# Male Lower Urinary Tract Symptoms (LUTS)

EDITED BY: Christopher Chapple and Paul Abrams
CONSULTATION CHAIRS: Christopher Chapple, Kevin McVary and Claus Roehrborn

An International Consultation on Male LUTS

Fukuoka, Japan, September 30 – October 4, 2012

SIU — SOCIÉTÉ INTERNATIONALE D'UROLOGIE

ICUD
International Consultation
on Urological Diseases

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Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible that these may change after publication. The reader is urged to review the product information (i.e. product monograph, package insert or leaflet, prescribing information) published by the manufacturers of the medications mentioned.

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# Abbreviations Used in the Text

| | |
|---|---|
| 5-AR | 5-alpha reductase |
| 5-ARI | 5-alpha-reductase inhibitor |
| AAPs | atypical anti-psychotics |
| ABP | acute bacterial prostatitis |
| ABs | alpha-blockers |
| Ach | acetylcholine |
| ACTH | adrenocorticotropic hormone |
| ADE | adverse drug event |
| ADH | antidiuretic hormone |
| ADR | adverse drug reaction |
| AE | Adverse event (abbreviation used in tables only, to save space) |
| AH | autonomic hyperactivity |
| ALF-ONE | alfuzosin once daily (a study name) |
| ALTESS | Alfuzosin Long-Term Efficacy and Safety Study |
| APF | anti-proliferative factor |
| ASA | American Society of Anesthesiologists |
| ATP | adenosine triphosphate |
| AUA | American Urological Association |
| AUA-SI | American Urological Association Symptom Index |
| AUASS | American Urological Association Symptom Score |
| AUR | acute urinary retention |
| AUS | artificial urinary sphincter |
| AVP | arginine vasopressin |
| B-TURP | bipolar TURP |
| BACH | Boston Area Community Health |
| BCI | bladder contractility index |

| | |
|---|---|
| BDs | bladder diaries |
| bFGF | basic fibroblast growth factor |
| BII | benign prostatic hyperplasia impact index |
| BK channels | large-conductance voltage- and calcium-dependent potassium channels |
| BMI | body mass index |
| BNI | bladder neck incision |
| BNP | brain natriuretic peptide |
| BoNT-A | Botulinum Neurotoxin type A |
| BOO | bladder outlet obstruction |
| BOOI | bladder outlet obstruction index |
| BOON | bladder outlet obstruction number |
| BOR | bladder outlet relation |
| BPE | benign prostatic enlargement |
| BPH | benign prostatic hyperplasia |
| BPO | benign prostatic obstruction |
| BTX | Botulinum Toxin A |
| BVE | bladder voiding efficiency |
| BWT | bladder wall thickness |
| $Ca^{2+}$ | calcium |
| cAK | cyclic adenosine monophosphate–dependent protein kinase |
| cAMP | cyclic adenosine monophosphate |
| CAMUS | Complementary and Alternative Medicine for Urological Symptoms |
| CBP | chronic bacterial prostatitis |
| CFS | chronic fatigue syndrome |
| cGK | cyclic guanosine monophosphate–dependent protein kinase |
| cGKI | cyclic guanosine monophosphate-dependent protein kinase-1 |
| cGMP | cyclic guanosine monophosphate |
| CI | confidence interval |
| CIC | coagulant intermittent cutting |
| CISC | clean intermittent self-catheterization |

| | |
|---|---|
| CLSS | Core Lower Urinary Tract Symptom Score |
| CombAT | Combination of Avodart and Tamsulosin (a trial name) |
| COPD | chronic obstructive pulmonary disease |
| CP | chronic prostatitis |
| CPC | Chronic Prostatitis Cohort |
| CPCRN | Chronic Prostatitis Collaborative Research Network |
| CPPS | chronic pelvic pain syndrome |
| CPSI | Chronic Prostatitis Symptom Index |
| CR | chronic retention |
| CT | computed tomography |
| DAN-PSS | Danish Prostatic Symptom Score |
| DECO | detrusor coefficient |
| DHEAS | Dehydroepiandrosterone |
| DHIC | detrusor hyperactivity with impaired contractility |
| DHT | dihydrotestosterone |
| DI | diabetes insipidus |
| DiLEP | diode laser enucleation of the prostate |
| DM | diabetes mellitus |
| DNA | deoxyribonucleic acid |
| DO | detrusor overactivity |
| DRE | digital rectal examination |
| DU | detrusor underactivity |
| DWT | detrusor wall thickness |
| Dx | diagnosis |
| EAU | European Association of Urology |
| ED | erectile dysfunction |
| EGF | epidermal growth factor |
| EjD | ejaculatory dysfunction |
| ELEP | eraser laser enucleation of the prostate |
| EMG | electromyography |
| EPICS | Enlarged Prostate International Comparator Study |

| | |
|---|---|
| EpiLUTS | Epidemiology of Lower Urinary Tract Symptoms |
| EPS | expressed prostatic secretions |
| ESWT | extracorporeal shock wave treatment |
| ET-1 | endothelin-1 |
| F | French (unit of measure) |
| FINNO | Finnish National Nocturia and Overactive Bladder |
| fMRI | functional magnetic resonance imaging |
| FPL | functional profile length |
| FVC | frequency volume chart |
| GFR | glomerular filtration rate |
| GITS | gastrointestinal therapeutic system |
| GOR | Grade of Recommendation |
| GRADE | Grading of Recommendations Assessment, Development, and Evaluation |
| Hb | hemoglobin |
| HDL | high-density lipoprotein |
| HIFU | high-intensity focused ultrasound |
| Ho:YAG | Holmium:YAG |
| HoLAP | holmium laser ablation of the prostate |
| HoLEP | holmium laser enucleation of the prostate |
| HoLRP | holmium laser resection of the prostate |
| HR | hazard ratio |
| HRQOL | health-related quality of life |
| hsCRP | high-sensitivity C-reactive protein |
| HTA | Health Technology Assessment |
| HUNT-2 | Nord-Trøndelag Health Study 1995–1997 |
| HUS | hours of undisturbed sleep |
| Hx | history |
| IBS | irritable bowel syndrome |
| IC | interstitial cystitis |
| ICIQ | International Consultation on Incontinence Questionnaire |
| ICIQ-FLUTS | ICIQ-Female Lower Urinary Tract Symptoms |

| | |
|---|---|
| ICIQ-OAB | ICIQ-Overactive Bladder |
| ICP | intracavernosal pressure |
| ICS | International Continence Society |
| ICS-'BPH' study | International Continence Society's benign prostatic hyperplasia study |
| ICUD | International Consultation on Urological Diseases |
| IDC | impaired detrusor contractility |
| IDC | involuntary detrusor contraction |
| IDEAL | Idea, Development, Exploration, Assessment, Long-term study |
| IFNγ | interferon gamma |
| IGF-1 | insulin-like growth factor |
| IGFBP-3 | insulin-like growth factor binding protein 3 |
| IIEF | International Index of Erectile Function |
| IIEF-EF | erectile function domain of the International Index of Erectile Function |
| IIEF-5 | International Index of Erectile Function questionnaire |
| IL | interleukin |
| ILC | interstitial laser coagulation |
| IPP | intravesical prostatic protrusion |
| IPSS | International Prostate Symptom Score |
| IPSS-QoL | International Prostate Symptom Score–Quality of Life |
| IR | immediate release |
| ISI | Incontinence Severity Index |
| IV | Intravenous |
| KTP | potassium-titanyl-phosphate |
| LBO | lithium triborate |
| LFE | low frequency electrotherapy |
| LH | luteinizing hormone |
| LHRH | luteinizing hormone–releasing hormone |
| LOE | Level of Evidence |
| LUT | lower urinary tract |
| LUTD | lower urinary tract dysfunctions |

| | |
|---|---|
| LUTS | lower urinary tract symptoms |
| M-TURP | monopolar transurethral resection of the prostate |
| MAP | mean arterial pressure |
| MCIC | minimal clinically important change |
| MCP-1 | monocyte chemoattractant protein-1 |
| MeSH | Medical Subject Headings |
| MIP-1-$\alpha$ | macrophage inflammatory protein 1-alpha |
| MIST | minimally invasive surgical therapy |
| MITs | minimally invasive treatments |
| MLUTS | male lower urinary tract symptoms |
| MOA | mechanism of action |
| MRI | magnetic resonance imaging |
| mRNA | messenger ribonucleic acid |
| MSAM-7 | multinational survey of the aging male |
| MSF-4 | Male Sexual Function 4-item |
| MSHQ | Male Sexual Health Questionnaire |
| MSHQ-EjD | Male Sexual Health Questionnaire for Ejaculatory Dysfunction |
| MTOPS | Medical Therapy of Prostatic Symptoms |
| MUCP | maximal urethral closure pressure |
| MUHC | McGill University Health Center |
| MVD | microvessel density |
| MVV | maximum voided volume |
| N-QoL | Nocturia Quality-of-Life Questionnaire |
| NGF | nerve growth factor |
| NHANES III | Third National Health and Nutrition Examination Survey |
| NHS | National Health Service |
| Ni | nocturia index |
| NICE | National Institute for Health and Clinical Excellence |
| NIH | National Institutes of Health |
| NIH-CPSI | National Institutes of Health Chronic Prostatitis Symptom Index |
| NIRS | Near Infrared Spectroscopy |

| | |
|---|---|
| NMDA | N-methyl-D-aspartate |
| NNES-Q | Nocturia, Nocturnal Enuresis and Sleep-interruption Questionnaire |
| NIH-CPSI | National Institutes of Health Chronic Prostatitis Symptom Index |
| NNT | number needed to treat |
| NO | nitric oxide |
| NOS | nitric oxide synthase |
| NP | nocturnal polyuria |
| NPi | nocturnal polyuria index |
| NSAID | non-steroidal anti-inflammatory drugs |
| OAB | overactive bladder |
| OAB-q | Overactive Bladder Questionnaires |
| OABSS | Overactive Bladder Symptom Score |
| OCAS | oral controlled absorption system |
| OR | odds ratio |
| OSA | obstructive sleep apnea |
| p | p-value |
| Pabd | abdominal pressure |
| PBS | painful bladder syndrome |
| PCAR | presumed circle area ratio |
| PCPT | Prostate Cancer Prevention Trial |
| PDE | phosphodiesterase |
| PDE5 | phosphodiesterase type 5 enzyme |
| PDE5-I | phosphodiesterase type 5 enzyme inhibitor |
| $P_{det}$ | detrusor pressure |
| $P_{det}Q_{max}$ | detrusor pressure at maximum flow |
| PDGF | platelet-derived growth factor |
| PDMS | polydimethylsiloxane |
| PFS | pressure flow studies |
| PG | prostaglandin |
| PICO | Patient, Intervention, Comparison, and Outcome |
| PIP | projected isovolumetric pressure |

| | |
|---|---|
| PLESS | Proscar Long-Term Efficacy and Safety Study |
| PM | after noon |
| PMC | pontine micturition center |
| PO | by mouth |
| PPMT | pre- and post-massage test |
| PSA | prostate-specific antigen |
| PSQI | Pittsburgh Sleep Quality Index |
| PUA | prostatic urethral angle |
| PUL | prostatic urethral lift |
| PV | prostate volume |
| Pves | vesical pressure |
| PVP | photoselective vaporization of the prostate |
| PVR | post-void residual |
| Qave | average flow rate |
| QH | quartz head |
| QHS | at bedtime |
| $Q_{max}$ | maximum flow rate |
| QOL | quality of life |
| Qqmax | Watts factor at maximum flow |
| RALP | robotic-assisted laparoscopic radical prostatectomy |
| RCT | randomized controlled trial |
| REDUCE | Reduction by Dutasteride of Prostate Cancer Events |
| RFA | radiofrequency ablation |
| RFITT | radiofrequency interstitial thermotherapy |
| RLS | restless legs syndrome |
| RNA | ribonucleic acid |
| ROC | receiver operating characteristic |
| ROCK | Rho-kinase |
| RR | relative risk |
| RRP | radical retropubic prostatectomy |
| SD | standard deviation |
| SE | standard error |

| | |
|---|---|
| SEP Q3 | Sexual Encounter Profile Question 3 |
| SF | side-firing |
| SHIM | Sexual Health Inventory for Men |
| SHR | spontaneously hypertensive rats |
| SIFO | Swedish Institute for Opinion |
| SSRIs | selective serotonin reuptake inhibitors |
| STD | sexually transmitted disease |
| STI | sexually transmitted infection |
| SUFU | Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction |
| SUI | stress urinary incontinence |
| TAMUS | Tampere Aging Male Urological Study |
| TEAP | transurethral ethanol ablation of the prostate |
| TGF-β | transforming growth factor beta |
| TGF-β1 | transforming growth factor beta 1 |
| ThuLEP | thulium laser enucleation of the prostate |
| ThuVaRP or TmLRP or TLVR | thulium vaporesection of the prostate |
| ThuVEP | thulium laser vapo-enucleation of the prostate |
| ThuVP or ThuVAP | thulium vaporization of the prostate |
| TIMES | tolterodine and amsulosin in men with LUTS (a trial name) |
| TNF? | tumour necrosis factor alpha |
| TRUS | transrectal ultrasound of the prostate |
| TRUSP | transrectal ultrasonography |
| TUEVP | trans-urethral electrovaporization of the prostate |
| TUIP | transurethral incision of the prostate |
| TUMT | transurethral microwave therapy |
| TUNA | trans-urethral needle ablation of the prostate |
| TURP | transurethral resection of prostate |
| TUVP | transurethral electrosurgical vaporization of the prostate |
| TWOC | trial without catheter |
| TZ | transitional zone |

| | |
|---|---|
| TZD | transitional zone volume |
| TZI | transitional zone index |
| UAB | underactive bladder |
| UDS | Urodynamics |
| UEBW | ultrasound-estimated bladder weight |
| UI | urinary incontinence |
| UK | United Kingdom |
| UPOINT | urinary, psychosocial, organ specific, infection, neurologic/systemic, and tenderness |
| UPP | urethral pressure profile |
| URA | urethral resistance factor |
| US | ultrasound |
| USD | American dollars |
| UTI | urinary tract infection |
| UUI | urge urinary incontinence |
| UWIN | Urgency, Weak Stream, Incomplete Emptying, and Nocturia |
| VA COOP | Veteran Affairs Cooperative Study |
| VEGF | vascular endothelial growth factor |
| VLAP | visual laser ablation of the prostate |
| WBC | white blood cell |
| WF | Watts factor |
| WFmax | Maximum Watts factor |
| WHO | World Health Organization |
| WIT | water-induced thermotherapy |
| Wmax | maximum bladder contractility |
| $\alpha$1-AR | alpha-1 adrenergic receptor |
| $\alpha$1AAR | alpha1A-adrenergic receptor |
| $\alpha$1BAR | alpha1B-adrenergic receptor |
| $\alpha$1DAR | alpha1D-adrenergic receptor |
| $\alpha$AR | alpha-adrenergic receptor |

# Preface

**Paul Abrams, MD**
Professor of Urology,
University of Bristol, UK

The worldwide adoption of the term "lower urinary tract symptoms" (LUTS) represents a paradigm shift from the days when the term "prostatism" was widely used. Lower urinary tract symptoms was introduced following a BMJ leading article in 1994. The arguments put forward in this article centred on the fact that many men's symptoms had little to do with the prostate. Male LUTS are now known to have a very similar prevalence and be of remarkable similarity to LUTS in age-matched women. The adoption of the term LUTS has led to some shift in focus when managing men with bothersome symptoms that were historically attributed to their prostate. The 1994 article also drew attention to the misuse of the term benign prostatic hyperplasia (BPH) and outlined the appropriate use of the terms BPH, benign prostatic enlargement (BPE) and benign prostatic obstruction (BPO). As the figure below shows, BPH, a histological term, is not necessarily associated with gland enlargement. If men live long enough, they will all develop histological BPH. Benign prostatic enlargement is the term used for gland enlargement and BPO is the term used when gland enlargement has caused the prostate to produce an obstruction to the urethra. Urodynamically, this is characterized by high voiding pressure and low urine flow rate. Benign prostatic obstruction is an example of bladder outlet obstruction (BOO) in the male. Other examples of BOO are bladder neck obstruction or urethral stricture. This terminology, initially recommended by the 1994 article, has subsequently been endorsed by the International Continence Society 2002 Terminology Report, the 2006 International Consultation on Urological Diseases (ICUD) Male LUTS Guidelines, and the 2011 American Urological Association Guidelines.

While there is general agreement on the intellectual correctness and proper use of the terms BPH, BPE, and BPO, much of the literature and activities around the scientific meetings still misuse the term BPH in expression, such as "the BPH patient" and "clinical BPH." Unfortunately these terms have become almost meaningless, as exemplified by a recent poster presented at the European Association of Urology: "Clinical efficacy and safety evaluation of imidafenacin as add-on treatment for residual overactive bladder symptoms in BPH patients with nocturia." In fact no prostatic size assessment, flow studies, or pressure flow studies had been carried out. Although all the men are likely to have had a prostate gland, the investigators had no knowledge whether men had histological BPH, let alone BPE or BPO. As such, this poster should have characterized the participants as men with nocturia, rather than BPH patients with nocturia. This example is, unfortunately, by no means unusual. The situation is not helped by regulatory authorities, such as the US Food and Drug Administration, insisting on using the term BPH. The argument centres on the misuse of words and results in many men being treated as if the prostate is the cause of their symptoms. For example, while overactive symptoms are as common in men as in women, only a quarter of the number of men are treated for overactive bladder compared to

women. Similarly, although nocturnal polyuria is the common cause of nocturia in older men (and women), it is poorly understood by the clinical community, and it is imagined that transurethral resection of the prostate will successfully treat nocturia, despite scientific literature showing that nocturia is the least responsive LUTS to prostatectomy.

This book represents a huge effort from a large international faculty, working in eight committees, as part of the ICUD-SIU Consultation on Male Urinary Tract Symptoms held in Fukuoka, Japan in September 2012, chaired by Chris Chapple, Kevin McVary, and Claus Roerhborn. Each chapter consists of the report of one committee, and the book is completed by the Scientific Report from the Consultation Scientific Committee, which consists of the chairs of the Consultation together with the chairs of all the committees. The Scientific Report details the consensus statements on patient care as well as reviews other topics, including epidemiology. The Scientific Report will be submitted separately for publication in a peer reviewed journal, as were the ICUD Guidelines from 2006. The Consultation committees reflect the change in emphasis as they assess not only prostatic obstruction, but also other important causes of male LUTS, such as detrusor overactivity. For the first time, there is also a committee on nocturia.

This book attempts to complete the paradigm shift from "prostatism" to LUTS/BPO. It is hoped that we have been consistent in the correct use of these terms. We hope that you enjoy reading the book and find it a vital and dependable source of data on male LUTS.
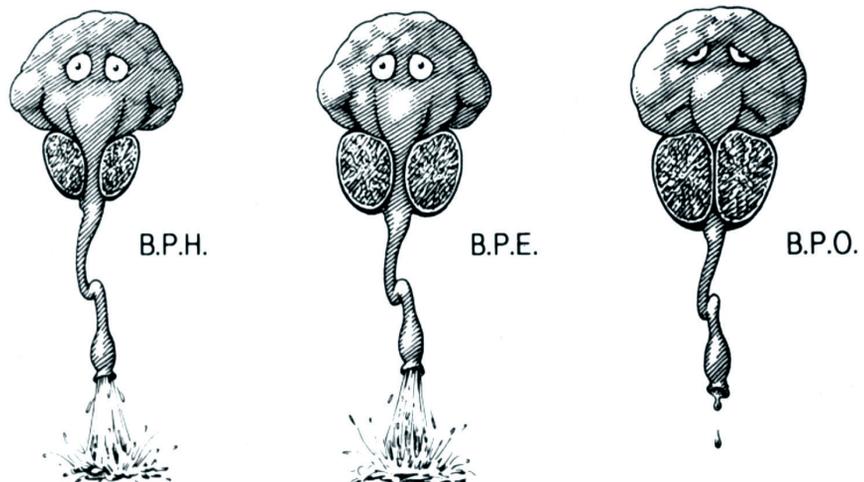


*Benign prostatic hyperplasia (BPH) vs benign prostatic enlargement (BPE) vs benign prostatic obstruction (BPO).*

**Paul Abrams**
United Kingdom

# Introduction



**Christopher Chapple**
United Kingdom

The proceedings of this consultation represent the consensus texts and recommendations of the eight committees involved in this, the ICUD International Consultation on Male Lower Urinary Tract Symptoms (LUTS).

On behalf of the International Consultation on Urological Diseases (ICUD), and its steering committee representing the major urological associations in the world (EAU, SIU, AUA, UAA, CAU, ICS), it is a great pleasure to thank the chairmen and committee members for all of their hard work in producing this impressive update on male lower urinary tract symptoms.

It is also a great pleasure, with this consensus document, to acknowledge the enormous contribution that Paul Abrams has made to the field by recognizing him as the Honorary Chairman of this meeting, and I would direct your attention to the foreword from him that follows this.

This consultation follows on the tradition which was first set in 1996 dealing with male lower urinary tract symptoms and in particular, I would like to acknowledge the enormous contribution made by our predecessors who edited the last edition, namely John McConnell, Louis Denis, and Saad Khoury, along with Paul Abrams and Clause Roehrborn who were heavily involved in this consultation.

This meeting was held in Fukuoka, Japan, on October 2nd, 2012, at the time of the 32nd Congress of the Société Internationale d'Urologie. The emphasis of this meeting was to provide a crisp update on key areas of interest, namely epidemiology and natural history, patient assessment, nocturia, the association between LUTS and sexual function, surgical treatment including new methods, the underactive bladder, chronic pelvic pain syndrome, and pharmacotherapy for lower urinary tract dysfunction in the male.

I would like to thank my co-chairs Kevin McVary and Claus Roehrborn for their strong support, and to acknowledge the hard work of the chairs of the committees and the individual members, whose enormous dedication made this monograph possible.

**Christopher Chapple**
United Kingdom

# Evidence-Based Medicine Overview of the Main Steps for Developing and Grading Guideline Recommendations

**P. Abrams, S. Khoury, A. Grant**

## Introduction

The International Consultation on Urological Diseases (ICUD) is a non-governmental organization registered with the World Health Organisation (WHO). In the last ten years, consultations have been organized on BPH, prostate cancer, urinary stone disease, nosocomial infections, erectile dysfunction and urinary incontinence. These consultations have looked at published evidence and produced recommendations at four levels: highly recommended, recommended, optional and not recommended. This method has been useful but the ICUD believes that there should be more explicit statements of the levels of evidence that generate the subsequent grades of recommendations.

The Agency for Health Care Policy and Research (AHCPR) have used specified evidence levels to justify recommendations for the investigation and treatment of a variety of conditions. The Oxford Centre for Evidence-Based Medicine have produced a widely accepted adaptation of the work of AHCPR. (June 5th 2001, www.cebm.net).

The ICUD has examined the Oxford guidelines and discussed with the Oxford group their applicability to the consultations organized by ICUD. It is highly desirable that the recommendations made by the consultations follow an accepted grading system supported by explicit levels of evidence.

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

## 1. First Step

Define the specific questions or statements that the recommendations are supposed to address.

## 2. Second Step

Analyze and rate (level of evidence) the relevant papers published in the literature.

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

## 2.1 What papers should be included in the analysis?

- Papers published, or accepted for publication in the peer-reviewed issues of journals.
- The committee should do its best to search for papers accepted for publication by the peer-reviewed journals in the relevant field but not yet published.
- Abstracts published in peer-reviewed journals should be identified. If of sufficient interest, the author(s) should be asked for full details of methodology and results. The relevant committee members can then "peer review" the data, and if the data confirms the details in the abstract, then that abstract may be included, with an explanatory footnote. This is a complex issue – it may actually increase publication bias as "uninteresting" abstracts commonly do not progress to full publication.

- Papers published in non-peer-reviewed supplements will not be included. An exhaustive list should be obtained through:
  I. The major databases covering the last ten years (e.g. Medline, Embase, Cochrane Library, Biosis, Science Citation Index).
  II. The table of contents of the major journals of urology and other relevant journals, for the last three months, to take into account the possible delay in the indexation of the published papers in the databases.

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

## 2.2 How are papers analyzed?

Papers published in peer-reviewed journals have differing quality and level of evidence. Each committee will rate the included papers according to levels of evidence (see below).

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

It is influenced by:
The type of study, whose hierarchy is outlined below:

- Systematic reviews and meta-analysis of randomized controlled trials
- Randomized controlled trials
- Non-randomized cohort studies

- Case-control studies
- Case series
- Expert opinion

### How well the study was designed and carried out

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

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

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

### How well the study was reported

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

### 2.3  How are papers rated?

Papers are rated following a level of evidence scale.

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

The levels of evidence scales vary between types of studies (i.e. therapy, diagnosis, differential diagnosis/symptom prevalence study) the Oxford Centre for Evidence-Based Medicine Website: www.cebm.net.

## 3.  Third Step: Synthesis of the Evidence

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

## 4.  Fourth Step: Considered Judgment (Integration of Individual Clinical Expertise)

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

## 5.  Fifth Step: Final Grading

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

The recommendations for grading follow the Oxford Centre for Evidence-Based Medicine. The levels of evidence shown below have again been modified in the light of previous consultations. There are now four levels of evidence instead of five.

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

## 6.  Levels of Evidence and Grades of Recommendation for Therapeutic Interventions

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

### 6.1  Levels of evidence

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

| Level of Evidence | Criteria |
|---|---|
| I | - Incorporates Oxford 1a, 1b<br>- Usually involves:<br>  - meta-analysis of trials (randomized controlled trials [RCTs]) or,<br>  - a good-quality RCT or,<br>  - "all or none" studies in which treatment is not an option (e.g. in vesicovaginal fistula) |
| II | - Incorporates Oxford 2a, 2b and 2c<br>- Includes:<br>  - *low-quality RCT* (e.g. <80% follow-up),<br>  - *meta-analysis* (with homogeneity) of *good-quality prospective cohort studies*<br>- May include a single group when individuals who develop the condition are compared with others from within the original cohort group.<br>- There can be parallel cohorts, where those with the condition in the first group are compared with those in the second group |
| III | - Incorporates Oxford 3a, 3b and 4<br>- Includes:<br>  - *good-quality retrospective case-control studies*, where a group of patients who have a condition are matched appropriately (e.g. for age, sex, etc.) with control individuals who do not have the condition<br>  - *good-quality case series*, where a complete group of patients, all with the same condition, disease or therapeutic intervention, are described without a comparison control group |
| IV | - Incorporates Oxford 4<br>- Includes *expert opinion*, where the opinion is based not on evidence but on "first principles" (e.g. physiological or anatomical) or bench research.<br>- The *Delphi process* can be used to give expert opinion greater authority:<br>  - involves a series of questions posed to a panel<br>  - answers are collected into a series of "options"<br>  - these "options" are serially ranked; if a 75% agreement is reached, then a Delphi consensus statement can be made |

## 6.2 Grades of recommendation

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

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

**Grade B** recommendation usually depends on consistent level 2/3 studies, or "majority evidence" from RCTs.

**Grade C** recommendation usually depends on level 4 studies or "majority evidence" from level 2/3 studies or Delphi processed expert opinion.

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

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

From initial discussions with the Oxford group, it is clear that application of levels of evidence/grades of recommendation for diagnostic techniques is much more complex than for interventions. The ICUD recommends that, as a minimum, any test should be subjected to three questions:

1. Does the test have good technical performance? For example, do three aliquots of the same urine sample give the same result when subjected to dipstick testing?

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

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

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

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

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

## Conclusion

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

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

**Summary of the International Consultation on Urological Disease Modified Oxford Centre for Evidence-Based Medicine Grading System for Guideline Recommendations**

| Levels of Evidence | Description |
|---|---|
| I | Meta-analysis of RCTs or high-quality RCT |
| II | Low-quality RCT or good-quality prospective cohort study |
| III | Good-quality retrospective case-control study or cohort study |
| IV | Expert opinion |

Abbreviation: RCT=randomized controlled trial

**Summary of the International Consultation on Urological Disease Modified Oxford Centre for Evidence-Based Medicine Grading System for Guideline Recommendations**

| Grades of Recommendation | Description |
| --- | --- |
| A | Usually consistent with level I evidence |
| B | Consistent level II or III evidence or "majority evidence" from RCTs |
| C | Level IV evidence or "majority evidence" from level II or III studies |
| D | No recommendation possible because of inadequate or conflicting evidence |

Abbreviation: RCT=randomized controlled trial

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Male Lower Urinary Tract Symptoms:
Medical Management and New Therapeutic
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# C1

# Epidemiology and Natural History of Male Lower Urinary Tract Symptoms

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# CONTENTS

## Epidemiology and Natural History of Male Lower Urinary Tract Symptoms

## 1.1  Introduction

Lower urinary tract symptoms (LUTS) are common in men and women, especially in aged populations. Lower urinary tract symptoms negatively affect health-related quality of life (HRQOL) of afflicted individuals and are associated with high health care costs (1–3). The etiology of male LUTS is multifactorial. One of the most common causes of LUTS in older men is benign prostatic hyperplasia (BPH), which induces benign prostatic enlargement (BPE) and bladder outlet obstruction (BOO). Bladder outlet obstruction interferes with urinary flow and may lead to acute urinary retention, urinary infection, bladder stones, hydronephrosis, or renal failure. Bladder outlet obstruction is also associated with bladder dysfunction, including detrusor overactivity, detrusor underactivity, and bladder hypersensitivity. Bladder dysfunction may occur independently from the prostate, as women develop similar changes in bladder function. Thus, male LUTS may be prostate associated and non-prostate associated. In practice, it is often difficult to distinguish these two phenotypes.

In this chapter, we describe the epidemiology and natural history of male LUTS. We acknowledge the distinction between prostate-associated and non-prostate associated phenotypes and devote a separate discussion to BPE and BOO. The epidemiology and natural history of nocturia, a common and bothersome complaint in men, is discussed in Chapter 3.

## 1.2  Descriptive Epidemiology

The majority of population-based epidemiology studies that evaluated LUTS among men were designed to report prevalence and not incidence of these symptoms. Most of these studies administered the International Prostate Symptom Score (IPSS) questionnaire to assess the prevalence of seven common LUTS. While, these studies describe proportions of individuals with moderate to severe symptoms (IPSS >7 points), they do not convey the prevalence of each individual LUTS, nor do they evaluate a wider spectrum of LUTS that includes all storage, voiding, and post-micturition symptoms.

Studies have shown that moderate (IPSS 8–19 points) to severe (IPSS >19 points) LUTS has a prevalence ranging from 16% to 52% (5–15). These studies demonstrated that LUTS are common among men and that the prevalence increases with age (5–12,16). Many publications focused specifically on the prevalence of urinary incontinence (UI) among community-dwelling men (16). Approximately 11% of men over the age of 40 had experienced an incontinent episode during the prior year, and the prevalence of daily UI may be as high as 9% among men over the age of 60 (16). A variety of questionnaires have shown UI prevalence estimates ranging from 5% among ages 19–44 years to 32% among those older than 80 years (16). Some country-specific disparities in LUTS and UI prevalence have been noted; however, these are most likely due to study design or methodological differences rather than true geographic variations (5–16).

During the past several years, population-based studies have reported both the prevalence of seven symptoms captured by the IPSS and a more complete list of voiding, storage, and post-micturition symptoms (17–23). These studies report variation in prevalence, ranging from 47% to 89% of the general male population reporting at least one lower urinary tract symptom (**Table 1**). In general, the most commonly reported storage symptom was nocturia, and the most common voiding symptom was terminal dribble. Post-micturition symptoms were reported less often than voiding or storage symptoms. These patterns are constant across countries (19). Several studies have confirmed a significant increase in prevalence with advancing age for both individual LUTS and for the total number of individual LUTS reported by men (17–19,22–24).

**TABLE 1**   Population-based Prevalence (%) of LUTS Among Men

| Symptom | Sweden 1992 *n*=7,763 | Finland 1994 *n*=4,256 | Scotland 1995 *n*=1,177 | Japan 2002–2003 *n*=2,100 | Sweden, Italy, UK, Germany & Canada 2005 *n*=7,210 | Korea+ 2006 *n*=888 | Sweden, UK & USA 2007–2008 *n*=14,139 |
|---|---|---|---|---|---|---|---|
| **Reference** | **22** | **17** | **18** | **20** | **19, 24** | **23** | **21, 26** |
| Any LUTS (at least 1 symptom) | NR | 89 | NR | NR | 47 | 54 | 72 |
| Storage symptoms | NR | NR | NR | NR | 27 | 27 | 46 |
| Nocturia* | 13 | 56† | 12‡ | 17§ | 21 | 10 | 29 |
| Urgency | 16 | 34 | 22 | 16 | 11 | 10 | 22 |
| Frequency | NR | 47 | NR | 52 | 7 | 14 | 21 |
| Urinary incontinence (UI) | 5 | NR | NR | NR | 5 | 3 | NR |
| Urge UI | 2 | 17 | NR | 7 | 1 | 1 | 9 |
| Stress UI | NR | 9 | NR | 3 | 1 | 1 | 1‖ |
| Mixed UI | NR | NR | NR | NR | 1 | NR | NR |
| Other UI | NR | 10 | NR | NR | 3 | 1 | 6 |
| Voiding symptoms | NR | NR | NR | NR | 26 | 29 | 57 |
| Intermittency | NR | NR | 10 | NR | 9 | 8 | 19 |
| Slow/weak stream | 27 | NR | 13 | 37 | 9 | 18 | 27 |

NR=gender specific prevalence not reported; *nocturia 2 or more times per night unless otherwise specified; §nocturia greater than 3x per night; ‡nocturia frequency not defined; †nocturia defined as mild, moderate, or severe; ‖prevalence defined as 'at least sometimes', SUI due to laughing, sneezing, coughing=1.2%; SUI due to physical activity=1.3%, other UI=leak for no reason; +some prevalence numbers extrapolated from graphs.

INTERNATIONAL CONSULTATION ON MALE LUTS

**TABLE 1** Population-based Prevalence (%) of LUTS Among Men, *Cont'd*

| Symptom | Sweden 1992 *n*=7,763 | Finland 1994 *n*=4,256 | Scotland 1995 *n*=1,177 | Japan 2002–2003 *n*=2,100 | Sweden, Italy, UK, Germany & Canada 2005 *n*=7,210 | Korea+ 2006 *n*=888 | Sweden, UK & USA 2007–2008 *n*=14,139 |
|---|---|---|---|---|---|---|---|
| **Reference** | **22** | **17** | **18** | **20** | **19, 24** | **23** | **21, 26** |
| Straining | NR | NR | 3 | NR | 7 | 10 | 8 |
| Terminal dribble | NR | NR | 23 | NR | 14 | 19 | 46 |
| Split stream | NR | NR | NR | NR | NR | NR | 20 |
| Hesitancy | 7 | 46 | 3 | NR | NR | NR | 20 |
| Post-micturition symptoms | NR | NR | NR | NR | 17 | 16 | 40 |
| Incomplete emptying | 23 | 30 | 8 | 26 | 14 | 14 | 23 |
| Post-micturition dribble | 32 | 63 | NR | NR | 6 | 8 | 30 |
| Other symptoms | NR | NR | NR | NR | NR | NR | NR |
| Bladder pain | NR | NR | NR | 2 | NR | NR | 5 |
| Dysuria | NR | 22 | 3 | NR | NR | NR | 3 |

NR=gender specific prevalence not reported; *nocturia 2 or more times per night unless otherwise specified; §nocturia greater than 3x per night; ‡nocturia frequency not defined; †nocturia defined as mild, moderate, or severe; ‖prevalence defined as 'at least sometimes', SUI due to laughing, sneezing, coughing=1.2%; SUI due to physical activity=1.3%, other UI=leak for no reason; +some prevalence numbers extrapolated from graphs.

