3 to 1.4 for spontaneous, from 0.6 to 2.4 for precipitated, and from 3 to 5.4% for surgery. The risk reduction for spontaneous AUR was therefore 7% in the lowest PSA tertile, 48% in the middle PSA tertile, and 77% in the highest PSA tertile. For surgery, it increased from 51 to 74%, and for the combined outcomes, AUR or surgery from 44 to 60%. Similar findings can be obtained regarding stratification by MRI-measured prostate volume although only 10% of the patients underwent prostate size measurement by MRI and thus, the division in tertiles yields less reproducible results. Figure 66 demonstrates that the risk reduction for either AUR or surgery increases because of the rapid increase in the risk for AUR with surgery in the placebo group, and the relatively stable risk for both outcomes in the finasteride group, while the baseline serum PSA is increasing. (Roehrborn, McConnell et al. 1999)

The odds ratios of patients in the placebo group to experience either AUR or BPO-related surgery compared to patients treated with dutasteride over two years in the dutasteride phase III trials is shown in Table 13. It shows the risk stratified by prostate volume and by transition zone index. Patients in the highest transition zone index had an odds ratio of 6.17 compared to those in the lowest transition zone index, while patients with the largest prostate volume and the highest transition zone index had an odds ratio of 3.29 to experience either AUR or BPO-related surgery. As is evident in this table, prostate volume and specifically, the volume of the transition zone, or the transition zone index, are powerful predictors not only of progression and outcomes, but also of the ability of 5alpha-reductase inhibitors to prevent such outcomes and progression events.

A similar analysis is shown in Figure 67 A through D for the MTOPS study. Here, stratification is by serum PSA and prostate volume in tertiles of prostate volumes less than 20, 20 to 40, and over 40 grams, and serum PSAs of less than 1.4, 1.4 to 3.9, and >4.0ng/mL. Figure 67 A demonstrates that AUR occurs with increasing frequency in the placebo group with increasing volume. In the smallest prostates, all three active drug treatments prevent episodes of retention, while in the intermediate size group, the alpha-blocker, doxazosin, reduces the risk by 50%. However, in the largest glands over 40 grams, the alpha-blocker is ineffective and only the 5ARI or combination therapy reduces the risk of retention. Figure 67 B shows a similar analysis for serum PSA, demonstrating again the reduction in risk for alpha-blockers in the low and intermediate groups, but not in the highest PSA categories where only the 5ARI and combination therapy were able to reduce this risk. Figure 67 C and D shows the same analysis for BPO treatment and basic therapy stratified by volume and by PSA. The alpha-blocker, doxazosin, in this case is ineffective in preventing invasive therapy for BPH for any volume size category, while the 5ARI in combination therapy reduce the risk for all sizes and all PSA values.

Figure 68 shows the BPO-related adverse outcomes in the Prostate Cancer Prevention Trial. (Thompson, Goodman et al. 2003). In this trial, BPO-related adverse outcomes were measured as the patients were either treated with placebo or finasteride. The relative risk for a diagnosis of BPE or BPO being made was 0.6 in the finasteride compared to the

Table 13. Risk of AUR and BPH-related surgery stratified by prostate volume tertiles and PVI tertiles from the Dutasteride phase III trials. The odds ratio of placebo versus dutasteride is shown. Patients in the highest PSA tertile have the highest risk of AUR or surgery compared to those in the lower prostate volume and lower PVI tertiles.
Figure 65 A - D. Incidence of outcomes in the placebo versus finasteride-treated patients over four years in PLESS. Spontaneous AUR (65 A), spontaneous and precipitated AUR (65 B), BPH-related surgery (65 C), and incidence of AUR or surgery (65 D). (Roehrborn, McConnell et al. 1999)

Figure 66. Cumulative incidence of AUR or BPH-related surgery over four years in PLESS stratified by baseline PSA threshold. The risk increase is linear and the magnitude of risk reduction is greater in patients with higher PSA baseline values. (Roehrborn, McConnell et al. 1999)
Figure 67 A–D. Prostate volume (A and B) and PSA (B and C) dependency of AUR (A and B) and surgery (C and D) in the four treatment groups of the MTOPS trial. (McConnell, Roehrborn et al. 2003)

Figure 68. BPH-related outcomes in PCPT with absolute and relative risk reduction.
placebo group for a risk reduction of 40%. The risk reduction for AUR was 33% and for TURP 46%.

**Table 14** presents an informative comparison of crude annualized progression events in the PCPT, MTOPS, PLESS and Dutasteride phase III trials. As is evident, a major difference between these trials was the baseline serum PSA and prostate volume in the men enrolled. It ranged from a PSA of 1.5 to 4.0, and a prostate volume from 33 to 54 ml. The crude annualized progression event for AUR and surgery are also depicted in this table. As is evident, the AUR events in the placebo group increased from 0.9 to 2.1%, and the surgery events from 0.23 to 2.1% per year.

**Figure 69 A and B** plots the annualized AUR (A) and surgery (B) endpoints for the placebo and 5alpha-reductase inhibitor-treated patients by plotting the individual studies and the mean serum PSA and prostate volumes on the X-axis, and the annual incidence of AUR (A) and surgery (B) along the Y-axis. Two observations are striking from this analysis. First, the annual incidence of AUR and surgery increases significantly in those studies with higher serum PSA and larger prostate volume, and, second, a gap between the placebo and 5alpha-reductase inhibitor-treated patients increases with increasing PSA and prostate volume for both outcomes.
Several conclusions can be drawn as follows:

- Alpha blockers appear to delay AUR overall and to prevent it in patients with smaller glands
- 5 ARIs prevent episodes of retention with the RR being 50-60% overall
- Alpha blockers do not appear to prevent surgical intervention
- 5 ARIs prevent surgical intervention with RR being 50-60 % overall
- Combination therapy does not add to the prevention of AUR or treatment intervention
- Larger glands/higher PSA are associated with greater baseline risk, and thus greater risk reduction

While it appears that prostate volume and serum PSA are reasonable predictors of progression and outcomes in men with BPO treated with placebo versus medical therapy, it is clear that a multivariate analysis, or a nomogram taking into consideration multiple baseline parameters may be even more useful to practicing physicians. Such effort is shown in Figure 70 A and B. Slawin et al. analyzed the symptom score, BPH Impact Index, prior treatment with an alpha-blocker, prostate volume, PSA, maximum urinary flow rate, and dutasteride therapy and utilized these parameters to predict the probability of AUR and/or surgical intervention within two years in the dutasteride phase III trials. Nomograms of this type have been developed for other outcomes utilizing other baseline parameters, most notably in the treatment of prostate cancer. Once transferred to an electronic calculator, PDA, etc., these algorithms might be used by practicing physicians to enter whatever baseline data are available, and thereby to calculate the risk of a given patient experiencing symptom progression, retention, or a need for surgery over a given period of time. Figure 71 shows a snapshot from a Web site www.oncovance.com where physicians can enter baseline parameters, and predict the likelihood of a person developing either AUR or surgery based on data from the MTOPS trial. It is possible that future efforts such as these will help physicians and other health care providers caring for patients with LUTS suggestive of BPO in the complex decision making process, if and when preventive efforts are available, and associated expenses are indicated or not.

IX. SUMMARY AND CONCLUSIONS

A careful examination of the literature suggests that there is significant evidence for LUTS and BPH/BPE/BPO, at least in many patients, being a progressive condition leading to worsening of symptoms, bother, interference with quality of life, deterioration of flow rate, urodynamic parameters and others, over time, and ultimately, to adverse outcomes such as urinary retention and the need for surgical intervention. From population-based studies and placebo-controlled arms of randomized clinical trials, such evidence can be obtained for worsening of these parameters as listed in Table 15. There is also significant evidence available regarding the prevention of such progression and outcomes. Much of this evidence is derived from randomized, placebo-controlled trials and thus, it can be rated as an evidence level I and grade A (Table 15).

Despite the considerable knowledge accumulated over time, we do believe that there are significant research gaps and priorities that are derived from our analysis of the literature, and in our attempt to sum-
Figure 70 A, B. Nomogram approach to predicting BPH progression. Baseline statistical analysis, various parameters proved to be predictive of BPH progression. The data can be expressed by a nomogram where for each baseline parameter the patient is assigned a certain point. The number of total points is established at risk for progression.
Figure 71. Example of a BPH progression nomogram on the Oncovance Web site.

Table 15. Rating of evidence and recommendations for prevention of BPH progression and outcomes derived from data in population-based studies and placebo groups for various parameters and various treatments.
marize the available literature and to make recommendations regarding the prevention of progression and outcomes. These research recommendations are briefly as follows.

- Better understanding of relationships between changes in continuous variables and subjective perception of worsening/improvement
- Conversion of transition within health states to transition between health states by converting continuous outcomes into categorical or dichotomous outcomes
- Better understanding of the role of dynamic change in variables as predictors, and their impact on health care seeking behavior
- Cost/benefit effectiveness as well as benefit to risk analyses to determine thresholds for initiation of therapies to prevent progression and adverse outcomes
- Population based studies and placebo control groups provide level 2 / 1 evidence that LUTS/BPH/BPE/BPO is a progressive condition
  - Symptoms, bother, QoL, Qmax, Volume, PSA, AUR, treatment intervention
- Population based studies and placebo control groups provide level 2 / 1 evidence for the role of baseline and dynamic factors to predict progression
  - Age, Symptom and bother severity, Qmax, Volume, PSA
- We recommend against initiating treatment to prevent progression/outcomes in men with low risk (young, PSA < 1.5, Vol < 25-30 ml) [1 A]

Our final recommendations in regards to prevention of progression and adverse outcomes in men with LUTS and BPH/BPE/BPO are summarized as follows. The available literature allows us to recommend strongly against initiation of any preventive treatment efforts to prevent progression/outcomes in men who are at low risk for such progression and outcomes. In general, these men are young, have a low serum PSA (less than 1.5 ng/mL), and a prostate volume (less than 25 to 30 ml). This recommendation carries a level I grade A.

The initiation of treatment to prevent progression or outcomes in men who are at higher risk, as defined by the parameters listed above, requires a consideration of the relative risks in each individual patient, and an analysis of the benefit to risk ratio based on the relative risks and the adverse events associated with the treatment, and certainly, consideration of the socio-economic circumstances of the individual, the society in which he resides, and the health care delivery system and available resources.

While there is evidence for strong recommendation level I, these circumstances must be taken into consideration in each case, which results in our opinion in an overall grade B recommendation.

**Figure 72** shows graphically the problem that the health care provider faces when making recommendations for the prevention of progression or outcomes. When we manage a patient who falls somewhere across a spectrum of increasing risk of progression and adverse outcomes along the X axis, we have to acknowledge that the risks and costs associated with the treatment to prevent such outcomes is

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*Figure 72. Across the “X” axis, the patients are based on various baseline parameters experiences an increased risk of progression of outcomes. At the same time, however, the side effects, costs, and other negative attributes of the potential treatments to prevent these outcomes remains stable across the entire spectrum of increasing risks. Thus, for each intervention and in each patient, and in each health care system, there presumably is a point by which the benefits of prevention of risks outweighs the harms at which point prevention of progression and outcomes become a reasonable strategy.*
constant across the spectrum of risks (red bar). However, inasmuch as the risk increases from left to right, the potential benefit of preventing the risk of progression and adverse outcomes increases also from left to right. (Green triangle). For every patient, in each and every situation and circumstance with a given set of baseline parameters, in a given society with a given health care system, and available resources, there is a breakpoint at which the benefit of preventing progression and adverse outcomes outweighs the risks and costs associated with the treatment to prevent progression and adverse outcomes. This would be the point at which it becomes cost-effective and, therefore, both economically and ethically feasible and reasonable to engage in a strategy to prevent progression and adverse outcomes in such patients. However, at present, it is impossible to state where exactly this break-even point is in each case, and as stated above, it depends on many other parameters that should be assessed by the individual health care providers and the individual patient situation.

The initiation of treatment to prevent progression or outcomes in men with higher risk requires

- Consideration of relative risk in the individual patient
- Benefit to risk ratio based on the relative risk of the individual patient and adverse events
- Consideration of socio-economic circumstances of the individual, society and health care delivery system
- While there is level 1 evidence, the listed circumstances must be taken into consideration resulting in an overall 1B recommendation

REFERENCES


Committee 9

New therapeutic targets in BPH and LUTS (Research priorities)

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For many years, medical treatment of the lower urinary tract symptoms (LUTS) associated with or suggestive of benign prostatic hyperplasia (BPH) has been based on mainly three types of agents, \( \alpha_1 \)-adrenoceptor (AR) antagonists [1, 2], 5\( \alpha \)-reductase inhibitors, [3-5] and phytotherapy. [6-8] Despite continued efforts, few new drug classes have been added to the therapeutic armamentarium. This is probably due to the fact that the pathophysiology of LUTS is multifactorial and that treatment targets are difficult to clearly define. It has not been established whether the most relevant target is within the prostate or whether extra-prostatic sites are more important [9]. However, focus has shifted from the prostate to the bladder as the source of some of the lower urinary tract symptoms, and as a therapeutic target [10, 11] (Figure 1). This has created a renewed interest in drugs used for treatment of the overactive bladder (OAB), characterized by urgency, frequency and urgency incontinence, i.e., equivalent to LUTS [12]. Increasingly, combinations of drugs are being evaluated in clinical trials and are being prescribed “off label” by physicians.

Some potential targets for future drugs, and some alternative treatment strategies, are reviewed in this chapter.

II. SUBTYPES OF \( \alpha_1 \)-ADRENOCEPTORS

It is well documented that the currently used \( \alpha_1 \)-AR antagonists are effective for treatment of LUTS associated with or suggestive of BPH [1, 2]. Whether or not treatment can be improved, either by increasing efficacy beyond that of existing drugs, reducing adverse effects, or both, has still not been determined, but is looking increasingly unlikely. Since targeting the predominant \( \alpha_1 \)-AR (\( \alpha_{1A/L} \)) in the prostate has not resulted in more effective drugs, [13] interest is now focussing on the \( \alpha_1 \)-ARs (\( \alpha_{1D} \)) in the bladder [14, 15]. \( \alpha_1 \)-ARs (Figure 2) may have effects on different locations in the bladder: the detrusor smooth muscle, the detrusor vasculature, the afferent and efferent nerve terminals and intramural ganglia.

The inter-relationship between the \( \alpha_1 \)-ARs in the human detrusor and the pathophysiology of LUTS is unclear. Most investigators agree that there is a low expression of these receptors [16]. In human detrusor studies Malloy et al. [17] found that 2/3 of the \( \alpha \)-AR mRNA expressed were \( \alpha_{1D} \), while there were no \( \alpha_{1B} \), and 1/3 were \( \alpha_{1A} \). In the rat detrusor, the \( \alpha_{1A} \)-AR distribution was different: the \( \alpha_{1A} \)-AR was predominating, 1/3 were \( \alpha_{1D} \)-AR, and there were very few \( \alpha_{1B} \)-AR. The subtype ratio was relatively consistent throughout the detrusor [18].

A change of subtype distribution may be produced by outflow obstruction. Hampel et al. [18] reported that there was a change in the obstructed bladder from \( \alpha_{1A} \)-AR to \( \alpha_{1D} \)-AR mRNA predominance. In humans, as described above, there is already an \( \alpha_{1D} \)-AR predominance in the normal detrusor, implying that a change in a similar direction as in the rat would be of minor importance, provided that the overall number of receptors did not increase. Indeed, Nomiya and Yamaguchi [19] have demonstrated that this was not the case. They confirmed both the low expression of \( \alpha \)-AR mRNA in normal human detru-
sor, and that there was no upregulation of any of the ARs with obstruction. Functionally, a similar situation was apparent. Nomiya and Yamaguchi [19] found a small response to phenylephrine at high drug concentrations with no difference between normal and obstructed bladders. Overall, in the obstructed human bladder, there seems to be no evidence for \( \alpha \)-AR upregulation or change in subtype, although this finding was challenged by Bouchelouche et al., [20] who found an increased response to \( \alpha_1 \)-AR stimulation in obstructed bladders. Whether or not this would mean that the \( \alpha_{1D} \)-ARs in the detrusor muscle are responsible for detrusor overactivity or OAB is unclear. Nakamura et al. [21] showed that the bladder of \( \alpha_{1D} \)-AR KO mice did not develop overactivity when stimulated with acetic acid. Chen et al. [22] studied micturition in \( \alpha_{1D} \)-AR KO mice and clearly showed that these mice have a larger bladder capacity and voided volumes than their wild type controls, supporting an important role for the \( \alpha_{1D} \)-AR in the control of voiding (Figure 3). However, it was not possible to draw any conclusions from their data about the location of the \( \alpha_{1D} \)-ARs receptors involved in micturition control. As discussed by

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**Figure 1.** Different bladder conditions which can result in lower urinary tract symptoms (LUTS)

**Figure 2.** \( \alpha \)-Adrenoceptor subtypes. The predominating subtype in the human bladder is the \( \alpha_{1D} \) receptor.
Chen et al. [22] the α1D-ARs in the detrusor and their levels of expression may not always be relevant for the functional importance of this receptor subtype.