Lower urinary tract symptoms often occur in clusters and not in isolation (24–27). Overactive bladder (OAB) is a common symptom cluster. The International Continence Society (ICS) defines OAB as urinary urgency, with or without urinary incontinence, usually with frequency and nocturia (28). The prevalence of these symptoms was the focus of at least 20 population-based studies during the past few years (19,22,23,29–46). Again, a wide variation in OAB prevalence rates (6%–84%) exists, with some geographic variation (**Table 2**). The majority of these studies (77%) reported the general population prevalence of OAB in men to be 10%–25% (**Table 2**). Several studies show that OAB prevalence among men increases with age, with the most dramatic increase occurring during the 6th and 7th decade of life (19,22–24,32,34,35,41–46). Except for one study, OAB with incontinence was reported less frequently than OAB without incontinence (**Table 2**).

## TABLE 2  Population-based Prevalence (%) of OAB Among Men

| Country | Ref | OAB Total | OAB without UI | OAB with UI |
|---|---|---|---|---|
| **Europe and the Americas** | | | | |
| France, Germany, Italy, Spain, Sweden, and UK (survey year not stated [*n*=7,048]) | 29 | 16 | NR | NR |
| Austria (survey year not stated [*n*=1,199]) | 30 | 10 | 8 | 2 |
| Canada  (survey year not stated [*n*=1,566]) | 38 | 15 | 13* | 2 |
| Sweden 1992 (*n*=7,763) | 22 | 16 | 14 | 2 |
| USA 2000–2001 (*n*=2,469) | 34 | 16 | 13 | 3 |
| Canada 2002 (*n*=475) | 39 | 13 | 9* | 4 |
| Brazil 2003–2004  (*n*=399) | 40 | 14 | NR | NR |
| Finland 2003–2004  (*n*=1,649) | 32 | 7 | 6 | 1 |
| Spain 2004 (*n*=824) | 31 | 15 | 5* | 10 |
| Italy, Germany, UK, Sweden, and Canada 2005 (*n*=7,210) | 19 | 11 | 8 | 3 |
| Italy | 12 | 9 | 3 | |
| Germany | 12 | 9 | 3 | |
| UK | 9 | 6 | 3 | |
| Sweden | 14 | 9 | 5 | |
| Canada | 9 | 5 | 4 | |
| USA 2005  (*n*=73,145) | 35 | 24 | 15* | 9 |
| Portugal 2008 (*n*=451) | 33 | 35 | NR | NR |
| Sweden, UK, and USA 2007–2008 (*n*=14,139) | 36 | NR | NR | NR |
| Sweden | 37 | 22 | NR | NR |
| UK | 24 | NR | NR | NR |
| USA | 27 | NR | NR | NR |

*Inputted from published data; NR=gender-specific prevalence was not reported; UK=United Kingdom.

INTERNATIONAL CONSULTATION ON MALE LUTS

**TABLE 2**  Population-based Prevalence (%) of OAB Among Men, *Cont'd*

| Country | Ref | OAB Total | OAB without UI | OAB with UI |
|---|---|---|---|---|
| **Asia** | | | | |
| Asia 1998 (*n*=2,369) | 41 | 30 | 13 | 17 |
| China | | 30 | NR | NR |
| Hong Kong | | 84 | NR | NR |
| India | | 14 | NR | NR |
| Indonesia | | 43 | NR | NR |
| Malaysia | | 27 | NR | NR |
| Pakistan | | 24 | NR | NR |
| Philippines | | 20 | NR | NR |
| Singapore | | 29 | NR | NR |
| Taiwan | | 23 | NR | NR |
| Thailand | | 63 | NR | NR |
| Taiwan 2000 (*n*=902) | 43 | 16 | NR | NR |
| Korea 2000 (*n*=1,000) | 44 | 21 | 13 | 8 |
| Japan 2002–2003 (*n*=2,100) | 42 | 14 | 8 | 6 |
| Japan 2003 (*n*=414) | 45 | 18 | NR | NR |
| Korea 2006 (*n*=888) | 23 | 10 | 9 | 1 |
| China 2009–2010 (*n*=7,359) | 46 | 6 | 4 | 2 |

*Inputted from published data; NR=gender-specific prevalence was not reported; UK=United Kingdom.

Studies of LUTS prevalence are difficult to compare for several reasons. There is evidence that results from self-reported LUTS data maybe be influenced by questionnaire administration method (e.g. mail surveys, telephone surveys, face-to-face interviews), which lead to sampling or measurement error due to differential response rates and data completeness (47–49). In addition, variations among study results may be attributed to the questionnaires administered and the operational LUTS definitions applied during analysis. The International Prostate Symptom Score, the most commonly used metric, lacks questions on incontinence and pain, two symptoms that often negatively affect HRQOL in men seeking medical care for LUTS (50). Population-based prevalence studies of self-reported LUTS are not necessarily reflective of medical diagnoses. Only about 50% of individuals reporting symptoms recall these symptoms as being bothersome, and an even smaller percentage of bothered individuals seek treatment (21,51). Future studies should implement standardized LUTS definitions and include consistent measurements of symptom burden, which will allow for better comparisons across settings.

There is a paucity of population-based research examining the incidence of individual LUTS. Thus, data on potential risk factors are restricted to cross-sectional studies. Longitudinal studies provide stronger evidence to better understand LUTS burden and elucidate LUTS risk factors for etiologic research. Once these risk factors have been clearly recognized, potential targets for prevention of symptom development can be identified.

## 1.3 Natural History

Information on the natural history of male LUTS derives from three types of sources: 1) longitudinal community-based studies, 2) control groups of men in randomized comparative studies, and 3) watchful waiting cohorts.

Overactive bladder and UI are highly prevalent (2,52). The EPIC study, based on current ICS definitions, found that approximately 11% of men and 13% of women in four European countries and in Canada reported OAB symptoms (19). The Epidemiology of Lower Urinary Tract Symptoms (EpiLUTS) study, also based on ICS definitions, found that the prevalence of both urge urinary incontinence (UUI) and stress urinary incontinence (SUI) is higher in women compared with men (UUI: 13.1% vs 4.5%, respectively; SUI: 14.8% vs 0.4%, respectively) (21). Literature on incidence and remission of male LUTS is still very scarce. There are few studies describing progression as well as remission of LUTS in men, especially long term.

Irwin *et al.* carried out a systematic review of OAB and UI longitudinal studies published in English between 1990 and 2010 (53). The search captured 21 randomly sampled population-based studies. Sample sizes ranged from 206 to 64,650. The majority of studies focused exclusively on women (16 studies) and on populations ≥40 years of age (16 studies). Only two studies dealt exclusively with men, and three studies investigated both men and women. These studies are described in **Tables 3** and **4**.

**TABLE 3** Longitudinal Studies in Men Performed Between 1990 and 2010

| First Author (Year) | Study Description | Gender | Age | Country | Population Source |
|---|---|---|---|---|---|
| **Studies of overactive bladder and UI based on ICS definitions** | | | | | |
| Malmsten (2010) | Cohort of men administered a prevalence survey about OAB using postal questionnaires in 1992 and 2003 | M | 56–103 y | Sweden | Population register |
| Dallosso (2004) | Data on urinary symptoms and diet were collected from men using a postal questionnaire | M | ≥40 y | United Kingdom | General practitioner registers |
| **Studies of UI alone not based on ICS definitions** | | | | | |
| Goode (2008) | Prospective cohort study of a random population of men and women with UI (stratified to be 50% black, 50% men, and 50% rural) administered a structured questionnaire by trained interviewers | M/F | 65–106 y | United States | Medicare beneficiaries |
| Liu (2002) | UI was assessed in a cohort of elderly men and women using a computer-assisted telephone interview | M/F | ≥70 y | Australia | State electoral database |
| Herzog (1990) | UI in men and women was assessed using an interviewer administered questionnaire | M/F | ≥60 y | United States | Multistage stratified area probability sample |

OAB=overactive bladder.

**TABLE 4** Symptom Progression and Remission

| First Author (Year) | Size | Follow-up Duration/ Interval | Recall Period | Symptom Definition | Progression/ Incidence | Regression/ Remission |
|---|---|---|---|---|---|---|
| **Studies of overactive bladder and UI based on ICS definitions** | | | | | | |
| Malmsten (2010) | 3257 | 11 y | – | ICS definitions used | Mean annual incidence OAB=3.7% UI=0.8% | Only a minority of men reported regression of symptoms. |
| Dallosso (2004) | 4887 | 1 y | – | ICS definitions used UUI: "Do you have such a strong desire to pass urine that you leak before reaching the toilet? (Y/N) Urgency: "When you need to pass urine, how strong is the urge usually?" Scored on a 5 point scale (overwhelming, very strong, strong, normal, weak) | 1 y incidence of OAB, 5.3% in men | – |
| **Studies of UI alone not based on ICS definitions** | | | | | | |
| Goode (2008) | 490 | 3 y | 6 mo | Women vs men reporting UI at 1 y after reporting no UI at baseline =15% vs 12% Women vs men reporting UI at 2 y after reporting no UI at 1 y =13% vs 12% Women reporting UI at 3 y after reporting no UI at 1 and 2 y =8% vs 8% | 3 y remission rates for women vs men reporting UI at baseline over 3 y=39% vs 55% | |
| Liu (2002) | 2087 | 2 y | – | UUI = "Do you have any difficulty holding your urine until you get to the toilet?" (often, occasionally, or never) SUI = "Do you accidentally pass urine?" (often, occasionally, or never) | Incidence of at least occasional UUI UUI=17.4% (men), 22.6% (women) at 1 y; UUI=30.4% (men), 37.5% (women) at 2 y; SUI=11.9% (men), 16.5% (women) at 1 y; SUI=20.7% (men), 30.8% (women) at 2 y | |
| Herzog (1990) | 1956 | 2 y | 1 y | UI = "In the past 12 months, about how many days have you lost any urine, even a small amount, beyond your control?" | Incidence UI=22.4% (women), 9.0% (men) from baseline to 1 y UI=18.6% (women), 9.2% (men) from 1–2 y | UI=11.2% (women), 26.7% (men) baseline to 1 y UI=13.3% (women), 32.3% (men) from 1-2 y (remission refers to no UI at 1 y or 2 y) |

ICS=International Continence Society; OAB=overactive bladder; MUI=mixed urinary incontinence; SUI=stress urinary incontinence; UI=urinary incontinence; UUI=urgency urinary incontinence.

Malmsten *et al.* demonstrated a dynamic progression of OAB symptoms from 1992 to 2003 in men (22). The proportions of men with OAB dry and OAB wet increased over that time period (**Figure 1**). Among men who were OAB dry in 1992, 49.5% remained OAB dry, while 12.6% reported symptom progression to OAB wet in 2003. Among men who were OAB wet in 1992, 51.1% remained OAB wet, and 42.2% reported symptom regression to OAB dry in 2003. The rate of complete remission of OAB symptoms was notably greater for men who were OAB dry (37.9%) compared with those who were OAB wet (6.7%). The mean annual incidence of UI and OAB was 0.8% and 3.7%, respectively. At both assessment points, UI and OAB had a negative influence on HRQOL, and men who developed UI or OAB had a greater deterioration in HRQOL than men who had no change in their UI/OAB status over time.

**FIGURE 1**

The dynamic progression of OAB symptom severity in men.

OAB symptoms showed dynamic changes in the percentage distribution of individuals with no OAB symptoms (No OAB), OAB without UI (OAB dry), and OAB with UI (OAB wet); reproduced from Malmsten UG, Molander U, Peeker R, *et al.*

Urinary incontinence, overactive bladder, and other lower urinary tract symptoms: a longitudinal population-based survey in men aged 45-103 years. *Eur Urol.* 2010;58:149-156 (Figure 3).

|  |  | 2003 | | | |
|---|---|---|---|---|---|
|  |  | No OAB, n | OAB dry, n | OAB wet, n | Total, n (%) |
| **1992** | No OAB | 1,166 | 680 | 109 | 1,955  (84) |
|  | OAB dry | 120 | 157 | 40 | 317  (14) |
|  | OAB wet | 3 | 19 | 23 | 45  (2) |
|  | Total, n (%) | 1,289 (56) | 856 (37) | 172 (7) | 2,317  (100) |
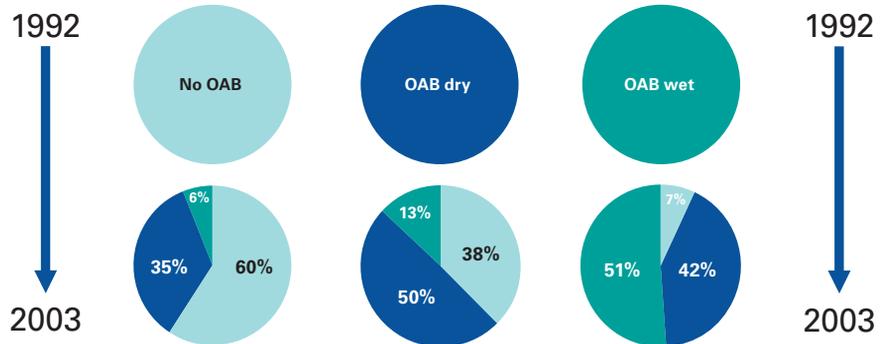


Dallosso *et al.* collected data on urinary symptoms in men aged ≥40 years using a postal question-naire (54). The 1-year incidence of OAB was found to be 5.3%. Goode *et al.* performed a prospective cohort study of a random population of men and women aged 65–106 years in the United States (55). The reported prevalence of UI 1 year after the start of the study in women and men who reported no UI at baseline was 15% and 12%, respectively. Three-year remission rates for women compared with men reporting UI at baseline were 39% and 55%, respectively. Liu and Andrews assessed UI in a cohort of elderly men and women from Australia using a computer-assisted telephone interview (56). The incidence of at least occasional UUI at 1 year was 17.4% for men and 22.6% for women. The corresponding figures for stress SUI were 11.9% for men and 16.5% for women. Herzog *et al.* assessed UI in men and women aged ≥60 years in the United States using an interviewer-administered ques-tionnaire (57). The incidence of UI from baseline at 1 year was 22.4% for women and 9.9% for men.

These studies clearly demonstrate an increasing incidence of OAB and UI over time, as well as a persistence of symptoms that illustrates the chronic nature of each condition. In addition, the severity of OAB and UI symptoms progresses dynamically over long time periods, as exemplified by the progression from OAB dry to OAB wet (22). While these studies indicate that symptoms reported at baseline generally continue at follow-up, there is evidence that OAB and UI symptom severity spontaneously wax and wane over time. The disparities in incidence rates between studies likely reflect confounders in epidemiologic studies based on survey questionnaires, including study population heterogeneity, age-related variations, population sampling procedures, self-selection and attrition, analyses of non-responders, survey methods, differences in symptom definitions, assessment, and quantification.

Overactive bladder and UI are highly prevalent and progress dynamically over time. In general, the results support the hypothesis that OAB dry progresses to OAB wet and that the severity of UI symptoms increases over time. Further longitudinal studies are needed to assess risk factors for symptom progression and regression or remission. Longitudinal studies assessing the natural history of OAB and UI are valuable in making accurate prognoses, determining causes and consequences, and predicting resource utilization.

# 1.4 Factors Associated with Lower Urinary Tract Symptoms

When reviewing the literature examining risk factors for male LUTS, the evidence sources fall into three main categories: 1) longitudinal community-based studies, 2) cross-sectional epidemiological or clinical studies, and 3) case-control studies. The majority of the research has been cross-sectional, demonstrating associations, but not causal pathways, of risk factors and conditions.

## 1.4.1 Aging and lifestyle factors

Aging is a risk factor for LUTS prevalence and severity (58–71). While LUTS have long been considered a normal part of the aging process, Parsons posits that there are modifiable risk factors during the aging process that can alter the onset of LUTS (72). The 5-year study of Parsons *et al.* of men aged 65 years and older found that increased physical activity had a protective effect against LUTS, whereas obesity (defined as body mass index [BMI] ≥30) was associated with a 41% increase in LUTS (73). Penson *et al.* found similar results in their 5-year Southern Community Cohort Study in a slightly younger, but more racially diverse, cohort of men (aged 40–79 years old) (73). Laven *et al.* examined a cross-section of 27,858 men and found that abdominal obesity and low birth weight were associated with an increased risk of LUTS (74). The findings regarding physical activity were further supported by two case-control studies (70,75) and one meta-analysis (76).

Both metabolic syndrome (a complex of hypertension, obesity, hyperlipidemia, and insulin resistance) and vascular risk factors (hypertension, dyslipidemia, diabetes, and smoking) have also shown to be associated with LUTS, though results have been mixed.

One longitudinal study with a 4-year follow-up examined lifestyle risk factors and LUTS and found that a history of coronary heart disease, depression, and alcohol intake (7 drinks or more per week) were associated with moderate to severe LUTS. Body mass index, hypertension, dietary intake, and physical activity, however, were not associated with LUTS (71).

In cross-sectional population cohort studies, however, the results were mixed. Storage symptoms were associated with abdominal fat, plasma glucose, low high-density lipoprotein (HDL), and obstructive sleep apnea in a sample of men in Australia (62). In a community sample of men in China, Gao *et al.* did not find any relationship between metabolic syndrome and LUTS (60). However, Wong *et al.* found that history of heart disease was associated with an increased risk of moderate to severe LUTS in their cohort of men in China (70). Joseph *et al.* found that hypertension and diabetes were associated with an increase in LUTS among a population cohort of African American men in the US (77), while Kim *et al.* reported that a culmination of three or more vascular disease risk factors had a 3-fold greater risk of moderate to severe LUTS (61). Interestingly, in this last study, only increasing age was an independent factor associated with LUTS. Ponholzer *et al.* (78) also looked at the number of risk factors versus individual risk factors and their association with LUTS, and found that two or more vascular risk factors were associated with symptoms. Further longitudinal and cross-sectional population cohort studies need to be conducted in various community samples to gain a better understanding of the relationship between metabolic syndrome and vascular risk factors to LUTS.

Using cross-sectional clinical samples of patients, Demir *et al.* found that waist circumference (>102 cm), fasting blood glucose (>110 mg/dL), and hypertension were associated with LUTS (79). Paick *et al.* reported that only elevated triglycerides were associated with moderate to severe LUTS, but not prostate-specific antigen (PSA), glucose, smoking, cardiovascular disease, BMI, hypertension, or diabetes (80). Similarly, three other cross-sectional clinical studies did not find a relationship between metabolic syndrome and LUTS (64,81,82). Ng *et al.*, however, found hyperuricaemia to be associated with LUTS (82).

The BACH investigators examined dietary intake and LUTS in a more detailed manner using a food frequency recall. In the baseline analysis of this study, dietary sodium and total energy intake (as well as waist circumference and diabetes) were significantly associated with LUTS, while carbohydrate and total fat intake were not (83). Additional analyses of the BACH data also found that dietary intake of carotenoids, lycopene, vitamin A, and vitamin C (with high-dose iron) was associated with decreased odds (40%–50%) of having LUTS; however, men taking high-dose supplemental vitamin C had increased odds (84).

The data regarding alcohol intake and smoking as risk factors for LUTS have been contradictory. Moderate alcohol intake appears to have a protective effect against LUTS (75), whereas heavy alcohol intake (defined as >72 g per day or >7 drinks per week) is associated with an increase in LUTS (71,77). However, several studies did not find any relationship between alcohol intake and LUTS

(70,80,85,86). Two studies reported that current and former smokers were at an increased risk for moderate to severe LUTS compared with non-smokers (77,82), while other researchers found no association between smoking status and LUTS (60,70).

While medications may cause LUTS (e.g. diuretics), there are a variety of medication classes that have not been evaluated. The association between psychoactive medications (atypical anti-psychotics [AAPs] and selective serotonin reuptake inhibitors [SSRIs]) and the prevalence of LUTS was examined in the BACH study (87). No association was found with either AAP or SSRI use and LUTS in men (although an association with AAP use and LUTS was noted among women). However, the longitudinal study of Kok *et al.* identified antidepressants and calcium antagonist use as significant risk factors predicting moderate to severe LUTS (85).

Finally, neither horseback riding nor motorcycle riding lifestyles were associated with an increase in the prevalence of LUTS, although LUTS appeared to be associated with erectile dysfunction (ED) in motorcyclists (63,88).

## 1.4.2  Inflammation

As inflammation is thought to be involved in the pathogenesis of LUTS, the presence of inflammatory markers may be used as objective risk factors for LUTS. This was demonstrated by Choi *et al.*, who found significantly greater high-sensitivity C-reactive protein (hsCRP) levels in men with moderate to severe LUTS than in men with mild or no LUTS (89). However, in their study of men from a urology clinic, Chang *et al.* did not find a relationship between hsCRP and LUTS, leaving the usefulness of hsCRP open to debate (90).

In a cross-sectional web survey of men over 30 years old, Breyer *et al.* found that HIV-infected men reported greater LUTS than men without HIV. As well, HIV-infected men with AIDS reported more moderate and severe LUTS than HIV-infected men without AIDS (91). The authors posit that the increased risk for LUTS among HIV-positive men is related to chronic urinary tract inflammation, weakened immune system, toxicity of treatments, and/or the HIV virus itself.

## 1.4.3  Hormones

Very little has been done to evaluate the impact of testosterone on LUTS (92). Chang *et al.* examined the impact of total testosterone, calculated free testosterone, and bioavailable testosterone, and found that low levels of calculated free testosterone and bioavailable testosterone, but not total testosterone, were related to the presence of severe LUTS (90). In Demir *et al.*'s clinical sample of men with LUTS, only total testosterone levels were examined, and no relationship was found between total testosterone and LUTS (79). The impact of testosterone on LUTS merits further investigation.

### 1.4.4   Erectile dysfunction

There is overwhelming evidence to support that ED and LUTS are related (8,59,62,63,65,66,70,79,85,93–97). However, there is no evidence to support that ED is a risk factor for LUTS or that LUTS precede ED. Common underlying pathophysiology between these two conditions have been hypothesized (98), but given that the vast majority of research in this area is cross-sectional, there is no indication that one condition precedes the other. However, the 6.5-year follow-up longitudinal study by Kok *et al.* provides some data regarding a causal link between LUTS and ED, where ED is a significant determinant of LUTS (85).

### 1.4.5   Genetics

There is a lack of research examining genetic influences on the development of LUTS. In their longitudinal study, Kok *et al.* found that a family history of prostate cancer was a significant predictor of moderate to severe LUTS (85). While Wennberg's longitudinal Swedish Twin cohort offers promise for the future, the most recent analysis of this study noted that there are too few men with LUTS in their cohort (age 20 to 46 years) to evaluate genetic influences (69).

In an analysis of over 184,000 men, racial/ethnic differences were reported in men with LUTS. Hispanic and black men were at higher risk for moderate LUTS than white men, though only Hispanic men were at greater risk for severe LUTS (68). Asian men were at lower risk than white men for moderate or severe LUTS.

## 1.5   Risk Factors for Clinical Progression

### 1.5.1   Prostate volume

Several longitudinal studies have confirmed age-related increases in prostate volume, although prostate volume has been noted to decrease with aging in a small proportion of men (99–103). Serum PSA, a valid surrogate marker of prostate volume in the absence of prostate cancer diagnosis (104,105), predicts future prostate growth (106). Prostate volume is likely to increase when the transition zone is either visible with a clear border (103,107) (**Figure 2**) or enlarged on trans-rectal ultrasound at baseline (108).

**FIGURE 2**

Change in prostate volume over 15 years in Japanese men. Prostates with a visible transition zone (TZ) tend to grow rapidly. The median prostate volume changes were 4.7, 6.5, and 17.3 mL for group 1, group 2, and group 3, respectively. TZ visible on TRUS with the borders not clearly delineated; Group 3: TZ clearly visible on TRUS (A). Adapted from Fukuta F, Masumori N, Mori M, *et al*. Internal prostatic architecture on transrectal ultrasonography predicts future prostatic growth: natural history of prostatic hyperplasia in a 15-year longitudinal community-based study. *Prostate*. 2011;71(6):597-603 (Figures 1 and 2) and Masumori N, Tsukamoto T, Kumamoto Y, *et al*. Age-related differences in internal prostatic architecture on transrectal ultrasonography: results of a community based survey in Japan. *J Urol*. 1997;157(5):1718-1722 (Figure 4).
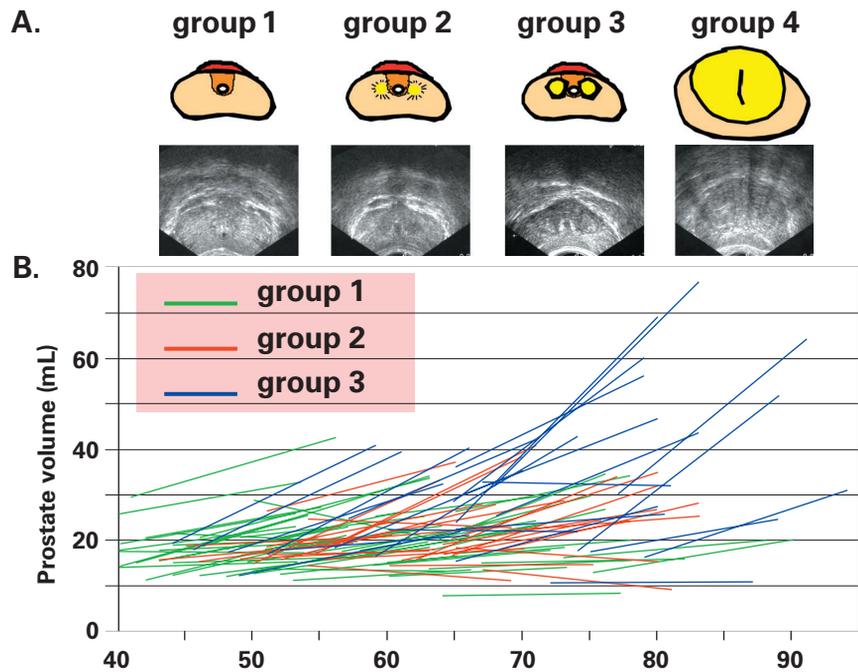


The growth rate of the prostate during follow-up is greater in men with BPH than in men in the general population (109,110). The Medical Therapy of Prostatic Symptoms (MTOPS) study, which observed patients on placebo or doxazosin for 4.5 years, reported that prostate growth could be predicted by baseline prostate volume and serum PSA levels (111). This suggests that prostate growth may not occur linearly with age and that prostate growth is more prominent in men with anatomical or clinical BPH.

## 1.5.2    Urinary flow rate

One longitudinal analysis demonstrated that younger men showed a smaller decrease per year of peak urinary flow rate than older men. Men in their 40s at baseline had a 1.3% per year decrease, whereas men in their 70s had a 6.5% per year decrease (**Figure 3**) (112). Detrusor underactivity due to long-lasting BOO and/or aging may be involved in enhanced decrease in urinary flow rate in the older population. On the other hand, a 15-year longitudinal community-based study in Japan

showed a significant decrease in peak urinary flow rate only in men in their 50s at baseline (113). However, this study may have underestimated the decrease of peak urinary flow rate, since men who received LUTS treatment during the long-term follow-up period were excluded from the analysis.

**FIGURE 3**

Change in peak urinary flow rate over 6 years in different age cohorts.

Younger men showed a lower percentage decrease per year of peak urinary flow rate than older men. Men in their 40s, 50s, 60s, and 70s at baseline had a 1.3%, 2.8%, 2.3%, and 6.5% per year decrease, respectively. Adapted from Roberts RO, Jacobsen SJ, Jacobson DJ, *et al.* Longitudinal changes in peak urinary flow rates in a community based cohort. *J Urol.* 2000;163(1):107-113 (Figure 2).



| Peak flow rate slope (%/y) | | | |
|---|---|---|---|
| 40–49 y | 50–59 y | 60–69 y | 70–79 y |
| −1.3 | −2.8 | −2.3 | −6.5 |
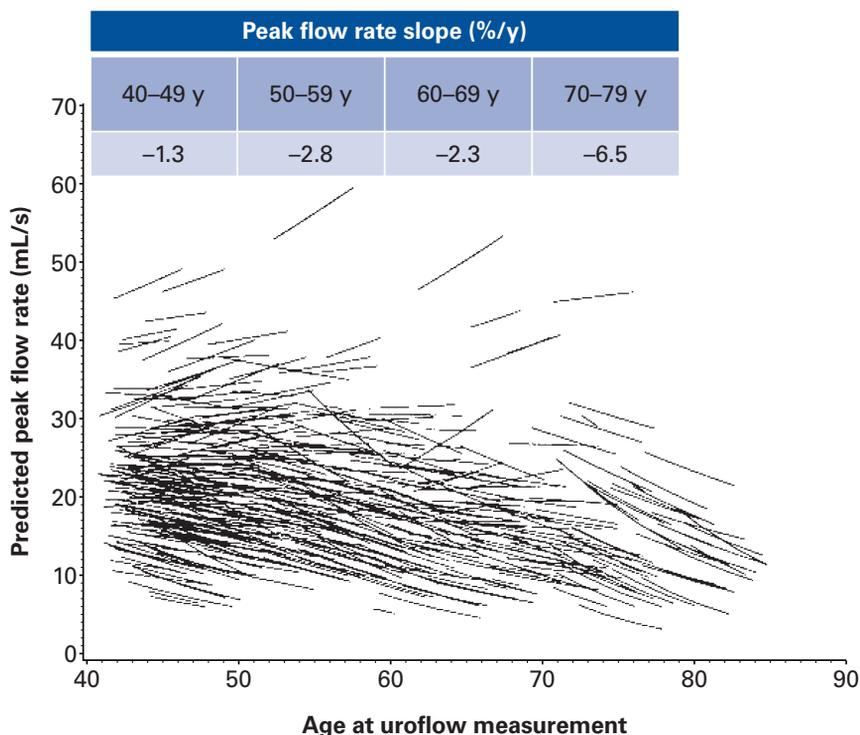
### 1.5.3 Cystometry and pressure-flow study

To our knowledge, no longitudinal data on cystometry and pressure-flow studies are available in the general population. Thomas *et al.* reported serial urodynamic parameters in 170 male patients with BOO who initially opted for a conservative approach (114). Although 141 patients remained untreated for an average of 13.9 years, pressure-flow studies showed no significant increase in BOO with time. However, a small but significant reduction in detrusor contractility was observed, and the prevalence of detrusor overactivity increased with follow-up. These changes in bladder function would explain the exaggerated voiding and storage symptoms in elderly men.

### 1.5.4 Health-care seeking

Health-care seeking behaviour depends on country, culture, medical environment, income, and education. A population-based study in Olmsted County revealed that health-care seeking behaviour was influenced by the severity of symptoms, particularly if they were bothersome and interfered with an individual's daily activities (115). There is a marginal overlap in the distribution of HRQOL

scores of the general population and patients with BPH in a Japanese study (116). Thus, regardless of country and race, it is likely that men with deteriorated HRQOL that is LUTS-related bother to seek medical care.

### 1.5.5 Acute urinary retention

Acute urinary retention (AUR) is an indicator of disease progression. The incidence of AUR in the general US population is 6.8 per 1000 person-years (117). Older age, a higher IPSS, peak urinary flow rate <12 mL/s, and prostate volume >30 mL are all risk factors for AUR in community-dwelling American men. Older age and greater prostate size (as indicated by prostate length on urethral pressure profile at baseline) were the only significant factors that predicted future failure, defined as either AUR or significant symptomatic deterioration leading to surgery in untreated men with BOO (114). The placebo arm in the MTOPS study demonstrated that baseline prostate volume >31 mL and serum PSA level ≥1.6 ng/mL are predictors of AUR, symptomatic progression, need for surgery, and clinical progression (118).

### 1.5.6 Need for surgical treatment

The Baltimore Longitudinal Study of Aging prospectively followed 1,057 healthy male volunteers for up to 30 years, and demonstrated that weak stream, incomplete emptying, and prostate enlargement on digital rectal examination are risk factors for subsequent prostatectomy (119). This risk increased with increasing number of factors (3.0%, 8.9%, 15.7%, and 36.6% in men with 0, 1, 2, and 3 risk factors, respectively). Probability of prostatectomy was double in men with prostate enlargement and voiding symptoms compared with those without these two symptoms (probability also increased with increasing age) (120). In the Olmsted County longitudinal community-based study, the probability of trans-urethral resection of the prostate (TURP) was related to age, symptoms, low urinary flow rate, prostate enlargement, and increased serum PSA levels (121). Men in their 70s at baseline were 51.7 times at risk for TURP compared with those in their 40s. Similarly, men with prostate volumes >30 mL and serum PSA >1.4 ng/mL had 9.2 and 9.3 times the risk for TURP compared with those with ≤30 mL and ≤1.4 ng/mL, respectively. In the Japanese longitudinal study, 0%, 4%, and 21% of men having mild (IPSS ≤7), moderate (IPSS 8–19), and severe symptoms (20–35), respectively, received TURP within 3 years (122). Prostate volume at baseline was higher in men who received TURP (53.9 mL) than those who did not (19.8 mL).

### 1.5.7 Failure of watchful and waiting

Studies have shown that male LUTS generally worsen progressively in men with BPH, although symptoms do improve or stabilize in some patients. Symptomatic deterioration, development of AUR, and conversion to BPH-related surgery tend to occur in patients with severe LUTS, large prostate volume, and high PSA levels at baseline (104,118,123). Wasson *et al.* reported that patients with affected HRQOL at baseline had a higher failure rate of watchful and waiting than those who were less affected (124). Thus, the option of watchful and waiting would not be recommended for patients with severe LUTS-with-bother, large prostate volume, or high PSA levels at baseline.

### 1.5.8 Other complications

A recent study has found that BPH-related deaths or comorbidities, such as hydronephrosis, renal failure, urinary tract infection (UTI), and bladder stones, are rare (111,124). In a study of 737 patients treated with placebo, only one patient developed recurrent UTI and none developed renal insufficiency during 4.5 years of follow-up (111).

# 1.6 Epidemiology of Benign Prostatic Hyperplasia

It is important to consider the substantial adverse consequences of BPH on the global health of older men. Despite widespread use of medical therapy, BPH continues to be associated with a substantial prevalence of urinary infections, bladder stones, urinary retention, and acute renal failure. It is also important to consider the costs associated with BPH diagnosis and treatment. In 2000, the most recent year for which comprehensive data are available in the US, BPH accounted for $1.1 billion in direct health care expenditures and over 4.4 million office visits, 117,000 emergency room visits, 105,000 hospitalizations, and 21 to 38 million hours in lost productivity. Estimated annual costs of BPH treatment in the US currently total $3.9 billion (125–127).

### 1.6.1 Age

The prevalence of BPH rises markedly with increased age. Autopsy studies have observed a histological prevalence of 8%, 50%, and 80% in the 4th, 6th, and 9th decades of life, respectively (128). Using several different metrics, observational studies from Europe, US, and Asia have demonstrated older age to be a risk factor for clinical BPH onset and progression (85,117,125,129–134). Prostate volume also increases with age; data from the Krimpen and Baltimore Longitudinal Study of Aging suggest a prostate growth rate of 2.0% to 2.5% per year in older men (101,106,135). Continued prostate growth is a risk factor for LUTS progression, and larger prostates are associated with BPE and increased risks of clinical BPH progression, urinary retention, and need for prostate surgery (102,136).

### 1.6.2 Genetics

Evidence suggests a strong genetic component to BPH. A case control analysis, in which men <64 years underwent surgery for BPH, noted that male relatives and brothers had a 4-fold and 6-fold increase, respectively, of age-specific risks for BPH surgery. These investigators further estimated that 50% of men <60 years undergoing surgery for BPH had a heritable form of disease (137). In a subsequent study, they observed that heritable disease was associated with larger prostate volume and younger age of onset compared with sporadic BPH (138). These and other (139) findings suggest an autosomal dominant pattern of inheritance. Data show monozygotic twin concordance rates of 26% (140) and strong associations of several gene polymorphisms in sex hormone metabolism with risks of enlarged prostate and BPH treatment (141).

### 1.6.3    Sex steroid hormones

Prostate tissue is composed of two basic elements: 1) a glandular element composed of secretory ducts and acini, and 2) a stromal element composed primarily of collagen and smooth muscle. In prostatic secretory cells, the 5-alpha reductase enzyme converts testosterone to dihydrotestosterone (DHT), a potent stimulator of prostate growth that, in addition to being necessary for prostate development, appears to play a central role in BPH pathogenesis.

#### 1.6.3.1    Testosterone
At least seven observational studies have reported no associations between serum testosterone (total, bioavailable, or free) and BPH, while another five studies have shown an inverse relationship (142–149). No studies to date have reported an increased risk of BPH with higher serum testosterone levels.

#### 1.6.3.2    DHT
Several studies have noted an increased risk of BPH with increased serum concentrations of DHT and its metabolites. In one prospective study of community men, those with the highest midlife levels of DHT had nearly 3 times the risk of subsequent BPH compared with those with the lowest levels (142). Another study demonstrated a 7-fold increased risk of prostate enlargement among Taiwanese men with the highest serum concentrations of DHT (150). These results are consistent with studies of serum concentrations of two DHT metabolites, 17b-diol-glucuronide and androstanediol glucuronide, surrogate markers for DHT activity. One cross-sectional and one prospective study have shown direct associations of these DHT metabolites with BPH (149,151). 5-alpha reductase inhibitors, such as finasteride, decrease serum concentrations of DHT (152). Consistent with epidemiological observations, a recent analysis of the US Prostate Cancer Prevention Trial observed that finasteride decreased the risk of incident clinical BPH in asymptomatic men by 40% (153).

#### 1.6.3.3    Estrogen
No clear patterns between estrogen, LUTS, and BPH have as yet emerged; prior studies have reported positive, negative, and null associations of endogenous estrogens with BPH (142,143,145–149).

#### 1.6.3.4    DHEAS
One prospective study has observed a positive association of dehydroepiandrosterone (DHEAS), an endogenous steroid hormone, with clinical BPH (142).

### 1.6.4    Lifestyle

It has increasingly been observed that modifiable lifestyle factors substantially influence the natural history of BPH.

#### 1.6.4.1    Metabolic syndrome and cardiovascular disease
Metabolic syndrome, resulting primarily from dietary and other lifestyle practices endemic to Westernized societies, increases the risk of cardiovascular disease (154). At least one study has demonstrated that men with heart disease are at significantly increased risk of clinical BPH (77,145).

### 1.6.4.2 Obesity

Studies have consistently observed that increased adiposity is positively associated with prostate volume–the greater the amount of adiposity, the greater the prostate volume. Body weight, BMI, and waist circumference have all been positively associated with prostate volume in multiple different study populations (72,155–159). In the Baltimore Longitudinal Study of Aging, each 1 kg/m$^2$ increase in BMI corresponded to a 0.41 mL increase in prostate volume, and obese participants (BMI ≥35 kg/m$^2$) had a 3.5-fold increased risk of prostate enlargement compared to non-obese (BMI <25 kg/m$^2$) participants (155). Epidemiological evidence also demonstrates that obesity increases the risks of BPH surgery, urinary symptom progression, and initiation of BPH medical therapy (73,159,160).

### 1.6.4.3 Diabetes and disruptions in glucose homeostasis

Disruptions in glucose homeostasis are associated with higher likelihoods of prostate enlargement and BPH. Higher serum concentrations of insulin-like growth factor (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3) have been associated with increased risk of clinical BPH and BPH surgery (161). Physician-diagnosed diabetes, increased serum insulin, and elevated fasting plasma glucose have been associated with increased prostate size and increased risk of prostate enlargement, clinical BPH, and BPH surgery in multiple cohorts (72,155,161–163).

### 1.6.4.4 Lipids

There are relatively little data on potential associations between lipids and BPH. Three studies have shown positive associations, while another two did not find any association between them (72,162,164,165).

### 1.6.4.5 Diet

There are some indications that both macronutrients and micronutrients may affect the risk of BPH, although the patterns are somewhat inconsistent. For macronutrients, increased total energy intake, energy-adjusted total protein intake, red meat, fat, milk and dairy products, cereals, bread, poultry, and starch all potentially increase the risks of clinical BPH and BPH surgery, while vegetables, fruits, polyunsaturated fatty acids, linoleic acid, and Vitamin D potentially decrease the risks of BPH (72,151,165). With respect to micronutrients, higher circulating concentrations of vitamin E, lycopene, selenium, and carotene have been inversely associated with BPH (72,151,166). Zinc has been associated with both increased and decreased risk (151,166).

### 1.6.4.6 Physical activity

Increased physical activity and exercise have been robustly and consistently linked to decreased risks of BPH surgery, clinical BPH, histological BPH, and LUTS (72,167,168). A meta-analysis of 11 published studies (n=43,083 men) indicated that moderate to vigorous physical activity reduced the risk of BPH by as much as 25% relative to a sedentary lifestyle, with the magnitude of the protective effect increasing with higher levels of activity (162).

### 1.6.4.7 Alcohol

Like exercise, moderate alcohol intake also appears to be protective against multiple outcomes related to BPH. A meta-analysis of 19 published studies (n=120,091 men) observed up to a 35% decreased likelihood of BPH among men who drank daily (86).

### 1.6.4.8    Smoking

One review notes that while several studies support the existence of an inverse, protective effect of smoking on the risk of BPH, several others have reported either no or increased risk (165). Thus, no definitive conclusions may be drawn at this time.

### 1.6.4.9    Inflammation

Many observational studies suggest that inflammation is intimately linked to the development of both BPH and prostate cancer. One potential explanation is that metabolic syndrome, which promotes systemic inflammation and oxidative stress, mediates the connection between the two (169). Inflammation has been implicated as a primary stimulus for prostate carcinogenesis, and it is possible that BPH represents a non-malignant pathway of unregulated prostate growth promoted by oxidative stress, inflammatory mediators, and insulin growth pathways.

There are strong links between BPH and histological inflammation in surgical specimens, with the extent and severity of the inflammation corresponding to the magnitude of prostate enlargement (170–173), as well as between BPH and systemic markers of inflammation (174). A history of infection with gonorrhea, Chlamydia, or trichomoniasis increases the risk of elevated PSA (175).

It would be reasonable to hypothesize, then, that inhibition of inflammatory pathways would potentially attenuate BPH risk. In the Olmsted cohort, men who reported daily non-steroidal anti-inflammatory drug (NSAID) or statin use had significantly decreased risks of both low urinary flow rate and prostate volume enlargement (176,177). However, use of NSAIDS was not associated with decreased risk of clinical BPH in other large cohorts (178,179).

## 1.6.5    Additional factors

### 1.6.5.1    Race

No clear patterns have as yet emerged with respect to BPH risk and race. Observational studies comparing black, Asian, and white men have produced variable results. Studies of black men in the US have observed an increased prostate transition zone and total volume compared with white men (180,181). Large analyses of the US Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and the Health Professionals Follow-Up Study observed no differences in clinical BPH risk between black and white men (182,183), while another study of 21,949 men living in the southeastern US noted that black men were half as likely to report a history of BPH diagnosis as white men, but were 65% more likely to report a history of TURP (184). Some data have suggested a decreased risk of clinical BPH in Asian compared with white men (182,183).

### 1.6.5.2    Prostate cancer

During the 1940s, autopsy studies noted an increased prevalence of histological BPH occurring in association with prostate cancer (185,186). Some investigators have since suggested that common initiating events may drive the concomitant development of BPH and prostate cancer (187,188). Epidemiological data have been conflicting, and connections of clinical BPH with prostate cancer remain unclear. A large cohort analysis of more than 3 million men from five national registries in Denmark concluded that men with clinical BPH had a 2- to 3-fold increased risk of subsequent prostate cancer diagnosis and were 2 to 8 times more likely to die from prostate cancer compared with

men without clinical BPH (186). However, a study of 5,068 men in the placebo arm of the Prostate Cancer Prevention Trial determined that there were no associations of symptomatic BPH with prostate cancer prevalence or prevalence plus incidence, as measured by three different definitions of clinical BPH (189). Other studies have noted a diminished likelihood of aggressive prostate cancer in patients with larger prostate volumes (190,191).

# 1.7  Summary

The Major findings of this chapter are:

1. Male LUTS, as assessed by validated questionnaires, are common in men, with nocturia and terminal dribble the most prevalent.
2. Voiding symptoms are predominant, and incontinence is rare in men compared with women.
3. LUTS symptoms are likely to wax and wane, but do slowly and steadily progress with aging.
4. The presence of LUTS is associated with age, metabolic syndrome or vascular risk factors, medications, inflammation, hormonal status, and erectile dysfunction.
5. Risk factors for clinical progression include age, enlarged prostate, elevated PSA, LUTS with bother, impaired HRQOL, and decreased urinary flow rate.
6. Risk factors for development of BPH are age, genetic predisposition, higher serum concentrations of DHT, metabolic syndrome, and some lifestyles.
7. LUTS negatively influences the HRQOL of individuals and imposes health care costs on society.

Limitations of the available data should be considered.

First, there is no standard assessment tool to measure male LUTS. IPSS, the most commonly used metric, lacks questions on incontinence and pain. Substantial variation of definition or questioning of OAB may have resulted in large differences in OAB prevalence among studies. There is no widely accepted working epidemiologic definition for "clinically important BPH," whether in terms of histological condition or clinical manifestations. The prevalence of "LUTS" or "BPH" is thus highly sensitive to the working definition applied. Future studies should focus on LUTS assessments that include a wider spectrum of symptoms related to urinary bother, which will allow for more robust comparisons across clinical settings.

Second, incidence studies of risk factors that explore temporal exposures-and-disease inferences are limited. The external validity of findings from studies performed within the placebo arms of clinical trials is questionable for community-dwelling men. Identification of the valid risk factors, especially modifiable lifestyles, may promote prevention of both clinical manifestations and LUTS consequences, thus lessening the individual and societal burden attributable to LUTS.

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# C2

# Lower Urinary Tract Symptoms in Men: Etiology, Patient Assessment, and Predicting Outcome from Therapy

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# CONTENTS

## Lower Urinary Tract Symptoms in Men: Etiology, Patient Assessment, and Predicting Outcome from Therapy

# 2.1 **Introduction**

Lower urinary tract symptoms (LUTS) in older men were historically linked to the prostate, and were usually referred to as prostatism until the late 20th century. The term prostatism was applied to almost all symptoms that referred to micturition in the older man. Furthermore, the term benign prostatic hyperplasia (BPH) or clinical BPH was used as an all-encompassing term that included prostate size, benign prostate histology, and all filling/storage or voiding/emptying symptoms thought to be related to the prostate pathophysiologically.

In the early 1990s, it was recognized that the so-called symptoms of prostatism were not always due to urodynamic obstruction, and that urodynamic obstruction was not always due to an enlarged prostate. This was visualized by the so-called Hald Rings (**Figure 1**) (1).

**FIGURE 1**

Hald Rings. This 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 (1).
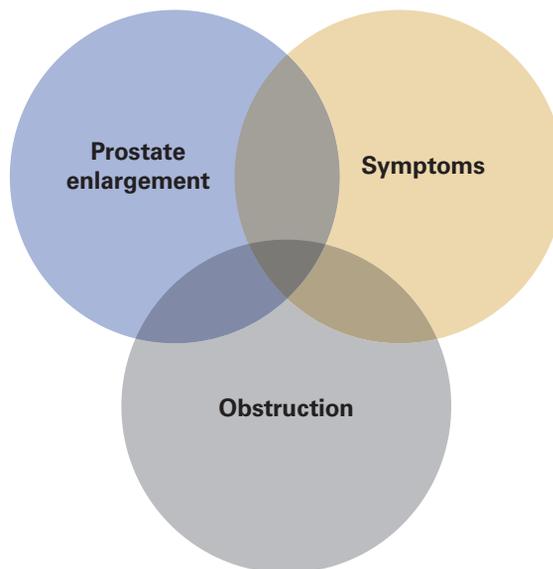


The typical syndrome of clinical BPH (as it was then called) was only present in the area where the rings for obstruction, enlargement, and symptoms overlapped. This representation of the clinical problem had two main disadvantages: it was organocentric (enlarged prostate) and in fact valid only for older men, thus ignoring the fact that symptoms of the lower urinary tract can also occur in women and younger men, and can also originate from organs like the bladder and the urethra.

By the mid-1990s, the term LUTS (2) had replaced the term prostatism as the proper terminology to apply to any patient, regardless of age or sex, with urinary symptoms, without implying the underlying problem. Lower urinary tract symptoms were initially divided into irritative and obstructive symptoms, but it became obvious that there was poor correlation between so-called obstructive symptoms and a urodynamic diagnosis of bladder outlet obstruction (BOO), 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 an infectious or inflammatory process.

Thus, a division of LUTS into filling/storage symptoms and emptying/voiding symptoms is clinically relevant (**Table 1**). Failure to empty can be related to outflow obstruction or detrusor underactivity, or a combination of both. Failure to store overlaps with overactive bladder (OAB).

**TABLE 1**  LUTS: Division into filling/storage, emptying/voiding, and post-voiding symptoms. The symptoms on a yellow background are part of the International Prostate Symptom Score (IPSS). The symptoms boxed in red are part of the OAB syndrome.

| Filling/storage symptoms | Emptying/voiding symptoms | Post-void symptoms |
|---|---|---|
| • Frequency | • Hesitancy | • Post-micturition dribble |
| • Urgency | • Straining to void | • Feeling of incomplete emptying |
| • Nocturia | • Poor stream | • Post-micturition incontinence |
| • Urgency incontinence | • Intermittency | |
| • Stress incontinence | • Dysuria | |
| • Nocturnal incontinence | • Terminal dribble | |
| • Bladder/urethral pain | | |
| • Absent or impaired sensation | | |

The terminology related to male LUTS is as follows:

**Benign prostatic hyperplasia:** This term is used and reserved for the typical histopathological pattern that defines the condition.

**Benign prostatic enlargement (BPE):** This term refers to the size/volume of the prostate, specifically prostatic enlargement due to a benign cause, generally histological BPH. If there is no prostatic histological examination available, then the term is presumptive of a benign cause for enlargement, usually assessed by digital rectal examination (DRE).

**Benign prostatic obstruction (BPO):** This is a form of BOO, defined by urodynamics (UDS; see below). This term may be applied when the cause of the outlet obstruction is BPE due to a benign cause, generally histological BPH.

**Bladder outlet obstruction:** This is the term for any cause of subvesical obstruction and is defined by UDS. It should be noted that there are causes of BOO other than prostatic enlargement (e.g. functional or anatomical bladder neck obstruction, urethral stricture, and meatal stenosis).

**Lower urinary tract symptoms suggestive of BPO:** This is the generic term to describe filling/storage or voiding/emptying problems in older men that are likely to be caused by an obstructing prostate. This definition is similar to that of the old term prostatism.

The 6th International Consultation on New Developments in Prostate Cancer and Prostate Diseases (3) and the International Continence Society's (ICS) 2002 Terminology Report emphasize the importance of using the terms BPH/BPE and BPO/BOO correctly (4).

By putting male LUTS into the 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 of tailoring management accordingly. It is therefore important to recognize that LUTS are not limited to the seven symptoms featured in the International Prostate Symptom Score (IPSS). For example, male urinary incontinence (UI) and post-micturition symptoms should be included in a comprehensive analysis of male LUTS.

With a focus on management, one can redraw the Hald Rings to highlight the possible causes of male LUTS: outflow tract obstruction (which includes, but is not restricted to, BPO); bladder dysfunction (which includes detrusor underactivity and overactivity, but is not restricted to these); and polyuria (**Figure 2**).

Consistent use of these terms will make it easier to communicate about the status of a patient's lower urinary tract, thereby facilitating management.

**FIGURE 2**

A change of focus from the basic features of LUTS suggestive of BPH to the causes of male LUTS: A non–prostate-centred view of three basic causes of LUTS.



Change of focus

Basic features of LUTS s/o BPO → Causes of Male LUTS

Prostate enlargement — Symptoms — Obstruction

Polyuria — Bladder dysfunction — Outflow tract pathology
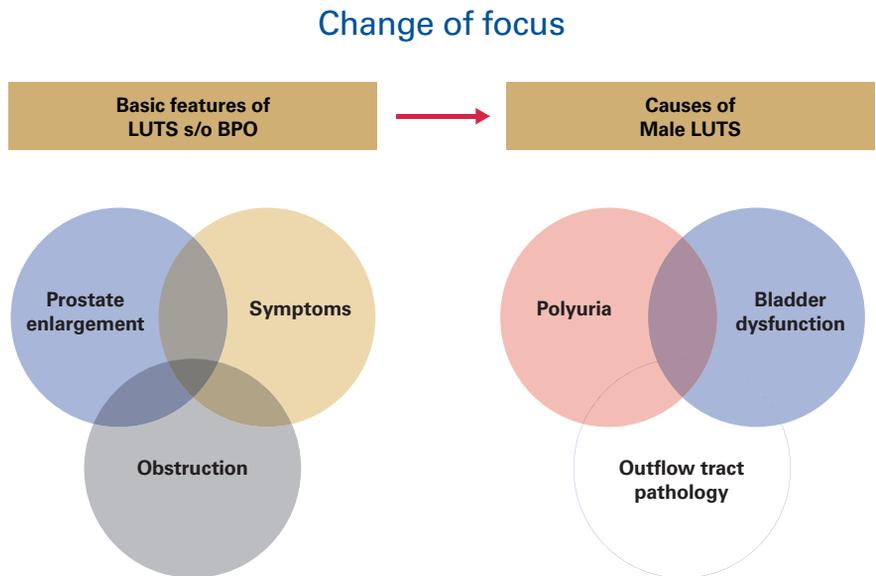
# 2.2 **Lower Urinary Tract Symptoms**

## 2.2.1 **Definition of symptoms**

lower urinary tract symptoms are equally bothersome to men and women, and greatly affect quality of life (QOL). These symptoms are not specific to prostatic obstruction in men and are almost as common in women (5).

The term LUTS is used to describe patients' urinary complaints without implying a cause (2). Lower urinary tract symptoms were defined by the Standardization Subcommittee of the ICS in 2002, and this terminology is now commonly used in clinical practice and research (4). Lower urinary tract symptoms are the subjective indicators of a disease or change in conditions as perceived by patients, carers, or partners, and may lead the patient to seek help from health care professionals. Symptoms are usually qualitative and may either be volunteered or described during the patient interview.

In general, LUTS cannot be used to make a definitive diagnosis, but can indicate pathologies other than LUTD, such as urinary tract infection (UTI) or even cardiovascular disease in the case of nocturnal polyuria. Clinicians must make their best efforts to exclude other causes of LUTS.

Lower urinary tract symptoms are categorized as storage, voiding, or post-micturition symptoms.

### Storage symptoms

Storage symptoms are experienced during the storage phase of bladder function and include increased daytime urinary frequency and nocturia.

**Increased daytime urinary frequency** is the complaint of a patient who feels that he/she voids too often during the day. This term is equivalent to pollakisuria, which is used in many countries.

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

**Urgency** is the complaint of a sudden compelling urge to pass urine, which is difficult to defer.

**Urinary incontinence** is the complaint of any involuntary leakage of urine. In each circumstance, UI should be further described by specifying relevant factors such as type, frequency, severity, precipitating factors, social impact, effect on hygiene and QOL, measures used to contain the leakage, and whether or not the individual seeks or desires help because of UI.

**Stress UI** is the complaint of involuntary leakage upon effort or exertion, or upon sneezing or coughing.

**Urgency UI** is the complaint of involuntary leakage accompanied by or immediately preceded by urgency. Although the ICS 2002 term is urge UI, it was recognized in a 2004 ICS standardization workshop as an inadvertent mistake and proposed urgency UI as a better term. However, in some languages, there is no difference between the words for urgency and urge. In those circumstances, it is probably best to use the translation for urge and speak about pathological urge (instead of urgency).

**Mixed UI** is the complaint of involuntary leakage associated with urgency and exertion, effort, sneezing, or coughing.

**Enuresis** is any involuntary loss of urine. If this term 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 (though rare) symptom in older men, as it may indicate high pressure chronic retention (6).

**Continuous UI** is the complaint of continuous leakage, only found after prostatectomy.

## Bladder sensation

Bladder sensation can be divided into four categories:

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

## Voiding symptoms

Voiding symptoms are experienced during the voiding phase of bladder function.

**Slow stream** is reported by individuals who perceive 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 an individual describes urine flow that stops and starts, on one or more occasions, during micturition.

**Hesitancy** is the term used when an individual describes difficulty initiating micturition, resulting in a delay of the onset of voiding after the individual is ready to pass urine.

**Straining to void** describes an increased muscular effort required 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.

## Post-micturition symptoms

Post-micturition symptoms are experienced immediately after micturition.

**A feeling of incomplete emptying** is a self-explanatory term for a feeling experienced by some individuals 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 onto his clothes after leaving the toilet.

## 2.2.2 Prevalence of lower urinary tract symptoms in relation to age

although male LUTS are common in the aged population, they are sometimes encountered in young men as well. In one prospective study, 85 men (18 to 45 years old) with LUTS were studied to determine the cause of LUTS in young men, and whether non-invasive testing and symptom scores are useful in deciding which patients to evaluate with video-UDS (7). Mean American Urological Association Symptom Index (AUA-SI) scores were as follows–total: 19.3, voiding: 10.8, and storage: 8.5.

Video-urodynamic diagnoses were primarily bladder neck obstruction (in 40 cases; 47%), dysfunctional voiding (in 12 cases; 14%), impaired contractility (in eight cases; 9%), sensory urgency (in seven cases; 8%), detrusor overactivity (DO) alone (in five cases; 6%), DO during filling and underactivity during voiding (in one case; 1%), external detrusor-striated sphincter dyssynergia (in one case; 1%), and normal (in five cases; 6%). Of these patients, nine could not void during UDS, and in six patients, no urodynamic diagnosis was made.

As illustrated by this report, LUTS in young men have a variety of underlying causes. Video-UDS was not considered helpful in patients with a normal or non-diagnostic study or sensory urgency only, but was an extremely helpful diagnostic test in men with abnormal uroflow and high voiding scores.

Even in asymptomatic young men, the IPSS was not zero and increased with age. Of asymptomatic men aged 18–29 years, 2% reported moderate symptoms (IPSS >7) compared with 12% of men aged 40–49 years (8). Moon *et al.* surveyed a population of younger men (a National Guard unit) for LUTS and found an IPSS ≥7 in 5% of men in their 20s. This rate rose to 15% among those in their 40s (9).

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, and South Korea, the prevalence of LUTS in men and women was studied with a population-based, cross-sectional survey (5). The percentages of men with an IPSS of 8–35 (indicating moderate to severe symptoms) were 0.7 (the Netherlands), 19.2 (France), 25.1 (UK), and 16.2 (South Korea). By age group, the percentages of men with moderate to severe symptoms were 10.6 (40–49 years old), 19.0 (50–59 years old), 30.5 (60–69 years old), and 40.4 (70–79 years old).

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. In each age group, there were no major cultural differences in the frequency of LUTS. However, in a study comparing Japanese and American men, within each age decade the median IPSS was higher for Japanese men than for American men, with little difference in the rates of increase with participant age or bother (10).

In Japan, an epidemiological population-based investigation of LUTS has been performed (11). 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. A total of 4,570 responses were available for analysis (46.0% men). The average age was 60.6 years for both genders (range: 40–100 years).

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% of the participants. The proportion of cases experiencing symptoms (≥once per week/≥once per day) was 27.0%/19.8% for decreased urine stream, 17.8%/12.0% for a feeling of incomplete emptying, 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. Prevalence increased with age and was generally greater in men, except for stress incontinence. In total, 78% of the people older than 65 years had some kind of LUTS. Daily activities were negatively influenced by urinary symptoms in 14.7%. More specifically, the impact was felt on mental health (10.2%), vitality (10.1%), physical activities (7.1%), work/house chores (5.9%), and social activities (4.0%). The average number of problematic symptoms was 2.0. 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 the negative impact of LUTS, only 18.0% of individuals had visited a physician. The prevalence of LUTS was generally higher in men and the aged population. Appropriate management and treatment should be encouraged by increasing public awareness of urinary problems.

In Sweden, the prevalence of LUTS was estimated in different age groups of men 45–79 years old in a large population-based study (12). Among the study population, 18.5% and 4.8% of the men were moderately and severely symptomatic, respectively; the prevalence of at least one symptom was 83%. Lower urinary tract symptoms 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 QOL resulting from the bothersomeness of LUTS (r=0.70). Among symptomatic subjects, 36% reported a poor QOL (fairly bad, very bad, or terrible). Only 29% of symptomatic subjects (IPSS >7) reported that they had been previously diagnosed for their urinary problems, and only 11% received medication. In Sweden, it is apparent that few men seek help for their urinary symptoms. Only a third of symptomatic men reported that they had been previously diagnosed for urinary problems. This emphasizes the need for better public education and awareness of the relatively high prevalence of LUTS in society.

Conducted in 2005, the EPIC study was the first population-based epidemiological study in which the prevalence of LUTS was surveyed based on the 2002 ICS terminology. This survey was conducted in Canada, Germany, Italy, Sweden, and UK in 58,139 men and women aged from 18 to > 70 years old (13). In total, 19,615 subjects were analyzed. The overall prevalence of having any LUTS was 62.5% in men and 66.6% in women. Storage symptoms were more common in women (59.2%) than in

men (51.3%), whereas voiding symptoms were more common in men (25.7%) than in women (19.5%). Post-micturition symptoms were more common in men (16.9%) than in women (14.2%). In men, the incidence of all symptoms increased with age. The most frequent symptom was nocturia, both in men (48.6%) and women (54.5%), followed by urgency (i.e. OAB) in men (10.8%) and women (12.8%).

The EpiLUTS study (14) was another population-based epidemiological study based on the 2002 ICS terminology. The Internet-based survey was conducted from 2007 to 2008 in the US, UK, and Sweden. Data from 30,000 people older than 40 years were analyzed. Among the men, 47.9% had LUTS with a frequency of "more than sometimes," and 72.3% had LUTS with a frequency of "more than often." A variety of investigations using data from the EPIC study and the EpiLUTS study have since been reported (15–18).

Risk factors associated with male LUTS have been investigated in several population-based epidemiological surveys (19–21). Determinants such as heart disease, diabetes, hypertension, hyperlipidemia, and lifestyle factors such as obesity (increased body mass index), alcohol consumption, smoking, and exercise were suggested to be related to LUTS. Prostate volume (PV), post-void residual (PVR) urine volume, IPSS, and social generic QOL were important determinants for seeking first consultation with a general practitioner during a 2-year period in community-dwelling men with LUTS (IPSS >7) at baseline (22).

## Conclusions

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

There is high-quality (Level 1) evidence that LUTS are relatively common in the community, with an increasing prevalence with age. It is important to note that prevalence is little affected by gender, suggesting the possibility that many men's and women's LUTS have similar etiologies.

There is also evidence that many men with LUTS do not seek help, despite having bothersome symptoms (Level 2).

The relationship between LUTS and risk factors such as heart disease, diabetes, hypertension, hyperlipidemia, and lifestyle factors such as obesity (increased body mass index), alcohol consumption, smoking, and level of physical exercise has recently been pointed out (Level 2).

## 2.2.3   Storage symptoms

The ICS–"BPH" study (23–25) showed that voiding symptoms were more prevalent, but that storage symptoms were more bothersome, with the exception of post-micturition dribble. Terminal dribble was seen in 94% of participants, reduced stream in 93%, intermittency in 88%, hesitancy in 83%, and incomplete emptying in 81%. The five most bothersome symptoms, however, defined by the

proportion of men who reported that the bother was at least "a bit of a problem," were post-micturition dribble (84%), urgency incontinence (84%), nocturnal incontinence (81%), miscellaneous incontinence (81%), and urgency (80%).

Voiding symptoms are most prevalent in men with LUTS suggestive of BPO. However, recent community-based epidemiological studies in men demonstrated that storage symptoms are more common and more bothersome to the patient than are voiding symptoms (13,26). Storage symptoms interfere to the greatest extent with daily life activities and have a considerable negative impact on QOL. Urgency, frequency, and urgency incontinence may cause social embarrassment or isolation, and nocturia may disturb sleep and induce fatigue or irritability during the daytime (24,27–28). Tikkinen *et al.* have shown that bother in relation to nocturia occurs mainly when the nocturnal voiding frequency is two or more times per night (29).

### 2.2.3.1 Lower urinary tract storage symptoms and their etiologies

A brief summary of the etiology of these symptoms follows, recognizing that the major symptoms are mostly a manifestation of the OAB syndrome (4). Theories regarding the pathophysiology of this syndrome, and its possible relationship to BOO, are considered subsequently.

#### Frequency

There are surprisingly few objective data on frequency in the normal population. Abrams cites two papers and personal experience in considering normal diurnal frequency to be between three and seven voids per day (25). Jepsen and Bruskewitz consider the normal 24-hour urinary frequency to be eight, and that more than 3 hours between successful voids is normal, whereas less than 2 hours is abnormal (30).

Two papers reported on a study of 284 asymptomatic males aged 18 to 66 years (8,31). Latini *et al.* used a 24-hour diary to study the voiding habits of this patient population. They found that subjects voided a median of seven times per 24 hours (range: 2–21), with 95% voiding fewer than 12 times daily. They also reported that even in asymptomatic men, the number of daily voids correlated with the IPSS. They cautioned against using a cut-off of eight 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 (31). Mueller *et al.* noted that 11% of men aged 18–49 and 31% of men aged 40–49 reported two or more nightly voids (8).

In the population-based Krimpen study, the normal 24-hour voiding frequency in men 50–78 years old ranged between 5.7 and 7.0 times (32).

The factors that contribute to increased urinary frequency are characterized as follows:

#### Normal voided volumes

In the Dutch population-based Krimpen study, 1,446 men aged 50–78 years completed 24-hour frequency-volume charts (FVCs). The median average volume per void was 246 mL (interquartile range: 192–349 mL). The median maximal voided volume (formerly known as functional bladder capacity) was 400 mL (interquartile range: 300–500 mL) (33).

A longitudinal analysis of the Krimpen population, followed for 6.5 years, showed that the median maximum and average voided volumes decreased with time from 400 to 380 and 245 to 240 mL, respectively, and were lower in older age groups, while 24-hour voided volume showed no change (34).

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 polydipsia, osmotic diuresis, or abnormal antidiuretic hormone production.

## Reduced voided volumes

This implies that the bladder capacity under general or regional anesthesia would be normal, but that the voided volumes are consistently low (<300 mL). The causes of this include the following:

- 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 DO who note that their problem increases with increasing bladder volume)
- Psychogenic causes other than fear of urinary retention or incontinence

## Reduced structural bladder capacity

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

## Urgency, urgency incontinence, and overactive bladder

Urgency is defined as a sudden compelling urge to pass urine that is difficult to defer (4). It is the primary driver of frequency, nocturia unrelated to polyuria, and–when correlated with DO that cannot be suppressed–urinary urgency incontinence (35–36). An earlier definition included the fact that the desire was compelling to avoid leakage or pain, and many feel that fear of leakage should be reinserted in the definition.

Urgency is the primary–and the only obligatory–symptom of the OAB syndrome (urgency, with or without urgency incontinence, usually with frequency or nocturia in the absence of infection or other obvious pathology) (4). One shortcoming of this definition is that it excludes patients with grossly impaired or no sensation, but with UI due to IDC.

A community-based epidemiological study in Japan demonstrated that the prevalence of OAB was 14% in men older than 40 years (26).

The EPIC study, which was the first population-based epidemiological study based on the 2002 ICS terminology, demonstrated the prevalence of OAB in men to be 10.8% (13). Of the men with OAB, 28% suffered from urgency UI. The prevalence of OAB rises with age in both sexes; this is another

piece of evidence that the symptoms that characterize this symptom syndrome cannot be due solely to the presence of an enlarged and/or obstructing prostate. In fact, among people under the age of 60, OAB is actually more prevalent in women than men, but the opposite is true above the age of 60 years.

Urinary urgency is not the same as urinary urge, which can be defined 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 urge 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 all of their micturition cycles are associated with urgency.

By definition, urgency is episodic and there is little or no degradation of the sensation. Thus, scales that attempt to define the intensity of urgency may be at odds with the definition of the symptom, if urgency is indeed a sensation that is either present or not. The physiological sensations of the urge to void (the first sensation of filling, a normal urge to void, and a strong urge to void) can, however, vary in intensity, and some measurement of the intensity of this urge may be useful in assessing symptom severity and the outcome of therapy for OAB.

Chapple's diagrams (**Figure 3**) illustrate 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 (e.g. 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 low-volume voids and reduced, variable inter-void intervals or urgency incontinence.

The time from the onset of the urgency episode to the void or to 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 is referred to as the refractory or urgency-free interval. The factors that influence whether incontinence occurs include the following: pelvic floor and urethral sphincter tone, mobility, toilet access, and timing of sensation (i.e. if sensation is delayed or impaired because of neurological disease or injury, then incontinence is more likely to occur).