Sugaya et al. [23] investigated the effects of intrathecal tamsulosin (blocking α1A/D ARs) and naftopidil (blocking preferably the α1D ARs) on isovolumetric bladder contractions in rats. Intrathecal injection of tamsulosin or naftopidil transiently abolished these contractions. The amplitude of contraction was decreased by naftopidil, but not by tamsulosin. It was speculated that in addition to the antagonistic action of these agents on the α1A-ARs of prostatic smooth muscle, both agents (especially naftopidil) may also act on the lumbosacral cord (α1D-ARs?). This observation is of particular interest considering the findings that in the human spinal cord, α1D-AR mRNA predominated overall [24]. Ikemoto et al. [25] gave tamsulosin and naftopidil to 96 patients with BPH for 8 weeks in a crossover study. Whereas naftopidil monotherapy decreased the I-PSS for storage symptoms, tamsulosin monotherapy decreased the I-PSS for voiding symptoms. However, this difference (which was suggested to depend on differences in affinity for α1-AR subtypes between the drugs) could not be reproduced in a randomized head to head comparison between the drugs [26]. Based on available evidence, it therefore cannot be concluded that the α1D-ARs on the detrusor muscle is an important therapeutic target. This does not exclude that α1D-ARs located elsewhere in the bladder (i.e., the vasculature; Das et al. [27]) or in other structures, might be of importance. The role of α1-

The expression of α1-AR was investigated in the transitional zone of 28 prostates with BPH [28]. Twelve (43%) were α1A-AR dominant, whereas 16 (57%) were α1D-AR dominant. The implications of these findings to the selection of α1-AR antagonist was further investigated. Curiously, naftopidil was shown to provide significant advantage in the treatment of α1D-AR dominant BPH patients [28].

The importance of the α1D-ARs for the generation of LUTS and the potential advantages of α1D-AR receptor blockade in the treatment of LUTS cannot be assessed until a drug with appropriate subtype selectivity becomes available for clinical evaluation.

### III. β3-AR AGONISTS

The detrusor muscle contains β-ARs, and 3 subtypes (β1, β2, and β3) have been identified in most species (Figure 5). Functional evidence for a role of the β3-AR in human detrusor suggests that the relaxation induced by adrenergic stimulation is mediated main-
ly through β3-AR activation [29-31]. Recent studies, using real-time RT-PCR, have revealed a predominant expression of β3-AR mRNA in human detrusor muscle [19, 32]. Thus, of the 3 subtypes of mRNA, 97% was represented by the β3-AR and only 1.5%, and 1.4% by the β1-AR and β2-AR, respectively. If the amount of subtype mRNA reflects the population of receptor protein, then the β3-AR is the most abundant in the human detrusor. Supporting an important role of β3-ARs, selective β3-AR agonists effectively relaxed isolated detrusor muscle from both normal and neurogenic bladders [19, 30, 31, 33, 34] (Figure 6).

The in vivo effects of β3-AR agonists on bladder function have been studied in animal models. It has been shown that compared with other agents (including antimuscarinic agents), β3-AR agonists increase bladder capacity with no change in micturition pressure and the residual volume [29, 35-37]. Thus, the above results suggest the β3-ARs as a potentially useful target for drugs intended for the treatment of OAB, including storage symptoms secondary to outflow obstruction.

IV. MUSCARINIC RECEPTORS

Storage symptoms, including urgency, frequency and urgency incontinence may be related to bladder dysfunction secondary to e.g., increased outflow resistance in BPH, but also to several other disorders [38]. Since muscarinic receptors mediate the main part of bladder contraction in many species, and par-
particularly in humans, it seems reasonable to assume that changes in their function can be related to LUTS [39]. Both M3 and M2 receptors may be involved in bladder contraction and micturition control. M3 receptors are primarily responsible for detrusor contraction both in the normal and overactive bladder. The role of the M2 receptors may increase in bladder pathologies including changes associated with prostatic obstruction [16]. A role for the M1 receptor in prostatic cell proliferation has been suggested [40]. However, the development of infravesical obstruction in men with BPH did not seem to be related to upregulation or altered binding affinity of muscarinic receptor receptor binding sites [41].

In humans, no direct contractile effect on prostatic smooth muscle of acetylcholine or carbachol was found by Hedlund et al. [42]. However, Abdelkhalik et al. [43]. found that strips of muscle from both the anterior capsule and prostatic urethra could be contracted by acetylcholine, and the investigators speculated on their role in the pathophysiology of BPH/LUTS. Muscarinic receptors may also be involved in the control of adrenergic activity and may thus also influence LUTS initiated from the prostate. More probable is that muscarinic receptors are involved in LUTS emanating from the bladder. Antimuscarinics are still the most widely used treatment for urgency, frequency and urgency incontinence [12, 44]. Based on urodynamic studies, detrusor contractility increases initially with the grade of obstruction in order to guarantee an optimal voiding despite an increased outlet resistance. If the main mechanism of action of antimuscarinics used for treatment of OAB were reduction of detrusor contractility, treatment with these drugs might be expected to result in increasing amounts of residual urine even to the extent of producing complete retention. However, antimuscarinics act mainly during the filling phase, and in the doses recommended for treatment of OAB, there is little effect on detrusor contractility [44]. The implication is that muscarinic receptors on other structures than the detrusor may be involved in LUTS generation [44]. On this basis it would not be unreasonable to consider these structures as potentially important targets for antimuscarinic drugs. Historically, the effect of antimuscarinics has been studied primarily in patients with OAB without BOO. In chronic obstruction, the morphological, biochemical and functional changes together with detrusor denervation make it reasonable to assume that blocking the muscarinic receptors in a damaged bladder can lead to a decompensation of the detrusor. However, at least two studies of antimuscarinics [45, 46] in patients with BOO have challenged, to a certain extent, these assumptions.

Additional studies on safety and efficacy of antimuscarinics in patients with BOO are needed to assess their usefulness. An important question is whether any of the currently used antimuscarinic agents are more efficacious or safer than the others, or whether an antimuscarinic with particular properties (target-
ing preferentially afferent mechanisms) would be advantageous in the treatment of LUTS. M₂ receptors were demonstrated in afferent fibers [47] and their blockade was shown to inhibit nociceptive sensory transmission. In addition, M₂ receptors were shown to occur in urothelial cells in close association with sub-urothelial sensory nerves. [48] Both M₂ and M₃ receptors [49] and their mRNA [50] have been demonstrated in the human urothelium/suburothelium with the same ratio M₂/M₃ as in the detrusor [49]. In a recent experimental study Kim et al. [51] suggested that antimuscarinic agents applied intravesically could be effective in treating overactive bladder by blocking muscarinic receptors in bladder afferent pathways. Nevertheless, at the present stage of knowledge, the clinical relevance of these findings is not known.

V. PURINOCEPTORS

ATP can be released by distension of the bladder, [52, 53] and released ATP may be able to activate the micturition reflex (Figure 7). Supporting this view, ATP, given intravesically induced pronounced detrusor overactivity in unanesthetized rats and mice [54].

The ATP receptor P₂X₃ is expressed on small diameter primary sensory neurons, [55-57] but also in the urothelium of rats and humans, [57] which suggests a role in sensory processes. Vlaskovska et al. [53] demonstrated release of ATP proportional to the extent of bladder distension in both normal and P₂X₃ receptor deficient mice, and found good evidence for a major sensory role for urothelially released ATP acting via P₂X₃ receptors on a subpopulation of pelvic afferent fibers. P₂X₃-deficient mice exhibited a marked reduction in urinary frequency as shown by cystometry, which revealed decreased voiding frequency, increased bladder capacity and voiding volume, but normal bladder pressures [58] (Figure 8). Thus, P₂X₃ receptors seem to be critical to the normal physiological regulation of afferent pathways controlling volume reflexes [52, 53, 59].

In studies of human bladder, P₂X₂ receptors were not seen to co-localize exclusively with sensory nerve fibers containing calcitonin gene-related peptide [57]. In particular, in the suburothelium, non-neuronal P₂X₃ receptor immunoreactivity was demonstrated near so-called “interstitial cells” or “myofibroblasts” [57]. These observations show that the sensory process is more complex than previously thought and emphasize the potential role of a newly described layer of suburothelial myofibroblasts [58, 59]. Electron microscope studies have also shown that these cells make close appositions with C-fiber nerve endings [59]. Thus, myofibroblasts interpose between urothelium and afferent nerve endings. Their intimate association with nerves suggest that they may respond to ATP released from the urothelium, and may influence afferent nerve function [60].
Most probably, a cascade of mediators, released from the urothelium and the suburothelial plexus of nerves in response to bladder distension, can initiate or depress activation of the bladder [63]. The firing of suburothelial afferent nerves, and the threshold for bladder activation, may be modified by both inhibitory (e.g., NO) and stimulatory (e.g., ATP, tachykinins, prostanoids) mediators. These mechanisms can be involved in the generation of detrusor overactivity, causing urgency, frequency and urgency incontinence, and thus seem to be potential targets for pharmacological intervention.

O’Reilly et al. [64] examined the role of P2X receptors in female patients with idiopathic detrusor overactivity. Bladder biopsies were obtained from the patients and from age and sex matched controls with a urodynamically proved stable bladder. In the patients, detrusor P2X2 receptors were significantly (50%) elevated, while other P2X receptor subtypes were significantly decreased. A purinergic component of nerve mediated contractions was not detected in control female bladder biopsy specimens but there was a significant component in overactive bladder specimens. It was concluded that in patients with idiopathic detrusor overactivity there is abnormal purinergic transmission in the bladder, which may explain symptoms. This pathway may be a novel target for the pharmacological treatment of the overactive bladder.

Which P2X receptor subtype is the most promising to target for drugs meant for treatment of OAB/detrusor overactivity has not been established. Antagonists of P2X3 receptors are in development.

VI. VANILLOID RECEPTORS

Intravesical administration of capsaicin or resiniferatoxin (RTX) — two members of the vanilloid family—has been shown to increase bladder capacity and decrease urge incontinence in patients with neurogenic, as well as nonneurogenic forms of detrusor overactivity [65]. Vanilloids are exogenous ligands of vanilloid receptor type 1 (TRPV1 or VR1), an ion channel present in the membrane of type C primary afferent nerve fibers innervating the bladder wall [66] and the peri-urethral zone of the prostate gland [67]. This receptor, which plays a key role in inflammatory pain perception and control of the micturition reflex, [68] may be upregulated by nerve growth factor (NGF), a neurotrophic molecule detected in high concentrations in overactive detrusors generated by chronic bladder outlet obstruction [69]. Vanilloids, by reducing uptake of NGF through sensory neurons, may counteract TRPV1 upregulation [65]. In addition, vanilloids decrease the response of already expressed TRPV1 receptors, a phenomenon known as desensitization [65].
Important sensory information from the prostate and bladder is conveyed by C fibers. Local anesthesia of the prostatic urethra was shown to increase bladder volume to first sensation to urinate and maximal bladder capacity, and also to reduce or abolish detrusor overactivity, in patients with benign prostatic enlargement [70, 71]. Likewise, intravesical lidocaine was shown to reduce involuntary detrusor contractions in patients with detrusor overactivity [72]. As lidocaine is more effective to anaesthetize C-than Aδ-fibers the contribution of prostate and bladder C-fiber input to abnormal detrusor activity is strongly suggested.

The ice water test triggers a capsaicin-sensitive spinal micturition reflex mediated by unmyelinated C fibers in the bladder and urethra [73]. Chai et al. [74] demonstrated a positive ice water test in 71% of subjects with bladder outlet obstruction (12 of 17), which was significantly higher than the 7% positive ice water test rate in nonobstructed subjects (3 of 44). The authors suggested this to be caused by an enhanced spinal micturition reflex, possibly due to plasticity of bladder afferents after BOO. If this is the case, intravesical treatment of patients with LUTS associated with BOO with intravesical vanilloids, by desensitizing C-fibers would be an interesting approach. Two preliminary studies with intravesical resiniferatoxin suggest that this may be the case [75, 76]. Dinis et al. [75] treated 12 males with a mean prostate volume of 45 ml by instilling a 50 nM RTX solution in 10% ethanol in the bladder during 30 minutes. RTX decreased by half the IPSS and QoL score, 91% of the patients having reported at least a 25% improvement. Cystometries performed in these patients showed that the mean volume at which patients reported the first desire to void and urgency to urinate increased by 90% and 55%, respectively. Kuo [76] performed multiple low dose (10 nM) RTX instillations in 20 patients with BPH and observed a reduction in the total IPSS score of 6 points. In a more detailed analysis, both studies concluded that the decrease of the IPSS score was predominantly due to an improvement of the storage symptoms. In contrast, improvement of voiding symptoms was marginal. Likewise, urodynamic parameters as maximum flow rate or post-voiding residual were not changed by the intravesical administration of the vanilloid [75, 76].

Another recent trial involving 18 BPH patients in whom urgency incontinence due to detrusor overactivity persisted in spite of having been submitted to prostatectomy also indicated that RTX may improve BPH associated storage symptoms [77]. RTX, 100 nM concentration, was instilled in the bladder in a 10% ethanol solution. In spite of being a subgroup of patients particularly difficult to handle, 11 patients (61%) improved due to either a decrease of 50% or more in the number of urge incontinence episodes.

A randomized, placebo-controlled study is needed to assess the therapeutic value of this approach.

VII. BOTULINUM TOXIN

Doggweiler et al. [78] injected botulinum toxin type A into the rat prostate and found that the toxin induced selective denervation and subsequent generalized atrophy of the gland (Figure 9). Apoptosis was seen diffusely throughout the gland.

Maria et al. [79] evaluated the therapeutic role of botulinum toxin injection in 30 men with benign prostatic hyperplasia in a randomized, placebo-controlled study. The patients received intraprostatic injections with a perineal needle inserted under ultrasound guidance. The control group received saline solution and the treated group received 200 U of botulinum toxin A. The outcome of each group was evaluated by comparing the symptom scores, serum prostate-specific antigen concentration, prostate volume, postvoid residual urine volume, and peak urinary flow rates. Thirty consecutive patients were enrolled. No local complications or systemic side effects were observed in any patient. After 2 months, 13 patients in the treated group and 3 in the control group had subjective symptomatic relief (P <0.0007). In patients who received botulinum toxin, the symptom score was reduced by 65% compared with baseline values and the serum prostate-specific antigen concentration by 51% from baseline. In patients who received saline, the symptom score and serum prostate-specific antigen concentration were not significantly changed compared with the baseline values and 1-month values (Figure 10). It was concluded that botulinum toxin injected into the prostate seems to be a promising approach for the treatment of BPH.

In a prospective study, Kuo [80] evaluated the effectiveness of prostate injection of botulinum A toxin in BPH patients who were poor surgical candidates. Ten patients with BPH and urinary retention or a large postvoid residual urine volume received 200 U botulinum A toxin injection into the transition zone of the prostate under visual endoscopic control. The
clinical results and urodynamic parameters at baseline and after treatment were compared. All patients had an improvement in spontaneous voiding after treatment. Of them, 8 had an excellent result (80%) and 2 had an improved result. Both voiding pressure and postvoid residual volume were significantly decreased after treatment. The total prostate volume was significantly reduced, and the maximal flow rate was significantly increased after treatment. The maximal effects of botulinum A toxin appeared at about 1 week and were maintained at 3 and 6 months after treatment. At 6 to 12 months of follow-up, no patient had had recurrence of urinary retention and the voiding condition in all patients remained at the post-treatment status. No adverse effect was noted.

Another three non-randomized clinical trials recently reported to International meetings and involving 37 symptomatic BPH patients support these results [81-83]. Prostates were injected with 100-150 UI Botox under transrectal ultrasound control. A significant symptomatic improvement occurred, as shown by a marked decrease in the IPSS score which could be detected, at least in some cases, within one week after injection and reached a maximum effect at one week.
Symptomatic improvement was accompanied by a marked decrease in the prostate volume and PSA serum levels [83]. These results are promising but further information is required concerning e.g., doses, duration of effect, effects on prostate size and PSA, and effects of repeated injections, to properly assess this potential treatment alternative. Randomized, sham-controlled studies are urgently needed.

**VIII. ENDOThELIN RECEPTORS**

Endothelins (ET-1, ET-2, ET-3) and ET (ET\(_A\), ET\(_B\)) receptors have been demonstrated both in the prostate and bladder. Since ETs can initiate both short-term (contraction) and long-term (mitogenesis) events in target cells in the bladder and urethra via their receptors, they may be of importance in the pathogenesis of LUTS.