## FIGURE 3

**A.** 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, shortening the inter-void 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 (35).



A

B

INTERNATIONAL CONSULTATION ON MALE LUTS
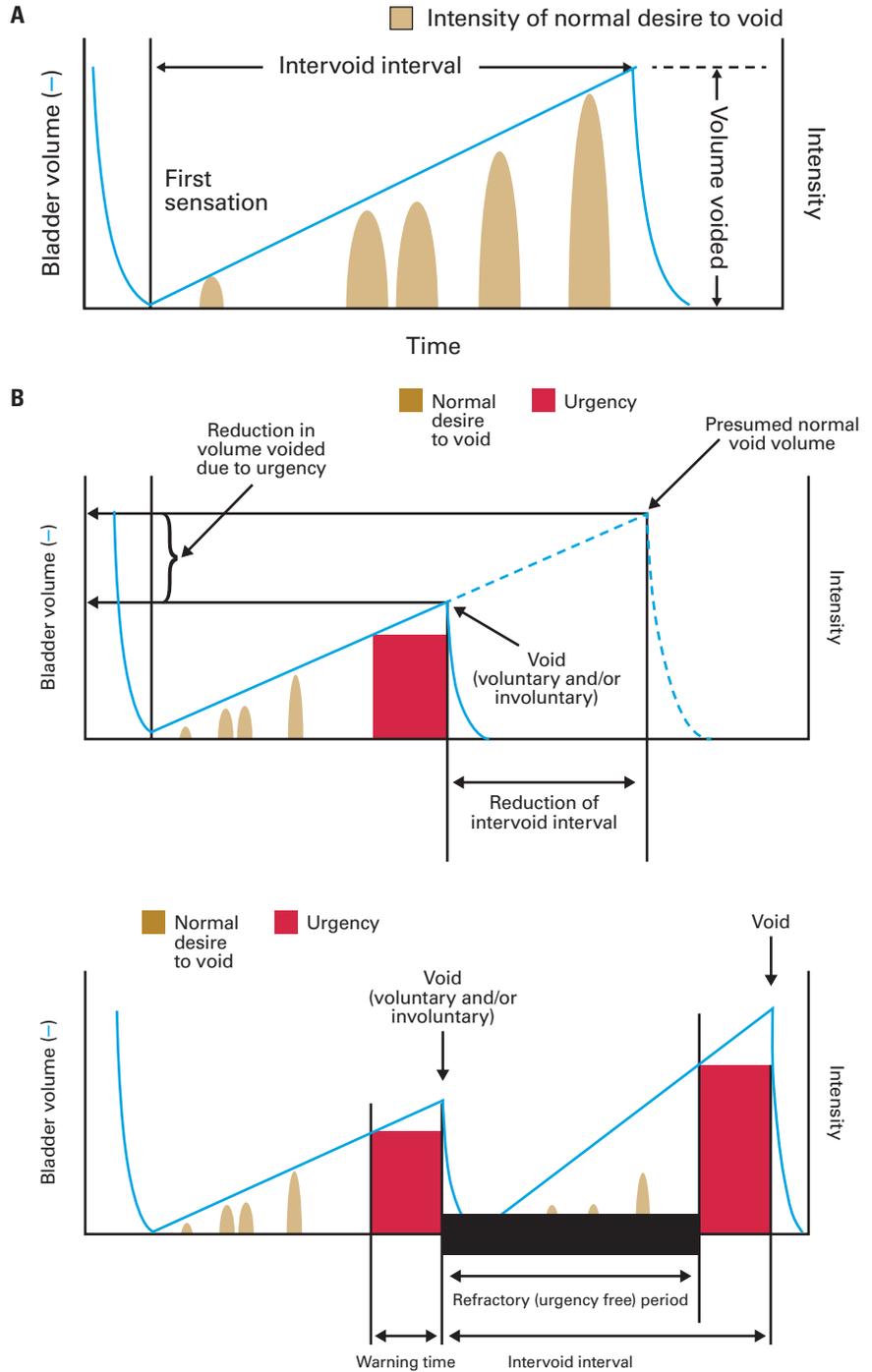
Urgency affects nocturia as well, but because nocturia is related to other factors than just nocturnal OAB, such as nocturnal polyuria, non-urological sleep disorders, and congestive heart failure, treatment that reduces urgency is not highly correlated with nocturia reduction.

Urgency is therefore the pivotal clinical symptom in OAB, as it is the driver of frequency, non-polyuria–related nocturia, and urgency incontinence. It is also a surrogate endpoint for patients having better control. There is no evidence to support the hypothesis that there is a continuum between the normal urge to void and urgency. A strong case can be made, however, for the suggestion that the definition of urgency be further qualified by adding the phrase "for fear of leakage," which was previously included in the definition. The ICS Standardization Committee, unfortunately, has compounded this problem by suggesting that synonymous terms for OAB include urgency/frequency syndrome and urge syndrome (4). However, the only obligatory symptom for a patient to be classified as suffering from OAB is urgency. Another issue that warrants discussion is that the difference between the terms urgency and urge may not translate well into other languages.

### Nocturia

Nocturia is defined as the complaint that the individual has to wake at night one or more times to void. Whereas voiding once at night may have no major impact on QOL, nocturia episodes of two or more may significantly affect QOL (29).

Bosch and Weiss (37) performed a systematic review of articles reporting nocturia prevalence in community-based populations. Prevalence rates in younger men (aged 20–40 years) were 11%–35.2% for one or more nocturia episodes per night, and 2%–16.6% for two or more episodes. In older men (>70 years), the rates were 68.9%–93% for one or more nocturia episodes per night, and 29%–59.3% for two or more episodes (**Figures 4** and **5**).

**FIGURE 4**

The prevalence of nocturia across age groups in men, based on a review by Bosch and Weiss (37).
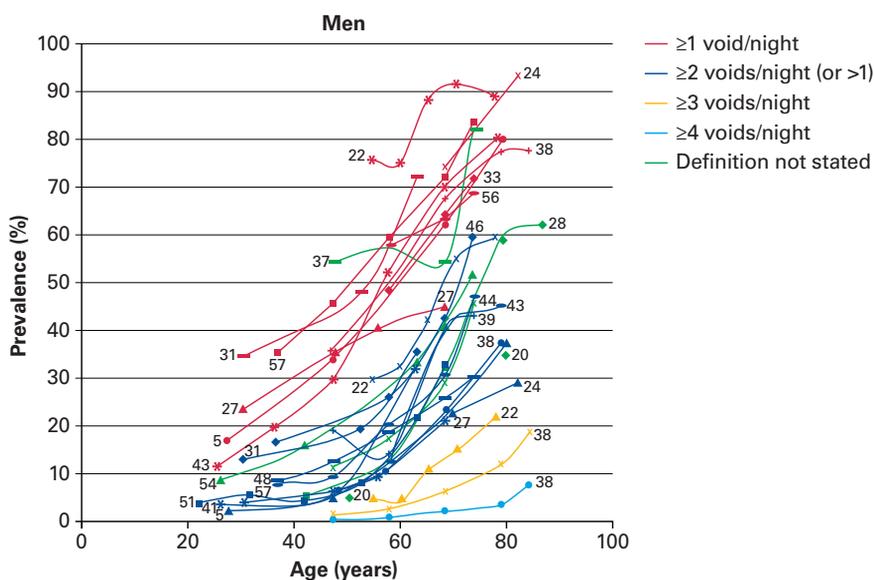
**FIGURE 5**

The overall prevalence of nocturia reported for full age range, studied by number of nocturia episodes per night in men, based on a review by Bosch and Weiss (37).
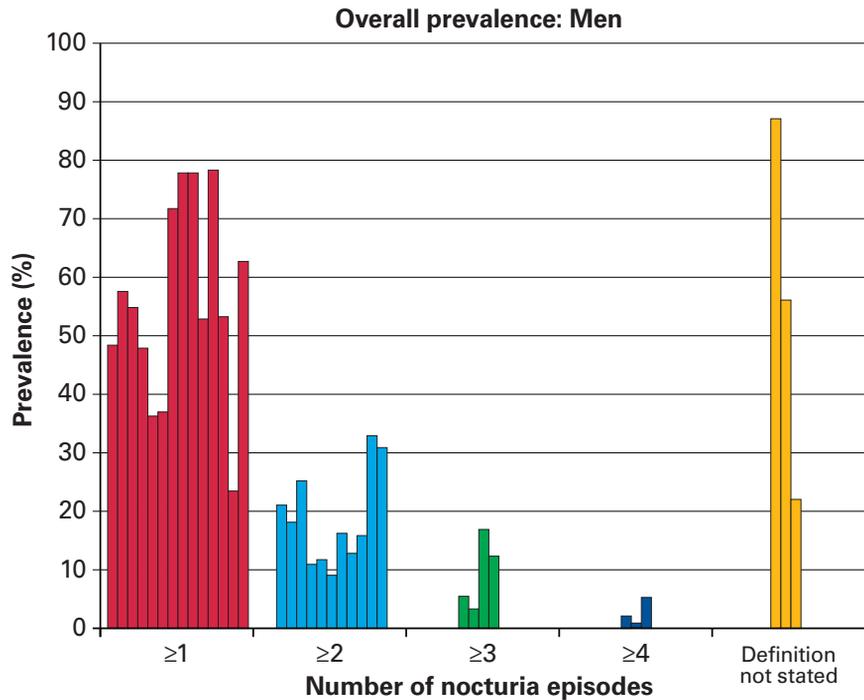
In the majority of patients, the symptom of nocturia has a multifactorial pathophysiological background that complicates analysis. Nocturia can be caused by any of the problems listed above as causing diurnal frequency. However, nocturnal polyuria and sleep disturbance due to a variety of etiologies can also result in nocturia. An in-depth discussion of nocturia and nocturnal polyuria are presented in the nocturia chapter of this consultation.

### Pain

Pain 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 has any particular relationship to BPH, BPE, or BPO. Advanced prostate cancer can invade the posterior bladder base and pelvic side walls and cause pelvic pain.

### Impaired or absent sensation

This may be due to a variety of neurological diseases or injuries, or to the effects of chronic bladder over-distension.

### 2.2.3.2 Pathophysiology of urgency detrusor overactivity and overactive bladder

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 is now called DO. This is undoubtedly the case with the latter two phenomena, but urgency without incontinence can exist without demonstrable DO on UDS, 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 determined.

In any case, the following list includes the relevant theories regarding the pathophysiology of OAB, DO, and urgency. Some of these bear potential relevance to BPH, BPE, and/or BPO.

## Neurogenic

Reduced suprapontine inhibition, damage of axonal paths in the spinal cord, loss of peripheral inhibition, increased lower urinary tract afferent input, and/or enhancement of excitatory neuro-transmission in the micturition reflex pathway can result in OAB (38–39). Evidence supporting this includes the following:

- Detrusor overactivity is associated with various supraspinal and spinal pathologies (40).
- Local anesthetic injected into the prostate in patients with DO inhibits the DO (41). Transurethral microwave thermotherapy (TUMT) and alpha-blockers have been hypothesized to act on prostatic or prostatic urethral sensory receptors.
- Yokoyama *et al.* (42) reported that mechanical stimulation of urethral afferent nerves causes bladder contraction, and that in BPH patients, IDCs were suppressed by mucosal anesthesia of the prostatic urethra with lidocaine. They demonstrated that relaxing the prostate gland and urethral smooth muscle with alpha-1 adrenergic receptor ($\alpha$1-AR) antagonists could suppress stimulation of the urethral C-fibre afferent and inhibit urethral-detrusor reflux, resulting in suppression of DO and improvement of storage symptoms (43).
- Capsaicin, a neurotoxin for unmyelinated C-fibre afferents, inhibits DO when given intravesically (44).
- Benign prostatic obstruction produces a positive ice-water test (a spinal reflex) in the majority of patients (45–46). This is abolished by capsaicin (45).
- Neuroplasticity following obstruction has been hypothesized to occur by a variety of mechanisms, resulting in spinal reflexes that may persist after the initial stimulus has been removed (47–50). 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. NGF blockade prevented the neural and micturition alterations.
- Comparing the effects of various therapies on symptoms recorded in the ICS-male questionnaire (51), it is interesting to note that the therapies that would be expected to ablate periurethral or prostate tissue produce the greatest reduction in storage symptoms, which would suggest to some that a neurological mechanism is involved, since the urodynamic results of surgery are greater than those produced by the minimally invasive ablative non-drug therapies.
- Andersson suggests that during filling/storage, acetylcholine and other neurotransmitters may be released from the urothelium and increase afferent nerve activity by exciting receptors in the urothelium or suburothelium (52). Presumably, either the release or the increased sensitivity would be heightened in patients with OAB/DO.
- Andersson (52) 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 (53), and previously described by Coolsaet and van Duyl (54).
- Gillespie (55) proposed that the inappropriate augmentation of autonomous myogenic activity and 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 of generating and modulating autonomous activity are different from those involved in micturition. The possible etiological factor could be regarded as myogenic, and links the two principle etiological theories.

## Myogenic

There is some evidence suggesting 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 (53,56–58).

- In approximately 25% 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) (59).

## Structural

Detrusor overactivity has been reported to be associated with a distinct ultrastructural (electron microscopy) pattern know as complete disjunction (60). This has been hypothesized to occur with aging in some individuals and to be responsible for DO in the absence of obstruction (61).

## Impaired detrusor blood flow

Impaired blood flow in the bladder, which is attributable to bladder overdistension associated with BOO, was recently thought to be an important cause of DO in BPH patients. In a rabbit model of chronic bladder ischemia caused by iliac artery injury, bladder ischemia enhanced overactivity and the carbachol-induced contractile response of the detrusor smooth muscles, suggesting that bladder ischemia may be the cause of DO (62).

Okutsu *et al.* (63) reported that overdistension of the bladder was followed by emptying-induced DO in rats, indicating that decreased blood flow was responsible for the development of overactivity. Decreased blood flow has also been reported in rat, rabbit, and pig models of BOO. In humans, reduced bladder perfusion was observed in BPH patients with persistent DO after trans-urethral resection of the prostate (TURP) (64).

Various hypotheses have been proposed for the mechanisms by which bladder ischemia induces DO, a few of which are included below. The post-synaptic fibres of the pelvic nerve within the bladder wall degenerate in the ischemic condition, which in turn causes denervation supersensitivity to acetylcholine in the detrusor muscle. Increased secretion of NGF from the detrusor smooth muscle in BOO enhances the micturition reflex. Overdistension and subsequent ischemia of the bladder wall release a variety of neurotransmitters (such as adenosine triphosphate, nitric oxide, prostaglandins, and acetylcholine) from the urothelium, which stimulate the sensory C-fibre afferents of the bladder wall.

More recently, the relationship between reactive oxygen species and DO has also been discussed. Various mechanisms, including those described above, are presumed to be associated with the overdistension and ischemia of the bladder caused by BOO.

The effect of $\alpha$1-AR antagonists on impaired bladder blood flow has recently been investigated at the experimental level. Mizuno *et al.* (65) investigated the effect of tamsulosin on bladder microcirculation in a rat ischemia-reperfusion model induced by overdistension and emptying of the bladder.

Blood flow failed to return to the basal level after reperfusion, demonstrating that reperfusion injury to bladder was caused by bladder overdistension and emptying. However, administration of tamsulosin prevented the impaired blood flow after reperfusion.

Okutsu *et al.* (63) demonstrated that tamsulosin improved the impaired bladder blood flow and DO caused by ischemia/reperfusion of rat bladder. In an earlier paper, Okutsu *et al.* (66) reported that tamsulosin increased the impaired bladder blood flow in BOO in rats. The α1B-AR subtype is known to be involved mainly in vasoconstriction, whereas various α1-AR subtypes play roles in the vasculature of individual organs. For example, α1A-AR is reported to play a role in the contraction of canine vesical arteries, similar to those in the prostate and urethra. The α1A and α1B subtypes are the most common in rat bladder arteries, while the α1B-AR subtype is virtually absent (66). However, localization of the α1-AR subtypes in human bladder vasculature has yet to be thoroughly investigated. The emerging role of α1-AR antagonists in bladder perfusion changes will lead to further basic and clinical studies.

## OAB symptoms, BPH, BPE, BOO, and BPO: other observations

It has often been assumed that the pathophysiology of LUTS in older men is the result of BPO associated with BPE, presumably because all of these phenomena increase with age. Girman *et al.* (67) and Barry *et al.* (68) investigated the relationship among maximum flow rate ($Q_{max}$), PV, and symptom score. There were no statistically significant correlations. Nitti *et al.* (69) also failed to find either clinical or statistical correlations between the severity of BOO based on pressure-flow UDS and LUTS. In males, LUTS may be associated with BOO, but neither storage nor voiding symptoms are diagnostic of urodynamic obstruction. The situation seems complex, and in those with BOO, both neurological and myogenic mechanisms have been suggested (see above).

### 2.2.3.3 The prevalence of storage symptoms

The prevalence of DO and its correlative symptom, urgency, increases with age, but the addition of prostatic obstruction does seem to further increase its occurrence. Detrusor overactivity is 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 trans-urethral prostatectomy (70). Urodynamic testing in 211 men with LUTS showed that approximately 30% had no urodynamic evidence of obstruction. The symptomatology in these patients was related to DO and low detrusor strength or speed (71). However, age-matched men without LUTS have been found to have a prevalence of DO between 25% and 63% (72–73).

The ICS–'BPH' study (23) was conceived because "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 today, it would be different, as views 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 will understand what the study was designed to investigate.

Ultimately, 1,256 patients >45 years of age who presented to urology departments in 12 countries with symptoms and possible BPO were recruited. A substudy was performed in a community-based group of men, in which all ambulatory men aged 40 years or over who were registered with a rural general practice in the UK were invited to complete the questionnaire, resulting in a sample of 423 individuals.

In the ICS–'BPH' study, the general pattern of a positive association with age is not evident, except for the symptom of nocturia and urgency incontinence in the ICS–'BPH' patients. In the clinic sample, the prevalence of nocturia (one or more episodes) increased from 66% in the men aged <60 years to 79% in those aged >70 years. Furthermore, the prevalence of urgency incontinence increased from 36% in the men aged <60 years to 56% in those aged >70 years. 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, which was reported by 41% of the community-based men >70 years, is probably due to the relationship between DO 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 BPH/BPE/BPO (singly or in any combination). However, until this is proven, one can only conclude that storage symptoms such as urgency, frequency, and nocturia are compatible with a diagnosis of BPH/BPE/BPO, but are by no means specific or even strongly suggestive of any of these.

Thomas *et al.* (74) followed neurologically intact men diagnosed with detrusor underactivity during voiding who initially opted for no specific treatment. Of those 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 had increased to 48%. However, the symptom of urgency, initially present 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.* (75) also followed a group of men initially diagnosed with BOO 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 indexes 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 DO on UDS increased from 35% to 70% ($p$<0.001). The mean age of presentation was 56.9 years and at follow-up 70.8 years.

Thomas *et al.* (76) also investigated at the natural history of LUTD following TURP for BOO. 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 the mean time since surgery was 13.0 years. Although there was significant

resolution of DO in the short term, 64% of patients demonstrated DO at follow-up, compared with 40% at original presentation. Interestingly, only 31% complained of urgency at follow-up, compared with 51% at presentation.

These observations 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 is also compatible with a neurological 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).

### 2.2.4 Voiding symptoms

The term voiding symptoms refers to the symptoms experienced by a 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 (4).

The terms obstructive symptoms and prostatism are still sometimes misused, but in modern terminology, the descriptive term voiding symptoms as part of LUTS should be used (2).

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

Voiding symptoms can be related to BOO, impaired detrusor contractility, or a combination of the two. In most individual patients, it is impossible to relate symptoms to pathophysiological mechanism or to 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 (6).

Post-void dribble is so common among men without prostatic problems that it is of little value as a discriminator. It is not a voiding symptom, but should be included with a feeling of incomplete emptying as a post-micturition symptom. Straining is a symptom with little relation to obstruction (77). 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 BOO or any of the other pathophysiological mechanisms (78). However, scoring systems have been based on these symptoms in community populations (79).

The lack of significance of voiding symptoms is not surprising, since–as in the case of limited bladder capacity–voiding symptoms can be the consequence of small-volume voids. Moreover, in patients with DO, 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 and of underactive detrusor.

## 2.2.5 Post-micturition symptoms

Post-micturition symptoms are symptoms that patients experience immediately after micturition: a feeling of incomplete emptying and post-micturition dribble. Although the new ICS terminology has defined post-micturition symptoms, overall, urological research to date has focused on voiding or storage symptoms; post-micturition symptoms have received relatively little attention, despite their potential burden on daily health-related QOL (HRQOL).

A feeling of incomplete emptying is a self-explanatory term for a feeling experienced by an individual after passing urine. This symptom had been regarded either as a storage or voiding symptom before it was categorized as a post-micturition symptom by the 2002 ICS terminology report. Post-micturition dribble is the term used when an individual describes the involuntary loss of urine immediately after he has finished passing urine, usually onto his clothes after leaving the toilet. This symptom had been commonly regarded as a voiding symptom before the 2002 ICS terminology report.

During the 2005 EPIC study (13), post-micturition symptoms were observed in 16.9% of the men. The prevalence of a feeling of incomplete emptying was 13.5%, while post-micturition dribble was observed in 5.5%. The EpiLUTS study (14) also reported the prevalence of incomplete emptying and post-micturition dribble among men. The prevalence of incomplete emptying at least sometimes was 22.7% and at least often was 5.4%. Post-micturition dribble was also common in men: at least sometimes in 29.7% and at least often in 14.9%.

Maserejian *et al.* (80) recently conducted an epidemiological investigation focused on post-micturition symptoms and their impact on HRQOL. Data were obtained through in-person interviews in the Boston Area Community Health Survey, studying a random population-based sample of 2,301 American men aged 30 to 79 years. The overall prevalence of post-micturition symptoms was 11.8%, and the prevalence increased with age. Post-void dribble contributed to many of the post-micturition symptoms. The presence of post-micturition symptoms, particularly incomplete emptying, was indicative of mildly impaired physical HRQOL, activities interference, and mental HRQOL.

These findings emphasize the need to routinely assess for post-micturition problems in patients complaining of voiding symptoms, keeping in mind that patients who report a feeling of incomplete emptying may be among those most bothered by their urinary problems. Gotoh *et al.* (81) also reported that post-micturition symptoms, especially a feeling of incomplete emptying, influenced patients' QOL independently of storage and voiding symptoms.

There is a lack of studies investigating the pathophysiology of post-micturition symptoms. In male patients, although some organic disorders of the urethra, such as urethral stricture and urethral valve disease, may be associated with post-micturition dribble or post-micturition incontinence, the cause of the symptom is functional and difficult to identify in most cases.

Bader *et al.* (82) investigated the pathophysiology of post-micturition dribble in patients undergoing radical prostatectomy, and reported insufficient urethral milking secondary to impaired sensitivity of the membranous–but not bulbar–urethra. Although the subjects in this study were

post-prostatectomy patients, they noted that post-void urethral milking was often already absent before surgery. Though the pathophysiology of insufficient post-void urethral milking remains to be elucidated, the increased incidence of post-micturition dribble with age may suggest that it is associated with the physiological changes seen in aging.

A feeling of incomplete emptying often coexists with voiding symptoms (80), and voiding dysfunction is closely associated with appearance of this symptom. However, patients sometimes have a feeling of incomplete voiding associated with storage symptoms such as urgency and frequency, and this symptom may also be associated with increased bladder sensation.

# 2.3 Patient assessment

## 2.3.1 History and physical examination/digital rectal examination

National guidelines (or guideline updates) on male LUTS since the 2006 Consultation have all recommended that, despite the lack of high-quality supporting evidence, a relevant history and clinical examination should be done when men present with LUTS.

The medical history should identify comorbidities and medications that might be relevant to the etiology and management of the LUTS. Physical examination should determine whether the bladder is palpable, and whether there is excoriation of the genitals secondary to UI or evidence of urethral discharge. It should include a focused neurological examination if relevant symptoms are present. Digital rectal examination of the prostate is also performed. Studies investigating the detection of prostate cancer have suggested that DRE is more useful than trans-rectal ultrasound (TRUS) without biopsy (83–84).

## Recommendations

Take a relevant history from men who present with LUTS (Level 4, Grade D).

Examine the abdomen, external genitalia, and prostate of men who present with LUTS (Level 4, Grade D).

### 2.3.2 Frequency-volume charts

A registration of the voiding pattern by recording voiding events in terms of time and volume yields an objective assessment of urinary frequency and voided volumes. Recordings concerning urgency, incontinence episodes, or fluid intake may also be added.

Such recordings have been referred to as micturition time charts (a simplified version omitting volume recordings), FVCs, micturition charts, urinary diaries, voiding diaries, or bladder diaries. This last term has been proposed by the ICS (4) to include data on urgency and incontinence episodes, because this term is more comprehensive than voiding diary or FVC. Here we use the term FVC, addressing the basic parameters of the voiding pattern, as a collective noun for all formats.

Frequency-volume charts have become an important part of the evaluation of LUTS, and their use is recommended in several guidelines (85–86). Most experts agree that these charts provide invaluable information about several voiding symptoms. There are a number of parameters that can be assessed by an FVC: total number of voids/24 hours; total number of daytime (awake) voids; total number of nighttime voids; total voided volume; maximum, minimum, and mean voided volume; and if appropriate, total fluid intake, number of urgency episodes, and number of incontinence episodes.

Despite the agreement on the usefulness of FVCs, the structure, content, and duration of chart-keeping for the evaluation of LUTS has not been standardized.

#### 2.3.2.1 Objective recordings vs. recall bias

Frequency-volume charts have been shown to be reproducible and more accurate than the patient's recall (32,87–89). For example, it has been shown that for nocturia, the majority of men are inaccurate in their estimation of the number of episodes per night (90–91). Measurements by patients using FVCs have a high accuracy (92).

#### 2.3.2.2 Ranges of frequency-volume chart parameters

Several reports have established the variance of FVC parameters within populations of normal men. The reported mean 24-hour urine production is 1,506–1,718 mL, with large variation in the studied populations (standard deviation [SD]: 600–800 mL) (31,33,93–97). Two studies showed that 24-hour urine production was related to age and had a parabolic curve, increasing until the fifth decade and then decreasing (94–95). Others have shown that the 24-hour voided volume does not decrease with age in community-dwelling men aged 50–78 years who were followed for 6.5 years (34). The reported mean 24-hour frequency ranges between five and eight and increases with age in most reports (33,93–97).

#### 2.3.2.3 Duration of frequency-volume charts

Due to intra-individual variation, FVC recordings differ on different days (98). The more days recorded, the more likely that the whole spectrum of variation will be captured by the recordings. The desired trade-off between patients' response rate and accuracy of the recordings, in terms of reliability and compliance, depends on the aim of the FVC. In large epidemiological studies, a high response rate is more important than individual accuracy, whereas accuracy is more important in the assessment of an individual's voiding pattern in a clinical situation.

Few data are reported on the intra-individual variations in FVC parameters (92,98–99). However, these variations have been used in statistical analyses leading to statements on the optimal duration of FVCs.

Recommendations for diary length vary considerably, including 24 hours (89,92), 3 days (100), or 7 days (101–103). This inconsistency is partially explained by differences between study populations in diagnosis, age, sex, and geography, and by differences in methods of analysis and interpretation of results.

Abrams and Klevmark favoured a 7-day FVC because the week is a unit of time in social terms (102). However, most reports on the optimal duration of FVCs have been based on compliance or reliability rates.

Compliance rates have been presented as the percentage of patients who completed the FVC at the end of the study period, and vary between 57% and 100% (104). In a study of 3-day FVCs in 188 BPH patients, 15% did not complete the first day (99). Of the remaining 160 patients, 91 completed 3 days, resulting in a 3-day compliance rate of 57% and an overall compliance rate of 48%.

In a group of incontinent men and women, 248 kept a 3-day FVC, and 40 kept a 7-day FVC. Of the 3-day FVCs, 90.7% were complete vs. only 50% of the 7-day FVCs. Therefore, the authors favoured the 3-day FVC (105).

In a group of 162 patients with incontinence and LUTS, Ku *et al.* found no differences in compliance rates among FVCs kept for 2 days, 3 days, or 7 days (106). However, they showed that the burden of an FVC increased with its duration. They suggested that the number of days required to evaluate voiding symptoms should be reduced to less than 7.

Several authors have reported on the reliability of FVCs. Groutz *et al.* used test-retest reliability of 1- to 3-day FVCs recorded over 2 weeks in 109 patients with UI and LUTS (89). They found a reliability of 0.83 for voiding frequency after a 3-day FVC, whereas the compliance for voided volumes decreased to 76% at day 3. They advocated a 24-hour FVC because on the second and third day, the improvement in reliability was small compared to the loss of compliance.

Gisolf *et al.* found only small variations in the 24-hour mean voided volume in 3-day FVCs recorded by 160 men with LUTS due to BPH, and concluded that a 24-hour FVC is sufficient and reliable (99).

Homma *et al.* analyzed the 1-, 3-, and 7-day FVCs of 74 patients with urinary frequency or incontinence (103). They showed that the intra-individual variability of FVC parameters decreased with increasing duration of the FVC. The magnitude of the decrease was different between different parameters. Thus, the optimal length of a diary varies depending on the parameter being assessed, as well as on the precision and sensitivity required. They contended that a 7-day FVC is a reasonable option for most patients with incontinence.

Brown *et al.* studied two 7-day FVCs of 21 men and 133 women with urge incontinence by test-retest analysis (107). The intraclass correlation coefficients were >0.80 for all parameters; furthermore, the intraclass correlation coefficients were only slightly lower for FVCs completed for 3 or 4 days.

By calculating the intraclass correlation coefficients of several parameters, Yap *et al.* compared each day of a 3-day FVC kept by 96 men with LUTS. Accuracy varied by parameter and by patient. Therefore, they concluded that a 1-day FVC is insufficient for diagnostic purposes or the evaluation of treatment (108).

In a mini-review of the reliability of FVCs, Yap *et al.* argued that using FVCs of ≥3 days might be the most defensible policy, but they reported no published data on compliance rates associated with a duration of ≥3 days (104). They also indicated that in some reports, reliability might have been overestimated.

Another review by Bright *et al.*, focusing on validation of FVCs, summarized that excessive duration reduces patient compliance, but too short a duration may produce unreliable measurements (109). They also noted that a validated urinary diary does not exist.

As a general conclusion (until further research has been conducted) one can state that when using FVCs of a particular duration, there will be a trade-off between precision and compliance. Compliance seems to decrease dramatically when the duration is longer than 3 days. In a clinical setting where a diagnosis has to be made in an individual patient, precision is very important and therefore the duration should be at least 3 days. In the setting of an epidemiological study, compliance is more important than individual precision and therefore a 1-day diary is optimal.

### 2.3.2.4  Frequency-volume chart content

Besides the discussion of the optimal duration of FVCs, various opinions exist in terms of the content and layout of FVCs. Whether urgency scales and incontinence recordings are required and useful depends on the type of symptoms. Layout and content seem to be related to patients' and doctors' preferences. Recently, a study was performed hoping to provide a starting point for the development and validation of a generic urinary diary, based on patients' and clinicians' views of importance. It was appreciated that the diary was unlikely to be a one-size-fits-all tool with the potential to replace all other diaries and that the final urinary diary may only be recommended for use in certain circumstances (110).

Most studies have used paper diaries to collect information. But as early as 1993, Rabin *et al.* found that a majority of 25 patients and 25 controls favoured a computerized voiding diary over a written diary (111). Concerns about fear of technology, especially in elderly or less intelligent people, were not confirmed in this study.

Quinn *et al.* compared the use of electronic and paper diaries in a cross-over study in 35 patients with OAB (112). They concluded that data collection was comparable, and suggested that the electronic diary was an appropriate and easy-to-use alternative to a paper-based method for assessing the symptoms of OAB. Stone showed electronic diaries (not voiding diaries) to have a much higher compliance than paper diaries (113).

Interpretation of FVCs requires simple calculations of FVC parameters, such as mean, maximum, and total voided volumes and frequencies. Currently, reports are lacking on how FVC data are processed. Digital processing of FVCs is likely to facilitate the assessment of FVC parameters. However, it remains unclear how clinicians interpret FVC data in routine clinical practice.

### 2.3.2.5 Diagnostic and therapeutic features

In clinical practice, FVCs are useful for determining a baseline that can be used to evaluate the effects of interventions. Frequency-volume charts are also useful in the diagnostic process of patients with LUTS. In analyzing nocturia, FVCs have been shown to be indispensable for proper categorization and thus treatment (113–115). The cornerstone of further analysis of nocturia is the completion of an FVC, with the length of nighttime stated (i.e. the period in bed with the intention to sleep, until waking with the intention of arising). It is obvious that the time spent in bed is relevant to the total number of nocturia episodes. It can also be useful to examine the timing of nocturia episodes, since this may relate to the pathophysiological background. Increased venous return tends to produce nocturia episodes earlier in the night, while some sleeping disorders or bladder problems tend to cause nocturia episodes in the second part of sleep.

Although several guidelines recommend using FVCs in the diagnostic work-up of patients with LUTS/BPH (85–86), no diagnostic discriminative values of FVC parameters have been established. Due to the wide variation in FVC parameters within populations, false-positive and false-negative rates are high, yielding a low predictive value. It is conceivable that certain parameters will show better diagnostic properties than others. For example, the median voided volume was reported as the most constant parameter by several authors (98–99). Combining FVC data with other examinations (e.g. symptom scores, uroflowmetry, and ultrasonography for measurements of the PVR volume or bladder wall thickness [BWT]) might add to the diagnostic abilities of FVCs.

### 2.3.2.6 Future perspectives

The optimal content and structure of FVCs need to be established, but will probably depend on the symptoms of interest and the aims of a patient's evaluation. Assessing the optimal duration of FVCs is an important goal and should take into account the reliability of FVC parameters, as well as patient compliance. Future studies should be aimed at elucidating the potential (additional) diagnostic value of FVCs.

## Recommendations for research

Determine the reliability of and compliance with FVCs in relation to the duration of the FVC.

Design a validated FVC.

### 2.3.3 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/test results and scores from symptom and QOL questionnaires
- To predict the response to treatment
- To assess the outcome of treatment

The following symptom scores for male LUTS have been evaluated and are discussed below:

- The IPSS: symptoms and QOL impact of LUTS
- The International Consultation on Incontinence Modular Questionnaire–Male LUTS (ICIQ-MLUTS): symptoms of LUTS and UI
- The Danish Prostatic Symptom Score (DAN-PSS): symptoms of LUTS and UI
- The OAB Symptom Score (OABSS): symptoms of OAB
- The Core LUTS Score (CLSS): symptoms of LUTS
- The Urgency, Weak Stream, Incomplete Emptying, and Nocturia Scoring Tool (UWIN): symptoms of LUTS

Over the past two decades, symptom scores have become a routine part of the evaluation of LUTS. Symptom scores have been used to quantify LUTS in terms of both prevalence and severity, to verify the influence of LUTS on QOL (including sexual function), and to determine the therapeutic efficacy of various treatments.

It is important that symptom scores have a wide applicability across a number of different cultures and languages. Ideally, symptom scores should also help to determine the underlying etiology of LUTS (e.g. BOO, DO, impaired detrusor contractility); 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, but it is clear that the worldwide use of such scores has helped in evaluating symptoms, treating patients, and communicating findings globally. Attempts to develop new and better indexes 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 IPSS, the ICS's ICS-male questionnaire (now known as the ICIQ-MLUTS), and the DAN-PSS. Although each was designed with the same purpose, only six symptoms are common to all three, including incomplete emptying, urgency, decreased stream, frequency, and nocturia.

As the concept of OAB defined by subjective symptoms such as urgency, daytime frequency, nocturia, and urgency incontinence has become widespread, a simple symptom questionnaire to quantitatively assess OAB symptoms, the OABSS, was developed and psychometrically validated. Other new symptom questionnaires to assess male LUTS include the UWIN and the CLSS. As yet, there is no validated symptom questionnaire that assesses post-micturition symptoms (post-micturition dribble and post-micturition incontinence).

### 2.3.3.1  The international prostate symptom score

The IPSS is the most commonly used tool to evaluate LUTS suggestive of BPO. In 1992, Barry *et al.* reported that the AUA-SI was a valid short questionnaire useful in the diagnostic work-up of voiding symptoms (116). Before the AUA-SI had been published, it was adopted by the World Health Organization (WHO) and renamed the IPSS after adding a disease-specific QOL score (117).

The IPSS was developed to examine how patients with BPH perceived their symptoms and how the symptoms affected their lives. It was also created as a tool to give clinicians a uniform and reproducible method of assessing symptoms and to facilitate comparisons of results in clinical studies (118).

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 (116). The committee (the AUA 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 that covered all symptom domains 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 contained questions that correlated with global bother questions, the committee decided on seven questions, with each symptom rated 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 QOL with LUTS may be answered on a scale of 0 (delighted) to 6 (terrible). Statistically, the index was shown to be internally consistent, highly reliable, and able to accurately distinguish BPH patients from controls. Symptoms are classified as mild (an AUA-SI score of ≤ 7), moderate (an AUA-SI score of 8–19), or severe (an AUA-SI score of 20) based on sensitivity cut-offs for BPH patients and specificity cut-offs for controls (119).

The IPSS has subsequently been routinely used in clinically practice and extensively used in clinical studies to evaluate the prevalence of LUTS and symptomatic BPH (12,120), 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 (making it efficient, less time-consuming, and without interviewer bias), sensitive to change, and generalizable to different populations and socio-economic groups (121–124). In cases where self-administration is not possible (e.g. due to visual impairment or illiteracy), interviewer administration is an acceptable substitute; however, the mode of administration should remain consistent for a given patient (119,121,125–126).

International Prostate Symptom Scores increase with age, as would be expected. Young asymptomatic men (age 50 or less) tend to have low scores (typically 8–9). 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 (127).

The IPSS has been shown to be sensitive to change. Barry *et al.* (128) calculated clinically significant changes in the score by examining patients' ratings of treatment, which ranged from markedly, moderately, or slightly improved, through unchanged to worse. Those who reported no improvement had a mean reduction of 0.7 points; those who reported a slight improvement had a mean reduction of 3.0 points; moderate improvement was associated with a mean reduction of 5.1 points; and marked improvement with a mean reduction of 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 differences 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 assessing the severity of LUTS suggestive of BPO, and for evaluating therapeutic outcomes (compared to baseline in individual subjects), it is not a diagnostic tool for BPO (129). LUTS are multifactorial and BOO, 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 (69,78,130–134). It also correlates poorly with free urinary flow rate, prostate size, and the volume of PVR urine (68). In addition, the IPSS is not strongly correlated with PV as determined by TRUS (133,135).

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 outcome 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 BOO than in those without (129).

## 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 greater 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 additional 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 and BPO.

Linguistically validated translations of the IPSS into a multitude of languages are available.

**Recommendation:** Grade A

### 2.3.3.2 The international consultation on incontinence modular questionnaire

The ICS-male questionnaire resulted from the ICS–'BPH' Study (23,25,129,136–137). The ICS-male questionnaire (now renamed the ICIQ-MLUTS as part of the ICIQ: www.iciq.net) was assessed by comparing patients visiting urological clinics who had urodynamically proven BOO with community-based men.

When the ICS-male was initiated, it was intended that a scoring system would be devised in terms of relationships with urodynamically confirmed BOO (25). 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 DO, even with the power of a study with a relatively large number of patients ($n$=1,271) (129). This is similar to what has been found with the IPSS, even though the ICS-male questionnaire was derived from patients who had urodynamically investigated BOO. This led the authors to conclude that "there are objective methods that quantify both urine flow rate and BOO. 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" (129). Unlike the IPSS, the ICS-male questionnaire assesses a number of incontinence symptoms.

The ICIQ-MLUTS contains 22 questions on 20 urinary symptoms and (for most questions) the degree of bother that the symptom causes (23). It has demonstrated acceptable levels of validity, reliability, and sensitivity to change following a range of treatments, including surgery, minimally invasive therapies, and drug treatments (25,51,138). After factor analysis, the long version has now been largely replaced by a scored short form: the ICIQ-MLUTS, formerly called the ICS-male-SF (137). It also continues to be used to assess LUTS in men and the results of minimally invasive therapies and drug treatments (139–141). The ICIQ-MLUTS consists of 14 questions: five assessing voiding symptoms; six assessing incontinence symptoms; and one question each on frequency, nocturia,

and QOL (137). The ICIQ-MLUTS may be divided into a voiding subscore (ICS-male-VS) and an incontinence subscore (ICS-male-IS). 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 that met at the end of the First International Consultation on Incontinence in 1998 supported the idea that a universally applicable questionnaire should be developed, which could be widely applied both in clinical practice and research. The hope was 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 to treat the same condition, in the same way that the IPSS has been used.

An 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. The first module to be developed was the ICIQ-UI Short Form. The ICIQ-UI Short Form has now been fully validated and published (142). Given the intention to produce an internationally applicable questionnaire, requests were made for translations of the ICIQ-UI Short Form at an early stage, in response to 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, 12 modules have been adopted that are direct (unchanged) derivations from already published questionnaires. As described above, the ICIQ-MLUTS is derived from the ICS-male-SF. It has the same questions as the ICS-male-SF except for the last question on QOL. In its place, there are subquestions related to degree of bother ("How much does this bother you?") after each question, which are scored from 0 (not at all) to 10 (a great deal).

## Conclusions

The ICIQ-MLUTS Long Form and the ICIQ-MLUTS have a high level of psychometric validity and reliability. The ICIQ-MLUTS is derived from the ICS-male-SF and has a 10-point bother question after each symptom question.

There is Level 1 Evidence to suggest that the ICS-male-SF is a useful tool to assess LUTS suggestive of BPO and to assess change from baseline after treatment.

Furthermore, this symptom score does take into account symptoms of incontinence, and it may be divided into voiding and incontinence subscores. Although linguistically validated translations of the ICIQ-MLUTS into many languages are available, this tool has not yet had the same widespread use in clinical practice as the IPSS.

**Recommendation:** Grade A

### 2.3.3.3  The Danish prostate symptom score

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 (79,143–144). The DAN-PSS was initially intended for use in the BPH patient without serious complications such as recurrent UTIs, 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 dribble, stress, and urgency incontinence. Each question is scored from 0 (not present) to 3 (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, and 3: severe problem). A composite score is achieved by the multiplication of the symptom score by the bother score, with a total range of 0 to 108 (143–144).

The DAN-PSS has excellent test-retest reliability and content and construct validity, and is able to discriminate between patients with LUTS suggestive of BPO and those without them (79,145). The DAN-PSS has also been shown to be appropriately responsive to change after surgery and medical therapy (145–147). A computer version of this questionnaire has been validated, and patients are said to appreciate the new version more than the paper version (148).

The DAN-PSS may be subdivided into an obstructive and an irritative part. Schou *et al.* claimed that with a cut-off point of 6 for the obstructive part, the DAN-PSS is to be able to discriminate men with BOO from men without significant obstruction (149). However, a subsequent study showed no correlation of the DAN-PSS (or obstructive subscore) with obstruction measured by standardized pressure-flow analysis (147). Furthermore that study showed that neither the pre-operative DAN-PSS nor the IPSS score could sufficiently predict the success or failure of TURP.

## Conclusions

The DAN-PSS is a psychometrically valid and reliable tool for the assessment of LUTS suggestive of BPO. It is unique among similar indexes in that it multiplies the severity of symptoms by the degree of bother. Thus, severe symptoms that cause no bother contribute nothing to the total score. The tool 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 Scandinavian countries.

**Recommendation:** Grade B

### 2.3.3.4 The overactive bladder symptom score

The OABSS is a four-item questionnaire to collectively express the OAB symptoms (daytime frequency, nocturia, urgency, and urgency incontinence) in a single score (150). The OABSS, originally developed in Japanese, has been psychometrically validated for reliability and validity (150) and has been used in Germany and Taiwan (151–153). Previous research examining the OABSS has suggested that it can be useful as a brief assessment tool for symptom severity as well as bother (154). In addition to validity and reliability, the OABSS proved to be responsive to treatment-related change in OAB symptoms, and the minimal clinically important change (MCIC) of the OABSS was suggested to be −3 points (81).

## Conclusions

The OABSS is a psychometrically valid and reliable tool for the assessment of OAB symptoms. The OABSS is also responsive to treatment-related changes, with an MCIC of –3 points.

It is not yet clear how well the OABSS performs in the male LUTS population. No reports on linguistically validated translations into languages other than Japanese and English have been published.

**Recommendation:** No recommendation is possible yet for male LUTS.

### 2.3.3.5 The core lower urinary tract symptom score

Ten LUTS (increased daytime frequency, nocturia, urgency, urgency incontinence, stress incontinence, slow urinary stream, straining, a feeling of incomplete emptying, bladder pain, and urethral pain) were selected as core symptoms from 25 LUTS defined by the ICS committee, and a symptom questionnaire to assess the core symptoms was developed as the CLSS (155).

Symptoms were scored according to their frequency (0: never, 1: slight, 2: sometimes, and 3: often) and their severity (0: none, 1: slight, 2: moderate, and 3: severe). The core LUTS all showed significantly higher scores in symptomatic patients than in the controls, and they were not correlated with other more prevalent symptoms. The CLSS questionnaire derived from the 10 symptoms was confirmed to show good test-retest reliability. The CLSS was compared with the IPSS in men with LUTS (156), and it was suggested that the CLSS is more comprehensive than the IPSS for symptom assessment of men with various diseases/conditions. The authors suggested that the CLSS provides overall assessment of relevant symptoms without omissions, and may be useful for new patients, patients with multiple diseases, and patients without a definite diagnosis, as well as before and after interventions that may cause other symptoms.

As yet, no reports on linguistically validated translations into other languages have been published.

**Recommendation:** Grade C

### 2.3.3.6 Modified American urological association symptom index

Development of a shorter form of the AUA-SI was attempted and called the UWIN. Complete AUA-SI data were collected from 8,731 men, and correlation analysis and area under the receiver operating characteristic (ROC) curve were used to determine the best reduced index and cut-off points in scores for the severity categories of mild, moderate, and severe (157). In addition, the correlation of the AUA-SI and the UWIN was investigated in 278 male (158). These studies validated that the UWIN questionnaire can be used in place of the AUA-SI. As with the original AUA-SI, the UWIN has no question on UI, and no reports on linguistically validated translations into other languages have yet been published.

### 2.3.3.7 Summary

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

The IPSS has been the most widely used (in many countries and languages), but neglects the symptom of urgency incontinence, a symptom that produces significant bother. The ICIQ-MLUTS is slightly longer, but takes into account the symptom of urgency incontinence, and may also 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. The DAN-PSS has been mostly used in Scandinavia.

Because LUTS are multifactorial, none of the symptom scores are condition specific and none are able to consistently predict obstruction. This has led to the conclusion that these valid and reliable methods of quantifying the presence and severity of symptoms, and the objective methods that quantify urine flow rate and BOO, measure different aspects of the clinical condition, and should be viewed separately in the evaluation and treatment decision of a patient presenting with LUTS (134).

A newly developed symptom questionnaire for OAB, the OABSS, is a simple and brief self-administered questionnaire. It has been subjected to psychometric testing and has been shown to be valid, reliable, and responsive to change. The performance of the OABSS in the male LUTS population still needs to be established. Linguistically validated translations into languages other than Japanese and English are still lacking.

Although epidemiological studies demonstrated that post-micturition symptoms were common and bothersome for patients, there is no validated symptom questionnaire to measure these symptoms, especially post-micturition dribble and post-micturition incontinence. Symptom scores and a functional assessment provide the optimal way to appreciate the total picture of the male with LUTS.

## 2.3.4 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. It is considered an inexpensive diagnostic test able to identify patients with UTI as indicated by the presence of leukocyte 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. Microscopic hematuria can be easily identified by dipsticking because of the presence of hemoglobin. The detection of hematuria is important because the condition is associated with a 4%–5% risk of a diagnosis of urological disorder or malignancy within 3 years (159).

No high-quality evidence has emerged since the 2006 Consultation to alter the recommendation that urinalysis should be done at initial assessment for LUTS. Doubt has been cast on the utility of urinalysis in the identification of either urinary infection or bladder cancer (159–160). A systematic review and economic evaluation of diagnostic tests and algorithms used to investigate hematuria concluded that the evidence base on which to determine the ideal means of investigating hematuria was insufficient (161). The recommendation that urinalysis should be done as part of the initial assessment of men with LUTS, however, remains in place.

## Recommendation

Do urinalysis in men who present with LUTS (Level 4, Grade D).

### 2.3.5 Biochemical testing

#### 2.3.5.1 Renal function testing

Epidemiological studies in community-dwelling men have shown an absence of any association between BPH and chronic kidney disease, suggesting that screening for renal function is not justified in patients with BPH (162). Diabetes and arterial hypertension appear to be the most important causes of elevated serum creatinine in men with BPH and renal failure (163). Recently, data from the Medical Therapy of Prostatic Symptoms (MTOPS) study showed that the risk of developing *de novo* renal failure in men with LUTS is low (<1%), suggesting that it is not necessary to monitor renal function in patients with BPH (164).

Since the 2006 Consultation recommended measuring serum creatinine, no clear evidence has emerged to reverse that recommendation. A study examining the association between LUTS and glomerular filtration rate (GFR) in South Korean men concluded that in older men without obvious enlargement of the prostate, as LUTS became more severe, GFR fell (165). This suggests that assessment of GFR remains a reasonable part of the initial assessment of men who present with LUTS.

## Recommendation

Measure serum creatinine in men who present with LUTS (Level 4, Grade D).

#### 2.3.5.2 Prostate-specific antigen

There remains no consensus as to the measurement of prostate-specific antigen (PSA) in patients with LUTS. The rationale for measuring PSA is two-fold: to screen for prostate cancer, and to measure a parameter with prognostic value for progression of BPH and response to treatment. Men over 50 years of age often consult their family doctor or a urology clinic for a prostate cancer check. Recent data have failed to support the use of PSA as an effective means of reducing mortality when used to screen for prostate cancer (166).

Major randomized studies from North America and Europe produced different conclusions, with the US study not finding a reduction in prostate cancer deaths after screening (167), whereas the European study did find evidence of a reduction in deaths from prostate cancer (168). An analysis from the UK screening study (ProtecT) showed a reduced risk of prostate cancer with raised PSA if LUTS were present (169). Risk calculators derived from the European Randomized Study of Screening for Prostate Cancer showed that PSA was not helpful in identifying prostate cancer in screening (84). It seems sensible to consider the use of PSA in men with LUTS according to the national guidelines in their own country.

Serum PSA is also a surrogate of PV. In the control arm of the MTOPS study, PSA was one of a number of variables that predicted clinical progression (170). Bohnen *et al.* showed that in men over 50 with no prostate cancer, PSA ≥1.5 ng/mL indicated that the PV was >30 cm$^3$ in more than 78% of the men (171). Because these data cannot be transferred to individual men, the utility of PSA is not sufficient to justify its uniform use.

## Recommendation

Offer PSA testing in men who present with LUTS, according to national recommendations (Level 4, Grade D).

### 2.3.6 Post-void residual

post-void residual 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. Post-void residual can be measured by ultrasound or catheterization. Post-void residual may be elevated due to detrusor underactivity, BOO, or a combination thereof. Thus, an elevated PVR is a non-specific indication of poor bladder emptying. For example, while men with LUTS and BPO may have an elevated PVR, an elevated PVR in isolation does not necessarily predict the presence of obstruction (172–173). PVR alone cannot be used to differentiate between obstructed and non-obstructed patients. Furthermore, there is no agreed-upon standard definition of exactly what constitutes an elevated PVR. The volume of PVR that may be significant has not been established, and probably varies by patient according to intrinsic characteristics of an individual's lower urinary tract. However, it is generally agreed upon that in some patients, an elevated PVR may be harmful. As a result, the 2012 AUA/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) UDS guideline (174) states that clinicians may perform PVR in patients with LUTS as a safety measure to rule out significant urinary retention both initially and during follow-up. This is a clinical principle and is not made based on evidence-based diagnostic, prognostic, or treatment criteria.

## Recommendation

The level of evidence for the measurement of PVR in the standard patient with LUTS is weak, and it is mainly based on expert opinion (Level 5, Grade D).

## 2.3.7 Uroflowmetry

Uroflow measurement is a non-invasive urodynamic assessment that provides an objective and quantitative indication of the integration of bladder function and the outlet. While an abnormal flow rate is indicative of a dysfunction of the voiding phase of micturition, uroflowmetry, like PVR, is limited by its inability to distinguish between a low flow rate due to outlet obstruction, bladder underactivity, or both. Furthermore, obstructed patients with high detrusor pressure ($P_{det}$) can maintain a normal flow rate. Uroflowmetry results show considerable variation in the $Q_{max}$ measured on either the same or different days (175).

In males, different studies have shown variability in the diagnostic accuracy of uroflow for detecting BOO ranging from moderately high to low (176–181). This reported variability may be due to a variety of factors. The specificity of $Q_{max}$ 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 a $Q_{max}$ of less than 15 mL/s were 38% and 82%, respectively (181). 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.

Smaller single-centre studies have suggested a higher specificity of up to 90% for this value of $Q_{max}$, in particular with multiple flows (180,182–183). However, for uroflowmetry to play a part in the diagnosis of BOO/BPO, the measurements need to be multiple. In this circumstance, the Level 2 Evidence allows a recommendation, Grade B, for the reliable diagnosis of BOO, but only when $Q_{max}$ is less than 10mL/s. The AUA/SUFU UDS Guideline Panel concluded that "although the literature fails to specifically identify clinical scenarios when uroflowmetry is useful, the test has value in the evaluation of disorders of voiding, even if further testing is required to make a specific diagnosis" (174). Uroflowmetry can also be used for monitoring treatment outcomes and correlating symptoms with objective findings. This leads to the following guidelines statement: "Uroflow may be used by clinicians in the initial and ongoing evaluation of male patients with LUTS that suggest an abnormality of voiding/emptying."

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**Recommendation:** Grade C

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## 2.3.8 Imaging

Since the previous Consultation, there has been some work published on the use of ultrasound to assess bladder weight, intravesical prostatic protrusion (IPP), and BWT. One study from Italy showed some promise for use in the assessment of men with LUTS. Bladder wall thickness and IPP correlated with urodynamic markers of outflow obstruction (184–185). Other studies of ultrasound have shown correlation between ultrasound findings and the urodynamic markers of obstruction (186–187).

Near-infrared spectroscopy (NIRS) has shown varying results in its use to attempt to avoid the need for pressure-flow studies (PFS) (187–190).

## Recommendation

Do not offer imaging in the initial assessment of men who present with uncomplicated LUTS (Level 4, Grade D).

### 2.3.8.1 Ultrasonic assessment of the prostate
#### Prostate size and shape

Trans-rectal ultrasound is the imaging modality used most frequently to assess PV, and it is more accurate than DRE (191). Magnetic resonance imaging (MRI) provides an even more accurate estimation of PV and can more easily detect drug-induced changes in volume (192).

The relationship between total PV and BOO has been investigated in several studies. A retrospective study involving 521 patients showed a weak but statistically significant correlation between prostate size and BOO ($r=0.32$, $p<0.001$) (193). The sensitivity and specificity for BOO of a PV greater than 40 mL were 49% and 32%, respectively. In another study of 525 patients, there was a similarly weak correlation between PV and BOO (r=0.28, $p<0.001$) (134).

With the failure of total PV 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 three zones: the central zone, the transitional zone (TZ), and the peripheral zone. The TZ is the major site for the development of BPH leading to BPE and is affected to a greater extent than the peripheral zone by medical treatment with finasteride (194) and dutasteride (195), with a correspondingly greater effect on $Q_{max}$ (195–196).

It also appears that prostate size and shape may affect the accuracy of trans-abdominal ultrasound in measuring prostate size. In a study of 202 men, Yang *et al.* (197) found that trans-abdominal ultrasound was inaccurate in determining the volume of smaller prostates. Comparing trans-abdominal ultrasound to computed tomography (CT), they found that the ellipsoid formula ($\pi/6 \times$ width $\times$ height $\times$ length) is not adequate to estimate prostate size, since the shape of the prostate changes as the gland grows bigger. By analytical modelling, these authors found three typical prostate shapes associated with three different stages of prostate hyperplasia. They introduced a formula to correct the eccentricity parameter to calculate prostate size. The CT-estimated PV was taken as the standard. The estimated volume of small prostates measured with trans-abdominal ultrasound differed by 28% from the CT-estimated volume. When using the corrected ellipsoid formula, this difference was reduced to 7.6%. For hypertrophied, round-shaped prostates, there is little difference between the volume estimate made by trans-abdominal ultrasound and that made by CT scan.

The TZ index (the ratio of TZ volume to total PV) is more strongly correlated with symptoms (r=0.75, $p=0.001$) and $Q_{max}$ (r=−0.71, $p=0.001$) than is PV alone, but it is only moderately correlated with a critical measure of obstruction ($P_{det}$ at $Q_{max}$; r=0.43) (198), and several investigators have concluded that it is not clinically useful for judging obstruction (199–201).

Though the prostate's size may be of some importance, its shape may be equally or more important in predicting BPO. Trans-rectal ultrasound can be used 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 1 as the prostate becomes more circular. The PCAR showed a stronger correlation with BOO than with the TZ index (r=0.487, $p<0.0001$ vs. r=0.331, $p<0.005$). The sensitivity and specificity for BOO of a PCAR value >0.8 were 77% and 75%, respectively (202), only a little lower than the limit imposed by intrinsic variability of obstruction. It has been shown by Watanabe *et al.* that when the ratio is greater than 0.75, BPO is likely (203). Similar findings were seen in a smaller study (204). It seems clear that the more circular the prostate, the more likely there is to be BOO.

## Intravesical prostatic protrusion

Intravesical prostatic protrusion has been used as a non-invasive determinant of obstruction. The postulated rationale is that as the prostate enlarges, it protrudes into the bladder, distorting the proximal urethral funneling and leading to BOO (205).

Intravesical prostatic protrusion is defined as the distance from the tip of the protruding prostate to the base at the circumference of the bladder, measured in the mid-sagittal plane on trans-abdominal ultrasound (206–207).

The measurement of IPP is affected by bladder volume and it has been suggested that IPP be measured at a comfortably full bladder volume of 100 to 200 mL (208). Intravesical prostatic protrusion is graded according to severity (grade 1: ≤ 5 mm, grade 2: 5–10 mm, grade 3: >10 mm) (206,209). As IPP grade increases, the severity of BOO also increases.

In one study, 79% of patients with grade-1 IPP were not obstructed, but 94% of patients with grade-3 IPP were obstructed (206). The positive predictive value of grade-3 IPP for BOO was 94%, while the negative predictive value was 79%. Intravesical prostatic protrusion 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 also seems to be a good predictor of failure of catheter trial in patients with acute urinary retention (AUR) (207). Lee *et al.* (210) used this grading scheme to study the clinical progression of BPE and found that higher grades of IPP are linked to a higher risk of progression. Another recent study (186) found that patients with IPP measured at a bladder volume of 100–200 mL had a higher bladder outlet obstruction index (BOOI) than did patients without IPP.

Lieber *et al.* (211) used TRUS in the sagittal plane to determine IPP in 2,115 men without any history of surgery, disease, etc. that would affect normal urinary function. They found that men with a high grade of IPP (>10 mm) were more likely to use medication for LUTS than were those with a lower grade of IPP, which was significantly related with PV, IPSS, and low $Q_{max}$. Intravesical prostatic protrusion may therefore be useful for evaluating patients.

### Prostatic urethral angle

The prostatic urethral angle (PUA) is the angle between the urethra pars prostatica and the urethra pars membranacea in the mid-sagittal plane. Ku *et al.* (186) investigated 260 males with moderate to severe LUTS who were 50 years or older and either scored >8 on the IPSS or had a $Q_{max}$ of <10 mL/s. Patients were evaluated with PFS, and BOOI was calculated as $P_{det}$ at $Q_{max}$ $-2/Q_{max}$.

A high PUA was linked with a high BOOI. It was concluded that a PUA of 35° or greater is predictive of BOO. There was no correlation between degree of PUA and IPP (determined on trans-abdominal ultrasound), indicating that lateral or median lobe enlargement does not affect the height of the bladder neck. It is unclear how the prostatic anatomy changes during voiding, because PUA is a static measurement; further investigation of PUA is needed to clarify this.

#### 2.3.8.2 Ultrasonic assessment of bladder wall thickness/weight

Bladder wall thickness has been used to assess BOO non-invasively. The postulated rationale is that prostatic obstruction is associated with detrusor hypertrophy, leading to increased BWT (60). Animal models confirm that detrusor hypertrophy decreases after release of obstruction (212). However, detrusor hypertrophy and increased BWT may also be related to DO. 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 (213).

In order to negate the effect of bladder volume on BWT, 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 (150 mL) (214). The mean BWT measured in this way at three sites was moderately strongly correlated with obstruction as measured by the Abrams-Griffiths number (r=0.6724, $p$<0.0001). In 58 patients with a BWT greater than 5 mm, 88% were obstructed on PFS. The specificity for BOO of a value of BWT >5 mm was 92%; however, the sensitivity was only 54%.

Another way to eliminate the effect of variable bladder filling volume is to calculate the ultrasound-estimated bladder weight (UEBW) (215), which has an SD of 5 g (12%) in repeated studies. In a group of 65 patients, there was a significant correlation between UEBW and the urodynamic parameters of obstruction (r=0.478, $p$<0.0001 for Abrams-Griffiths number; r=0.543, $p$<0.0001 for Schäfer grade) (215). With a cut-off value of UEBW >35 g, the sensitivity of the test for obstruction was 85%, with a specificity of 87%.

### 2.3.9 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. Endoscopy provides an estimation of prostate size by evaluating prostate length and the morphology of the prostate and bladder neck. However, bladder endoscopy (cystoscopy) has a low prognostic value for the diagnosis of BOO.

No new evidence regarding the utility of cystoscopy in men with LUTS has emerged since the 2006 Consultation, and so it is still not a recommended option in the initial assessment of men with uncomplicated LUTS (who constitute the majority of men with LUTS). The indications for cystoscopy in men include symptoms such as hematuria and recurrent UTI (216–217).

## Recommendation

Do not use routine cystoscopy as part of the initial assessment in men who present with LUTS (Level 3, Grade C).

# 2.4 Urodynamics

## 2.4.1 Introduction

Urodynamics is the term used to describe testing and measurements of the function of the lower urinary tract. It allows for assessment of the two essential functions of the lower urinary tract: the storage of urine at low pressure and the voluntary evacuation of urine. Low-pressure storage is essential to protect kidneys and assure continence, while voluntary evacuation allows for the elimination of urine in socially acceptable situations without fear of leakage or over-distension. When one or both of these functions are disrupted, the result often manifests as symptoms bothersome to the affected individual. These LUTS have been well categorized earlier in this chapter.

In some cases, a precise assessment of storage and emptying is helpful or even necessary to optimally treat patients. Urodynamics includes the actual tests that are performed (urodynamic studies) and the observations made during the testing (urodynamic observations) (4,218). Although UDS consists of a number of tests that can individually or in combination assess lower urinary tract function (uroflow, cystometry, abdominal pressure [Pabd] monitoring, and electromyography of the urethral sphincter), the term urodynamic study generally implies that a cystometrogram is performed (with or without other tests) to measure bladder pressure during filling and voiding.

In this section, we will discuss the use of UDS in the assessment and treatment of LUTS in men.

There are several urodynamic findings as defined by the ICS (4) that are commonly associated with LUTS:

- **Bladder outlet obstruction:** A urodynamically diagnosed condition characterized by increased $P_{det}$ and decreased urine flow during voiding
- **Detrusor overactivity:** A urodynamic observation characterized by IDCs during the filling phase, which may be spontaneous or provoked; DO may be phasic or terminal (a single involuntary contraction at cystometric capacity)
- **Detrusor underactivity:** A detrusor contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span
- **Impaired compliance:** An impaired relationship between change in bladder volume and change in $P_{det}$, which occurs when pressure increases significantly with increasing volume in the absence of a detrusor contraction

Bladder outlet obstruction and detrusor underactivity are diagnosed during the voiding phase of UDS, while DO and impaired contractility are diagnosed during the filling phase. Many times, these conditions coexist. Detrusor underactivity can be a consequence of long-term BOO, as the bladder decompensates for increased retention of urine and constant high-pressure contraction against an obstructed outlet. It can be challenging to diagnose BOO in the presence of detrusor underactivity, as high-pressure low flow is required for the diagnosis. Finally, impaired compliance, though relatively rare, can be a long-term sequela of BOO. In the absence of obstruction, impaired compliance can occur secondary to structural changes in the bladder due to conditions like radiation cystitis and tuberculosis.

Over the past decade, there has been some evolution of views about the urodynamic evaluation of LUTS in men with possible BPO. Men in middle or older age present with LUTS that may be, but are not necessarily, related to prostatic changes such as benign or malignant enlargement and obstruction. Lower urinary tract symptoms may be due to dysfunction anywhere in the complicated mechanical and neural control system that allows normal lower urinary tract function.

It has previously been stated that the aim of UDS should be to reproduce specific LUTS while taking measurements that will reveal their cause. However, because the number of possible causes is quite large, it is often useful to go beyond the mere reproduction of the symptom and to document the complete function of the lower urinary tract during both filling and voiding phases. 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 because unsuspected abnormalities may contribute to the incontinence. As well, testing may reveal urethral obstruction, poor voiding, elevated residual urine, or possible neuropathy, which may change the interpretation of the symptoms, alter the presumed diagnosis, or change the choice of treatment. Thus, when one commits to performing UDS, an attempt should be made to correlate an abnormality with the symptoms, but also to perform a complete evaluation of lower urinary tract storage and emptying functions to possibly uncover other irregularities that may be associated with the patient's symptoms or may represent a treatment target. The results of UDS represent just one aspect of the assessment of male LUTS (with other aspects including symptoms and anatomical abnormalities). Adhering to this view means that it is not necessary in all cases to reproduce the symptoms during UDS. However, performing complete UDS is still warranted.

With a multitude of possible underlying causes of LUTS in men, one obvious question is how necessary is it to make a specific UDS diagnosis of the cause(s) and LUTS before instituting treatment (or observation)? In some cases, the answer is that UDS is not necessary. However, there are specific instances where UDS is very helpful, depending on specific patient characteristics, response to prior treatment, planned treatment, etc. The role of UDS in clinical practice has been nicely summarized by Hosker *et al.* (219), and this role certainly extends to the evaluation of men with LUTS.

Urodynamics may be used to:

1. Identify or rule out factors contributing to LUTD (e.g. UI) and assess their relative importance
2. Obtain information about other aspects of lower urinary tract function or dysfunction
3. Predict the consequences of LUTD on the upper urinary tract
4. Predict the outcome, including undesirable side effects, of a contemplated treatment
5. Confirm the effects of intervention or understand the mode of action of a particular type of treatment (especially a new one)
6. Understand the reasons for failure of previous treatments for symptoms (e.g. UI) or for lower urinary tract function in general

Ultimately, the main aim of UDS in clinical practice is to guide therapy and improve outcomes. Its ability to do this must be judged based on the evidence provided by trials and cohort studies. Urodynamics is also very important as a research tool, where the main aim is to gather knowledge about the diseases encountered and how best to treat them (i.e. to ensure that medical practice is knowledge-based).

When a condition is first widely encountered, there is a phase in which clinical research is crucial to generate new knowledge. Once etiology has been established, the debate can shift to whether routine clinical UDS is necessary for a specific condition (e.g. Should UDS be limited to selected difficult cases or performed more widely?). Because UDS remains the only way of objectively establishing the pathophysiological situation, urodynamic evaluation always remains necessary in at least the difficult cases.

Since the previous International Consultation (3), there has been some evolution of views about the urodynamic evaluation of LUTS in men with and without possible BPO. In the present report, these views are updated bearing in mind the historical perspective and focusing on publications from 2005 onward. We once again cover the topic of UDS investigation of LUTS in prostate cancer and its treatment, updating the literature since the previous Consultation in 2005 (3).

### 2.4.2 Diagnosing detrusor overactivity and impaired bladder compliance

Normally, the bladder stores urine at a low pressure and does not contract involuntarily. Once capacity is reached or voluntary voiding is desired, intravesical pressure increases (voluntary detrusor contraction). This is preceded by a relaxation of the external sphincter.

Detrusor overactivity is a urodynamic observation characterized by IDCs during the filling phase, which may be spontaneous or provoked. Detrusor overactivity may be further characterized as neurogenic DO, which means that it is associated with a relevant neurological condition (e.g. spinal cord injury or multiple sclerosis) or idiopathic DO, which mean that there is no defined cause (it is non-neurogenic) (4).

Characteristically, DO is associated with symptoms such as urgency, frequency, and urgency incontinence. However, this 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 is often obscure. For example, it has been argued that DO may be caused by urethral obstruction, and this is discussed further below. In other cases, there is no obvious cause, and the DO is called idiopathic. Sometimes it may even be a normal variant.

As stated above, DO is often (but not always) associated with urgency and urgency incontinence. But not all patients with urgency or urgency incontinence demonstrate DO on UDS studies. In the first study correlating the latest ICS OAB terminology with UDS findings, Hashim *et al.* (220) showed that the bladder is a better and more reliable witness in men than in women, with a greater correlation between OAB symptoms and urodynamic DO. This was even more apparent in OAB wet than in OAB dry patients. Men with urgency incontinence had DO in 84.2% of cases vs. 59.8% of those without. Those with urgency had DO in 78.6% of cases vs. 46.5% of those without. The symptom of frequency did not increase the likelihood of finding DO.