In the prostate, ET-like activity is prominent in the glandular epithelium, but not in the stroma [84]. ET receptors have been demonstrated and characterized in prostatic tissue by many investigators; [85-94] in patients with BPH, the density of these receptors was found to be increased [87, 88]. Mumtaz et al. [94] used high affinity ET\(_A\) and ET\(_B\) -receptor-specific radioligands to determine the density and distribution of ET receptor subtypes in prostatic tissues obtained from patients with symptomatic benign prostatic hyperplasia (BPH). They demonstrated dense ET\(_A\) and ET\(_B\) receptor-binding sites in the prostatic stroma. The ET\(_B\) receptor-binding sites were predominantly seen in the prostatic stroma, whereas ET\(_A\) receptor-binding sites were prominent on the prostatic epithelium. ET-1, at sub-threshold concentrations, significantly enhanced \(\alpha_1\)-AR receptor-mediated prostatic smooth muscle contractile responses. Confirming previous reports, [84, 89, 95, 96] ETs were found to contract prostatic smooth muscle, and both ET\(_A\) and ET\(_B\) receptors were involved.

Saenz de Tejada et al. [97] demonstrated ET-like immunoreactivity in the transitional epithelium, serosal mesothelium, vascular endothelium, smooth muscles of the detrusor (nonvascular) and vessels, and in fibroblasts of the human bladder. This cellular distribution was confirmed in *in situ* hybridization experiments. The authors suggested that ETs may act as an autocrine hormone in the regulation of the bladder wall structure and smooth muscle tone, and that it may regulate cholinergic neurotransmission by a paracrine mechanism. The density of ET receptors was significantly lower in bladders from patients with BPH than in men without this disorder [87, 88]. ET-1 is known to induce contraction in animal as well as in human detrusor muscle [98]. The contractile effect of ETs seems to be mediated mainly by the ET\(_A\) receptor, and the ET\(_B\) receptor could not be linked to contraction. [99] However, in human bladder smooth muscle, ETs may not only have a contractile action, but could also be linked to proliferative effects. Supporting this view, Khan et al. [100] found that ET\(_A\) and ET\(_B\) receptor antagonists inhibited detrusor and bladder neck smooth muscle cell proliferation, and they suggested that ET-receptor antagonists may prevent smooth muscle cell hyperplasia associated with partial bladder outflow obstruction.

In rat urinary bladder, NANC neurotransmission is facilitated by ET-1 via the ET\(_A\) receptor, [101] and in rat vas deferens ETs potentiated the postjunctional effects of ATP, acting at P2X receptors [102]. Considering the potential role of purinergic transmission in the pathogenesis of detrusor overactivity, [64] such effects may be of importance in the pathogenesis of LUTS.

Many authors have suggested that ET may play a pathophysiological role in bladder outlet obstruction associated with BPH. ETs have a direct contractile effect on prostatic smooth muscle, they may enhance \(\alpha_1\)-AR receptor-mediated prostatic smooth muscle contractile responses, and they may stimulate cell proliferation. In the bladder, they may be implicated in detrusor hypertrophy and its functional consequences, including LUTS.

However, there is presently no clinical evidence available that ET receptor antagonists are effective against LUTS, or that they can influence the disease process in BPH.

**IX. ANGIOTENSIN RECEPTORS**

Several mitogenic factors may induce proliferation in the periurethral tissue of the prostate, including angiotensin. Dinh et al. [103, 104] showed the existence of angiotensin receptors type 1 (AT1) in normal human prostate and BPH. Other work showed elevated prostatic levels of local angiotensin-converting enzyme (ACE) in BPH and that the expression of the AT1 receptor might be affected by this [104, 105]. The intriguing question is what role Ang II plays in prostate physiology and pathophysiology (Figure 11).
Wennemuth and Aumuller [106] studied the occurrence of angiotensin I (AT1) and angiotensin II (AT2) receptors in human primary cultures of the prostate stromal compartment, and on human prostate tissue-embedded in paraffin. They also applied pharmacological tools in combination with photometry experiments to characterize the physiological activity of AT1 and AT2 receptors in primary human prostate cells. Only the AT1 receptor was detected in Western blot analysis. Immunocytochemistry of primary human prostate cells showed that the AT1 receptor was present in both the smooth muscle type and the fibroblastic type. In the stromal compartment of human prostate tissue, immunoreaction with antibodies against the AT1 receptor was detectable. In human prostate cells a linear rise in free intracellular calcium was elicited by angiotensin II in concentrations of 10$\mu$M. This effect could be inhibited by losartan.

In the isolated human detrusor, Andersson et al. [107] found that both angiotensin II and angiotensin I caused concentration-dependent contractions. The contractile effect was immediate, and was completely blocked by saralasin (blocking AT1 receptors), but was not affected by pre-treatment of the preparations with captopril or enalaprilate. A subsequent study showed that the conversion of angiotensin I to angiotensin II was produced not only by ACE, but also by a serine protease [108]. Waldeck et al. [109] characterized angiotensin II formation in human isolated bladder by selective inhibitors of ACE and human chymase. They confirmed that angiotensin II is a potent contractile agent in the human isolated detrusor muscle, and showed that the serine protease responsible for angiotensin II formation in the human bladder in vitro is human chymase or an enzyme similar to human chymase.

In rats with partial bladder outflow obstruction treated with losartan, Persson et al. [110] found no evidence for involvement of angiotensin II in development of bladder hypertrophy. The effect of angiotensin II on bladder smooth muscle tone was minor but was mediated by stimulation of the AT1 subtype receptor. Palmer et al. [111] arrived at a similar conclusion, showing that neither captopril nor losartan significantly ameliorated the histological or biochemical features of partial bladder outlet obstruction in the rat.

Whether or not blockade of angiotensin II generation or angiotensin receptors can block prostate growth or has any positive effects on LUTS remains to be established.

**X. VITAMIN D$_3$ RECEPTORS**

Analogues of vitamin D$_3$ were shown to inhibit BPH cell proliferation and to counteract the mitogenic activity of potent growth factors for BPH cells [112-114]. Receptors for vitamin D were demonstrated in rat and human bladder (Crescioli et al 2005), [115] which makes it conceivable that the bladder may also be a target for vitamin D. Experiments in rats with bladder outflow obstruction [116] showed that one of the analogues, BXL-628, at non-hypercalcemic doses, did not prevent bladder hypertrophy, but reduced the damage to the bladder smooth muscle which occurs with increasing bladder weight. BXL-628 has been selected for a phase II clinical trial in patients with benign prostate hyperplasia.
In the human prostate, there is a dense nitrergic innervation of the fibromuscular stroma, glandular epithelium, and blood vessels. Particularly secretory cells were found to be surrounded by a dense network of NOS-containing nerve terminals [117-119]. In BPH, this nitrergic innervation is reduced [118].

NO and electrical stimulation of nerves relaxed noradrenaline-contracted preparations of human prostatic smooth muscle; inhibition of synthesis of NO abolished the electrically induced relaxations [119, 120]. These findings suggest that NO can be a regulator of prostatic smooth muscle tone. However NO may have effects not only on stromal smooth muscle, but also on secretory cells and on vessels. Theoretically, lack of NO may lower the threshold for afferent firing leading to detrusor overactivity and LUTS associated with BPH. However, there is so far no clinical evidence showing that this may be the case.

In male neuronal NOS (nNOS)-deficient mice, Burnett et al. [121] found markedly dilated bladders with muscular hypertrophy, findings compatible with deficient urethral relaxation and increased outflow resistance. Supporting that the bladder changes were caused by disturbances in outflow relaxation, the decrease in tension produced by low frequency stimulation of nerves of isolated urethral preparations from wild-type controls, was absent in preparations from nNOS-deficient mice.

Evidence that baseline NOS activity prevents uninhibited bladder contractions also exists from urodynamic studies performed in a fetal lamb model [122]. If the nitrergic nerves observed in the detrusor, and particularly within and beneath the urothelium, are afferent terminals, NO may be involved in the regulation of the threshold for bladder afferent firing. Supporting such a view, intravesical oxyhemoglobin, a nitric oxide scavenger, induced detrusor overactivity in normal rats [123]. It was suggested that intravesical oxyhemoglobin induced detrusor overactivity by interfering with nitric oxide (NO) generated in the urothelium or suburothelially, and that NO may be involved in the regulation of the threshold for afferent firing in the bladder. Inhibition of the L-arginine/NO pathway by NOS inhibitors also lead to detrusor overactivity and decreased bladder capacity [124]. Furthermore, mice lacking cyclic GMP-dependent protein kinase I (cGKI, PKG I) showed detrusor overactivity characterized by decreased intercontraction intervals and non-voiding bladder contractions [125]. This further supports the view that the L-arginine/NO pathway is involved in the control of detrusor activity.

iNOS does not seem to be expressed in the normal bladder, but enhanced expression is seen early after BOO [126]. An enhanced function seen in bladders from mice lacking iNOS after longer periods of obstruction (5 weeks) in comparison to WT bladders suggests that reactive nitrogen species-induced protein nitrosylation may be involved in the loss of contractile function observed after more prolonged periods of obstruction [127]. Felsen et al. [128] showed that pharmacological or genetic decreases in iNOS resulted in amelioration of functional and fibrotic changes in the bladder after partial BOO, suggesting that NO contributes to the pathophysiology of BOO.

Gradini et al. [129] found that iNOS could not be detected in normal prostate, while it was expressed in the prostate of BPH patients, even in the absence of prostatitis or systemic signs of an inflammatory condition. Romih et al. [130] showed that in patients with BOO, some superficial urothelial cells lacked the asymmetric unit membrane, suggesting focal compromise of the blood-urine permeability barrier. In such relatively undifferentiated urothelial zones there was an accompanying increase in the expression of iNOS, which marks perturbed urothelial differentiation and may modulate bladder response to the outlet obstruction.

In an open prospective study Klotz et al. [131] studied the effects of orally given nitrates on micturition in 32 subjects. Fifteen patients suffered from obstructive symptoms, and 17 had no subjective micturition problems. In symptomatic patients, the authors found a significant improvement of peak urinary flow rates, IPS score and a significant decrease of residual urine volume. No significant changes of micturition parameters were found in asymptomatic patients.

The usefulness of NO donors in the treatment of LUTS remains to be established.

Use of NOS inhibitors to prevent the negative effects of the increased iNOS expression in BOO is exciting. However, further investigations are necessary to explore the potential of this approach.
Uckert et al. [132] characterized the PDE isoenzymes from human prostatic tissue by molecular biology and protein chemistry, and also investigated the effects of various PDE inhibitors on $\alpha_1$-AR mediated tension in isolated human prostatic strips. Reverse transcriptase-polymerase chain reaction revealed messenger RNA transcripts encoding for PDE 1, 2, 4, 5, 7, 8, 9 and 10 in the various anatomical regions of the human prostate, including the peripheral, central and transition zones. Except for complementary DNA encoding for PDE 1C, complementary DNA fragments encoding for PDE 1A, 1B, 2A, 4A, 4B, 4C, 4D, 5A, 7A, 8A, 9A and 10A were found at almost even ratios in the different histological regions of the prostate. The hydrolytic activities of PDE 4 and 5 were present in the cytosolic fraction of prostatic tissue, whereas in the particulate fraction only the hydrolytic activity of PDE 4 was detected. $\alpha_1$-AR mediated tension in prostatic strip preparations was reversed by forskolin, sodium nitroprusside, and inhibitors of PDE 4 and 5. The authors considered their studies to support the possible use of inhibitors of PDE 4 and 5 for treating urinary obstruction secondary to BPH. Sairam et al. [133] found that treatment with sildenafil appeared to improve urinary symptom scores in men with ED and LUTS in an open study, giving support to the conclusion drawn by Uckert et al. [132] Truss et al. [133, 135] demonstrated the presence of five PDE isoenzymes in human detrusor and suggested that the cAMP pathway and the calcium/calmodulin-stimulated PDE (PDE 1) could be of functional importance in the intracellular regulation in this tissue in vitro. They also presented preliminary clinical data with the PDE 1 inhibitor vinpocetine in patients not responding to standard antimuscarinic therapy, which suggested a possible role for vinpocetine in the treatment of urgency, frequency, and urge incontinence [134]. The results of a larger randomized, double-blind, placebo-controlled, multicenter trial with vinpocetine showed a tendency in favor of vinpocetine over placebo; however, statistically significant results were documented for one parameter only [135].

To assess the value of PDE inhibition (PDE 4 and 5) alone or in combination, further placebo controlled randomized trials are required.

XIII. RHO-KINASE

In BPH/LUTS there seems to be an increased smooth muscle activity contributing to the pathophysiology and development of symptoms. This may be attributed to increased sympathetic activity and increased stimulation of smooth muscle $\alpha$-ARs. However, in the pathophysiology of BPH/LUTS several other contraction-mediating transmitters than noradrenaline may be involved such as endothelins, angiotensins and prostanoids [136]. The question is whether or not there is a common pathway through which the different contractile transmitters/mediators can mediate contraction of the smooth muscle (Figure 12)?

Figure 12. Rho-kinase activation increases the sensitivity to Ca$^{2+}$ in the smooth muscle of the lower urinary tract by inhibiting myosin light chain phosphatase (MLCP). Since only phosphorylated myosin light chains (MLC) can interact with actin to produce contraction, inhibition of Rho-kinase decreases the calcium sensitivity of the contractile proteins and the smooth muscle relaxes. IP$_3$=inositoltrisphosphate; CaM=calmodulin; MLCK=myosin light chain kinase.
During recent years, regulation of the myosin light chain phosphatase (MLCP) has received much attention. One main pathway for inhibition of the MLCP and inducing Ca\(^{2+}\)-sensitisation involves a specific kinase (Rho-kinase), which is activated by RhoA via G-protein coupled receptors.\[137-139\] RhoA is a small, GTP-binding protein, which regulates a wide range of cellular processes including cytoskeletal function, secretion and smooth muscle contraction. Once activated, RhoA has several downstream targets, but for smooth muscle contraction the downstream target is 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\(^{\text{P}}\)) is maintained and smooth muscle remains contracted\[137-139\].

Rees et al.\[140\] showed that Rho-kinase is present in the cytosol and located in the perinuclear region in human and rat prostatic smooth muscle cells. Y-27632 decreased the proliferation of human and rat prostatic smooth muscle cells, and inhibited noradrenergic contractions elicited by electrical field stimulation and exogenous phenylephrine in rat prostatic strips.

Lindberg et al.\[141\] demonstrated an intense staining for RhoA in spontaneously hypertensive rats (SHR) prostatic smooth muscle cells. In comparison, immunoreactivity detected in prostatic smooth muscle from Wistar Kyoto (WKY) control rats was weaker in intensity amounting to 53 ± 4% of that obtained in SHR (p<0.05). Western blot analysis verified upregulated expression of RhoA in prostates from SHR compared to WKY. It was suggested that the increased activity of the RhoA/Rho-kinase pathway in prostatic smooth muscle from SHR may explain why prostatic tissue from these animals exhibit enhanced nerve-induced \(\alpha_{1}\)-AR-mediated contractions.

If Rho-kinase is upregulated in the prostate and the bladder in BPH, and contributes to increased smooth muscle activity both in the prostate and the bladder, this enzyme would be an interesting target for the treatment of BPH/LUTS. Fasudil is currently the only Rho-kinase inhibitor available for clinical use, and it is approved in Japan for the prevention of vasospasm in patients with subarachnoid hemorrhage\[142\]. Rho-kinase may represent a new target aimed for treatment of BPH/LUTS and studies are needed to define the therapeutic potential of Rho-kinase inhibitors.

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**XIV. CYCLOOXYGENASES/PROSTANOID RECEPTORS**

Prostanoids (prostaglandins and thromboxanes) are generated locally in both detrusor muscle and mucosa,\[143-144\] and synthesis is initiated by various physiological stimuli such as stretch of the detrusor muscle, but also by injuries of the vesical mucosa, nerve stimulation, and by agents such as ATP and mediators of inflammation, e.g., bradykinin and the chemotactic peptide\[136, 145-146\]. Prostanoids are synthesized by cyclooxygenase (COX) in the bladder\[144\]. This enzyme exists in two isoforms, one constitutive (COX-1) and one inducible (COX-2). It has been suggested that in the bladder, the constitutive form is responsible for the normal physiological biosynthesis, whereas the inducible COX-2 is activated during inflammation.

Even if prostanoids cause contraction of human bladder muscle,\[98\] it is still unclear to what extent they contribute to the pathogenesis of OAB/DO. More important than direct effects on the bladder muscle may be sensitization of sensory afferent nerves, increasing the afferent input produced by a given degree of bladder filling. Involuntary bladder contractions can then be triggered at a small bladder volume. If this is an important mechanism, treatment with COX inhibitors could be expected to be effective OAB/DO. However, clinical evidence for this is scarce.

Cardozo et al.\[147\] performed a double-blind controlled study of 30 women with DO using the nonselective COX inhibitor flurbiprofen at a dosage of 50 mg 3 times daily. The drug was shown to have favourable effects, although it did not completely abolish DO. There was a high incidence of side effects (43%) including nausea, vomiting, headache and gastrointestinal symptoms. Palmer\[148\] studied the effects of flurbiprofen 50 mg x 4 versus placebo in a double-blind, cross-over trial in 37 patients with idiopathic DO (27% of the patients did not complete the trial). Active treatment significantly increased maximum contractile pressure, decreased the number of voids and decreased the number of urgent voids compared to baseline. Indomethacin (non-selective COX inhibitor) 50 to 100 mg daily was reported to give symptomatic relief in patients with DO, compared with bromocriptine in a randomized, single-blind, cross-over study\[149\]. The incidence of side effects was high, occurring in 19 of 32 patients. However, no
patient had to stop treatment because of side effects. Sprem et al. [150] administered ketoprofen (non-selective COX inhibitor) intravesically once a day for 4 weeks in a double-blind, placebo-controlled cross-over study to 30 women with urodynamically verified idiopathic DO. Both symptomatic and urodynamic improvement was demonstrated. Eighteen out of 30 patients became symptom-free after treatment, and no side effects were observed.

Schroder et al. [151] investigated whether the PGE2 receptor EP1 was involved in the regulation of normal micturition, the response to intravesical PGE2 administration, and the development of bladder hypertrophy and overactivity due to BOO. Moderate BOO was created in EP1 receptor knockout (EP1KO) mice and their wild type (WT) counterparts. After 1 week cystometry was performed in conscious animals before and after PGE2 instillation. Findings were compared to those in unobstructed control animals. There was no difference between unobstructed EP1KO and WT mice in urodynamic parameters, but EP1KO mice did not respond to intravesical PGE2 instillation, while WT mice showed detrusor overactivity. The lack of EP1 receptor did not prevent bladder hypertrophy due to BOO. After BOO, WT mice had pronounced detrusor overactivity, while this was negligible in EP1KO mice. It was concluded that the EP1 receptor appears not to be essential for normal micturition or the mediation of bladder hypertrophy due to BOO, but to have a role in the development of detrusor overactivity caused by PGE2 and outlet obstruction.

Prevention and/or termination of inflammation and infiltration with lymphocytes in the prostate represent another potential new treatment concept for LUTS. Chronic inflammation is consistently associated with BPH and with precursor lesions of prostate cancer as well [152-154]. There is good evidence that this process lasting over years and decades, contributes to the development of benign hyperproliferation and in consequence LUTS. Interesting new therapeutic targets are therefore likely also to be found among the regulators of chronic inflammation of the prostate.

The predominating infiltrating cell type in inflammatory BPH lesions were characterized to be activated CD3+ T lymphocytes suggesting an autoimmune response as the underlying mechanism [155-156]. Accompanying prostate autoantibodies in the serum of BPH patients, directed for example against PSA [157] support this hypothesis. The chronic activation of infiltrating immune cells can cause tissue damage and thus may contribute to the pathogenesis of prostate diseases. Inflammatory infiltrates produce a variety of cytokines among them substances with autocrine stimulatory activity for prostate cells like IL6 or IL8 that likely contribute to hyperproliferation [158-161].

One potential class of drugs available for interfering with inflammation and inflammatory effects on the tissue are the non-steroidal anti-inflammatory drugs (NSAIDs), and among them especially the COX-2 inhibitors. They are used as potent pain relievers in diseases associated with inflammation and in addition are considered and tested as promising tumor chemopreventive agents for cancers such as colon and prostate cancer [162-163]. In the prostate highest level of expression of COX-2 were found in tumor cells, thus the interest to use substances like rofecoxib or celecoxib for chemoprevention of prostate carcinogenesis and tumor progression [164]. However, COX-2 is also induced in BPH lesions and smooth muscle cells of the prostate [165-166]. This pattern of expression nourishes hope that COX-2 inhibitors might also be effective in BPH. So far studies of COX-2 inhibitors in the treatment of LUTS are scarce. Di Silverio et al. [167] tested a combination of finasteride and the COX-2 inhibitor refecoxib versus finasteride alone in forty-six consecutive men with LUTS and BPH. Especially during the first weeks of therapy the improvement of symptoms was significantly better in the combination group, later on this difference levelled-off. This result is promising and would justify extension of these studies. However, recent findings of cardiovascular toxicity associated with prolonged use of COX-2 inhibitors resulting in withdrawal of some of these compounds from the market will make the conduct of appropriately designed long term placebo controlled studies very difficult.

1. GABAPENTIN

Gabapentin was originally designed as an anticonvulsant GABA (y-aminobutyric acid) mimetic capable of crossing the blood-brain barrier [168]. The effects of gabapentin, however, do not appear to be mediated through interaction with GABA receptors, and its mechanism of action remains controversial [168]. It has been suggested that it acts by binding to a subunit of the α2δ unit of voltage dependent calcium channels [169].
Gabapentin is also widely used not only for seizures and neuropathic pain, but for many other indications, such as anxiety and sleep disorders, because of its apparent lack of toxicity.

In a pilot study, Carbone et al. [170] reported on the effect of gabapentin on neurogenic detrusor overactivity. These investigators found a positive effect on symptoms and significant improvement in urodynamic parameters after treatment with gabapentin, and suggested that the effects of the drug should be explored in further controlled studies in both neurogenic and non-neurogenic detrusor overactivity. Kim et al. [171] studied the effects of gabapentin in patients with OAB and nocturia not responding to antimuscarinics. They found that 14 out of 31 patients improved with oral gabapentin. The drug was generally well tolerated, and the authors suggested that it can be considered in selective patients when conventional modalities have failed. It is possible that gabapentin and other α2δ ligands (e.g., pregabalin and analogs) will offer new therapeutic alternatives.

2. ALTERNATIVE STRATEGIES - COMBINATIONS

Combining the current α1-adrenoceptor antagonists with other agents might theoretically provide improved symptom relief. One such example is the combination of α1-adrenoceptor antagonists with 5 α-reductase inhibitors, which has proven to improve clinical outcomes and reduce the incidence of BPH and LUTS progression measured as symptom worsening, retention or progression to surgery [172]. Other combinations have also been tested with varying degrees of success. Traditionally muscarinic receptor antagonists have been contradicted in patients with BPH due to fears of urinary retention. However, this dogma has been questioned recently, [39] and several studies have been performed in which α1-adrenoceptor antagonists are combined with muscarinic receptor antagonists with promising results [173-174].

As mentioned above, Di Silverio et al. [167] found that combination with the COX-2 inhibitor rofecoxib and finasteride compared favourably to finasteride alone in a short-term interval (4 weeks). It was hypothesized that the association of rofecoxib with finasteride induces a more rapid improvement in clinical results until the effect of finasteride becomes predominant.

Speculatively, other combinations can be suggested: α1-adrenoceptor antagonists combined with ET-receptor antagonists may potentially offer both short-term and long-term benefits. Also a combination between an α1-adrenoceptor antagonist and a Rho-kinase inhibitor seems attractive.

3. TARGETS WITHIN THE CENTRAL NERVOUS SYSTEM

Several CNS transmitters may modulate voiding, but few drugs with a defined CNS site of action have been developed for treatment of voiding disorders, including LUTS associated or suggestive of BPH [16, 175]. Drugs affecting γ-aminobutyric acid, opioid, serotonin, noradrenaline, dopamine, or glutamatergic receptors and mechanisms are known to influence micturition, and potentially such drugs could be developed for clinical use. However, a selective action on the lower urinary tract may be difficult to obtain. Recently, the inhibition of the intracellular MAP kinase ERK 1, 2 signaling cascade (Figure 13) in lumbosacral spinal cord neurones was shown to reduce the frequency of reflex bladder contractions in anaesthetised rats with cyclophosphamide-induced chronic bladder inflammation (Figure 14), but not in normal rats [176].

The selective effect of ERK1, 2 inhibitors, designed to evaluate the role of this signalling cascade, on bladder function is attractive as a therapeutic tool, but future studies specifically focusing on bladder changes accompanying chronic BOO are needed.

XVI. CONCLUSIONS

Theoretically, there may be several possibilities to improve current medical treatment of LUTS associated with or suggestive of BPH (Figure 15; Table 1). Subtype selective α1-AR antagonists (α1D3), β3-AR agonists, muscarinic receptor antagonists (as single treatment or in combination with α1-AR antagonists), ET-receptor antagonists (alone or together with α1-AR antagonists), drugs acting at vanilloid receptors, angiotensin receptors, vitamin D3 receptors, and intraprostatic botulinum toxin all seem to have a certain potential. Nitric oxide donors, PDE inhibitors, iNOS inhibitors, Rho-kinase inhibitors, COX inhibitors, drugs blocking purinoceptors, and drugs like gabapentin, may offer new opportunities. Drugs acting on targets within the CNS seem to have a potential, but selective effects on LUTS may be difficult to obtain.
Figure 13. The ERK1/2 pathway in spinal cord neurones stimulated by bladder afferents.

Figure 14. The ERK 1/2 pathway in the spinal cord can be activated by physiologic bladder distension, an effect that can be inhibited by the mitogen-activated protein kinase kinase 1/2 (MEK 1/2) inhibitor PD98059.

Figure 15. Possible new therapeutic principles in the treatment of BPH/LUTS.
Table 1.

<table>
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<td>α1D-Adrenoceptor</td>
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<td>+++</td>
<td>Documented effects Practical problems</td>
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<td>+++</td>
<td>Documented effects Promising</td>
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<td>Endothelin receptor / converting enzyme</td>
<td>Endothelin receptor / converting enzyme inhibitors</td>
<td>++</td>
<td>-</td>
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<tr>
<td>Angiotensin receptor / converting enzyme</td>
<td>Angiotensin receptor / converting enzyme inhibitors</td>
<td>++</td>
<td>-</td>
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<td>+++</td>
<td>+</td>
<td>Under development. Promising?</td>
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<td>++</td>
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<td>iNOS inhibitors</td>
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<td>++</td>
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<td>Central nervous system active drugs</td>
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<td>+</td>
<td>Promising, but no positive proof of concept studies</td>
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Grading
- Evidence lacking
? Evidence not yet available

Evidence, preclinical:
+ Effect suggested – limited evidence
++ Effect demonstrated in several models
+++ Effect demonstrated in relevant in vivo models

Evidence, clinical:
+ Effect demonstrated – clinical implications unclear
++ Effect demonstrated – limited information
+++ Effect demonstrated in controlled clinical trials
REFERENCES


76. Kuo H-C. Multiple intravesical instillation of low dose resiniferatoxin is effective in the treatment of detrusor overactivity refractory to anticholinergics. BJU Int. 95: 1023-1028. 2005


Committee 14

Androgen Therapy in Men at Risk for Prostate Disease

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#### RECOMMENDATIONS (insofar as indications for androgen substitution)

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2. PROSTATE AND BREAST SAFETY – I
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4. PROSTATE SAFETY – III
Currently the major concern for the therapy for male late-onset hypogonadism is whether androgen replacement affects the safety of prostate. This section discusses the molecular aspects of the potential effect of androgen replacement on the prostate of aging male.

Prostate cancer is the absolute contraindication of androgen replacement. However recent studies show that low androgen milieu itself contributes to more aggressive prostate cancer [1, 2, 3]. These findings may invite speculation that androgen level in the prostate might modulate the oncogenic process of prostate cancer. To this date, there is no proof of evidence that androgen replacement therapy does increase the chance of prostate cancer. Thus the practical approach would be to discuss the potential molecular effect of testosterone administration on the precancerous lesions.

1. PROLIFERATIVE INFLAMMATORY ATROPHY AND TESTOSTERONE

Several lines of evidence suggest that chronic inflammation establishes a microenvironment for a precancerous lesion of many types of malignancies in humans, including prostate cancer. Inflammatory cells produce an array of oxygen-containing mutagenic chemicals, including superoxide, nitric oxide (formation of peroxynitrite), hydrogen peroxide, and hypochlorous acid [4, 5]. Oxygen radicals can cause tissue damage, and moreover they can directly attack DNA, which results in the accumulation of potentially pro-mutagenic oxidized DNA bases, such as 8-hydroxydeoxyguanosine [6]. Oxygen radicals are now considered to have a place in the prostate carcinogenesis since several studies show that antioxidants, such as carotenoid lycopene, vitamin E and selenium, decrease oxidative genomic damage in prostate cells, and may also reduce the risk of prostate cancer [7,8,9]. When a tissue becomes damaged as a result of inflammation, the consequent tissue regeneration processes usually involve increased cellular proliferation. De Marzo et al. proposed that a prostatic lesion called proliferative inflammatory atrophy is a precursor to prostatic intraepithelial neoplasia and prostate cancer [10]. The frequent association of lesions of proliferative inflammatory atrophy with chronic inflammation suggests that these lesions arise as a consequence of the regenerative proliferation of prostate epithelial cells in response to injury caused by inflammatory oxidants [10]. Indeed PIA lesions that are exposed to inflammatory oxidants induce GSTP1 expression as a defense against oxidative genome damage [11]. In aging males, the tissue level of androgens decreases as the blood level of testosterone does [12]. A thorough deprivation of circulating androgens results in diffuse prostatic atrophy. However whether partial decrease in androgen signal triggers focal atrophy which may be related to PIA remains unknown. Testosterone probably has two opposite effects on the prostate with inflammation. First of all, in relatively low androgen level, testosterone has anti-inflammatory effects. For example, in patients with hypogonadism, supplementation of androgens reduces serum inflammatory cytokines [13]. In an animal model, the inflammation
of the spontaneous nonbacterial chronic prostatitis of rats is worsened by castration, and it is blocked by replacement with testosterone [14,15,16]. Estrogen induces exaggerated inflammation and activates proinflammatory genes in the rat prostate [17], while testosterone inhibits the inflammation [18]. These experimental data indicate that testosterone may have anti-inflammatory effects on the prostate with low androgen milieu.

However, testosterone also has prooxidative effects which lead to activate AP-1 and NF-kB [19]. AP-1 is a transcriptional factor stimulating cell proliferation. NF-kB is a pro-inflammatory molecule and plays significant role in carcinogenesis. Furthermore, testosterone also activates MAPK and PI3K-Akt cascades, which contribute to cell proliferation [20]. These facts propose a serious question whether addition of testosterone to Pla, a potential precancerous lesion of prostate cancer, further enhances inflammation, aberrant cell proliferation, and genetic instability. In experimental carcinogenesis, short-term treatment of rats with chemical carcinogens or chronic treatment with testosterone produces a low incidence of prostate cancer. Thus testosterone itself may not be genotoxic enough to initiate carcinogenesis. However, combination of chronic treatment with testosterone following administration of carcinogens such as N-methyl-N-nitrosourea (MNU) and 3,2’-dimethyl-4-aminobiphenyl (DMAB) results in a high carcinoma incidence. Testosterone markedly enhances prostate carcinogenesis even at doses that do not measurably increase circulating testosterone. These data indicate that testosterone is a strong tumor promoter for the rat prostate [21].

2. TESTOSTERONE AND P27

Testosterone exerts strong proliferative effect on developing prostate epithelial cells. Prostate epithelium chronically requires physiological levels of androgens for their maintenance to avoid apoptosis [22]. After castration, a majority of secretory cells of the rat prostate are rapidly lost (60%–70% within 7 days of androgen deprivation). Androgen administration to mature castrated rats can trigger the regrowth of the prostate gland, which will eventually return to its original size [23]. However this regenerative process is timely regulated since proliferation rates decline to the baseline levels once the organ has attained adult size despite further androgen treatment [24]. At the same time that androgens exerts mitogenic activity, androgens induce glandular differentiation [25,26]. Recent study utilizing cDNA microarray identified that androgen responsive genes are involved in metabolism, chaperoning, trafficking, cell cycle, apoptosis, protein synthesis, extracellular matrix and scaffold, which are presumably involved in prostate differentiation [27]. In this switch from proliferation to differentiation, a cyclin kinase inhibitor, p27, plays a significant role in controlling the regrowth by limiting the proliferation of epithelial cells and inducing their differentiation [28,29,30]. p27 belongs to the Kip (Kip1) family of CKIs and is involved in multiple fundamental cellular processes, including cell proliferation, cell differentiation, and apoptosis. p27 was initially identified as an inhibitor of cdk2/cyclin E complex activity, and it was found to induce cell cycle arrest when overexpressed in cultured cells [31]. Moreover, p27Kip1 is a putative tumor suppressor gene that appears to play a critical role in the pathogenesis of several human malignancies, and its reduced expression has been shown to correlate with poor prognosis in cancer patients [32]. Androgens regulate the expression of p27 in both normal and neoplastic prostate epithelial cells. This regulation is dependent on the androgen receptor and achieved through modulation of its specific degradation by the ubiquitin-proteasome proteolytic system. p27 is widely expressed in differentiated prostate secretory cells. The expression of p27 is lost in cancer, PIN, and Pla [33]. Especially, it is noteworthy that PIN features hyperproliferative or intermediate state. The specific mechanism by which androgens regulate p27 degradation is unknown. However in the loss of p27, the transitional process from proliferation and differentiation would be disrupted, and androgen might direct towards proliferation in precancerous and malignant lesions. Back to 1964, Franks, LM et al. reported that prostates in old mice showed the atrophy and hyperproliferation of epithelial cells. This atrophy was reversed by the replacement of androgens. However, androgens did not normalize the increased cell proliferation [34].