The presence of DO during UDS must be interpreted in the context of the patient's symptoms and condition. Ideally, a patient's symptoms should be reproduced during UDS, so we would expect DO to be accompanied by urgency or urgency incontinence, although it can occur and be significant without being symptomatic, particularly in neurogenic DO. However, DO can also be test induced or clinically insignificant, and has been reported in 14%–18% of healthy asymptomatic volunteers undergoing UDS (221–223). Several studies have investigated UDS findings in men prior to prostate cancer surgery and the incidence was 17%–60%, with some studies reporting DO of significant pressure magnitude (224–229).

The specific characteristics of DO can also be noted. Detrusor overactivity can manifest as a single event or as multiple IDCs. It can be phasic (continuous), sporadic, or terminal (occurring at the end of filling, near capacity). The ICS specifically defined three patterns of DO (4):

1. Phasic DO has the characteristic wave form and may or may not lead to UI.

2. Terminal DO is defined as a single IDC occurring at cystometric capacity that cannot be suppressed and results in incontinence, usually resulting in bladder emptying (voiding).

3. Detrusor overactivity incontinence is incontinence due to involuntary detrusor contraction.

Other characteristics of DO have also been reported, such as maximum $P_{det}$ during IDC and volume at first IDC.

Subclassifying DO in this way may be valuable in certain circumstances. For example, Kageyama *et al.* (230) showed that OAB symptoms associated with obstruction had a higher likelihood of resolving with intervention (e.g. TURP) when DO occurred as a single terminal IDC rather than continuous or sporadic IDCs.

More recently, Shahab *et al.* (231) investigated the relationship of DO profiles (including the amplitude of DO or the maximum DO pressure, the time to reach maximum DO pressure, the ratio of amplitude to time, the total time of DO, the bladder volume at the first DO, and the $P_{det}$ at the first DO) and DO patterns (terminal vs. phasic), and their correlation with symptoms. The authors retrospectively reviewed the UDS of 231 men with BPE who underwent TURP. Terminal DO was found in 127 patients (55.0%), while phasic DO was found in 104 patients (45.0%). Incontinence absence at DO was found in 104 (45%), while incontinence presence at DO was found in 127 (55%). Multiple DO was found in 83 patients (35.9%), while single DO was found in 148 patients (64.1%). No correlation was found between DO profiles and the severity of symptoms related to OAB. However, the scores of the urgency symptoms were significantly higher in terminal DO than in phasic DO, while the nocturia symptom scores were found to be significantly higher in single DO in comparison to those found in multiple DO. Terminal DO has higher amplitude and duration of DO contraction. The authors postulated that because of this, terminal DO accounts for more severe urgency symptoms, due to activation of sensory afferent nerves by increased $P_{det}$ and duration of contraction. They did not comment on outcomes of TURP.

Bladder compliance describes the relationship between change in bladder volume and change in $P_{det}$. The normal bladder is highly compliant: i.e. during artificial filling, the $P_{det}$ rises by at most 10 or 15 cm $H_2O$, while the bladder is filled to a volume of about 500 mL. If natural filling by diuresis is used, the pressure rise is even smaller. A steeper pressure rise (in the absence of DO) implies abnormally low compliance–a "stiff" bladder wall.

Compliance is calculated by dividing the volume change by the change in $P_{det}$ during that change in bladder volume. It is expressed in mL/cm $H_2O$. A variety of means of calculating bladder compliance have been described. The ICS (4) recommends that two standard points should be used for compliance in most circumstances. Both points are measured excluding any detrusor contraction:

1. The $P_{det}$ at the start of bladder filling and the corresponding bladder volume (usually zero)
2. The $P_{det}$ (and corresponding bladder volume) at cystometric capacity or immediately before the start of any detrusor contraction that causes significant leakage (and therefore causes the bladder volume to decrease, affecting compliance calculation)

Low compliance appears to always reflect pathology, and is well known to be associated with upper tract damage secondary to pressure transmission from the bladder to the kidneys, by reflux or ureteral obstruction. An association between low compliance and urethral obstruction has been reported but is uncertain. While it is known that some patients with obstruction develop impaired compliance and/or bladder decompensation, these events cannot be predicted early on before structural changes occur. Therefore, a critical level of obstruction has not been defined; there are no evidence-based studies to suggest when surgical relief is indicated to prevent bladder decompensation. Leng and McGuire (232) did show that relieving BPO with TURP led to improved bladder compliance in a small cohort of men with BOO and significantly impaired compliance.

What then can be said about the utility of diagnosing DO and impaired compliance in the male with LUTS? This is probably best summarized in the recently published AUA/SUFU UDS guidelines, which state: "Clinicians may perform multichannel filling cystometry when it is important to determine whether DO or other abnormalities of bladder filling/urine storage are present in patients with LUTS, particularly when invasive, potentially morbid, or irreversible treatments are considered."

This guideline is based on expert opinion, as the panel found no relevant studies that met the inclusion criteria regarding the usefulness of cystometry for guiding clinical management in patients with LUTS (174). Even though cystometry is the diagnostic standard for LUTS and some conditions associated with LUTS, it often fails to explain symptoms (233), and the reproducibility of finding DO from one study to another in the same patient can vary whether the studies are performed consecutively or on different days (234). The panel also found considerable variation in studies attempting to determine the usefulness of UDS to help predict prognosis after treatment of LUTS. However, despite that fact that the presence or absence of DO has not been shown to consistently predict specific treatment outcomes, the panel believes that there are instances in which a particular treatment for LUTS might be chosen or avoided based on the presence of DO and (more importantly) impaired compliance, particularly when invasive or irreversible treatment is planned, as it could aid in patient counseling. While there are no data to support or refute this recommendation, the AUA/SUFU UDS Guidelines Panel felt that for many clinicians, the presence of DO or impaired compliance remains an important piece of information in treatment decisions.

## 2.4.3 Pathophysiology of detrusor overactivity and bladder outlet obstruction

It has long been argued that urethral obstruction is responsible for the relatively high prevalence of DO found in men with LUTS, and in particular, for its post-operative decrease. However, the pathophysiological link between obstruction and DO is still not entirely clear and while there is definitely an association between the two, the cause-and-effect link is less clear.

In the previous Consultation, it was noted that the prevalence of DO in men with BOO was 45%–82%, and it was shown that the severity of obstruction correlated with the presence of DO (134,235–236). However, it was also noted that there was a great deal of overlap in obstruction severity (Schäfer grade) between those with and without DO. Also, it has been suggested that in obstructed men with LUTS, the DO may be caused by a neurological response, with activation of C-fibre afferents causing an abnormal voiding reflex (237–238).

Ultrastructurally, it is thought that in response to BOO, detrusor smooth muscle remodels in an effort to increase its force-generating capability. A key aspect of this remodeling is an increase in bladder mass, which is mediated by the hypertrophy of detrusor smooth muscle cells. Therefore, the detrusor becomes overactive, with spontaneous and involuntary contractions.

It has been previously shown that large-conductance voltage- and calcium-activated potassium (BK) channels play a role in DO (239). BK channels work as negative feedback regulators to limit smooth muscle contraction by regulating cytosolic calcium levels. Chang *et al.* (240) using a rabbit model of partial BOO, showed that both BK channel $\alpha$ and $\beta$ subunits were significantly decreased in detrusor

smooth muscle in obstructed rabbits. They also did a small translational study and found that men with BPH and associated DO had significantly less BK channel expression than did men with BPH and no DO, as well as controls. They concluded that obstruction-induced DO is associated with down-regulation of BK channel expression in the rabbit model, and this finding can be translated to human BPH patients with DO.

Recently, several authors have focused on BOO and DO, as well as factors other than obstruction that can cause DO. In a retrospective analysis of UDS on 213 men with LUTS caused by BPE, Aganovic *et al.* (241) found age to be significantly associated with a number of UDS parameters. They divided men into three age groups: <60, 60–69, and ≥70. They found that degree of bladder compliance impairment, incidence of obstruction, DO, and impaired contractility increased with age. Furthermore, decreased bladder compliance was directly linked to aging and obstruction, leading to an increased incidence of DO (from 2.5% with preserved compliance to 22.8% and 74.7%, with varying degrees of impaired compliance in the three age groups; $p<0.0001$). Thus, aging causes the bladder to be less responsive to functional demands (notably in patients with BOO). In these conditions, the bladder may overcompensate, perhaps secondary to muscle hypertrophy, when it over-responds to small volumes of urine by generating insufficient premature contractions. Furthermore, the bladder wall thickens and results in detrusor impairment/inability to empty the bladder efficiently.

Oelke *et al.* (242) reviewed the UDS tracings of 1,418 men who presented with clinical BPH (defined as LUTS, BPE, and/or suspicion of BOO) in men aged 40 years or older in the absence of other diseases that were more likely to have caused symptoms. The overall incidence of DO was 60.9%. In univariate analysis, men with DO were significantly older and more obstructed, and had larger prostates, higher irritative IPSS subscores, a lower voiding volume at free uroflowmetry, and a lower bladder capacity at cystometry. Multivariate analysis showed that age and BOO grade were the only variables independently associated with DO. The prevalence of DO rose continuously with increasing BOO grade, ranging from 51.4% in Schäfer grade 0 to 83.3% in Schäfer grade 4.

Oh *et al.* (243) also argued in favour of an association (and even a cause-and-effect relationship) between BOO and DO. They investigated 193 men with clinical BPH (defined as LUTS, BPE, and/or suspicion of BOO) in men 40 years of age and older. Among these patients, DO was noted in 49 (25.8%) and BOO in 44 (56%). Men with DO tended to be older. The authors noted a positive linear association between BOOI and prevalence of DO, with the prevalence of DO rising continuously with increasing BOOI (correlation coefficient: 0.402, $p=0.001$). On logistic regression analysis, among all clinical and urodynamic parameters, BOOI and maximal bladder capacity were the factors associated with DO, with odds ratios (ORs) of 1.046 and 0.981, respectively.

Blaivas *et al.* (244) performed an observational descriptive study of men diagnosed with OAB (as opposed to LUTS or clinical BPH) based on a previously validated OAB questionnaire who underwent UDS. Of these, 79% percent had DO. While this was a very heterogeneous population of patients seeking treatment, the authors did note that the incidence of true idiopathic OAB was only 5%, and that the most common UDS findings were BPE (32%), BPO (22%), and prostate cancer complications (20%). They concluded that "considering this differential diagnosis intellectually engages the

physician to consider new diagnostic and treatment algorithms that may be more precise and effective." However, this conclusion is not backed up by evidence-based outcomes, and it is not clear whether those treated empirically for OAB symptoms would have fared worse.

In a diagnostically unselected population of patients, Rodrigues *et al.* (245) reviewed the records of 3,830 male patients with LUTS submitted for UDS evaluation. These men did not necessarily have LUTS secondary to presumed obstruction from BPE. In this population, the authors found an inverse relationship between age and obstruction. Detrusor overactivity was diagnosed in 38.4% of the men; in 73.9% of the obstructed cases and 22% of the unobstructed subjects. Detrusor overactivity showed an increasing prevalence with increased age, despite the relative absence of obstruction. The authors concluded that as obstruction diminishes along all age strata, it may mean that DO occurs due to the aging process itself (perhaps related to cerebral aging or functional detrusor disarrangements), rather than due to BOO. They also found that $Q_{max}$ decreased with age and concluded that the findings indicated a progressive decrease in detrusor contractility rather than BOO.

Kuo (246) reviewed the UDS studies of 1,407 men (aged 45–96) referred over a 10-year period with storage and voiding LUTS (based on IPSS) who did not have clinically established BPO. Urodynamic findings included DO in 57.3% (including 5.8% with detrusor hyperactivity with impaired contractility–DHIC), BPO in 29.4%, other functional obstruction in 23.6%, and detrusor underactivity in 10.6%. More than 90% of patients with or without BPO complained of frequency, and more than 80% of patients of both groups complained of a slow stream and straining. Detrusor overactivity was found in 80.9% of patients with BPO, but in only 39.3% of patients without BPO. Conversely, BPO was found in 46.3% of the patients with DO and in 11.5% of those without DO. The authors found that there was increased incidence of BPO, DO, and DHIC with aging, while a hypersensitive bladder and poor relaxation of urethral sphincter were more commonly seen in younger patients.

## Conclusions

The recent literature suggests a strong association of DO with the presence of BPO. However there is a significant population of men with DO without obstruction. One must carefully consider the patient population being studied (i.e. patients with obstruction that is suspected clinically vs. a more general OAB population) prior to drawing conclusions regarding associations between DO and BPO. Age seems to be a risk factor for DO either with or without obstruction.

### 2.4.4 Diagnosing bladder outlet obstruction by pressure-flow studies

#### 2.4.4.1 Introduction

It is now accepted that, although symptomatic management of LUTS is important, BOO associated with BPE (i.e. BPO) is equally important, since it may lead to disease progression and occasionally cause harmful effects on the bladder and the kidneys (247–249). However, it has been emphasized that there are no data to predict which men might develop complications (250). Therefore, assessing BOO is an important part of the evaluation of men with LUTS. The currently accepted gold standard measure of BOO is the PFS of voiding (251). In fact, PFSs are the basis of the definition of obstruction, and therefore remain the only objective means of establishing or ruling it out.

## 2.4.4.2 Pressure-flow studies

for a PFS, vesical pressure (Pves) and Pabd, usually obtained rectally) are measured during voiding, simultaneously with the urine flow rate. The $P_{det}$ is calculated by subtracting Pabd from Pves. The results of three typical studies are shown in **Figures 6**, **7**, and **8**.

**FIGURE 6**

Typical PFS 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 $P_{det}$ should be viewed as artifacts. The green circles mark the $Q_{max}$ and $P_{det}.Q_{max}$.
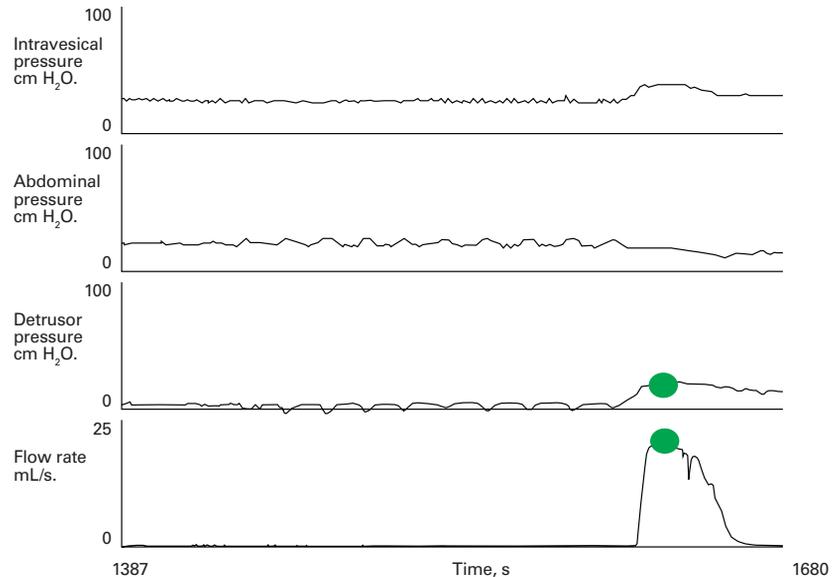
**FIGURE 7**

Pressure-flow study in an obstructed individual. $Q_{max}$ is low and $P_{det}.Q_{max}$ is elevated to over 100 cm $H_2O$ (see red circles), indicating BOO. The negative value of the Pabd before voiding suggests a slight artifact due to incorrect levelling of the transducers.
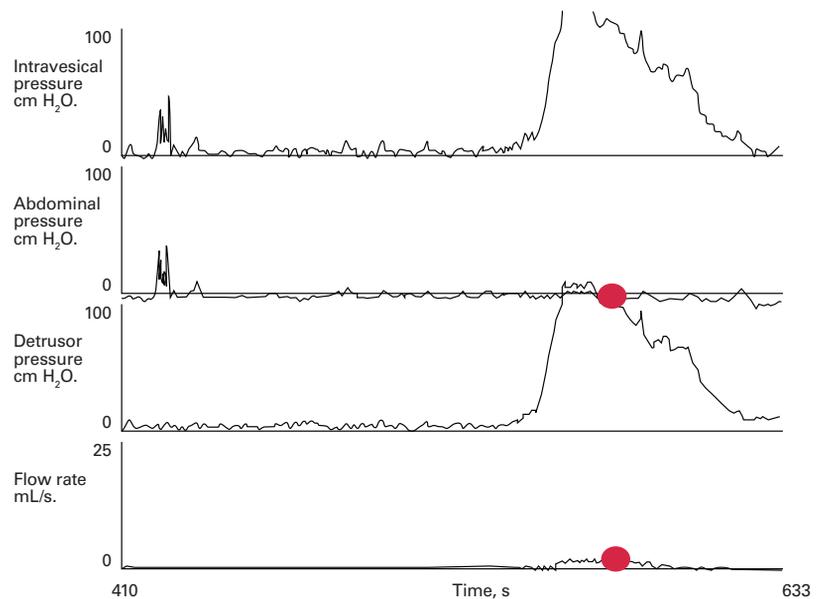
**FIGURE 8**

Pressure-flow study with intermediate values of $Q_{max}$ and $P_{det}.Q_{max}$ (yellow circles). Small rectal contractions are visible in Pabd and therefore also in $P_{det}$ as downward deflections.
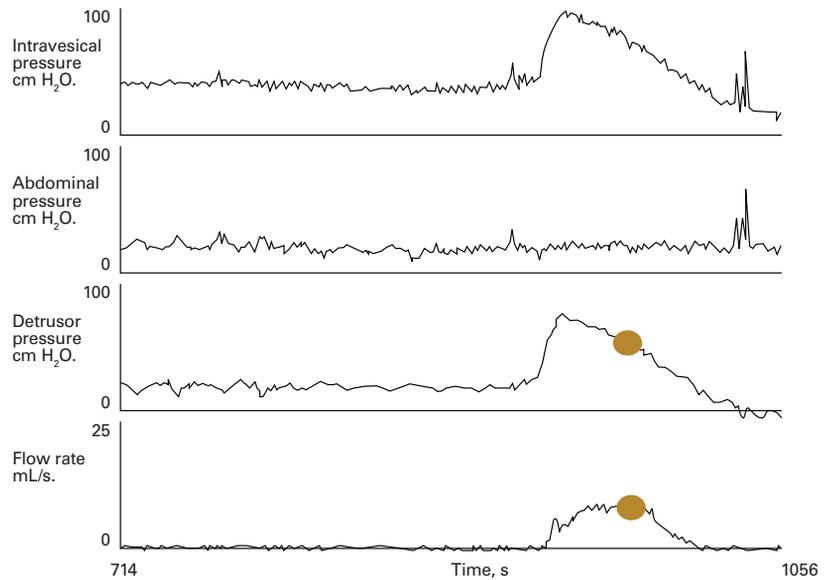


Urethral resistance classes:

- Low $P_{det}$ and normal flow rate = unobstructed
- High $P_{det}$ and low flow rate = obstructed

Detrusor contractility classes:

- Low $P_{det}$ and low flow rate = weak detrusor contraction (detrusor underactivity)
- High $P_{det}$ and high flow rate = abnormally strong detrusor contraction

Numerous ways of quantifying these descriptions have been suggested. The ICS recommends that the ICS nomogram shown in **Figure 9** (251) be used to diagnose both the presence and the severity of BOO in men. A point representing the value of the $Q_{max}$, and the corresponding $P_{det}$ ($P_{det}.Q_{max}$) is plotted on the nomogram, which has three areas: unobstructed, obstructed, or equivocal. The first two areas are consistent with the two urethral resistance classes just described. The third, equivocal area (or grey zone) allows for normal physiological variation and measurement errors. Even when the ICS nomogram is not available, a patient can be placed into one of the three zones by calculating the BOOI (252):

$$BOOI = P_{det}.Q_{max} - 2Q_{max}$$

- Unobstructed: BOOI <20
- Equivocal: BOOI=20 to 40
- Obstructed: BOOI >40

The well-established BOOI cut-off point of 40, defining the boundary between obstructed and equivocal, has had some recent support from a PFS study in 37 younger men (253), which also defined 40 as the upper limit of normality.

**FIGURE 9**

International Continence Society pressure-flow nomogram showing the three pressure-flow curves from FIGURES 6, 7, and 8 (251).
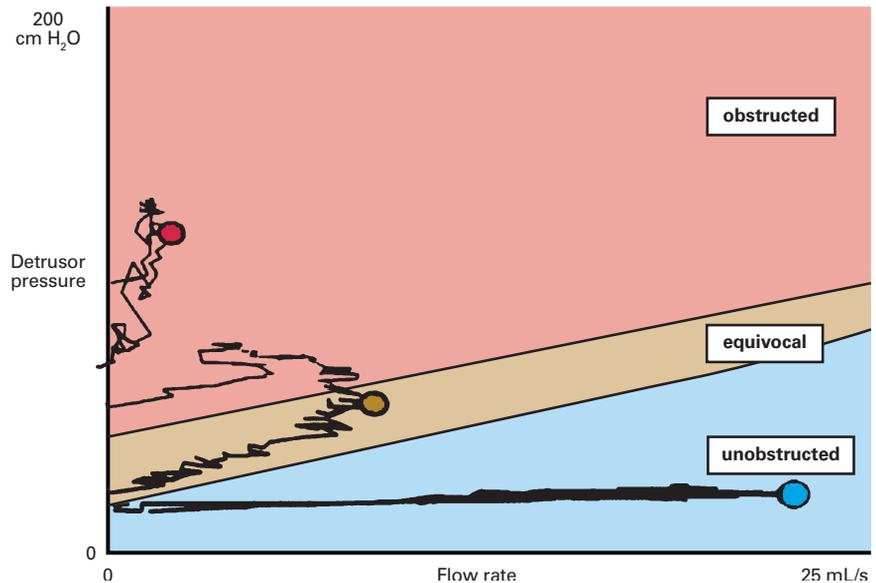
## 2.4.4.3 Reliability of urodynamics in men with lower urinary tract symptoms

In a previous Consultation (254), it was concluded that random variations of about 9–14 cm $H_2O$ in pressure measurement and about 0.4–2 mL/s in $Q_{max}$ occur. In repeated studies during the same session, there is usually a systematic decrease of up to 4 cm $H_2O$ in $P_{det}$ and 0.4 mL/s in $Q_{max}$. 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. It was stated that "a catheter of size 8 French gauge seems to be acceptable." Klausner *et al.* (255) examined the effect of catheter size on assessment of BOO in 31 patients with LUTS suggestive of BPO. Using 5-French (F) and 10-F catheters in random order, they observed that the 10-F catheter caused a decrease in $Q_{max}$ and an increase in $P_{det}.Q_{max}$, indicating a detectable obstructive effect over and above that of a 5-F catheter. On the Abrams-Griffiths nomogram, 10 of the 31 patients (32%) were categorized as obstructed with the 10-F catheter but not with the 5-F catheter. Overall, 17 of the 31 patients went from a less to a more obstructed category when the 10-F catheter was used. The authors' conclusion was that 10 F catheters should be avoided because of their obstructive effect.

More recently, Harding *et al.* (256) compared men catheterized with two catheters (4 and 10 F) with men having an 8-F dual-lumen catheter. While the men with two catheters had a reduction of $Q_{max}$, the $Q_{max}$ in the single catheter group was no different from the $Q_{max}$ at free flow (without any catheter). Therefore, one can conclude that any catheter remaining during the voiding phase should be 8 F or smaller.

Some centres perform PFS with their patients standing, and others with them seated. Unsal and Cimentepe (257) compared flow rates and residual urine in the two positions in 44 men with LUTS suggestive of BPO and 44 healthy men. No 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.

Tammela *et al.* (258) reported on PFS of three consecutive voids in 216 men with symptoms possibly associated with BPO. All were measured with no catheter present in the urethra. The mean value of $P_{det}.Q_{max}$ decreased significantly in successive voids, from 71 to 66 to 63 cm $H_2O$. Correspondingly, the proportion of patients classified as obstructed by the Abrams-Griffiths nomogram fell from 67% to 64% to 59%.

Kranse and van Mastrigt (259), in 131 unselected male patients, observed less pronounced systematic variations from one PFS to the next, but considerable random variability. In 35% of patients, the classification of obstruction based on the ICS nomogram changed between measurements. The authors investigated the possible causes of this variability using 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 PFS was therefore not a disadvantage, but a reinforcement of its importance as the only means to study bladder outlet resistance, detrusor contractility, and their physiological variations. Using PFS 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.* (260) yield an overall accuracy of 83%, and a 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 the editorial comments following the Sonke article [260]).

Two recent studies have reported on the variability in men of other urodynamic variables. Most recently, Hashim *et al.* (261) repeated PFS at an interval of 6 months in 114 men; 81% of whom remained in the same BOO category. Of those whose initial BOOI was 65 or more, all remained in the obstructed group. Indeed, only 5 of the 103 with an initial BOOI of 50 or more changed category to the equivocal group.

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. However, if a man has significant BOO, then the first PFS is completely reliable, and less than 5% of men change category if their BOOI is over 50. If it is clinically important, men with a BOOI of less than 50 should have a second PFS to validate the results of the first.

Some new mathematical approaches to the interpretation of studies of pressure and flow, based on computer manipulation of urodynamic variables, have been proposed (262–263). 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 a more reliable interpretation.

### 2.4.4.4  Detrusor contractility in men with lower urinary tract symptoms

Detrusor contraction strength during voiding (an aspect of detrusor contractility) can be judged from another nomogram suggested by Schäfer (**Figure 10**). On the basis of $P_{det}.Q_{max}$ and $Q_{max}$, it categorizes contraction strength into one of four classes, from very weak to strong (later subdivided to yield a finer gradation). Again, the same classification can be obtained by calculating the bladder contractility index (BCI) (3), also known as projected isovolumetric pressure (PIP); or the detrusor coefficient (DECO), which is almost identical (264).

$BCI=P_{det}.Q_{max}+5Q_{max}$
- Very weak: BCI <50
- Weak: BCI=50 to 100
- Normal: BCI=100 to 150
- Strong: BCI>150

**FIGURE 10**

The voids of Figures 6, 7, and 8 classified for detrusor contractility by the Schäfer nomogram. The position of the maximum flow point (coloured dots) in the four bands indicates the strength of the contraction (VW = very weak, W = weak, N = normal, S = strong). The strengths for these three voids are normal, normal, and weak, respectively.
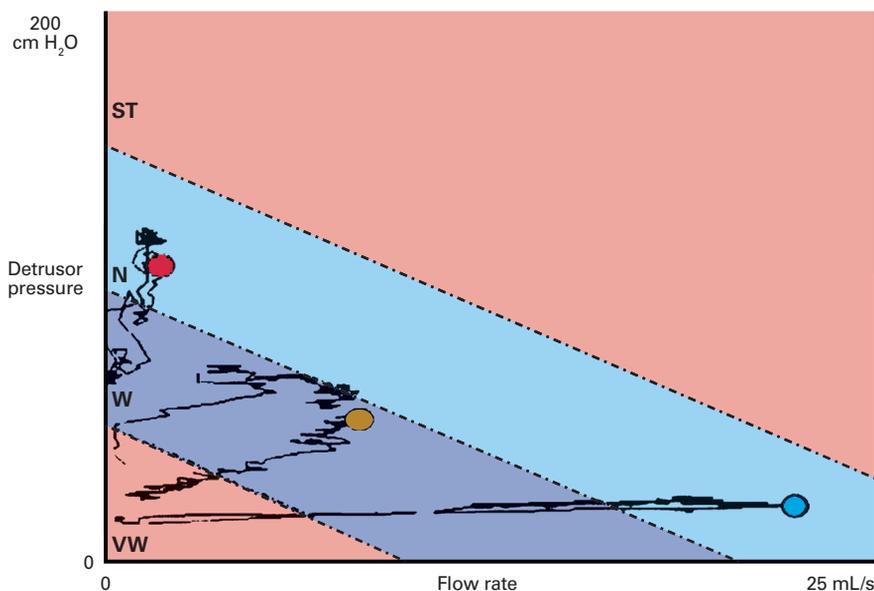


It is now widely recognized that impaired detrusor contractility can cause poor flow rate, incomplete emptying, and corresponding symptoms, even in the absence of urethral obstruction (254,265), and that this is especially likely in the frail elderly (266).

A detrusor contraction of normal strength can produce either a high $P_{det}$ (if there is BOO) or a high flow rate (if urethral resistance is low), but not both at once. A weak detrusor contraction can produce neither a high flow rate nor a high $P_{det}$. Thus, to assess detrusor contraction strength, both pressure and flow rate have to be considered. It is particularly important to understand that a low

$P_{det}$ 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 BCI (3) or DECO (264) during voiding at the moment of maximum flow.

The values of $P_{det}.Q_{max}$ and $Q_{max}$ can be plotted on a nomogram that shows the strength categories (**Figure 10**). Detrusor contraction strength can be estimated more reliably by measuring the isovolumetric $P_{det}$ during a mechanical stop test (264,267) (i.e. by eliminating the possibility of flow altogether); however, a significant proportion of patients are unable to interrupt their flow reliably.

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. Zhang *et al.* (268) 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.* (76) found that among a large series of 2,066 neurologically intact men with LUTS, 224 showed detrusor underactivity (defined as a $P_{det}$ at $Q_{max}$ <40 cm $H_2O$, with $Q_{max}$ <15 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, or that relieving the obstruction surgically improves contractility (74,269).

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

### 2.4.4.5  Why are urodynamic pressure-flow studies not more widely performed?

Despite the above, in many places PFS are not widely performed in routine clinical practice. One reason for this is the perceived invasiveness and morbidity associated with UDS (270). A second reason 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 UDS is low (270–272), although temporary dysuria is common (33% to 76%). Bacteriuria is found in up to 8% of cases, and symptomatic infection in 0.5%–4%. Mild macroscopic hematuria (in 6% of cases) (270) and post-investigational urinary retention (in 5% of men with obstruction) (271) 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.* (273) reported on the expectations and experience of 78 men and 88 women undergoing UDS. Men expected little or no embarrassment, and most (90%) found the test better or the same than they had expected. More older than younger individuals found it better than expected. Thus, the patient population with prostate problems–predominantly older males–is in fact the group that finds UDS the least troublesome.

With respect to the issue of the clinical utility of UDS in men with bothersome LUTS and possible BOO, there has never been a randomized controlled trial (RCT) to compare patients' qualitative and quantitative outcomes in relation to the cost of the procedure. The Health Technology Assessment (HTA) program of the UK's National Health Service (NHS) has recently (in August 2012) requested such a study, which could start in 2013.

## 2.4.5 Relationships between pressure-flow studies and other measurements

### 2.4.5.1 Introduction

Because of the above drawbacks to invasive UDS, 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 the following categories:

- Symptoms and symptom scores
- Ultrasound-derived parameters, including size and shape
- Post-void residual (measured by ultrasound)
- Uroflowmetry
- Non-invasive bladder pressure measurements (via a penile cuff or a condom catheter)
- Near-infrared spectroscopy

What can reasonably be expected of non-invasive surrogate measures of obstruction? Pressure-flow studies themselves are not perfect. Repeated measurements in one subject give quite variable results, especially in patients with an intact nervous system, who constitute 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% (259–260), limiting sensitivity and specificity to about 80% if both are maximized simultaneously.

In this section, the various tests are 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 much 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.

### 2.4.5.2 Symptoms and symptom scores

As the earlier section on LUTS, their etiologies, and their assessment demonstrated, LUTS (and in particular, voiding symptoms) lack any worthwhile specificity for BPO. This has been confirmed in large trials such as the ICS–'BPH' Study (129), and summarized in a previous International Consultation on BPH (254).

Eckhardt *et al.* (134) examined a cohort of 565 men with LUTS suggestive of BPO. Of these, 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 DO 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.

Despite their weak relationship with urodynamic parameters (in particular, obstruction), symptom scores such as IPSS are still useful tools, because they can be assessed easily and non-invasively. 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 under-treatment of patients with BPO or over-treatment of those without it.

## (Level 3, but Grade A due to the large volume of evidence)

### 2.4.5.3 Ultrasonic assessment of the prostate and bladder wall

The ultrasonic assessment of the prostate and bladder wall, and its relationship with urodynamic parameters, is reviewed in Section 2.3.8 – Imaging.

### 2.4.5.4 Post-void residual

Post-void residual 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. Post-void residual can be measured by ultrasound or catheterization. Post-void residual may be elevated due to detrusor underactivity, BOO, or a combination thereof. Thus, an elevated PVR is a non-specific indication of poor bladder emptying. For example, while men with LUTS and BPO may have an elevated PVR, an elevated PVR in isolation does not necessarily predict the presence of obstruction (173).

Post-void residual alone cannot be used to differentiate between obstructed and non-obstructed patients. Furthermore, there is no agreed-upon standard definition of exactly what constitutes an elevated PVR, and the volume of PVR that may be significant has not been established and probably varies by patient according to the intrinsic characteristics of an individual's lower urinary tract. However, it is generally agreed upon that in some patients, an elevated PVR may be harmful. As a result, the 2012 AUA/SUFU UDS guidelines (174) state that clinicians may perform PVR in patients with LUTS as a safety measure to rule out significant urinary retention both initially and during follow-up. This is a clinical principal, and is not made based on evidence-based diagnostic, prognostic, or treatment criteria.

### 2.4.5.5 Uroflowmetry

Uroflow measurement is a non-invasive urodynamic assessment that provides an objective and quantitative indication of the integration of bladder function and the outlet. While an abnormal flow rate is indicative of a dysfunction of the voiding phase of micturition uroflowmetry, like PVR, this measure is limited by its inability to distinguish between a low flow rate due to outlet obstruction, bladder underactivity, or both. Furthermore, obstructed patients with a high $P_{det}$ can maintain a normal flow rate. Uroflowmetry results show considerable variation in $Q_{max}$, whether it is measured on the same day or different days (175).

In males, a variety of studies have shown variability in the diagnostic accuracy of uroflow for detecting BOO ranging from moderately high to low (176–181). This reported variability may be due to a variety of factors. The specificity of $Q_{max}$ 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 a $Q_{max}$ less than 15 mL/s were 38% and 82%, respectively (181). Thus, this value of $Q_{max}$ is too non-specific to be useful. For a $Q_{max}$ <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.

Smaller single-centre studies have suggested a higher specificity (up to 90%) for this value of $Q_{max}$, in particular with multiple flows (180,182–183). However, for uroflowmetry to play a part in the diagnosis of BOO/BPO, the measurements need to be multiple. In this circumstance, the Level 2 Evidence allows a Grade B recommendation for the reliable diagnosis of BOO, but only when $Q_{max}$ is less than 10mL/s. The AUA/SUFU UDS Guidelines Panel (174) concluded that "although the literature fails to specifically identify clinical scenarios when uroflowmetry is useful, the test has value in the evaluation of disorders of voiding, even if further testing is required to make a specific diagnosis. Uroflowmetry can also be used for monitoring treatment outcomes and correlating symptoms with objective findings."