Extrapolating this observation to patients who are receiving androgens based on the findings of current molecular biology, the administration of androgens on the p27- or any other molecules that regulate cell cycle-deficient prostate might further increase cell proliferation and jeopardize for the progression of prostate cancer. Currently there is no evidence on the influence of androgen replacement on Pla. This could be further clarified with clinical studies in patients with long term androgen replacement and having frequent prostate biopsies to observe the change of pathology more closely even at lower range of PSA.
REFERENCES


II. ANDROGEN THERAPY AND PROSTATE DISEASE

1. INTRODUCTION

One of the main concerns regarding testosterone therapy is the possibility of causing or promoting prostate disease, especially prostate cancer. This concern originates from two historical observations:

Metastatic prostate cancer regresses with castration or with pharmacologic lowering of serum testosterone to castrate levels, [1] and under experimental conditions, normal and malignant prostate cells die or regress in the absence of testosterone, and resume growth with restoration of physiologic levels of testosterone.

These observations have led to the concern that higher testosterone levels, via the use of testosterone replacement therapy (TRT) may cause growth of occult prostate cancer, converting these into clinical cancers. Since benign prostatic hyperplasia is also androgen-dependent, [1] there is an additional concern that testosterone supplementation may cause progression of benign prostatic hyperplasia and associated lower urinary tract symptoms (LUTS). Although these beliefs are widely held, clinical results largely fail to support these concepts. Key studies are briefly reviewed below.

2. TESTOSTERONE REPLACEMENT THERAPY AND BENIGN PROSTATIC HYPERPLASIA

Eugonadal men who received supra-physiologic doses of testosterone failed to demonstrate any increase in PSA, [2] suggesting that there exists a threshold, or saturation level for testosterone-dependent stimulation of prostatic tissue. In contrast, several studies have shown that TRT in hypogonadal men does result in a rise in PSA and prostate volume [3-6]. This increase is modest, at approximately 15%. Of interest is that the PSA and prostate volumes rise to levels similar to those of eugonadal men, [3] again suggesting a saturation point for stimulation of prostate growth. Clinically, however, these studies have shown no evidence for worsening of voiding symptoms, with unchanged prostate symptom scores. Urine flow rates and post void bladder residual urine measurements were also unchanged, and there has been no evidence that complications such as urinary retention occurred more frequently among TRT patients than for placebo control patients.

Although this experience with TRT and BPH is reassuring, individuals with severe voiding symptoms may note exacerbation of such symptoms with TRT. Consideration should therefore be given to treatment of LUTS prior to initiation of TRT in men with severe voiding symptoms.

3. TESTOSTERONE THERAPY AND PROSTATE CANCER

a) Clinical trials

Although there are no long-term, large-scale placebo-controlled clinical trials of TRT, the available data fail to support the contention that TRT results in a substantially increased risk of prostate cancer, or cancer progression [7]. A compilation of TRT trials revealed a cancer detection rate of 1%, which is similar to detection rates in large-scale screening programs for prostate cancer [7].

Moreover, one year of TRT among hypogonadal men at high risk for prostate cancer based on the presence of high grade prostatic intraepithelial neoplasia (PIN) resulted in only one case of cancer among 20 men (5%) [8]. The natural history of men with PIN is the development of cancer in 25% over three years. Although one must be cautious in comparing one-year to three-year data, it would certainly appear that TRT failed to cause a substantially increased rate of prostate cancer in a high-risk population.

b) Population-based studies of endogenous testosterone levels and prostate cancer risk

In 2001 Hsing reviewed twelve prospective population-based studies examining the relationship of endogenous testosterone levels to prostate cancer risk [9]. The hypothesis of such studies is that men who develop prostate cancer would demonstrate higher testosterone levels than men without cancer based on frozen serum samples from years prior to the clinical diagnosis of cancer. None of these twelve studies showed that men who developed prostate cancer had higher testosterone levels than men who did not develop cancer.

Moreover, men with the highest testosterone levels did not exhibit a greater risk of prostate cancer compared to men with the lowest testosterone levels. Although one study did claim an association for higher testosterone and prostate cancer, [10] this result was obtained only after simultaneous adjustment for four other hormones, representing a statistical manipulation that is unlikely to have clinical relevance.
4. Prostate cancer prevalence among men with low serum testosterone

If high testosterone is believed to represent a risk factor for prostate cancer, then it follows that low testosterone should be protective against prostate cancer. However, this does not appear to be true. Prostate biopsy performed in a group of 77 hypogonadal men with normal digital rectal exam and PSA <4.0 revealed cancer in 11 men, for a detection rate of 14% [11]. This rate is similar to the 15% cancer detection rate among men with PSA <4.0 in the placebo arm of the Prostate Cancer Prevention Trial who underwent biopsy as part of the study protocol. [12]. Although cancer rates in that latter trial were reduced by 25% among men receiving finasteride (which lowers dihydrotestosterone), [13] this drug does not substantially alter serum testosterone levels, and thus one cannot draw any conclusions from that study regarding the potential impact of TRT on prostate cancer risk.

5. Conclusions

In the absence of large-scale, long-term clinical trials of TRT, one must be cautious in assessing the risk of TRT with regard to prostate cancer. Nevertheless, the effect of testosterone on the prostate has been investigated extensively, and from a variety of research approaches. As noted above, normalization of testosterone among hypogonadal men causes a modest rise in PSA and prostate volume to levels seen with eugonadal men, but no higher, and does not impact voiding except in rare cases. Clinical trials of TRT have shown a low prevalence of cancer detection with treatment, and even high-risk populations fail to demonstrate any striking increase in cancer detection or progression. Moreover, multiple studies have failed to show that higher endogenous testosterone is a risk factor for subsequent cancer development. Furthermore, the presence of low testosterone does not appear to reduce this risk.

How does one resolve the lack of worrisome clinical data with the original observations that prostate cancer regresses with castration? The answer is that TRT is not the opposite of castration, since most hypogonadal men presenting for treatment already have substantially higher circulating testosterone levels than castrates. Saturation of testosterone receptors in cancer cells at hypogonadal levels would explain why no further stimulation of prostate cancer growth has been shown in clinical trials. This hypothesis merits laboratory investigation.

Although it is possible that further research may ultimately provide evidence that higher testosterone levels or TRT increases prostate cancer risk, to date there is no compelling evidence to support this contention. Indeed, this belief flies in the face of the inescapable, yet rarely acknowledged fact that prostate cancer becomes prevalent at a time of life when testosterone levels are in decline, and that clinical prostate cancer is almost never seen during the early decades of life when testosterone levels are highest. As others have previously postulated, [14] this observation leads to the possibility that long-term studies may even show that TRT is protective against the development of prostate cancer.

REFERENCES

Serum levels of the adrenal androgen dehydroepiandrosterone (DHEA) peak in men in the 3rd decade of life and thereafter decrease progressively with age. This decreased secretion of DHEA and DHEA-S by the adrenals is responsible for a parallel decrease in androgen and oestrogen formation in peripheral tissues by the steroidogenic enzymes specifically expressed in each cell type in individual target tissues [3]. The consequences of decreased DHEA production are still matter of debate. Because DHEA can serve as a precursor to more potent androgens and estrogens, like testosterone (T), dihydrotestosterone (DHT), and oestradiol (E2), supplemental DHEA use may pose a cancer risk in patients with nascent or occult prostate cancer.

ADRENAL ANDROGENS FUNCTION AS AN ANDROGEN SOURCE WITHIN PROSTATE AND ANDROGEN TARGET TISSUE

Up-to-date only a few studies have investigated the effects of DHEA on the prostatic cell. Experiments in male Wistar-Unilever rats demonstrated that non-toxic doses of DHEA confer significant protection against prostate carcinogenesis in rats. The efficacy of delayed administration of DHEA suggested that the compound confers protection against later stages of prostate cancer induction and could suppress the progression of existing preneoplastic lesions to invasive disease [1].

Koh E. et al. [4] compared the ability of three human prostatic cancer cell lines to metabolise the adrenal androgens, DHEA, and androstenedione under living culture conditions. Androgen-independent cell lines PC-3 and DU145 and androgen-dependent cell line LNCaP were investigated [2]. The findings show that the adrenal precursor pool has the potential to contribute to the regulation of prostatic cells. In another study with steroid responsive human LNCaP prostate cancer cells, containing a functional, but mutated androgen receptor (AR) the effects of DHEA were compared with those of T, DHT, and E2 on cell proliferation, and protein and/or gene expression of AR, PSA, IGF-I, IGF-I receptor (IGF-IR), IGF-II, IGF binding proteins -2,3, and 5, (IGFBPs-2-5), and oestrogen receptor-beta (ERbeta). Cell proliferation assays revealed significant stimulation by all four steroids. DHEA and E2- induced responses were similar, but delayed and reduced, compared with those of T and DHT.

Since the drug is unregulated and easily available as over the counter “nutritional supplement” in some countries, the use of DHEA should be considered to have the same contraindications that apply to T regarding prostate safety. Further studies of the mechanisms of DHEA effects on prostate cancer epithelial cells of varying AR status, as well as on prostate stromal cells, will be required to discern the implications of DHEA supplementation on prostatic health.

REFERENCES


Relatively few studies have examined the effects of GH on the prostate. Prostate hypertrophy is found in acromegaly and reduced size of the prostate in patients with GH deficiency. Overall and cancer mortality in acromegaly have been shown to correlate with the degree of GH control; if post therapy GH is controlled, both the overall and cancer mortality do not appear to differ from that of the normal population. Neither prostate nor breast cancers have been consistently shown to have an increased prevalence in acromegaly, but larger prospective epidemiological studies are required to study this further [1].

The effects of GH are transmitted through the insulin-like growth factor 1 (IGF-1). Although IGF-1 appears to exert a permissive effect on tumorigenesis, there is no clear evidence that tumour initiation is triggered by IGF-1 in acromegaly. However IGF-1 and its main binding protein, IGFBP-3, modulate cell growth and survival, and are thought to be important in tumour development. An evaluation of 21 studies comparing 3609 cases and 7137 controls showed that circulating concentrations of IGF-I might be associated with an increased risk of cancer, whereas IGFBP-3 concentrations could be associated with a decreased cancer risk, but these associations were modest and varied between sites [2].

Although laboratory methods need to be standardised, these epidemiological observations could have major implications for assessment of risk and prevention of cancer. In men below 59 years of age however P. Stattin [3] found a significant rise in prostate cancer risk with increasing IGF-1 levels. This amounted to odds ratio of 1.67 for those with the highest compared to the lowest levels. Even after adjustment for IGFBP-3, the ratio remained at 1.47. For men who were aged less than 59 years at recruitment, the odds ratio was 4.12. Moreover, the odds ratio for advanced cancer was 2.87 times greater in men with the highest versus the lowest IGF-1 levels. Thus the researchers conclude that the association appears particularly strong “for IGF-1 measurements made at a comparatively young age and for advanced disease”.

GH has been shown to increase the rate of cell proliferation in prostate cancer cell lines and the co-expression of GH and GH receptor (GHR) mRNA isoforms in the ALVA41, PC3, DU145, LNCaP prostate cancer cells by reverse transcription polymerase chain reaction has been demonstrated. Sequence analysis confirmed that these cell lines express the pituitary form of GH mRNA and also the placental mRNA isoform. The presence of GH and GHR proteins in these cell lines by immunohistochemistry was also shown [5]. Weiss-Messer et al. [6] in a recently published study demonstrated mRNA expression of GHR and of its exon 9-truncated isoform (GHR(tr)) in benign prostate hyperplasia (BPH) and prostate adenocarcinoma patient tissues, as well as in LNCaP, PC3 and DU145 human prostate cancer cell lines. GH-induced activation of signalling pathways, and its effects on AR protein in LNCaP cells and the isoform-specific regulation of GHR in prostate cancer patient tissues, suggest that GH, most likely in concert with other hormones and growth factors, may play an important role in progression of human prostate cancer.

Colao et al [4] investigated whether GH replacement therapy in adult patients with GHD has adverse effects on the prostate. The effects of 12-month GH or GH plus testosterone replacement on prostate pathophysiology in 24 adult patients with GHD (11 euandrogenemic and 13 hypoandrogenemic), compared to 24 age-matched healthy controls were evaluated. GH replacement restored prostate size to normal in both young and elderly patients, with no increase in prostate abnormalities. Prostate-specific antigen (PSA) and free PSA did not change, whereas PSA density was significantly reduced after treatment in hypoandrogenemic patients. Because the simultaneous treatment with GH and testosterone induces an increase of prostate size by 50% of baseline on average, care is suggested in elderly patients with prostate hyperplasia to avoid any risk of prostate symptoms. In these cases, GH replacement might be performed sequentially to reduce the hypertrophic effect of combining GH and testosterone.

Very recent, as yet unpublished data from the KIMS study database following more than 6400 patients receiving GH replacement therapy showed a very slightly increased rate of prostate cancer incidence, but this might be biased by the relatively high age of the treated patients (personal communication).

**RECOMMENDATIONS**

Surveillance for prostate cancer in elderly males with high IGF-1, especially if also receiving testosterone replacement therapy, is recommendable, by measurement of serum PSA, rectal examination and/or prostatic ultrasound [7].

However, GH administration is contraindicated in...
the presence of any cancer to which prostate is not an exception; as it is suspected to play a causal role in CaP. It is prudent, therefore, to consider that the same concerns and contraindications apply to GH as to androgens in relation to prostate health.

REFERENCES


V. SELECTIVE ANDROGEN RECEPTOR MODULATORS (SARMs)

The term selective androgen receptor modulator (SARM) was introduced by A. Negro-Vilar in 1999 to name synthetic androgen agonists targeting the androgen receptor with a great degree of tissue selectivity, designed to eliminate undesired side effects (i.e. prostate stimulation, aggressive behavior…) and to maintain or enhance the positive, protective effects (i.e. anabolic) normally regulated by endogenous androgens [17].

The complete action of testosterone on male sex accessory organs, especially prostate and seminal vesicles, depends upon its reduction to 5α-dihydrotestosterone (DHT) whereas the action on most other tissues does not. Because DHT is a 6-7 times more potent androgen than testosterone, its action on proliferation is amplified in tissues where such reduction occurs. Since DHT mediates several untoward actions, including prostate diseases, the ideal steroid for therapeutic androgen replacement in the adult male would be, like SARMs, a potent testosterone agonist that does not undergo 5α-reduction to DHT but can be aromatized to estradiol.

1. STEROIDAL ANDROGEN RECEPTOR MODULATOR: MENT

The synthetic androgen 7α-methyl-19-nortestosterone (MENT) is believed to be more biopotent overall than testosterone both because 19-nor-testosterone derivatives in general demonstrate this property [12] and also because the 7α-methyl group in MENT greatly enhances its binding affinity for the androgen receptor and increases subsequent nuclear retention [15]. In contrast to testosterone, MENT shows no binding to sex hormone binding globulin [13]. In a study on castrated rats, MENT was 4 times more potent than testosterone in maintaining the weights of ventral prostate and seminal vesicles but was 10 times the effect of testosterone on the weights of bulbocavernous plus levator ani muscles and 12 times that of testosterone in the suppression of gonadotropin levels [11]. The physiologic half-lives of MENT and testosterone are similar, suggesting that the increased biological activity of MENT is not determined by reduced clearance. The use of a 5α-reductase inhibitor had no influence on the activity of MENT, whereas cyproterone acetate, an antian- drogen that competitively binds to the androgen receptors, inhibited the action of MENT and testosterone on the prostate as well as on the muscle. The response of seminal vesicles or kidney weights to either testosterone or MENT replacement may differ according to different animal strains [18]. Similar results were obtained in non human primates in which MENT has 10 times more antigonadotropic and anabolic potency than testosterone, but is only 2-3 times more potent at stimulating prostate growth [5]. In the castrated male monkey, the minimal testosterone dose required to suppress LH stimulated prostate growth to twice normal size, whereas the minimal MENT dose for LH suppression maintained approximately normal prostate size [5]. Moreover, these effects were associated with unaltered HDL and increased HDL2 [5]. In hypogonadal men previously treated with testosterone, prostate volume and serum PSA were found to fall during MENT administration on a 24 weeks trial [2]. In the latter study,
according to MENT dosage, lean mass increased whereas fat mass and serum leptin concentration were shown to fall.