This leads to the following guidelines statement: "Uroflow may be used by clinicians in the initial and ongoing evaluation of male patients with LUTS that suggest an abnormality of voiding/emptying."

**Recommendation:** Grade C

### 2.4.5.6 Non-invasive urodynamic pressure measurement

The principle underlying techniques to assess voiding pressure in a non-invasive manner 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 two 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.

### Condom catheter method

For the external condom method (274), the patient voids through a condom catheter. At maximum flow, the catheter is blocked and the isovolumetric pressure is measured. The best data obtained for this method showed an overall accuracy of 90% for diagnosing BOO, (275–276) but only when the obstructed and equivocal groups on ICS nomogram were combined. On the comparative PFS, the accuracy of agreement is only 67% for the ICS obstructed group alone (277), a value that should be compared with accuracies of 82% to 83% for PFSs themselves.

### Penile cuff

The penile cuff is a flexible inflatable cuff that is placed around the shaft of the penis (278). Two methods of use have been suggested: the deflation technique and the interruption technique.

For the deflation technique (279), 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 1 mL/s is detected by the flowmeter, the cuff is deflated rapidly.

For the interruption technique, an automatically inflated penile cuff is used to interrupt the flow after voiding has commenced (280). 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 UDS showed that the isovolumetric $P_{det}$ was reliably estimated by this method, although the mean cuff pressure over-estimated the bladder pressure by $14.5 \pm 14$ cm $H_2O$ (280). The test-retest variability was 0 (SD: 20.3 cm $H_2O$) in patients with a voided volume of at least 150 mL (281), and inter-observer agreement in the analysis of the results has been shown to be good (282).

In conclusion, in spite of technical pitfalls (283) and the fact that it measures intravesical pressure and not $P_{det}$, non-invasive urodynamic 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). However, it remains unclear whether the extra complication required is worth the relatively small improvement in diagnostic accuracy over uroflowmetry.

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**No recommendation yet possible**

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### 2.4.5.7  Near-infrared spectroscopy

Near-infrared spectroscopy measures changes in chromofore concentration using infrared light. It measures the concentration of two chromofores: oxyhemoglobin and deoxyhemoglobin. During normal, unobstructed voiding, there is a rise of oxyhemoglobin and deoxyhemoglobin, called reactive hyperemia. When there is outlet obstruction, there is less hyperemia, as the concentration of oxyhemoglobin and deoxyhemoglobin lowers.

Two recent studies compared NIRS to conventional PFS with contradictory results. Stothers *et al.* (188) found a relationship between obstruction in urodynamic studies and NIRS, while Chung *et al.* (189) concluded that the NIRS algorithm is still not clinically useful, because it does not correlate strongly enough with obstruction. This may relate in part to standardization and technology. Hence, more studies are needed to evaluate this technique.

### 2.4.5.8  Combinations of single measures

Because of the shortcomings of individual non-invasive parameters for diagnosing BOO, many different combinations have been investigated.

$Q_{max}$ and total PV can be used to estimate BOOI (284). Data from 384 men suggest that estimated BOOI = antilog10($2.21 - 0.5\log Q_{max} + 0.18\log PV$). In 42% of the population, an estimated BOOI index of greater than 40 showed a sensitivity of 92% for obstruction or equivocal obstruction. Using $Q_{max}$ alone provided a sensitivity of 86% for predicting BOO, but could be used in only a minority of the study population (17%).

The combinations of AUA-SI score and $Q_{max}$ with the highest specificity for BOO were determined in 134 patients (285). With $Q_{max}$ <10 mL/s and AUA-SI score >20, specificity and sensitivity for obstruction were 98% and 38%, respectively. Conversely, with $Q_{max}$ >15 mL/s and AUA-SI score <10, specificity for no obstruction was 98%, but sensitivity was only 22%. Only 20% of the population studied were categorized as obstructed or unobstructed using this approach. If PV (>40 g) was added to the algorithm (286), specificity increased to 100%, but sensitivity remained only 26%, and the population diagnosed remained low, at 20%.

$Q_{max}$, PV and relative residual volume (PVR volume as a percentage of pre-void bladder volume) can be used to calculate a BOO number (BOON) as follows (287):

BOON=PV (from TRUS, in mL) − $3Q_{max}$ + (0.25 × relative residual volume). In a population of men with LUTS, the majority of whom were obstructed on UDS, a value of BOON >−2 diagnosed 50% of men with BOO (Schäfer grade ≥2), with a sensitivity of 90%. However, for Schäfer grade ≥3 (equivalent to obstructed on the ICS nomogram), the discrimination between obstruction and no obstruction disappeared. The equation was later refined (288) to use voided volume instead of relative residual volume.

$Q_{max}$, PV, and PVR have been combined in a simple categorical nomogram to determine the probability of obstruction (133). This method has not been validated in an independent set of patients.

$Q_{max}$, PV, PVR, and voided volume (289) were measured in 871 elderly patients and used to obtain a clinical score (in which $Q_{max}$ 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.

$Q_{max}$, flow pattern, PVR, PV, 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 (178). 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 UDS to determine the presence of BOO. The generalizability of the results to non-Asian populations is uncertain.

Intravesical prostatic protrusion and Doppler ultrasound appear to offer high sensitivity and specificity for obstruction. Intravesical prostatic protrusion and Doppler ultrasound were recently compared with PFS in 30 patients (290). The combination of these parameters, with the same cut-off values, gave a sensitivity of 100% (5/5), with a specificity of 91% (10/11) (290). These impressive values were 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 PFSs 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. These values require independent testing and confirmation in a larger population.

Intravesical prostatic protrusion and detrusor wall thickness (DWT) have recently been used in combination to predict BOO. Using trans-abdominal ultrasound, Franco *et al.* (184) measured IPP and DWT in 100 patients with LUTS. All patients with an enlarged median lobe were excluded; thus, only obstruction due to lateral lobe enlargement was evaluated. All patients were assessed with a blinded PFS. The ultrasound examination was done with a bladder volume of approximately 200 mL.

A combination of IPP >12 mm and DWT >7 mm was used to reliably predict obstruction. If one of these investigations was positive, there was a 90% probability of finding obstruction in a PFS. If both investigations were negative, the likelihood of finding no obstruction was 66%. The authors noted that ultrasound investigations are highly operator dependent. Since IPP and DTW are dependent on bladder filling, bladder volume needs to be standardized for future tests. Furthermore, the thickness of the bladder mucosa and musculature increases when a patient has an infection or urinary bladder malignancy.

## 2.4.6 Clinical utility of non-invasive measurements

Of the many non-invasive parameters currently available for assessing obstruction in patients with LUTS, which are the most clinically useful? Only a few achieve both a high specificity and sensitivity for BOO. 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 a large prostate, low $Q_{max}$, and severe symptoms); but for these, such methods represent no improvement over clinical experience.

As was stated in the previous Consultation, further research is required to provide evidence that these methods will reduce the need for PFS. Moreover, to be clinically useful, a 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. 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 UDS, still require the attendance of the investigator. Moreover, the current non-invasive urodynamic methods are no more accurate than is 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 are maintained in wider practice. With ultrasound readily available in clinics, enabling tests such as those listed above to be performed, the need for UDS before surgical intervention may be reduced to patients with obstruction that remains equivocal after non-invasive (ultrasound) assessment. However, it must also be realized that many of the more specialized ultrasound techniques described in various studies were performed by one operator to exclude variations between operators, but in a urological outpatient clinic, the results will vary among urologists (291). Thus, these methods must be validated for use by clinicians in practice.

A number of distinct measurement techniques have also been published, using BWT, DWT, or UEBW. As a result, different threshold and reference values were established, causing confusion. In a report by the International Consultation on Incontinence–Research Society, Oelke (292) proposed that for the purpose of quality control, all future reports should provide information about the

frequency of the ultrasound probe; bladder filling volume at measurement; whether BWT, DWT, or UEBW was measured; the enlargement factor of the ultrasound image; and one ultrasound image with marker positioning.

## 2.4.7 When is obstruction clinically significant?

In the previous section, we focused on the non-invasive diagnosis of obstruction, ultimately defined 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 QOL, obstruction (if not relieved in time) may lead to disease progression and affect organ function. In less-developed parts of the world, obstruction still leads to mortalities.

Until recently, attention was paid only to the back pressure effects of obstruction on the kidneys. More recent studies have suggested that BOO affects bladder function, leading to structural changes as well. Because these changes may eventually become irreversible, some argue that management should be directed at early relief of significant obstruction (247–249). However, as pointed out above, there are no data to suggest that patients can be readily identified as being at risk of BOO complications (250).

Bates *et al.* (293) reported on 93 men with a PVR of >250 mL who were treated conservatively because of comorbidity, lack of symptoms, or refusal of surgery. These men were followed for an average of 5 years (range: 3–10 years). The PVR was unchanged or decreased in 80%; only two patients experienced rising serum creatinine, seven developed acute retention, and 14 had worsened symptoms. The authors commented that conservative treatment could be justified as long as proper follow-up was carried out. They also could not predict which patients would deteriorate from baseline data.

When is the level of obstruction clinically significant? Is the ICS definition of obstruction, based on PFS, clinically significant? If the BOOI is >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 PFS, the results of surgical relief are not as good (76,294). Indeed, patients can usually be reassured that there is unlikely to be significant deterioration in their voiding function over the medium term. Thomas's work in both patients with BOO (75) and those with detrusor underactivity (74) showed that those who received no surgical treatment for more than 10 years (mean of 13 years), experienced no overall deterioration and came to no harm.

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. 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 UDS 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. There are no natural history data indicating that storage function is affected by BPO, except when BPO leads to a significant PVR with increased frequency, and nocturia with voiding of small volumes.

Suitable tests are:
- Measurement of voided volume; this can be done easily and non-invasively by asking patients to keep a voiding diary
- Measurement of residual urine
- Ultrasound of kidneys to look for hydronephrosis

Patients with pronounced obstruction may occasionally have bilateral hydronephrosis, and because they do not have bothersome symptoms, seek treatment late. Unfortunately, measurement of serum creatinine is not sensitive enough to detect this complication until the kidneys have lost significant function. As surgeons, we must detect this complication early, and the best clinical tool is trans-abdominal ultrasound. In less-developed countries, chronic retention of urine with bilateral hydro-nephrosis (and impaired renal function in about 6% of cases) is still a common urological problem (250). However, this argument would logically demand screening of the entire older male population, which is likely to remain impractical.

### Summary
We do not know what severity of BOO is dangerous and will inevitably lead to complications. Current guidelines mandate physical examination, which should detect a PVR of >250 mL but only if the man is slim; if he isn't, then abdominal ultrasound is useful in measuring PVR and excluding hydronephrosis.

## 2.4.8 Urodynamics in prostate cancer

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 centres among different patient populations. It is usually suggested that the possible abnormalities are similar to those seen in men with LUTS associated with BPH: BOO and DO. The age ranges of the patients are usually similar (though quite wide). In a study of urine flow rates (295), among 125 men examined prior to radical retropubic prostatectomy (RRP) for prostate cancer, 38% had a $Q_{max}$ of 10 mL/s or less. Dubbelman *et al.* found a median pre-operative $Q_{max}$ of 8.4 mL/s (interquartile range: 6.2–11.6 mL/s) in 66 men before RRP (296).

Data from studies in men with LUTS (see above) suggest that the majority (about 90%) of the 38% who have a $Q_{max}$ of 10 mL/s or less likely have BOO caused by an enlarged prostate. A direct assessment of obstruction by invasive urodynamic measurements prior to RRP was performed by Dubbelman *et al.* They found that the median value of the urethral resistance factor (URA)–an

obstruction parameter–was 29.0 (interquartile range: 19.8–37.5 cm $H_2O$) (296). With a reported URA cut-off value of 29 cm $H_2O$ (297–298) as an indicator of obstruction, this indicates that about 50% of the men were urodynamically obstructed before RRP. The median value of URA dropped to 16.5 cm $H_2O$ (interquartile range: 10.5–28.5 cm $H_2O$), indicating that at least 75% were unobstructed following RRP (296).

The incidence of DO during filling cystometry has been noted in several studies. Constantinou and Freiha (224) examined 29 patients, with a mean age of 63 years, prior to surgery for prostate cancer. Of these, 16 patients (55%) demonstrated DO, with quite high maximum $P_{det}$ (mean ± SD: 59 ± 28 cm $H_2O$). Golomb *et al.* (225) reported on 20 patients with a diagnosis of prostate cancer. Detrusor overactivity with $P_{det}$ exceeding 15 cm $H_2O$ was demonstrated in 12 of the 20 patients (60%). Kleinhans *et al.* (226) studied 66 patients in the week before surgery for prostate cancer. Detrusor overactivity was observed in 21 of the 66 (32%). Aboseif *et al.* (227) evaluated 92 men (mean age: 64 years) prior to prostate cancer surgery; 19 of them (21%) showed DO. Hammerer *et al.* (228) examined 82 patients pre-operatively. Detrusor overactivity was observed in 14 of the 82 (17%). Song *et al.* reported DO in 38% before RRP (299). Giannantoni noted a relatively high prevalence of DO, at 61.2% (300). Dubbelman *et al.* (296) performed urodynamic studies in 66 men before and after RRP and found pre-operative DO in 26%.

The incidence of pre-operative DO seems to average between 25% and 30% in the above-mentioned studies. This is similar to what would be expected in age-matched men with and without LUTS who do not have prostate cancer.

There are relatively few systematic prospective studies on urodynamic evaluation after cancer treatment. The majority of studies have focused mainly on the changes produced by surgery, or on the risk and mechanism of incontinence. Among the few urodynamic data available, there are no consistent urodynamic parameters that predict post-treatment continence or incontinence.

A study by Kumar *et al.* (301) suggested that, among a group of 50 men with prostate cancer and moderate or severe LUTS pre-operatively, there were significant improvements post-operatively in $Q_{max}$ (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 eight men with mild LUTS (16% of the group), the symptomatic improvement was much less.

Constantinou and Freiha (224) found that, in 13 post-operative patients, the $Q_{max}$ was 13 ± 2 mL/s and maximum voiding $P_{det}$ was 39 ± 4 cm $H_2O$. These values are within normal ranges, suggesting that the most severe outlet obstruction had been removed by surgery.

Montorsi *et al.* (302) found that, in 150 patients after radical prostatectomy, mean maximum uroflow was 16.9 ± 1.3 mL/s and PVR was 11 ± 2 mL. A total of 22% patients were still obstructed post-operatively, by a stricture in 12% and because of denervation in 10%.

Dubbelman *et al.* saw $Q_{max}$ increase from 8.4 mL/s (interquartile range: 6.2–11.6 mL/s) to 11.9 (interquartile range: 6.9–20.0 mL/s) at 6 months after RRP, whereas the median PVR decreased from 15 mL (interquartile range: 0–86 mL) to 0 mL (interquartile range: 0–30 mL) (296).

According to Masters and Rice (295), among 125 men, mean $Q_{max}$ post-operatively was 17 mL/s, rising to 24 mL/s at 20 months. This high value suggests that urethral obstruction had 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.* (303) performed UDS pre- and 3 months post-treatment by external beam radiotherapy in 15 patients. This therapy caused no significant change in BOO, although there was a significant decrease in PVR. Henderson *et al.* (304) found that 27 out of 100 patients had to use a catheter after prostate brachytherapy treatment or suffered AUR. This seems to have been due mainly to urethral obstruction (new or pre-existing) post-treatment.

### 2.4.8.1 Incontinence after radical prostatectomy and radiation

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 also 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% (305), depending on the surgical technique, the definition of incontinence and how it is quantified (306–307), who performs the evaluation of the incontinence (physician or patient) (308–309), and (because of spontaneous improvement) the time between the surgery and the evaluation. However, at 12 months post-surgery, the prevalence of incontinence is probably about 15%–20% (310).

Jacobsen *et al.* (311) prospectively compared incontinence rates for laparoscopic vs. open radical prostatectomy performed by 10 surgeons using a relatively strict definition of incontinence: a 24-hour pad test greater than 8 g. This RCT found no significant difference in incontinence rates at 1 year between the two procedures (17% vs. 13%). But importantly, this study provides a prospective assessment of the risk of relatively strictly defined incontinence, which seems to be about 15% after 1 year. However, it should be noted that even this definition does not strictly identify all men who are completely dry (i.e. those who are strictly continent in the way they were continent before the procedure).

It is also important to note that many studies report post-operative continence at 1 to 2 years. We now know that for some men, continence may deteriorate over time. In a study of 1,213 men, Penson *et al.* (312) showed that the percentage of men with frequent urinary leakage or no control peaked at 6 months, decreased to 10.4% at 24 months, then increased to 13.9% at 60 months. This would seem to be important information for patients considering surgery.

More recently, robotic-assisted laparoscopic radical prostatectomy (RALP) has become the most popular procedure. However, it has become clear that patients who undergo RALP are more likely to be regretful and dissatisfied than are men who undergo open RRP; possibly because of higher expectations about this innovative high-tech procedure (313).

In a study of 953 patients after RALP, one of the factors that independently predicted decisional regret was post-operative continence, as categorized by the use of 0, 1, or ≥2 pads daily. Patients who required a daily safety pad were significantly more regretful of their decision than patients who were completely dry. Post-operatively, strict continence (i.e. completely dry) was achieved in 73% of the 703 responders to the questionnaires, and in 60% of the 250 non-responders. In this study, strict continence was therefore achieved in 68.4% (314).

Henderson *et al.* (304) reported no incontinence after radiation/brachytherapy treatment in a total of 100 patients. Choo *et al.* (315) reported that four 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.

Chen *et al.* (316) reported on 36-month functional outcomes after nerve-sparing radical prostatectomy, non–nerve-sparing radical prostatectomy, external beam radiotherapy, and brachytherapy; 43%, 58%, 18%, and 17%, respectively, of the men with normal baseline function who underwent these procedures reported UI.

The true incidence of incontinence and voiding dysfunction after external beam radiotherapy and brachytherapy must take into account the morbidity associated with the occurrence and treatment (i.e. TURP) of BOO after radiation therapy. About 3% of men undergoing brachytherapy are catheter dependent early after the treatment and about half of these will remain catheter dependent or need TURP as a late complication (317). Those who have larger prostates (>50 cm$^3$) have a three-fold higher risk for obstructive complications, even if the PV has been reduced by androgen deprivation before brachytherapy is given (318). Of those needing TURP to relieve obstruction, 11%–70% will develop UI (319).

Androgen deprivation alone is also associated with UI. In a recent systematic review, Wilt *et al.* found that urine leakage one or more times per day was reported in 35% of men after radical prostatectomy, in 12% after radiotherapy, and in 11% after androgen deprivation (320). Perhaps androgen deprivation causes apoptosis of the external sphincter, leading to incontinence.

### 2.4.8.2 Can pre-operative urodynamics predict post-operative continence and lower urinary tract symptoms after radical prostatectomy?

It seems that pre-operative DO is not a predictor of incontinence or other LUTS after radical prostatectomy. However, there are very few studies that have systematically performed UDS before and after radical prostatectomy in a large enough group of men. Golomb *et al.* (225) showed that among 12 out of 20 patients who demonstrated DO pre-operatively, only two manifested urgency incontinence pre-operatively, and five complained of urgency incontinence post-surgery. Five of the original 20 had mild stress incontinence. There was no significant association between pre-operative DO and post-operative incontinence.

Hammerer *et al.* (228), examined 82 patients pre- and post-operatively. Detrusor overactivity increased to 41% after surgery, from 17% pre-operatively. Do *et al.* (303) and Choo *et al.* (315) performed UDS pre- and post-radiotherapy in 15 patients. There were no significant changes in DO. In fact, the amplitude of DO can remain quite high post-operatively (mean: 49 cm H$_2$O) (224). Kleinhans *et al.*

(226) examined 44 patients at a mean of 8 months after radical prostatectomy, out of 66 examined pre-operatively. Of these patients, 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. Dubbelman *et al.* performed a multivariate logistic regression analysis of prognostic factors for persisting incontinence after radical prostatectomy and found no statistically significant predictors among maximum bladder contractility (Wmax) ($p=0.215$), cystometric capacity ($p=0.563$), URA ($p=0.561$), the presence of DO ($p=0.073$), and bladder compliance ($p=0.073$) (229). Therefore, no pre-operative bladder function parameters predicted post–radical prostatectomy incontinence.

Urethral pressure measures done pre-operatively do not seem to consistently predict continence after radical prostatectomy. Hammerer *et al.* (228) did show that maximum urethral pressure decreased in 82 patients, from a pre-operative mean of 90 cm $H_2O$ to 65 cm $H_2O$ post-operatively. John *et al.* (321) measured a number of urodynamic parameters in 34 patients pre- and post-operatively. Maximal urethral closure pressure (MUCP) was $49 \pm 10$ cm $H_2O$ pre-operatively and was reduced significantly after radical prostatectomy. Furthermore, at 6 weeks it was significantly lower in incontinent patients ($11 \pm 9$ cm $H_2O$) than in continent patients ($35 \pm 6$ cm $H_2O$); at 6 months, the corresponding figures were $23 \pm 6$ cm $H_2O$ and $42 \pm 9$ cm $H_2O$, respectively.

Rudy *et al.* studied 14 patients pre- and post-RRP, and surprisingly found no mean decrease in MUCP, but did find a 63% decrease in functional profile length (FPL) (322). Dubbelman *et al.* prospectively examined urethral pressure profiles (UPPs) in 66 men undergoing RRP, and found that those who were incontinent 6 months after the surgery had a median MUCP of 49.7 cm $H_2O$ (interquartile range: 42.7–58.7 cm $H_2O$), while those who were continent 6 months after RRP had a significantly higher median MUCP of 66.2 cm $H_2O$ (interquartile range: 57.9–76.0 cm $H_2O$) ($p=0.001$). The authors also noted that after RRP, the MUCP and FPL decreased by 41% and 64%, respectively (296).

These observations show that damage to the urethral striated sphincter decreasing MUCP and FPL is prominent even in patients who are continent post–radical prostatectomy. Those with low pre-operative values run a greater risk of not regaining continence after the radical prostatectomy.

Several authors have reported on imaging parameters that may predict post-operative continence after radical prostatectomy. Konety *et al.* (323), in a cohort study of 2,000 men, reported an association between ultrasound-measured PV and recovery of continence. However, others (324–326) have not noted such an association. Von Bodman *et al.* (326) did report that longer membranous urethral length and higher membranous urethral volume may be associated with a more rapid recovery of continence (measured at 6 and 12 months). They suggested that parameters such as these determine further exploration.

### 2.4.8.3 Mechanism of post-operative incontinence

Incontinence encountered after treatment of prostate cancer may be due to sphincter dysfunction, bladder dysfunction, or a combination of both. A number of studies have explored this. Most have studied incontinent patients, but a few have compared continent and incontinent patients. For example, Presti *et al.* (327) noted a shorter FPL (2.1 vs. 3.6 cm, $p<0.001$), a lower MUCP (39 vs. 74 cm $H_2O$, $p<0.001$), and a lower MUCP during strain (107 vs. 172 cm $H_2O$, $p<0.002$) in incontinent

vs. continent patients after radical prostatectomy. Detrusor overactivity was only weakly associated with incontinence. John *et al.* (321) showed a decrease in MUCP after prostatectomy, with an even lower MUCP in incontinent vs. continent men.

As stated above, Dubbelman *et al.* noted that after RRP, the MUCP and FPL decreased by 41% and 64%, respectively. The authors also noted that of those who were continent after 6 months, 68% had a pre-operative MUCP above the median value for the entire group (i.e. 53.1 cm $H_2O$), while only 40% of the incontinent men had an MUCP above this value (296).

These comparisons of incontinent and continent patients suggest that intrinsic sphincter deficiency is a major contributor to post-prostatectomy incontinence.

The majority of the literature is based on urodynamic observations in incontinent patients only (although some patients are difficult to classify because the authors use terms that are non-standard or use terms in non-standard ways). These studies showed that the prevalence of urodynamic stress incontinence ranges from 88% to 100%.

While bladder dysfunction in terms of DO or impaired compliance is common (26%–35%), it is rarely found as the sole cause of incontinence (3%–7%) (328–333). Ficazzola and Nitti (331) also showed that the symptom of stress incontinence had a 95% positive predicative value and a 100% negative predicative value for the diagnosis of urodynamic stress incontinence.

These studies all suggest that sphincter dysfunction is the predominant cause of post–radical prostatectomy incontinence, and that detrusor dysfunction (DO or low bladder compliance) is rarely the sole cause, but can exacerbate its severity. However, it must be realized that the cohorts studied may have been selected (for example) for pre-operative UDS prior to surgery and may over-represent the true prevalence of sphincter vs. bladder dysfunction.

Three studies have shown a relatively high incidence of impaired bladder contractility or detrusor underactivity in men after radical prostatectomy. Groutz *et al.* (332) found that 82% of men with post-prostatectomy incontinence had evidence of impaired contractility on UDS. Chung *et al.* (334) found the prevalence to be 49%. They also found that 48% of men voided by Valsalva. Similarly, Chao and Mayo (328) found that 42% of post-prostatectomy incontinent men voided by Valsalva and did not have a detrusor contraction on UDS.

It is not clear however, that these men truly have impaired contractility (presumed to be a result of surgery) vs. a testing artifact, and the fact that many of these patients can void by Valsalva may contribute to the over-diagnosis of detrusor underactivity. Indeed, Dubbelman *et al.* recently showed that detrusor contractility, as determined by the parameter Wmax, did not change significantly as a result of radical prostatectomy (229). Another recent retrospective study showed no increased risk of post-operative urinary retention after slings in men with a urodynamic diagnosis of impaired contractility; it should be noted, however, that selection bias cannot be ruled out, due to the retrospective nature of this study (335).

### 2.4.8.4 Does urodynamics predict outcomes of stress incontinence surgery?

While few would argue that empiric treatment of urgency incontinence with behavioural therapy and/or pharmacological treatment is unreasonable, the treatment of sphincter dysfunction usually requires surgery after conservative therapy fails. Most experts feel that it is important to rule out conditions such as impaired compliance prior to artificial urinary sphincter or sling placement. Dubbelman *et al.* found that the prevalence of impaired compliance (<20 mL/cm $H_2O$) increased from 12% pre–radical prostatectomy to 18% post-operatively (229).

Three studies have shown that the demonstration of bladder dysfunction, even impaired compliance on UDS prior to artificial urinary sphincter placement, does not negatively impact outcomes (336–338). In addition, one small study of 16 men with bladder dysfunction (339) demonstrated improvement in bladder capacity and compliance and a reduction in DO after artificial sphincter placement. Ballert and Nitti (340) also showed that men with DO did not have worse outcomes of sling procedures than did those without DO.

Some have argued that impaired detrusor contractility or bladder underactivity may be a risk factor for urinary retention after sling procedures, as Valsalva voiding may not be possible after sling placement. However, Han *et al.* (335) found no statistically significant difference in post-operative PVR (at a mean 4 months post-operation), urinary retention, or overall outcomes in men with impaired contractility (BCI <100), or in those who voided by Valsalva vs. those with normal contractility prior to sling placement. The authors concluded that the UDS findings of impaired contractility or Valsalva voiding may not represent true bladder function. In spite of these considerations, temporary urinary retention is seen in 5%–36% of men treated with a male sling, with sling over-tensioning and sling malposition being the main causes (341).

## 2.4.9 Recommendations: what urodynamic study should be done and when?

UDS in Patients with LUTS Suggestive of BPO
- Pressure-flow studies remain the only means of establishing or ruling out the presence of BOO (Grade A).
- Non-invasive methods of assessing obstruction are not yet able to fill that role, although some may ultimately be able to do so.
- The filling phase of micturition should also be assessed, as symptomatic DO may have a bearing on the outcome of treatment (Grade C).
- Patients being submitted to TURP, with its attendant risks, should have a definitive diagnosis of outlet obstruction (Grade B).
- If PFSs are not planned prior to invasive treatment, then the patient should be made aware of the diagnostic limitations of uroflowmetry (Grade B).
- In the research setting, PFSs 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.

UDS in Patients with Prostate Cancer (Pre- and Post-Treatment)

- Until RCTs are available, comprehensive UDS should be considered if there is UI that persists for >6 months after surgical treatment of prostate cancer and does not respond to conservative management/treatment in a patient who is considering more invasive treatment. The aim should be to determine the type of incontinence (e.g. urodynamic stress incontinence) and any exacerbating factors (e.g. DO) (Grade C).
- Periodic monitoring of urine flow during the recovery period post-surgery may help in early detection of stricture (Grade D).

# 2.5 Predicting Outcome after Therapy

Several reports have been published since the previous International Consultation on Male LUTD held in 2005, evaluating predictors of outcomes in patients undergoing virtually every kind of therapy for male LUTS.

We performed three literature searches in April 2012 using the MEDLINE database.

The searches included a free-text protocol using the following terms:

1. [Male LUTS OR benign prostatic hyperplasia] AND [watchful waiting OR active surveillance OR conservative management]
2. [Male LUTS OR benign prostatic hyperplasia] AND [dutasteride OR finasteride OR tamsulosin OR alfuzosin OR terazosin OR silodosin OR doxazosin OR tadalafil]
3. [Male LUTS OR benign prostatic hyperplasia] AND [TURP OR HoLEP OR PVP OR simple prostatectomy OR laser]

The records of all the papers published after 2003 were screened, identifying 321 records with search #1; 2,064 records with search #2, and 2,784 records with search #3. All of these abstracts were screened, identifying 284 papers suitable for the purpose of this review. After evaluation of the full-text publications of those 284 papers, 47 papers were used for this chapter.

## 2.5.1 Watchful waiting

Watchful waiting is an appropriate strategy for the treatment of patients with uncomplicated, not bothersome, mild or mild-to-moderate LUTS.

Prior literature, already summarized in the 2005 report of the International Consultation on Male LUTD, suggested a role for PSA as a predictor of the need for invasive surgery for BPH (342).

In a secondary analysis of the placebo arm of the MTOPS study involving 737 men, with a mean follow-up of 4.5 years, Crawford *et al.* evaluated several baseline factors as predictors of clinical progression (170). The authors found that total PV ≥31 mL was associated with a significantly higher

risk of BPH progression ($p<0.0001$), a significantly greater worsening over time of AUA-SI ($p=0.001$), a significantly greater risk of AUR ($p=0.034$), and a significantly greater need for invasive surgical treatment ($p=0.0005$) relative to that of subjects with baseline total PV <31 mL.

Similarly, patients with a baseline PSA ≥1.6 ng/dl had a significantly higher risk of clinical progression ($p=0.0009$), a significantly greater worsening over time of AUA-SI ($p=0.028$), a significantly greater risk of AUR ($p=0.003$), and a significantly greater need for invasive surgical treatment ($p=0.018$) compared with patients with PSA ≤ 1.5 ng/dl.

With regard to $Q_{max}$ at uroflowmetry, the same study demonstrated that patients with a baseline $Q_{max}$ <10.6 mL/s had significantly higher risk of BPH progression ($p=0.011$), greater worsening over time of AUA-SI ($p=0.005$), and a significantly greater need for invasive therapy ($p=0.033$) than did those patients on placebo with a $Q_{max}$ ≥10.6 mL/s.

Finally, the same study demonstrated that PVR volume ≥40 mL was associated with significantly greater risk of BPH progression ($p=0.0008$), a significantly greater worsening over time of AUA-SI ($p=0.003$), and a significantly greater need for invasive therapy ($p=0.004$) compared with patients on placebo with <40 mL PVR (170). However, all these observations were made using univariate analyses, whereas multivariate models evaluating the independent predictors of BPH progression, worsening of symptom index, AUR, and surgical therapy for LUTS were lacking.

In a secondary analysis of the Alfuzosin Long-Term Efficacy and Safety Study (ALTESS), a large, randomized, double-blind, placebo-controlled, parallel-arm 2-year RCT that randomized more than 1,500 patients to either alfuzosin 10 mg or placebo, Roehrborn evaluated predictors of ≥4 points IPSS worsening, AUR, and BPH-related surgery in the patients randomized to placebo (343). The study demonstrated that severe baseline symptoms (adjusted hazard ratio–HR: 0.64), and baseline PVR >93 mL (HR: 2.04) were significantly associated with IPSS worsening, whereas baseline PSA >3.9 ng/mL was associated with the need of surgery (HR: 5.95). Conversely, none of the evaluated covariates was associated with AUR (343).

There is Level 3 Evidence that higher PSA, higher PV, lower $Q_{max}$, and higher PVR predict failure with watchful waiting.

## 2.5.2  Drug treatment

Alpha-blockers, 5-alpha-reductase inhibitors, and their combinations are all standard treatments for uncomplicated bothersome LUTS. Moreover, anti–muscarinic receptor antagonists, alone or in combination with alpha-blockers, may be used in patients with predominant storage LUTS. Finally, although not yet widely used, a phosphodiesterase type 5 inhibitor (tadalafil 5 mg) has recently been approved for treatment of male LUTS in patients with or without concomitant erectile dysfunction.

With regard to alpha-blocker therapy, in the same secondary analysis of ALTESS cited above, Roehrborn also evaluated predictors of outcome in the patients randomized to alfuzosin10 mg (343). The study identified only baseline patient age ≥65 years as an independent predictor of IPSS

worsening (HR: 1.6), whereas non-statistically significant trends were demonstrated for baseline symptoms and PVR as predictors of IPSS worsening; for PSA, PV, and baseline PVR as predictors of AUR; and for symptoms as predictors of need for surgery (343).

Further data on the outcome prediction in patients undergoing alpha-blocker monotherapy come from a study of alfuzosin once daily (ALF-ONE), a prospective study enrolling more than 3,500 men with LUTS of all severity treated with alfuzosin 10 mg once daily for 6 months (344). After 6 months of treatment, about 0.7% of the patients experienced AUR and 1.3% had BPH-related surgery. The authors found that prior history of AUR (HR: 6.3; $p<0.01$), and ≥4 points IPSS worsening during treatment (HR: 3.3; $p=0.03$) were independent predictors of AUR.

Similarly, history of AUR (HR: 3.2; $p<0.01$), and symptom worsening during treatment (HR: 2.5; $p<0.01$) were associated with AUR and/or need for surgery (344). In both cases, neither patient age, nor baseline PSA, nor baseline IPSS was found to be associated with outcome during treatment, likely due to the low number of events observed during the short follow-up duration.

Similarly, a further extended analysis of the ALF-ONE dataset on more than 6,500 patients reconfirmed the role of prior AUR (HR: 10.6; $p<0.001$) and symptom worsening on IPSS (HR: 3.7; $p=0.003$) as predictors of AUR, and of prior AUR (HR: 3.5; $p=0.002$), baseline IPSS (HR: 2.0; $p=0.01$), and IPSS worsening (HR: 4.7; $p<0.001$) as predictors of surgery. Bother score >3 during treatment was the strongest predictor of surgery (HR: 7.61; $p<0.001$) (345).