The effects of MENT on behavior seem not to be uniform. The sexual behavior in male castrated rats or mice, as judged on the percent of animals with mounts and intromissions, is fully restored at a dose between 1/2 and 1/20 of the effective dose of testosterone [16, 18]. In the castrated male hamster, MENT is approximately 4 to 5 times more potent than testosterone to sustain mating behavior [25], equivalent to the relative binding affinities of MENT and testosterone for the androgen receptor. In contrast, testosterone was much more effective than MENT to restore aggressive behavior in male castrated mice [18]. However, the relative contributions of androgenic and estrogenic metabolites in male sexual and aggressive behaviors cannot be generalized. In a short term study in hypogonadal men, MENT was as effective as testosterone in improving spontaneous nocturnal and waking erections, and sexual interest [1]. The ability of MENT to provide adequate support to sexual behavior and erectile function was confirmed in a 24 weeks replacement study [2] and in another one for contraceptive purpose [23]. The effects on mood were less consistent and partly conditioned by cultural differences [1].

Thus, in a clinical setting, MENT may maintain important androgenic, anabolic, antigonadotropic and behavioral functions without hyperstimulation of the prostate or promotion of aggressiveness. The dose required for androgen replacement in human is estimated to be 300-700µg/day, according to the severity of hypogonadism and the tissue selectivity [21]. This quantity could be delivered subdermally in currently available sustained release formulations, such as subdermal implants of MENT acetate, that should last for up to 8-12 months [1, 20].

As with others androgen derivatives, it is unclear how to determine with certainty androgen replacement in the absence of an ability to measure serum testosterone. Normal hemoglobin concentration and hematocrit seemed to be sensitive markers of an adequate androgen stimulus in a mid-term study in hypogonadal men [2]. Part of the effect of testosterone on the maintenance of BMD in men is mediated by conversion to estradiol. Although MENT is a substrate for aromatase [14], it was shown that physiological androgen replacement with MENT did not provide adequate support to the skeleton with a fall in BMD at the lumbar spine [2]. The high potency of MENT as an androgen, by reducing the dosage requirement, might become disadvantageous when metabolism by aromatase is required. On the other hand, aromatization end-products of MENT might be less potent activators of estrogen receptors than estradiol itself [2]. Obviously, more data are needed to further evaluate the effects and long-term safety of MENT.

2. NONSTEROIDAL SELECTIVE ANDROGEN RECEPTORS MODULATORS

Although MENT is considered one of the first tissue-selective androgens, some suggest to reserve the acronym SARM for androgens with a partial agonist/antagonist profile like the classical selective estrogen receptor modulator (SERM) raloxifene [6]. The steroidal compound mifepristone (RU34486) has partial agonist and antagonist actions [3]. Nonsteroidal ligands have a better receptor selectivity than steroidal ligands and demonstrate tissue-selective actions with diverse activity profiles that may serve specific therapeutic needs. Nonsteroidal androgens can neither be potentiated upon 5α-reduction nor aromatized to estrogenic compounds. The tissue selectivity of nonsteroidal androgen action may depend upon ligand-induced AR conformation and recruitment of a tissue-specific repertoire of coregulatory factors that function as coactivators or corepressors [4].

The tissue selectivity of nonsteroidal SARMs has been demonstrated in animal models, with a partial agonist action in prostate and seminal vesicles and a full anabolic action in the levator ani muscle [26]. In intact rats, the tissue selectivity of the SARM designated S1 decreased prostate weight with efficacy similar to that of the 5α-reductase inhibitor finasteride without affecting the levator ani muscle or altering the plasma levels of T, LH, or FSH [7]. When administered to orchidectomized rats, LGD2226 [19] and S-40503 [8] showed an osteoanabolic effect with an increase of BMD and biomechanical strength of femoral cortical bone but no elevation of prostate weight over the normal. Both products also exerted anabolic activity on the levator ani muscle [8, 19].

Thus, the strong agonist activity of tissue-selective nonsteroidal androgens in DHT-independent tissues could be used to help to reduce androgen depletion syndromes and to treat muscle wasting, osteoporosis and age-related frailty. However, the development of these compounds is at an early stage, and no information is yet available on the effects of these new androgens in humans.
3. CONCLUSION ON SARMs

In theory, SARMs should be safer than testosterone with regard to prostate hypertrophy and with regard to stimulating the growth of incipient prostate cancer. But the results of the Prostate Cancer Prevention Trial [22] raises an important question concerning a possible useful physiological function mediated by 5α-dihydrosteroids that would not be subserved by an androgen that resists 5α-reduction. The incidence of prostate cancer in the finasteride group was 18.4%, as compared with 24.4% in the placebo group. Moreover, the incidence of tumors with a Gleason score 7-10 was 37.0% in the finasteride group vs 22.2% in the placebo group [22]. The second estrogen receptor (ER-β) may have a role in this outcome [9]. ER-β is silenced in human cancers that are not well differentiated [27] and knock-out mice for ER-β show failure of the prostatic epithelium to differentiate fully, whereas the epithelial cells continue to proliferate [10]. The natural ligand for ER-β may be a steroid, 5α-androstane-3β,17β-diol (3 β-androstanediol), a metabolite of DHT [24]. Imamov et al. [9] suggest that finasteride, by blocking the conversion of testosterone to DHT, inhibits the production of 3 β-androstanediol, thus suppressing ER-β and preventing the differentiation of epithelium, accounting for the higher incidence of poorly differentiated tumors in the finasteride group in the Prostate Cancer Prevention trial. While the tissue selectivity and prostate-sparing effect of SARMs have been demonstrated in animal models, clinical trials with SARMs suppressing endogenous testosterone and 5α-reduction to DHT should address this potential major drawback in the future.

REFERENCES


VI. ANTIESTROGENS AND SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs)

A diagnosis of primary gonadal failure is made when a decreased serum level of testosterone is associated with an elevated level of gonadotropin and, on the other hand, normal or low level of gonadotropin in the presence of a lowered serum level of testosterone lead to a diagnosis of secondary or hypogonadotropic hypogonadism. In the latter group of patients, it is necessary to exclude patients with hyperprolactinemia and patients with a structural lesion of the hypothalamic-pituitary area.

However, a group of men exists who have a low level of serum testosterone and normal or low levels of prolactin and gonadotropin with no demonstrable anatomic abnormality of the hypothalamus or pituitary gland and no conditions known to cause hypogonadotropic hypogonadism (physical stress, psychotic illness, head injury, acute critical illness, alcohol intake, multiple medications…). This phenomenon of testosterone levels that decline without an increase in the gonadotropins has been reported to be related to age. Secondary hypogonadism refers to a low free testosterone level that is not compensated for by an increase in LH secretion.

The normal LH and FSH responses to GnRH suggest that the cause of reduced basal gonadotropins in the presence of reduced testosterone is a result of inadequate stimulation of pituitary gonadotrophs by properly timed release of GnRH pulses [4].

1. ANTIESTROGENS : CLOMIPHENE CITRATE AND TAMOXIFEN

Clomiphene [8] and tamoxifene [7] are believed to stimulate endogenous production of GnRH by the hypothalamus by their antiestrogen action, probably reflecting the primacy of estrogen over testosterone in the negative feedback regulation of male gonadal function. In men with erectile complaints and secondary hypogonadism, administration of clomiphene resulted in elevation of the levels of LH, FSH, and free and total testosterone similar to that reported in patients with intact pituitary and gonadal function [3, 4]. Clomiphene citrate was effective on both clinical and biological data in hypogonadotrophic hypogonadism induced by exercise in a male endurance athlete [1] and by steroid abuse in a 30-year-old male [9]. Tamoxifen had the same favourable effect in a man with hypogonadism caused by sports activity together with an impaired testicular function (cryptorchidy) [7]. The hypothalamus can be challenged with 50-100mg of clomiphene citrate for 5-7 days [3, 9] and the treatment resumed to 25-50mg 3 times a week [5].

2. SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

Recent data suggest that estrogen deficiency may play an important role in age-related bone loss in elderly men. Lasofoxifene, a selective estrogen receptor modulator, has been shown to prevent bone loss by inhibiting bone turn-over associated with aging and orchidectomy in adult male rats [6]. Further, lasofoxifene did not affect the prostate weight. Raloxifin, a SERM with an agonist action on bone without feminization, has been used during 6 months in 50 aging men, showing an osteoanabolic effect in patients with a low estradiol [2].

These results suggested that SERMs such as raloxifene or lasofoxifene might be useful agents for the prevention of osteoporosis in elderly men with some degree of hypogonadism.
3. CONCLUSION ON SERMS

Endogenous testosterone elevation from antiestrogens stimulation in hypogonadotropic hypogonadism raises PSA levels as exogenous testosterone does [5]. Determining PSA levels before and during treatment with an anti-oestrogenic drug is therefore strongly recommended.

REFERENCES


VII. INDICATIONS AND CONTRAINDICATIONS FOR TESTOSTERONE TREATMENT

In clinical practice there are only a few valid and specific reasons not to consider treatment for men with documented symptomatic late onset hypogonadism SLOH. In fact, the case for treatment is compelling, although some simply consider androgen substitution to be a quality of life issue. In a retrospective historical review of castrati who lived between the XVI and XIX Centuries, Nieschlag et al [1] found that life expectancy among these 50 men was not different than that of contemporary controls. However, a recent retrospective study suggests a contrary view: standardized mortality ratio was significantly higher in men with untreated gonadotropin deficiency as compared to those treated (with sex steroids) and healthy controls [2].

This section deals primarily with long-term androgen treatment. As explained later, treatment should not be instituted until a satisfactory work up has been completed. It is also understood that this section focuses on the adult male –the common victim of both prostate diseases and hypogonadism- eligible for androgen supplementation in whom androgen deficiency has been clearly diagnosed. The physician should be satisfied that the patient has signs and symptoms of SLOH and that the clinical picture is supported by biochemical findings. The decision tree summarizes in a practical way the views expressed here. 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.

1. MANAGEMENT OF MEN WITH BPH AND SLOH.

As with most clinical situations where evidence-based guidelines do not exist, knowledge and good medical judgment play a crucial role. From the considerations on the effect of androgens on BPH, it is clear that some modest increase in the volume of the gland is to be expected after T treatment in a hypogonadal man. Men with modest residual urine volumes and minimal symptoms of bladder outlet obstruction due to BPH (I-PSS < 8) can be safely treated with supplemental androgens. The situation...
is less well defined in the moderate category (I-PSS between 8-15). Obviously, a man with severe symp- toms and significant residual volumes can be tipped over into urinary retention by the administration of T; therefore, ART is contraindicated. But the benefits of ART should not be denied to a properly selected candidate because of the presence of mild, stable lower urinary obstructive symptoms. Treatment should only be postponed in those with moderate to severe obstructive symptoms until they have been successfully treated according to well established criteria [3].

2. MANAGEMENT OF MEN WITH SLOH AND AT RISK OF PROSTATE CANCER.

Current standard of practice establishes categorically that the administration of androgens is absolutely contraindicated in men suspected of or harboring prostate (and breast) cancer. This includes those with an abnormal digital rectal examination (DRE) and/or abnormal prostate specific antigen (PSA) in whom the diagnosis of carcinoma has not been excluded beyond doubt. However, a sub-clinical cancer can easily escape detection [4]. The presence of prostatic intraepithelial neoplasia (PIN) represents a major dilemma for the urologist. The experience on this is minimal and the information available limited to the extreme. Although Rhoden et al [5] concluded that ART “is not contraindicated in men with a history of PIN” their study included only 75 men followed for 12 months. These results must be viewed with caution until further independent information is available.

The increasing use of T preparations has made the issues involving ART and prostate cancer an important area of controversy with immediate clinical consequences. At present there are no studies available to answer the question: does T administration induce prostate cancer? This, beyond a doubt constitutes the most important issue regarding safety in men receiving androgens. The IOM report [6], in its extensive review of the situation regarding ART recommended that prostate safety be considered a high priority in future clinical trials. Unfortunately the IOM also recommended that small studies be conducted initially to document the efficacy of T treatment and only after efficacy has been confirmed, should the matter of prostate safety -among other safety issues- be addressed. This puts the clinician in a precarious situation when dealing with a man with SLOH. Obviously, it is inappropriate to wait for 15 or more years until those important concerns are eventually settled. As mentioned above, limited studies have already clearly demonstrated efficacy of ART in the treatment of most of the manifestations of SLOH (for a recent and thorough review see reference [7]). In many of these studies the changes induced in the prostate gland have been assessed directly (digital rectal examination, ultrasonography, biopsy) or by surrogate measures (urine flow, post-micturation residual volumes, PSA). All of those studies, however, are relatively small and lack sufficient power and follow-up for definitive answers. In short, these results although reassuring are far from definitive.

The increasing prevalence of localized CaP results in a large number of men undergoing curative procedures. Some of these men will present with SLOH. This presents a truly challenging situation. Should they receive androgen supplementation? If so when? Let us start admitting that today’s physicians have an ingrained desire for deterrence of T use in men with a history of prostate cancer. However, if one such man is considered cured and suffers from SLOH, should he be denied treatment? The facts are

1) most men undergoing curative surgery for CaP do not undergo simultaneous castration,
2) most men undergoing radical surgery have normal serum T levels,
3) although not fully recognized, serum T levels increase after radical prostatectomy and
4) early evidence is being presented indicating that no detrimental effects have occurred in patients receiving T after radical prostatectomy.

With these facts and a commitment for close follow-up, the prudent treatment of SLOH with testosterone supplementation appears warranted. Once again, definitive evidence is simply not available.

The following recommendations are adapted from the Consensus Conference held in Paris in 2003 [8]. They reflect the current state of knowledge but must be seen as “work in progress”. As new and better documented information becomes available the recommendations must be adapted to fresh realities. They are provided only as a general guide with global applicability.
1. **MONITORING – PROSTATE**
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.

2. **PROSTATE AND BREAST SAFETY – I**
Androgen administration is absolutely contraindi- cated in men suspected of harboring carcinoma of the prostate or breast.

3. **PROSTATE SAFETY – II**
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.

4. **PROSTATE SAFETY – III**
Androgen supplementation is contraindicated in men with severe bladder outlet obstruction due to an enlarged, clinically benign prostate. Moderate obstruction represents a partial contraindication to ART. After successful treatment of the obstruction, the contraindication can be lifted.

**REFERENCES**

INTRODUCTION

The 6th International Consultation on New Developments in Prostate Cancer and Prostate Diseases met from June 24-28, 2005, in Paris, France, under the co-sponsorship of the Union Internationale Contre le Cancer (UICC), to review new developments in prostate cancer, lower urinary tract symptoms (LUTS), benign prostatic disease, prostatitis and chronic pelvic pain syndrome (CPPS) and other related fields.

The recommendations are based on a thorough review of the available literature, and the global subjective opinion of recognized experts serving on focused committees. The individual committee reports were developed and peer-reviewed by open presentation and comment. Final recommendations were then refined by the Scientific Committee, consisting of the Chairmen of all the committees. The recommendations are graded whenever possible according to the International Consultation level of evidence and grading system adapted from the Oxford system.

The recommendations apply only to the standard patient defined below. Patients falling outside the definition of a standard patient may require diagnostic evaluation and treatment beyond the scope of these recommendations.

These recommendations agreed upon in 2005 will be periodically re-evaluated in the light of clinical experience and technological progress.
1. Terminology and Definitions

Lower urinary tract symptoms (LUTS) include storage and/or voiding disturbances which are very common in aging men.

LUTS may be due to structural or functional abnormalities in one or more parts of the Lower Urinary Tract (LUT) which comprises of bladder, bladder neck, prostate, distal sphincter mechanism and urethra. It must also be remembered that LUTS may result from abnormalities of either or both the peripheral and central nervous systems which provide neural control to the LUT. LUTS may also be secondary to cardiovascular, respiratory or renal dysfunction or disease.

This Consultation endorses the previously recommended nomenclature from the 5th International Prostate Consultation (2000) and detailed in the International Continence Society’s Terminology Report published in 2002.

- **LUTS** is divided into
  - **Storage Symptoms** which are experienced during the storage phase of the bladder and include daytime frequency and nocturia.
  - **Voiding Symptoms** which are experienced during the voiding phase

- **Overactive Bladder Syndrome** (OAB) is defined as urgency with or without urge incontinence, usually with frequency and nocturia.

- **Detrusor overactivity** (DO) is a urodynamic observation characterized by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked.

- **Benign Prostatic Hyperplasia** (BPH) is reserved for the histologic pattern the phrase describes.

- **Benign Prostatic Enlargement** (BPE) is used when there is gland enlargement. It is usually a presumptive diagnosis based on the size of the prostate.

- **Benign Prostatic Obstruction** (BPO) is used when obstruction has been proven by pressure-flow studies or is highly suspected from flow rates, and if the gland is enlarged.

- **Bladder Outlet Obstruction** (BOO) is the generic term for all forms of obstruction to the bladder outlet (eg urethral stricture), including BPO.

Therefore, terms such as “BPH patient”, “symptomatic BPH”, “clinical BPH”, “drugs for BPH” and “BPH treatment” are imprecise, cause confusion and are not recommended.

The Physicians Desk Reference (PDR) lists as indication for alfuzosin and tamsulosin the “treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)”, and for finasteride and dutasteride the “treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate”. It is clear from the above discussion that these definitions are less than ideal. “Alpha blockers are effective in treating LUTS, while 5-α reductase inhibitors are effective in treating LUTS in men with Benign prostate enlargement (BPE)” would be a more appropriate listing of indications.

The standard (usual) patient is a man over the age of 50 years consulting a qualified health care provider for lower urinary tract symptoms (LUTS). These symptoms may or may not be associated with an enlarged prostate gland, bladder outlet obstruction (BOO), or histologic benign prostatic hyperplasia (BPH).

A qualified health care provider is a person (physician, physician assistant, nurse practitioner or other mid-level provider) knowledgeable in diseases affecting the urinary tract, in particular the prostate gland, who has the expertise to perform the tests required as an initial evaluation, and who has been trained and has demonstrated competence in performing digital rectal examination (DRE).

LUTS consensus recommendations do not apply when other pathologies are known to be responsible for the patient’s LUTS, such as prostate cancer or other genitourinary tract malignancies, or due to significant comorbidities (eg severe diabetes mellitus) or significant concomitant medications, prior pelvic surgery or trauma. As well as being responsible for the symptoms, these diseases/conditions affect the proposed treatment in a manner not consistent with the consensus recommendations.
2. Diagnostic work-up of men presenting with lower urinary tract symptoms (LUTS)

The following categorization was utilized to classify diagnostic tests and studies:

- **A recommended test** is a test that should be done on **every patient** during the initial evaluation.
- **An optional test** is a test of proven value in the evaluation of **selected patients**. In general, optional tests are done during a **specialized evaluation** usually performed by a urologist.

### A. BASIC EVALUATION

#### RECOMMENDED TESTS

The basic evaluation should be done on every patient presenting to a health care provider with lower urinary tract symptoms (LUTS).

#### 1. History

A **relevant medical history** should be obtained focusing on the:

- **nature** and **duration** of reported genitourinary tract symptoms,
- **previous surgical procedures** (in particular, as they affect the genitourinary tract),
- **general health issues**, sexual function history,
- **medications** currently taken by the patient, and
- the **patient’s fitness** for possible surgical procedures or other treatments.

#### 2. Assessment of Symptoms and Bother

At least a **semi-quantitative** assessment of symptoms and bother is **strongly recommended** to grade the **severity** of lower urinary tract symptoms and to understand the patient’s **degree of bother** caused by those symptoms.

Excellent quantitative assessment tools have been developed and validated such as the International-Prostate Symptom Score (IPSS) with Bother Score (BS) (see page 14). Other questionnaires include the DANPSS, the ICIQMLUTS and the “BPH” Impact Index.

#### 3. Physical and Digital Rectal Examination

- **A focused physical examination** should be performed to assess:
  - **the suprapubic area** to rule out bladder distension,
  - **overall motor and sensory function** focused on the **perineum and lower limbs**.
- **A digital rectal examination** (DRE) should be performed to evaluate the **anal sphincter tone** and **prostate gland** with regard to approximate size, consistency, shape, and abnormalities suggestive of prostate cancer.

#### 4. Urinalysis

The urine should be analyzed using any of the widely available **dipstick tests**. These tests are done to determine if the patient has hematuria, proteinuria, pyuria, or other pathological findings (e.g., glycosuria, ketonuria, positive nitrite test etc). Examination of the urinary **sediment and culture** is indicated if the result of the dipstick is abnormal. The results of urinalysis may guide **further and additional testing** independent of the evaluation for LUTS.

#### 5. Serum Prostate-Specific Antigen (PSA)

The **benefits** and **risks** of PSA should be **discussed** with the patient, including the possibility of false-positive and false-negative results, the **possible complications** of subsequent transrectal ultrasound-guided-biopsy, and the possibility of a false-negative biopsy. Given the **uncertainties** surrounding prostate cancer detection, physicians must use **clinical judgment** in determining which patients should or should not undergo transrectal ultrasonography and prostate biopsy in response to a particular value of PSA.

Serum PSA is a **reasonable predictor** of prostate **volume** in men with LUTS, and can be used in this capacity in clinical decision making.

#### 6. Frequency - Volume Chart (Voiding Diary or Time and Amount Voiding Charts)

Frequency-Volument Charts are particularly useful when **nocturia is the dominant symptom**. The time and voided volume is recorded for each micturition over several 24-hour periods (usually 3) and will help to identify patients with **nocturnal polyuria** or **excessive fluid intake**, which are common in the aging male (a model of a chart is reproduced on page 15).
When patients present with LUTS, the use of a short, self-administered questionnaire, in the appropriate language, for the objective documentation of symptom frequency from the patient’s perspective is highly recommended. Three short, patient-completed questionnaires are recommended, the IPSS, and the ICIQMLUTS, both of which include a single quality of life question, and the DAN-PSS-1.

a) The IPSS (Page 14) is used to assess the frequency of three storage symptoms (frequency, nocturia, urgency) and four voiding symptoms (feeling of incomplete emptying, intermittency, straining, weak stream). The Bother Score assesses the degree of bother associated with the seven questions queried in the IPSS symptom severity score cited above. The “BPH” Impact Index can be used with the IPSS and has four questions asking how the symptoms affect the patient’s everyday life and interfere with daily activities, thus capturing the impact of the condition. This gives useful additional information to the single QoL question “If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?”

b) The ICI-QMLUTS assesses the frequency and bother of eight storage symptoms (frequency, nocturia, urgency, plus five questions on types of incontinence: urgency, stress, unconscious enuresis and post-micturition dribble) and five voiding symptoms (feeling of incomplete emptying, intermittency, straining, weak stream, hesitancy). Bother is evaluated using a 0 to 10 linear analog scale. Additional ICIQ modules on QoL (ICIQM-LUTSqol) and sexual function (ICIQMsex) can be used with the ICIQMLUTS. The advantage of ICIQMLUTS is that it recognizes and assesses symptoms due to causes other than BPO in the pathogenesis of LUTS, such as OAB.

2. Flow Rate Recording

Urinary flow rate measurement is useful in the initial diagnostic assessment and during or after treatment, to determine response. Because of the non-invasive nature of the test and its clinical value, it is recommended as part of the specialized evaluation, to be performed prior to embarking on any active therapy. Maximum urinary flow rate (Qmax) is the best single measure, but a low Qmax does not distinguish between obstruction and decreased detrusor contractility. Because of the intra-individual variability and the volume dependency of the Qmax, at least two flow rates ideally, both with a volume > 150 ml of voided urine, should be obtained. If such a voided volume cannot be obtained by the patient, despite repeated recordings, the Qmax results at the available voided volumes should be considered.

3. Residual Urine

The determination of post-void residual (PVR) urine is useful in the initial diagnostic assessment of the patient and during subsequent monitoring as a safety parameter. The determination is best performed by non-invasive transabdominal ultrasonography. Because of the marked intra-individual variability of residual urine volume, the test should be repeated to improve precision, particularly if the first residual urine volume is significant and suggests a change in the treatment plan.

4. Pressure Flow Studies (PFS)

Recommended prior to invasive therapies in men with a Qmax of greater than 10ml/sec. If Qmax is < 10ml/sec obstruction is very likely and PFS are not necessarily needed. PFS are of proven value in the evaluation of patients prior to invasive therapies, or when a precise diagnosis of BOO is important. Pressure-flow urodynamic studies are the only method with the potential to distinguish men with a low urinary flow rate due to detrusor outlet obstruction from those with bladder outlet obstruction. This is done by relating the detrusor pressure at the time of the maximum urinary flow rate to the maximum flow rate.

If patients are found not to have BOO, yet suffer from severe LUTS, they are less likely to benefit from invasive treatments, such as surgery, designed
to relieve outlet obstruction. Consequently, it is recommended that these patients have their symptoms treated in an appropriate fashion. Such treatment can consist of therapy aimed at other underlying disease processes, including anticholinergics, bladder behavioral training, biofeedback, etc.

The most important parameter of the pressure-flow study is the detrusor pressure (pdet) at the time of the maximum urinary flow rate (Qmax).

II. OPTIONAL TESTING

1. Imaging of the Prostate by Transabdominal or Transrectal Ultrasound (TRUS)

When residual urine is determined by transabdominal ultrasound with a machine generating real-time B-mode images, prostate shape, size, configuration, and protrusion into the bladder may be simultaneously evaluated.

Outside this context, imaging of the prostate by transabdominal or transrectal ultrasound (TRUS) is optional in selected patients. The success of certain treatments may depend on anatomical characteristics of the prostate gland (e.g., hormonal therapy, thermotherapy, stents, TUIP). When such treatments are planned, transabdominal or transrectal ultrasonography may be used to assess prostatic size and shape.

In men with serum PSA levels elevated above the locally accepted reference range, transrectal ultrasonography (TRUS) is the method of choice to evaluate the prostate, and to guide a needle biopsy of suspicious areas, or to perform biopsies in an attempt to rule out prostate cancer.

2. Imaging of the Upper Urinary Tract by Ultrasonography or Intravenous Urography (IVU)

Although imaging of the upper urinary tract is not recommended as a routine procedure, imaging is indicated in patients presenting with one or more of the following signs or symptoms:

- history of or current upper urinary tract infection,
- hematuria (microscopic or macroscopic),
- history of urolithiasis,
- renal insufficiency (in this case, ultrasonography is the preferred imaging study)
- recent onset nocturnal enuresis

3. Endoscopy of the Lower Urinary Tract

Endoscopic evaluation of the lower urinary tract is not recommended in an otherwise healthy patient with an initial evaluation consistent with BOO although it has certain indications, as described above for imaging.

There are treatment alternatives in which success or failure depend on the anatomical configuration of the prostate (e.g., TUIP, thermotherapy, etc.). Endoscopy is recommended if considered helpful when such treatment alternatives are contemplated.
### 3. Treatment Recommendations

#### I. BASIC MANAGEMENT

| A. Initial evaluation demonstrates the presence of LUTS associated with one or more of the following findings: |
| • DRE suspicious of prostate cancer  
• Hematuria  
• Abnormal PSA  
• Pain  
• Recurrent infection (infection should be assessed and treatment started by the practitioner before referral)  
• Palpable bladder  
• Neurological disease  
These patients need to be referred to a specialist (urologist) for appropriate evaluation before advising treatment. |

No further evaluation is recommended and the patient is reassured and can be seen again if necessary. This recommendation is based on the opinion that this category of patients with non-bothersome LUTS is unlikely to develop significant health problems in the future due to their condition.

| B. Initial evaluation demonstrates the presence of LUTS only, with or without some degree of non-suspicious prostate enlargement: |
| 1. If the symptoms are not significantly bothersome to the patient, or if the patient does not want treatment: |

If medical treatment is considered, the physician can proceed with therapy based mainly on:

1. Altering modifiable factors such as:
   - Concomitant drugs
   - Regulation of fluid intake especially in the evening
   - Lifestyle changes (avoid sedentary life) and
   - Dietary advice (avoid dietary indiscretion, such as excessive intake of alcohol and highly seasoned or irritative foods).

2. Pharmacological treatments
   (See pages 10-12)

   The patient should be followed to assess treatment success or failure and possible adverse events. The time interval after initiation of therapy for the assessment of treatment success varies according to the pharmacological treatment prescribed. It is usually 2-4 weeks for α-blocker therapy and 3 months for 5α reductase inhibitor.

   - If treatment is successful and the patient is satisfied, follow-up should be repeated approximately once a year by repeating the initial evaluation as outlined previously. The follow-up strategy will allow the physician to detect any changes that have occurred over the past year, more specifically, if symptoms have progressed or become more bothersome, or if a complication has developed creating an imperative indication for surgery.

   - If treatment fails and the patient is not satisfied, the patient should be referred to a urologist for further evaluation and possibly interventional treatment.

   | If interventional therapy is chosen, |

   - If the patient gets out of bed to void 2 or more times per night then he should be asked to complete a frequency-volume chart (FVC) for 3 days.

   The FVC chart will show polyuria when present. This may be either 24-hour polyuria or nocturnal polyuria. 24-hour polyuria has been defined as about ≥ 3 liters output. In practice, patients with symptoms are advised to aim for a urine output of 1 liter/24 hour.

   Nocturnal polyuria is diagnosed when more than 33% of the 24-hour urine output occurs at night. The patient should be managed according to the nocturia algorithm (see page 7). If his symptoms do not improve sufficiently, he should be treated along the same lines as men without predominant nocturia.

   b) If the patient has no polyuria

   If the patient has predominant significant nocturia:

   a) If patient has nocturnal polyuria:

   | a) If patient has predominant significant nocturia: |

   | • If the patient gets out of bed to void 2 or more times per night then he should be asked to complete a frequency-volume chart (FVC) for 3 days. |

   The nocturia algorithm (see page 7) may be used.

   If his symptoms do not improve sufficiently, he should be treated along the same lines as men without predominant nocturia.

   If interventional therapy is chosen, the patient should be referred to the specialist.
Basic Management of LUTS in Men

LUTS CAUSE LITTLE OR NO BOTHER

- ALTER MODIFIABLE FACTORS
  - DRUGS
  - FLUIDE & FOOD INTAKE

- LIFESTYLE ADVICE
  - BLADDER TRAINING

LUTS CAUSE LITTLE OR NO BOTHER

REASSURANCE AND FOLLOW-UP

PREDOMINANT SIGNIFICANT NOCTURIA

FREQUENCY-VOLUME CHART

Polyuria

1. Polyuria 24-hour output ≥ 3 liters
   - Lifestyle and fluid intake is to be reduced

2. Nocturnal polyuria ≥ 33% output at night
   - Fluid intake to be reduced Consider desmopressin

BOthersome LUTS

SUCCESS IN RELIEVING BOTHERSOME LUTS:

- ALTER MODIFIABLE FACTORS
  - DRUGS
  - FLUIDE & FOOD INTAKE
- LIFESTYLE ADVICE
- BLADDER TRAINING

Drug Treatment

Failure

RECOMMENDED TESTS:

- RELEVANT MEDICAL HISTORY
- ASSESSMENT OF LUTS
  - SYMPTOM SEVERITY AND BOTHER
- PHYSICAL EXAMINATION INCLUDING DRE
- URINALYSIS
- SERUM PSA
- FREQUENCY-VOLUME CHART

Complicated LUTS:

- SUSPICIOUS DRE
- HEMATURIA
- ABNORMAL PSA
- PAIN
- INFECTION
- PALPABLE BLADDER
- NEUROLOGICAL DISEASE

1 When life expectancy is > 10 years and if the diagnosis of prostate cancer can modify the management.
2 When significant nocturia is a predominant symptom.
3 Assess and start treatment before referral.
4 In practice, advise patients with symptoms to aim for a urine output of about 1 liter/24 hours
5 See pages 10-12.

SPECIALIZED MANAGEMENT
II. SPECIALIZED MANAGEMENT

For Persistent Bothersome LUTS after Basic Management

The specialist will use additional testing beyond those recommended for basic evaluation:

- Frequency -Volume Chart
- Detailed LUTS questionnaire
- Urine flow studies
- Ultrasound estimate of residual urine

A. If storage symptoms predominate (OAB) and no indication of BOO

Overactive Bladder (OAB) due to idiopathic detrusor overactivity is the most likely cause if there is no indication of Bladder Outlet Obstruction (BOO) from flow study and ultrasound estimates of PVR. The treatment options of lifestyle intervention, behavioral modification (bladder training and pelvic floor muscle exercises) and pharmacotherapy (antimuscarinic drugs) should be discussed with the patient.

The best results are obtained by combined therapy using all three modalities. Should improvement be insufficient and symptoms severe, then newer modalities of treatment such as botulinum toxin and sacral neuromodulation can be considered.

B. If there is evidence of Bladder Outlet Obstruction (BOO)

The treatment options should be discussed in the categories of drug therapy or interventional procedures.

1. If Drug Therapy is Considered:

Drug therapy decisions will be influenced by two factors: coexisting overactive bladder (OAB) symptoms and the size of the prostate or serum PSA level.

a) Coexisting BOO+OAB symptoms

This condition has been treated with alpha blocker and antimuscarinic combination therapy with increasing evidence of safety and efficacy.

b) BOO symptoms predominant

α1-adrenergic blocking agents are the treatment of choice for LUTS due to BOO. However, combination therapy with a 5α-reductase inhibitor has shown the highest efficacy when the prostate is enlarged and/or if the serum PSA is > 1.5 ng/ml.

The patient should be followed to assess treatment success or failure and possible adverse events. The time interval after initiation of therapy for the assessment of treatment success varies according to the pharmacological treatment prescribed. It is usually 2-4 weeks for α-blocker therapy and at least three months for 5α-reductase inhibitors.

- If treatment is successful and the patient is satisfied, the follow-up should be repeated approximately once a year by repeating initial evaluation as outlined previously. The follow-up strategy will allow the physician to detect any changes that have occurred over the past year, more specifically, if symptoms have progressed or become more bothersome, or if a complication has developed creating an imperative indication for surgery.

- If treatment fails and the patient is not satisfied, reassess and consider other therapies.

2. If Interventional Therapy is Considered

- If the patient elects to have interventional therapy, and there is sufficient evidence of obstruction, e.g., Qmax < 10ml/s, patient and physician should discuss the benefits and risks of the various interventions. TURP is still the “gold standard” for interventional treatment, but when available, new interventional therapies could be discussed. The techniques accepted for clinical use are summarized in Table 1 (page 12).

- If the patient’s condition is not sufficiently suggestive of obstruction, e.g., Qmax > 10 ml/s, pressure-flow studies are indicated, as treatment failure rates are somewhat higher in the absence of obstruction. If interventional therapy is planned without clear evidence of the presence of obstruction, the patient needs to be informed of possible higher failure rates of the procedure.
**Specialized Management for Persistent Bothersome LUTS after Basic Management**

**Recommended Tests:**
- Validated Questionnaires
- FVC (Frequency-Volume Chart)
- Flowrate Recording
- Residual Urine

**Evidence of BOO**
- Discuss Rx Options
- Shared Decision

**Medicai Therapy Option**

**Mixed OAB and BOO**

**Predominant BOO**

**Larger Gland and/or Higher PSA**
- \( \alpha \)-Blockers + 5\( \alpha \)-Reductase Inhibitors

**Small Gland and/or Low PSA**
- Antimuscarinics & \( \alpha \)-Blockers

**Reassess and Consider Invasive Therapy of OAB**
- Botulinum Toxin and Neuromodulation

**Failure**

**Offer MIST or Surgery to Patient**

**Evaluation clearly suggestive of Obstruction? (Qmax < 10ml/s)**
- **YES**
- **NO**

**Pressure-Flow Studies**

**Obstruction?**
- **YES**
- **NO**

**Treat appropriately. If interventional therapy is pursued, patients need to be informed of possibly higher failure rates**

**Proceed with selected technique**

---

**OAB**: Overactive Bladder  
**BOO**: Bladder Outlet Obstruction  
**MIST**: Minimally Invasive Surgical Treatment

1. PSA < 1.5 ng  
2. PSA > 1.5 ng
For a treatment to be considered as an acceptable option, it must meet the following criteria:

1. **Effectiveness and safety** of the treatment must have been shown in trials according to the guidelines established by the International Consultation on Prostate Diseases.

2. Any treatment of this disease should either **improve symptoms** and/or **prevent long-term complications** of the disease by either shrinking the enlarged prostate and/or reducing obstruction or by other modes of action.

3. The risk of **morbidity** and **mortality** associated with treatment must be considered in the context of the treatment:

   *New interventional treatments* should be compared to sham, similar treatments of proven efficacy, or TURP.

   *Pharmacological treatments* should be compared to placebo, have minimal morbidity, be acceptable to the patient, should not interfere with the patient’s sense of well-being or his quality of life and must not be unacceptably hazardous to his health.

4. After a new treatment is considered as an acceptable treatment option, **long-term studies** should be conducted to demonstrate durability and:
   
   - Continued effectiveness and safety.
   - Continued effectiveness relative to existing treatment options.
   - Cost-effectiveness related to existing and emerging therapeutic options.

   The results of such long-term studies could lead to a treatment being firmly established in routine practice, or to it being rejected as an unacceptable option.

The patient must be informed of all available and acceptable treatment options applicable to his clinical condition and the related benefits, risks, and costs of each modality.

LUTS associated with benign prostatic obstruction can significantly affect the quality of life in aging men, but are rarely life-threatening. Moreover, a significant number of men with histologic BPH or even gland enlargement (BPE) do not have disease progression. 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 (shared decision making). Some patients with very bothersome symptoms might opt for surgery, while other patients might opt for watchful waiting or medical therapy, depending on their individual views of benefits, risks, and costs.

**A. Watchful Waiting**

Progression of LUTS, BPE and/or BPO in terms of symptoms, future prostate growth, and long-term complications has been shown to be more likely in men with larger glands and higher serum PSA levels (i.e., >1.5 ng/ml or greater). Many men with smaller glands and/or lower serum PSA may have minimal progression of their symptoms over time. Moreover, the level of symptoms individual men may tolerate before being bothered by them is highly variable.

For these reasons, watchful waiting is an accepted management option for patients with mild, moderate or even severe symptoms, as long as they are not bothered by them and have not developed one of the imperative indications for surgery (mainly today upper tract dilatation and/or elevated creatinine).

If, after being adequately informed of the various treatment options and their consequences, the patient chooses watchful waiting as the preferred form of management, he should be followed approximately yearly by repeating the initial evaluation as outlined previously. This follow-up strategy will allow the physician to detect any changes that have occurred over the past year, specifically if symptoms have progressed or become more bothersome, or if a complication has developed, creating an imperative indication for surgery.
Patients initiated on medical therapy **should be followed** at appropriate intervals by repeating the initial evaluation, assessing treatment success or failure, and possible adverse events, and determining whether an alteration in treatment plan is indicated. Once patients are **stable on treatment**, **follow-up intervals** should be at least yearly.

Before deciding on a specific medical therapy, the physician should discuss the benefits and risks of the available drugs with the patient.

### 1. α-Adrenergic Receptor Antagonists (α-Blockade)

- **α-AR** antagonists are **effective, improve quality of life**, and have **acceptable safety**, as documented in properly conducted randomized clinical trials.
- **α-AR** antagonists are an **acceptable treatment** option for “LUTS” patients with bothersome symptoms, thought to be due to BPO, who have not developed serious complications.
- The **long-term efficacy and safety** of treatment with **α-AR** antagonists have been documented in open-label extension investigations, but continued study for example of cost-effectiveness, is recommended.
- Clinical efficacy on symptoms and safety of **α-AR** antagonists cannot be reliably predicted from **preclinical data**. However, effects on flow may be predicted.
- The **most advantageous** subtype selectivity profile for an **α-AR** antagonist has not been established.
- **Clinical uroselectivity**, as defined by the International Consultation on “BPH”, (“desired effect on obstruction and lower urinary tract symptoms related to adverse effects”), is still a **valid concept**.
- All clinically available **α-AR** antagonists can be associated with dizziness, asthenia, and orthostatic hypotension, and have the potential to lower blood pressure. The frequency of side effects of **α-AR** antagonists may vary between individual agents and the choice of a particular **α-blocker** might be influenced by the cardiovascular and sexual status of the patient. Dizziness and asthenia may be mediated by the CNS.
- Adequate head-to-head comparisons between different **α-AR** antagonists are still scarce, making fair comparisons between different agents difficult. More such studies are needed.

- The clinical action of **α-AR** antagonists is **rapid**. The treatment’s success is usually assessed after 2-4 weeks of treatment.
- **α-AR** antagonists are first-line medical treatment for “BPO”.
- In patients with “BPO” and **hypertension**, **α-AR** antagonists remain a first-line treatment for “BPO”. Associated hypertension and cardiovascular diseases should be treated independently according to established guidelines.

### 2. 5 α-Reductase Inhibitor (5 α-RIs) Therapy

- Of the available forms of hormonal therapy (androgen ablation, antiandrogens, and 5α-reductase inhibitors), only the **5 α-reductase inhibitors** have demonstrated both **efficacy** and **acceptable safety** in properly conducted, randomized clinical trials. 5 α–RIs are less effective with regard to symptom relief and flow rate in men who do not have clinically enlarged prostates. It is considered an acceptable first-line treatment option in patients with **clinically enlarged prostates** and bothersome symptoms who have not developed serious complications.
- The **long-term efficacy** and **safety** of 5 α–RIs have been demonstrated in open-label extension investigations, but continued study for example, of cost-effectiveness, is recommended.
- Available data show that 5 α–RIs have a **preventive influence** on the progression of benign prostatic enlargement (BPE) and significantly **reduce clinically important endpoints** such as acute urinary retention and the need for surgery.
- 5 αRIs lower serum PSA, but this can be corrected with sufficient clinical accuracy by multiplying the value by two. To date, there is no evidence that 5 α–RIs mask the detection of prostate cancer.
- The most common side effects of 5 α–RIs are sexual adverse events (diminished ejaculation, diminished libido and impotence).
- After initiation of therapy, the time interval for the **assessment** of treatment success is at least 3 months.
3. Combination treatment

The combination of an \( \alpha \)-adrenergic receptor antagonist and a 5 \( \alpha \)-reductase inhibitor (combination therapy) is an appropriate and effective treatment for patients with LUTS associated with demonstrable prostatic enlargement.

4. Alternative Treatments

Alternative medical treatment for LUTS mainly includes phytotherapeutic preparations and derivatives of polyene substances. The use of alternative medical treatments for LUTS varies greatly in different countries due to the evolution of treatment traditions and structures of the health care systems. In some countries, it is regarded as drug treatment and partly or totally reimbursable, while in others it is not reimbursed, but still considered as drug treatment, or merely considered as a dietary supplement.

Most phytotherapeutic preparations are plant extracts with different components, manufactured by different extraction procedures, which complicates comparison of the various preparations even though they originate from the same plant. Progress has been made towards isolation of various components of these preparations and their possible mechanism(s) of action.

Randomised clinical studies against placebo have been conducted with one extract of *Serenoa Repens* (Permixon extract) and suggest superior efficacy against placebo. Comparative studies of this extract with other medical treatments are not conclusive as these studies do not include a placebo arm. Other products (extracts from *Pygeum africanum*, preparations containing high concentrations of \( \beta \)-sitosterol and mepartmicin) have not been evaluated in adequate studies to draw significant conclusions.

Further studies according to the guidelines of the International Consultation are needed. Long-term follow-up is lacking. These studies are encouraged, as the Consultation considers this approach an interesting direction for further pharmaceutical and clinical research.

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### C. INTERVENTIONAL THERAPIES

**Standard surgical approaches** produce the most significant, long-term symptom improvement with acceptable risks. However, there is increasing acceptance of minimally invasive therapies that produce variable degrees of symptom improvement with risks that (in some cases) may be less than surgery. Evidence of durability is lacking, however, and it remains uncertain whether these new technologies are more cost-effective in the long-term than standard surgery (e.g., TURP).

The present status of the various available techniques is summarized in Table 1.

**Table 1: Clinically acceptable interventional techniques (present state).**

<table>
<thead>
<tr>
<th>Interventional therapies</th>
<th>Abbreviation</th>
<th>ICBPH 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transurethral resection of the prostate</td>
<td>TURP</td>
<td>A</td>
</tr>
<tr>
<td>Open prostatectomy</td>
<td>OP</td>
<td>A</td>
</tr>
<tr>
<td>Transurethral electrovaporization</td>
<td>TUVP</td>
<td>A</td>
</tr>
<tr>
<td>Laser-vaporization</td>
<td>LV</td>
<td>A</td>
</tr>
<tr>
<td>Transurethral microwave therapy</td>
<td>TUMT</td>
<td>A</td>
</tr>
<tr>
<td>Transurethral needle ablation</td>
<td>TUNA</td>
<td>A</td>
</tr>
<tr>
<td>Interstitial laser coagulation</td>
<td>ILC</td>
<td>A</td>
</tr>
<tr>
<td>Urethral stents</td>
<td>A/R</td>
<td></td>
</tr>
</tbody>
</table>
4. Standard Evaluation of New Treatment in Clinical Trials

All new investigational drugs and devices intended for use in LUTS, BPE, BOO and/or BPO should undergo rigorous testing in phase III clinical trials of at least 12 months duration in which they are compared with either standard treatments, or placebo/sham treatments to document their efficacy.

For commercial products, these trials may be sponsored by patent holder/owner/device manufacturer/pharmaceutical industry; however, third party monitoring of all trial-related source documents at each investigational site is mandatory to avoid either real conflicts of interest or the appearance thereof.

All new investigational drugs and devices should undergo additional testing in phase IV clinical trials to document efficacy over the long term (>12 months).

Additional recommended trial designs are community-based effectiveness and cost-effectiveness trials.

All trials involving humans must follow the Declaration of Helsinki Principles as revised by the World Medical Association in October 2000* and must be approved by an Institutional Review Board (IRB) which may either be local or central.

All trials should be planned, administered and conducted in close consultation with biostatisticians to assure proper sample sizes and data analysis and interpretation.

Inclusion and exclusion criteria, outcomes and efficacy parameters should be carefully chosen with the anticipated effect of the drug or device to be tested on the disease process in mind.

Rather than creating new symptom scoring instruments, all investigators should make use of widely available, validated, and in many cases translated and additionally culturally and linguistically validated instruments such as the I-PSS.


Reports should include a detailed listing of inclusion/exclusion criteria, and a flow diagram detailing how the participants pass through the various stages of the trial (JAMA 272:1926-1931, 1994).

Outcomes, efficacy and safety parameters should be reported in a clear and concise manner, avoiding the combination of two or more parameters into “global indices” and the reporting of proportions of patients who achieve X% improvement in parameter A and/or Y% improvement in parameter B.

Absolute as well as percentage changes should always be reported. If percentages and proportions are reported, the absolute changes should also be presented. All reported variables should be reported including measures of central tendency (mean, median) and measures of variance (SD, SE or CI).

To relate improvements in symptoms and, bother, quality of life scores to patients’ perceptions, standardized global subjective assessment questionnaires, should be administered during several of the follow-up visits in the pivotal trials.
INTERNATIONAL-PROSTATE SYMPTOM SCORE (I-PSS)

1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Less than 1 time in 5</th>
<th>Less than half the time</th>
<th>About half the time</th>
<th>More than half the time</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

2. Over the past month, how often have you had to urinate again less than two hours after you finished urinating?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Less than 1 time in 5</th>
<th>Less than half the time</th>
<th>About half the time</th>
<th>More than half the time</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

3. Over the past month, how often have you found you stopped and started again several times when you urinated?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Less than 1 time in 5</th>
<th>Less than half the time</th>
<th>About half the time</th>
<th>More than half the time</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

4. Over the past month, how often have you found it difficult to postpone urination?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Less than 1 time in 5</th>
<th>Less than half the time</th>
<th>About half the time</th>
<th>More than half the time</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

5. Over the past month, how often have you had a weak urinary stream?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Less than 1 time in 5</th>
<th>Less than half the time</th>
<th>About half the time</th>
<th>More than half the time</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

6. Over the past month, how often have you had to push or strain to begin urination?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Less than 1 time in 5</th>
<th>Less than half the time</th>
<th>About half the time</th>
<th>More than half the time</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?

<table>
<thead>
<tr>
<th>None</th>
<th>1 time</th>
<th>2 times</th>
<th>3 times</th>
<th>4 times</th>
<th>5 or more times</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Total I-PSS Score =

BOROTHER SCORE DUE TO URINARY SYMPTOMS (BS)

1. If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?

<table>
<thead>
<tr>
<th>Delighted</th>
<th>Pleased</th>
<th>Mostly satisfied</th>
<th>Mostly dissatisfied</th>
<th>Unhappy</th>
<th>Terrible</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Bother Score (BS) =
## Urinary Diary

### Example

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume of Urine Passed</th>
<th>Urgency</th>
<th>Leakage?</th>
<th>Drinks</th>
</tr>
</thead>
<tbody>
<tr>
<td>6:15 AM</td>
<td>200</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10:00</td>
<td>150</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11:30</td>
<td>275</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12:30</td>
<td>150</td>
<td>0</td>
<td>0</td>
<td>250 mL</td>
</tr>
<tr>
<td>3:00 PM</td>
<td>220</td>
<td>0</td>
<td>0</td>
<td>300 mL</td>
</tr>
<tr>
<td>3:45</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5:30</td>
<td>175</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7:45</td>
<td>200</td>
<td>0</td>
<td>0</td>
<td>300 mL</td>
</tr>
<tr>
<td>9:30</td>
<td>175</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10:30</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>250 mL</td>
</tr>
</tbody>
</table>
| Go to bed

### Day 1

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume of Urine Passed</th>
<th>Urgency</th>
<th>Leakage?</th>
<th>Drinks</th>
</tr>
</thead>
</table>

### Day 2

<table>
<thead>
<tr>
<th>Time</th>
<th>Volume of Urine Passed</th>
<th>Urgency</th>
<th>Leakage?</th>
<th>Drinks</th>
</tr>
</thead>
</table>

Please indicate the times you get up and go to bed.