More data are available on the effect of IPP on outcome in patients on alpha-blockers. Specifically, IPP was measured during TRUS as the vertical distance from the tip of the protrusion to the circumference of the bladder at the base of the prostate gland (290). In a small series of South Korean patients with LUTS treated with tamsulosin 0.2 mg, Park *et al.* found that IPP was an independent predictor of IPSS improvements (OR: 0.2; $p=0.044$) and $Q_{max}$ improvements (OR: 0.79; $p<0.001$), once adjusted for the effect of PSA, PSA density, baseline PSA, baseline $Q_{max}$, total PV, and TZ volume (346).

With regard to 5-alpha-reductase inhibitors, interesting data were provided by a cumulative analysis of two phase 3 RCTs enrolling more than 4,200 patients with moderate to severe symptoms, PV of at least 30 mL, and PSA ranging from 1.5 to 10 ng/mL, treated with dutasteride or placebo for 2 years (347). On the whole, 6.8% of the patients randomized to placebo experienced AUR or surgery. Benign Prostatic Hyperplasia Impact Index (HR: 1.35; $p=0.008$), prior therapy with alpha-blockers (HR: 1.58; $p=0.001$), PV (HR: 1.29; $p=0.001$), PSA (HR: 1.35; $p=0.002$), $Q_{max}$ (HR: 0.6; $p=0.001$), and therapy with dutasteride (HR: 0.5; $p=0.001$) turned out to be independent predictors of AUR or surgery. Based on these variables, the authors provided a nomogram able to predict 2-year risk of AUR or BPH-related surgery (347). Unfortunately, external validation of that nomogram is still pending.

No evidence is available regarding predictors of failure during therapy with anti–muscarinic receptor antagonists or phosphodiesterase type 5 inhibitors.

There is Level 3 Evidence that baseline patient age, IPSS, BPH Impact Index, PSA, PV, PVR, prior history of AUR, ≥4 points IPSS worsening, and bother score >3 during treatment may predict failure from medical therapy with alpha-blockers or 5-alpha-reductase inhibitors.

There is Level 4 Evidence that IPP may predict failure of medical therapy with alpha-blockers.

No evidence is available regarding predictors of failure during therapy with anti–muscarinic receptor antagonists or phosphodiesterase type 5 inhibitors.

### 2.5.3 Trial without catheter after acute urinary retention

It is now widely accepted that administration of an alpha-blocker increases the success rate of a trial without catheter (TWOC) in men with BPE after a first episode of AUR. That clinical practice is supported by several RCTs that demonstrated that alpha-blocker therapy before TWOC significantly increased patients' ability to void successfully (348–352). Specifically, meta-analysis performed by the National Institute for Health and Clinical Excellence (NICE) panel for LUTS guidelines demonstrated that use of alpha-blockers significantly increased the probability of successful voiding (risk ratio: 1.3; $p=0.003$) and reduced the risk of recatheterization (risk ratio: 0.79; $p=0.05$) as compared to placebo (216).

Recent literature provides insights on the predictors of successful TWOC. Specifically, in a prospective, multi-institutional international survey that enrolled more than 6,000 patients with AUR, it was demonstrated that patients' age at AUR (<70 years vs. ≥70 years; OR: 0.73; $p<0.001$), type of AUR (precipitated vs. spontaneous; OR: 0.7; $p<0.001$), amount of drained urine (<1,000 mL vs ≥1,000 mL; OR: 0.62; $p<0.001$), use of alpha-blockers before TWOC (OR: 1.92; $p<0.001$), LUTS severity before AUR (severe vs. mild; OR: 0.61; $p<0.001$), and PV (≤ 50 vs. >50 g; OR: 0.63; $p<0.001$) were all independent predictors of successful TWOC (353).

In a small prospective study, Mariappan *et al.* evaluated the role of IPP as a predictor of the outcome of TWOC. The authors found that patients with successful TWOC had lower PV (55 vs 70 mL, $p=0.012$) and lower IPP (7.2 vs. 16.5 mm, $p<0.001$), with IPP having a higher area under the curve than PV in ROC curve analysis (354). However, a formal multivariate model was not reported.

In a secondary analysis of an RCT evaluating the efficacy of alfuzosin 10 mg in TWOC, McNeill found that PSA measured 1 month after TWOC and post-TWOC residual volume were predictors of AUR relapse (HR: 4.2; $p=0.0095$ for PSA; and HR: 1.01; $p=0.0035$ for post-TWOC residual volume) and need for BPH surgery (HR: 2.7; $p=0.0125$ for PSA; and HR: 1.009; $p=0.009$ for post-TWOC residual volume) (351).

There is Level 1 Evidence that alpha-blockers are efficacious in improving the probability of successful voiding and reducing the risk of recatheterization following TWOC.

There is Level 3 Evidence that lower age at AUR, type of AUR, lower volume of drained urine, lower LUTS severity before AUR, and lower PV were all independent predictors of successful TWOC.

There is Level 3 Evidence that PSA measured 1 month after TWOC and post-TWOC residual volume were predictors of AUR relapse and need for BPH surgery.

There is Level 4 Evidence that IPP is associated with successful TWOC.

### 2.5.4 **Surgical treatment**

Trans-urethral resection of the prostate has historically been the most widely performed surgical treatment for patients with moderate to severe LUTS secondary to BPH, and for patients with BPH-related complications, and it is still the surgical procedure with the most solid long-term evidence of efficacy, based on studies with follow-up durations longer than 10 years (75,355). However, over the previous decade, several surgical procedures have been proposed as alternatives to TURP, in order to reduce the morbidity of the procedure, especially in patients with a large prostate or at high risk of bleeding. These alternative include bipolar TURP, trans-urethral holmium laser enucleation of the prostate (HoLEP), and photoselective vapourization of the prostate (PVP).

Given that TURP is such an established and standardized treatment, the number of relevant publications addressing predictors of outcome has been quite limited since the previous International Consultation on Male LUTD. Publications summarized in the Consultation's prior report clearly demonstrated that the patients who benefit most from TURP are those with unequivocal BOO and normal detrusor contractility (356–357). However, Masumori *et al.* recently reported the 12-year outcome in a small series of 93 patients treated with TURP. The authors observed that although there was a gradual deterioration with time, improvements in IPSS were similar for patients with and without BOO, and with and without detrusor underactivity (355), demonstrating that TURP may provide a long-term benefit regardless of pre-operative urodynamic findings. However, the study is limited by its small sample size, which might have made the statistical analysis underpowered. Similarly, van Venrooij *et al.* showed that grade of obstruction was slightly associated with patients' symptoms and poorly predicted TURP outcome (358).

Conversely, detrusor contractility was associated with the presence of storage LUTS following TURP. Seki *et al.* studied 298 patients with BOO treated with TURP, and demonstrated that baseline degree of detrusor contractility was an independent predictor of ≥50% improvement over the pre-operative measurements of urgency, frequency, and nocturia (OR: 2.16–9.52; $p<0.005$) (359).

Park *et al.* evaluated the ratio of resected tissue in comparison with the prostate TZ volume as predictor of outcome in a series of 263 patients undergoing TURP. About 68% of the patients had a resection ratio >50% (i.e. the volume of the resected tissue was >50% of the TZ volume), whereas 32% had a ratio <50%. Six months after surgery, IPSS and $Q_{max}$ improvements were similar regardless of the resection ratio, suggesting (in the opinion of the authors) that complete prostate adenoma resection may not be essential (360). However, the study is limited by its short follow-up duration, and it might be hypothesized that larger significant differences might have been identified with longer follow-up.

With regard to HoLEP, Shah *et al.* evaluated the influence of PV on outcome in a series of 354 patients, stratified into three groups according to PV (≤ 60 mL vs. 60–100 mL vs. >100 mL). At the 12-month follow-up, HoLEP had resulted in a 75% decrease in the mean AUA-SI score (from 19.35 to 4.77), a 225% increase in the mean $Q_{max}$ (from 7.86 to 17.70 mL/s), and an 86% decrease in mean PVR (from 142.7 to 19.5 mL). Although some minor differences were present in the outcomes across the three groups, the observed improvements were comparable, demonstrating that prostate HoLEP can be performed with similar efficacy across the spectrum of PV, and that PV was not a factor in determining success (361).

Anderson *et al.* compared the outcome of HoLEP in patients presenting with and without AUR (362). The outcome of 31 patients with AUR undergoing surgery was compared with that of 56 patients without AUR, and similar improvements in AUA-SI and QOL score were seen in both groups during the first year after surgery (362).

With regard to PVP, several studies have evaluated the impact of PV on surgical outcomes. In a secondary analysis of an RCT comparing 120-Watt PVP with monopolar TURP, Capitán *et al.* found that PV (categorized as $\leq$ 50 mL vs. >50 mL) was not associated with differences in improvement in 24-month IPSS, QOL scores, or $Q_{max}$ among PVP and TURP groups, suggesting that the two procedures were similarly effective regardless of PV (363).

Ruszat *et al.* analyzed a series of 500 patients treated with 80-Watt PVP and evaluated at a mean follow-up duration of 30.6 months. They demonstrated that 1-, 2-, 3-, 4-, and 5-year improvements in IPSS score, QOL score, $Q_{max}$, and PVR were similar in patients with PV <40 mL, PV ranging from 40 to 80 mL, and PV >80 mL, although the prevalence of some complications (i.e. hematuria, dysuria, and bladder neck strictures) varied across groups (364). Similar findings were demonstrated in other smaller series involving 80-Watt PVP (365–366).

On the other hand, Otsuki *et al.*, in a series of 400 Japanese patients treated with 80-Watt PVP, found that greater improvements were observed in patients with larger prostates at similar reduction ratios. A larger absolute reduction of volume in patients with larger prostates (categorized as <30 mL vs. 30–50 mL vs. 50–70 mL vs. >70 mL) was associated with greater improvement in IPSS, QOL score, $Q_{max}$, and PVR (*p*<0.01) (367).

Regardless of baseline PV, prostate configuration (i.e. the presence of a median lobe) was also evaluated in a small series of patients treated with 120-Watt PVP, demonstrating similar improvements in AUA-SI, QOL score, and PVR in patients with and without a median lobe (368).

Prior AUR and the presence of an indwelling catheter at the moment of PVP were also evaluated as predictors of surgical outcome. In the above-mentioned secondary analysis of an RCT comparing 120-Watt PVP with monopolar TURP, Capitan *et al.* found that a prior indwelling catheter was not associated with differences in improvements in 24-month IPSS, QOL scores, or $Q_{max}$ among PVP and TURP groups, suggesting that the two procedures were similarly effective regardless of prior AUR (363).

Similarly, Ruszat *et al.* compared the outcome of 70 patients with refractory urinary retention and an indwelling catheter undergoing 80-Watt PVP to that of 113 patients without urinary retention before surgery, demonstrating similar complication rates and 24-month efficacy with regard to $Q_{max}$, IPSS, IPSS-QOL, and PVR in the two subgroups of patients (369).

The predictive role of some urodynamic parameters was evaluated in PVP patients. Choi *et al.* compared the outcome of 239 patients with BOO to that of 132 men with BOO and detrusor underactivity, both treated with 120-Watt PVP. In both groups, the procedure was significantly effective, with similar improvements in IPSS, $Q_{max}$, and PVR observed during the first year after surgery in both groups (370).

Monoski *et al.* evaluated a small group of 40 patients with pre-operative complete urinary retention or large PVR (>400 mL) treated with PVP. Of these patients, 30 (75%) had DO and eight (20%) had detrusor underactivity. The patients without pre-operative DO had a significantly lower IPSS than did those with pre-operative DO at 1 month of follow-up only, whereas no differences were observed in the 3-, 6-, or 12-month data. Similarly, patients without pre-operative detrusor underactivity had significantly better IPSS and PVR volume at 1 month of follow-up only, whereas no differences were observed in 3-, 6-, or 12-month data. However, $Q_{max}$ at the 1- and 6-month follow-ups in men with pre-operative detrusor underactivity was significantly lower than it was in men without (371). On the whole, these data indicate that the presence of pre-operative DO or detrusor underactivity may affect the outcomes of patients with pre-operative urinary retention undergoing PVP.

## Summary

The predictive parameters for the outcome of the various therapies for LUTS suggestive of BPH are summarized in **Table 2**. The following evidence summary applies to the invasive treatments TURP, HoLEP, and PVP.

### TURP

- There is controversial evidence concerning the effect of BOO and normal detrusor contractility on TURP outcome.
- There is Level 4 Evidence that resection ratio (i.e. volume of the resected tissue/TZ volume) does not affect short-term outcome following TURP.

### HoLEP

- There is Level 4 Evidence that PV and prior AUR do not affect short-term outcome following HoLEP.

### PVP

- There is Level 3 Evidence that PV and prior AUR do not affect short-term outcome following PVP.
- There is Level 4 Evidence that the presence of a median lobe does not affect short-term outcome following PVP.
- There is Level 4 Evidence that the presence of detrusor underactivity does not affect short-term outcome following PVP.
- There is Level 4 Evidence that the presence of detrusor underactivity and DO may affect short-term outcome following PVP in patients with large PVR or complete urinary retention.

**TABLE 2** Overview of parameters that have been shown to predict outcome after therapy

| Treatment | Parameters | Predictive ability |
|---|---|---|
| Watchful waiting | PSA, PV, $Q_{max}$, PVR | Predictors of failure |
| Medical treatment | Baseline patient age, IPSS, BPH Impact Index, PSA, PV, PVR, prior history of AUR, ≥4 points IPSS worsening, bother score >3 during treatment | Predictors of failure with alpha-blocker or 5-alpha-reductase inhibitor therapy |
| | IPP | Predictor of failure with alpha-blocker therapy |
| TWOC after AUR | Age at AUR, type of AUR, amount of drained urine, LUTS severity before AUR, PV, IPP | Predictors of TWOC success |
| | PSA at 1 month after TWOC, post-TWOC PVR | Predictors of AUR relapse and need for BPH surgery |
| Surgical treatment | Baseline degree of detrusor contractility | Predictor of TURP outcome |
| | Detrusor underactivity and DO | May affect PVP outcome in patients with pre-operative urinary retention |

# 2.6  Research Directions

1. Conservative treatments such as behavioural modification, including self-management of fluid intake and lifestyle changes, have been used in the management of male LUTS. What are the predictive parameters for the success or failure of this type of treatment?

2. Combination medical therapies have become more popular. What are the predictive parameters of treatment success for combination therapy with alpha-blockers + anticholinergics or alpha-blockers + 5-alpha-reductase inhibitors?

3. Clinical data suggest that no single parameter can accurately predict the outcome of a specific therapy. Is it possible to construct well-validated, useful nomograms based on multiple independent parameters to predict the probability of success or failure in surgical therapies? Few nomograms have been proposed.

4. Design a validated FVC.

5. What is the reliability and compliance of an FVC in relation to the duration of the FVC?

6. With respect to the issue of the clinical utility of UDS in men with bothersome LUTS and possible BPO, an RCT needs to be done to compare patients' quantitative and qualitative outcomes in relation to the cost of the procedure. (Such a study could start in 2013 in the UK.)

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# C3

# Nocturia

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# CONTENTS

## Nocturia

# 3.1 Introduction

This chapter focuses on nocturia in men. As much of the published evidence reports populations of both genders, nocturia in women is also discussed in this chapter, where it illustrates principles relevant to male lower urinary tract symptoms (LUTS). The full scope of peer-reviewed professional research literature was examined, and evidence was weighted to enable recommendation gradings according to the system of the International Consultation on Urological Diseases (ICUD) (1).

# 3.2 Evidence Base

Nocturia is a symptom that reflects a diverse spectrum of clinical conditions, with many individuals potentially affected by more than one relevant condition. It is characterized by idiosyncratic response, with nocturia of equivalent severity producing very different effects on quality of life for different people. Speed of progression of nocturia is likely to influence propensity to present for medical consultation; implicitly, slower progression will enable coping adaptations that ameliorate bother, the latter being the ultimate arbiter of whether medical opinion is sought. Speed of progression is difficult to capture, as are other crucial influences, such as contextual environmental influence, personality trait, and coping strategies, and thus the complex interplay between severity and bother remains unclear.

Measuring nocturia is a challenge. Day-by-day variation, habitual differences between work and non-work days, and temporal fluctuation over extended time periods hamper the reliable capture of a severity score. The terminology needs to not only be straightforward and manageable, but also deal with varied circumstances, such as shift workers (for whom nocturia may be a daytime event). Correspondence between retrospective subjective impression and actual severity of nocturia is implicitly unreliable–and probably influenced by bother level. Objective measurement by frequency volume chart (FVC) is perceived to be onerous (though in reality, the burden to the patient is probably overestimated). Crucially, science has yet to validate a tool for measurement of "reason for waking" (i.e. whether the person woke because they needed to pass urine, or passed urine having woken because of another cause) and "intention" (e.g. the person wanted to go back to sleep after a void but could not, or was in bed to sleep rather than to read). As the current International Continence Society (ICS) definition (1,2) of the symptom of nocturia includes a reason ("waking to void") and an explanatory note which includes intention ("prevents the individual from getting back to sleep as he/she wishes"), the measurement of nocturia unavoidably requires pragmatic compromise.

Furthermore, the medical priority accorded to nocturia does not reflect the potential seriousness of possible underlying conditions. Many physicians disregard nocturia occurring on average once per night, stating that it does not bother the patient or represent a health risk. This is probably a mistake, as it is a state that has progressed from no nocturia, and may continue to progress to bother the patient subsequently. Thus, nocturia once per night might represent an opportunity for screening and instigation of measures to prevent progression to bothersome nocturia. There is merit to ascertaining severity thresholds above which nocturia becomes clinically significant or below

which adequate therapeutic benefit can be claimed. However, it is essential that these are defined for specific populations and not extrapolated to all patients. For example, a threshold value for a healthy working person is likely to differ from that of a healthy older person or someone with neurological disease where multiple causes of sleep disturbance may be present.

All these provisos must be remembered when evaluating the nocturia literature. As the most widespread symptom tool used in male LUTS–the International Prostate Symptom Score (IPSS)–includes nocturia, which is the subject of a single question, number 7. Studies using IPSS question 7 as their primary outcome measure, rather than a specific symptom-assessment tool, and which do not use a FVC, cannot be accorded the same weight as those that use tools properly validated for nocturia and define the pathophysiological basis. Even with the greater strength of proper assessment, inability to capture the issues alluded to above mandates caution in interpreting results.

The extensive evidence base concerning nocturia is reflected in this chapter, but much of it fails to meet contemporary standards for high-quality evidence. Despite evident difficulties of conducting high-quality trials in nocturia, some studies have delivered valuable data for some patient groups, compensating for the considerable placebo response in LUTS management and going some way to addressing the complex influences. However, until the quality of research is raised to an adequate level, it is hard to envisage reliable treatment response becoming the norm for one of the more difficult-to-manage LUTS. When some of the interventions are potentially morbid, a strong case for their use is needed; without scientifically rigorous evaluation, such interventions should be avoided.

# 3.3 **Terminology**

The Standardisation Committee of the ICS has standardized relevant definitions (see **Table 1**) (2–4). The symptom of nocturia is the complaint that the individual has to wake at night one or more times to void. This definition does not include any reference to bother; many physicians regard nocturia once per night as not being clinically significant. However, some people can be substantially bothered by nocturia once per night, and the potential for symptom progression or a serious underlying medical condition means that a single episode of nocturia per night may have more importance than it is often given credit for.

"Nighttime" in this context relates to the hours of sleep–with adjustment needed for people with atypical sleep patterns, such as shift workers. Nocturia frequency includes only those voids preceded and followed by sleep. Thus, the first morning void after a night's sleep is counted toward diurnal frequency rather than nocturia.

**TABLE 1** Terminology of nocturia standardized by the ICS (3).

| Term | Definition |
|---|---|
| Nocturia | The number of voids recorded during a night's sleep: each void is preceded and followed by sleep |
| Nocturnal urine volume | Total volume of urine passed during the night including the first morning void |
| Nocturnal polyuria | Nocturnal volume >20–33% of total 24-hour volume (age dependent) |
| Polyuria | 24-hour voided volume of >2.8 L in a 70-kg adult (>40 mL/kg) |
| Night | The period of time between going to bed with the intention of sleeping and waking with the intention of rising |
| Nighttime frequency | The number of voids recorded from the time the individual goes to bed with the intention of sleeping, to the time the individual wakes with the intention of rising |
| First morning void | The first void after waking with the intention of rising |
| Maximum voided volume | The largest single voided volume in a 24-hour period |
| Nocturnal enuresis | Voiding occurring during sleep |

The nocturnal urine production is given by adding the first morning void to the nocturnal voided volume. It is the nocturnal urine production which determines the diagnosis of nocturnal polyuria (NP). The ICS Standardisation Committee defined NP as nocturnal urine production exceeding 20% of 24-hour output in younger adults and 33% in older adults (2). Alternative criteria for NP include nocturnal diuresis of greater than or equal to 0.9 mL/min (5), or nocturnal urine volume exceeding 10 mL/kg (6). The functional reservoir capacity of the lower urinary tract and the nocturnal urine production can be linked using a nocturia index (Ni) derived from an FVC (7). Ni in excess of 1.0 indicates that nocturnal urine production exceeds the largest voided volume, such that the need to pass urine overnight will be inevitable.

Nocturnal enuresis signifies voiding while remaining asleep and, technically, should be considered part of the nocturnal voided volume, though difficult to quantify in practice. Nocturnal enuresis does not count as nocturia, as the patient fails to wake when passing urine, but it clearly has to be factored into any evaluation of LUTS and nocturnal urine production. The terminology in current use necessarily involves some compromise (8,9), and the area is one in which debate and consensus is ongoing.

# 3.4 **Epidemiology**

In general, epidemiological research focuses on prevalence, incidence, impact, and risk factors of a certain condition or phenomenon. This Nocturia Epidemiology section explores most epidemiological aspects of nocturia, including: 1) prevalence of nocturia (including impact of age, sex, race/ethnicity, and socio-economic status on prevalence); 2) incidence of nocturia ("natural history"); and 3) impact of nocturia. Other risk factors are covered in the Nocturia Pathophysiology section.

Epidemiological research on male LUTS has previously focused on situations described as being "suggestive of benign prostatic hyperplasia (BPH)." During the last decade, however, nocturia has been recognized as a clinical entity in its own right, and there is a growing interest in nocturia (10–12). In general, the definition of a condition is a crucial factor in the evaluation of its epidemiology; nocturia is no exception (13). Several definitions, with minor differences, exist for nocturia (11,14,15). According to the ICS, nocturia belongs to "urinary storage symptoms." The ICS defines nocturia as "the complaint that the individual has to wake at night one or more times to void…each void is preceded and followed by sleep" (11). Other definitions with marginal differences have been published (14,15). However, it has been suggested that if the definition needs to address the issue of sleep following the void, it may be the intention of going back to sleep after voiding which might be more clinically relevant (16). Overall, these definitions are conceptually easy to use, but their detailed specificity makes them challenging to apply in practice. Furthermore, they lack the consideration of bother, impact, or severity. Hence, they do not elaborate the point at which nocturia becomes clinically meaningful, and worth evaluation and treatment (17,18). A single nighttime void would meet criteria for nocturia by these definitions (11,14,15), and yet there is a lack of evidence that it is suitable criterion for general clinical purposes (19). Nonetheless, a single episode of nocturia should not be disregarded if the patient reports he is adversely affected.

## 3.4.1 **Prevalence**

Estimates for nocturia prevalence have varied, mainly due to methodological differences in symptom assessment and definitions, populations, and data collection methods (13,18,20). Earlier studies, most of them conducted among elderly men, found that nocturia is a very common symptom in the elderly population (21-29), and that the prevalence increases with aging. These findings have been confirmed in comparative studies conducted in both men and women with wide age ranges (17,20,30–33,34–37) (see **Figure 1**).

In the population-based Finnish National Nocturia and Overactive Bladder (FINNO) study, approximately one of eight men (and women) aged 18–79 years reported at least 2 voids per night. Furthermore, as one-third reported 1 void per night, approximately 40% reported at least 1 void per night (17). Young women had more nocturia compared with young men. Prevalence equalized only after middle age, and in the oldest age groups, nocturia in men exceeded that in women (17). For instance, at ages 70–79 years, approximately 44% of men and 34% of women voided at least twice per night (20). Many other recent studies have supported these findings of a higher prevalence for nocturia among young women than young men, and an equalization of prevalence in middle age

(30–35). As the gender difference has been found across different continents (Europe, Asia, Australia, North America), it is unlikely due to a specific country, lifestyle, climate, or culture (17,20,30–37). The reasons for the excess of nocturia among older men remain unknown.

The community-based Krimpen study conducted in the Netherlands among elderly men (38) is one of the few studies where nocturia was longitudinally assessed by voiding diaries and FVCs. Averaged from information on 2 to 3 nights, one and a half (1.5) or more voids per night was present in 60% of men aged 70–78 years, and at least 2.5 voids per night was present in 20%. These proportions are comparable with questionnaire studies. Most elderly people void at least once per night (18) (see **Figure 1**).

**FIGURE 1**

Prevalence of at least 2 voids per night across age groups by sex in population-based studies conducted among both sexes with wide age range [17, 30-34, 36, 37]. All population-based studies assessing prevalence of nocturia in adults of both sexes were reviewed. To identify these studies, a PubMed search (articles published before September 2012) was carried out with the strategy ((nocturia. mp) and ((prevalence.mp)). Population-based (including community-based) studies published in English and conducted among both sexes with a wide age range (at least 40 years) which reported percentage data were included.
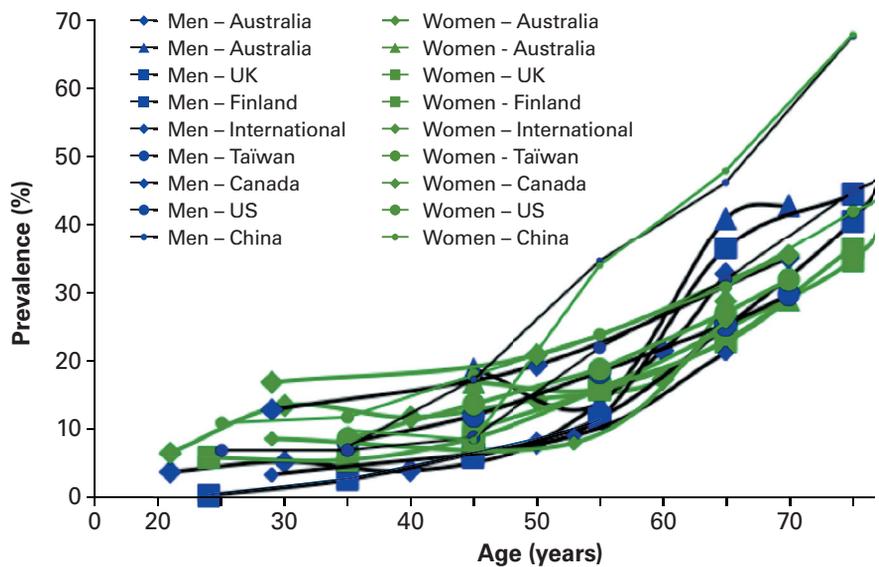


In several US studies, black men were observed to report nocturia more often than other ethnic groups (39–42). This effect persisted, although attenuated (39,40), after adjusting for comorbidities and socio-economic status. Similar effects were reported for women participating in the Boston Area Community Health (BACH) Survey (43), and the Penn Ovarian Aging Study (44), with black women being almost twice as likely to report nocturia even after multivariable adjustment. In an Internet-based survey in the US (42), nocturia (≥2 voids/night) was reported by 20% and 25% of white men and women, 25% and 27% of Hispanic men and women; and 29% and 37% of black men and women, respectively. In secondary care–seeking populations (45,46), black women also reported more nocturia. However, although most US studies found differences between different ethnic groups in prevalence for nocturia, conflicting results were found in a Kaiser Permanente study (47). Much less is known about the relationship between ethnicity and nocturia outside the US.

In small studies in Taiwan (48,49) and Scotland (50), associations between nocturia and ethnicity were found. In the Scottish study, the prevalence of NP was significantly higher in Caucasian men compared with Asian men.

Why might some ethnic groups have more nocturia than others? Are earlier studies limited in their ability to measure confounding factors? Indeed, in most studies, many of the potentially causal factors of nocturia, such as sleep apnea, remained unmeasured. Furthermore, in the recent Internet-based study, response rates were highest among whites and lowest among blacks (42). Earlier research has shown that lower response rates are related with higher prevalence estimates (51,52). Overall, the underlying mechanisms for the possible association of nocturia with race/ethnicity remain unknown.

## 3.4.2 **Incidence**

Not much is known about the incidence and natural history of nocturia (12). This is probably due to several reasons, including: 1) longitudinal studies are more difficult to perform than cross-sectional studies; and 2) there is uncertainty about the definition of "incident nocturia" (53–55) and about the appropriate time interval for repeated sampling (56). The fluctuation of nocturia contributes to these uncertainties (57), and as research into nocturia is relatively young, it is unsurprising that only few longitudinal studies exist (11).

In a community-based study among elderly people (conducted in 1983–1984 in the US) (58), participants were seen in their homes, and nocturia was assessed during the baseline and at first- and second-year follow-ups. Incidence of nocturia was defined by following those with no nocturia at baseline (defined as 0 or 1 episodes) to year 2. Of the 738 individuals with no nocturia at baseline, 34.6% (incidence rate, 213 cases/1,000 person-years) reported having nocturia (2 or more) at follow-up. Of the 357 individuals who had 2 or more episodes at baseline, 66.3% (remittance rate, 497 cases/1,000 person-years) reported 1 or fewer at 2-year follow-up (55).

In a study conducted among elderly men in one county in Finland (Tampere Aging Male Urological Study [TAMUS]) (59), the crude incidence of nocturia for men from no nocturia to 1 or more voids per night was 75 cases per 1,000 person-years during the first 5-year period and 126 during the second 5-year period. Younger cohorts (50 years old) had a lower incidence (61 cases/1,000 person-years) than did the two older cohorts (60- and 70-year cohorts, 91 and 93 cases/1,000 person-years, respectively). In all age cohorts, the observed incidence was higher during the second 5-year period than during the first: 102, 168, and 167 cases per 1,000 person-years, respectively. However, one should interpret this somewhat cautiously, as the prevalence for 60-year-olds was higher at 10-year follow-up than was the prevalence for 70-year-olds at baseline. The incidence of nocturia at 3 or more times per night (from 2 or fewer times/night) was substantially less across all age groups (3, 12, and 16 cases/1,000 person-years, respectively, for the age cohorts). This study is difficult to compare with other studies, as no information on incidence of nocturia from <1 episode to >2 or more episodes is available (59).

In a study from the city of Gothenburg (Sweden), questionnaires were mailed to 10,456 men (aged 45–99 years) (60). Follow-up was performed 11 years later when 3,257 men replied (3,000 men had died, and 691 had emigrated or were not available in the register). The authors presented prevalence data at two time points: at least 2 voids per night was reported by 13% at baseline and by 50% after 11 years. Incidence and remission estimates remained unreported (60).

In the Krimpen study conducted in a Dutch municipality (38), FVCs were used for assessment of nocturia incidence. The incidence was highest among the oldest and lowest among the youngest men. The overall incidence and remission rates (for nocturia defined as ≥2 voids/night) were 23.9% and 36.7% after approximately 2 years, respectively. However, the authors concluded (57) that "due to this fluctuation it is almost impossible to provide reliable incidence rates of nocturia in community-dwelling older men."

A 15-year follow-up study from Japan was recently published (61). In that study, 682 men were contacted in 1992, and 319 participated. Of them, 185 survivors were contacted in 2007 and 135 participated again, and of them 91 reported LUTS information. Mean IPSS nocturia score was 1.1 at baseline and 1.6 at follow-up.

In Denmark, 278 (of 305) women responded at 5 years and 242 at 12 years after their first pregnancy (62,63). Of 157 women who had no nocturia (≥2 voids/night) during pregnancy, not a single one developed it at 3 months after delivery. Of those having no nocturia at 3 months follow-up, 2.7% developed nocturia by 5 years, and 5.9% of those who had no nocturia at 5 years developed nocturia at 12 years. Of those 69 women who had nocturia during pregnancy, it had resolved in 99% of women (68/69) at 3 months postpartum (62).

### 3.4.3 Bother and impact on quality of life

Nocturia has been associated with adverse consequences for quality of life, morbidity, and mortality. Sleep disturbance is an important mechanism underlying subjective complaints and broader health consequences of nocturia. In a survey of US adults 18 years and older, the need to go to the bathroom was the most commonly cited reason for nocturnal awakening (64). This observation was consistent across all age groups and increased with age, from 39.9% among the 18–44-year-olds to 77.1% among those 65 years and older. Data from the 2003 National Sleep Foundation Survey in America corroborates these findings among older adults aged 55–84 years, with more than half of the respondents reporting nocturia as the cause of disturbed sleep, 4-fold higher than pain–the next most common reason cited for disturbed sleep (65). Similar results have also been reported by other studies (66,67). However, it is also possible that other conditions, such as insomnia or depression, can lead to sleep disruption, and nocturnal voids once awake then represent a secondary phenomenon (14,15). A US sleep centre study found that events during sleep (snoring, leg movements, apnea episodes) occurred surrounding the time of most nocturia episodes (68). Sleep loss associated with nocturia has been associated with daytime fatigue and reduced quality of life (69). Bother associated with nocturia has been shown to be related to both quantity and quality of sleep (70–72). Difficulty initiating sleep, as well as difficulty returning to sleep after an awakening play an important role (73,74).

The frequency of nightly voids that constitutes a threshold for significant or meaningful impact on well-being is a pertinent practical and theoretical question. Although more frequent nocturia causes more bother, the relationship is not perfectly correlated (19,28,29,32,69,75–79). The relationship of the number of nightly voids to bother and quality of life was investigated by age and gender using data from the population-based FINNO Study (19). Most respondents reported any degree of bother from nocturia with ≥2 episodes per night, and moderate bother only with ≥3 nocturia episodes. Similarly, two voiding episodes per night were associated with substantial impact on health-related quality of life compared with those without nocturia, and at least three episodes of nocturia resulted in further impairment of similar magnitude (19). These results indicate that two episodes of nocturia constitute a threshold beyond which nocturia has adverse effects on well-being, whereas 1 void per night does not identify subjects with interference from nocturia (19). Several other studies concur with this finding (32,77,78). An association of nocturia with depression has also been consistent across studies (80–82). While most studies were conducted among older adults, results from the BACH Survey suggest that the magnitude of the association is larger in younger age groups (<50 years) rather than in the elderly (80). While a significant trend in increased odds of depression with increased voids per night was observed in the BACH Survey, the temporal sequence between nocturia and depression has not been established. Longitudinal results from the TAMUS among men aged 50–79 years showed no association between nocturia at baseline and depression at follow-up (83). However, untreated depression at baseline was predictive of incident nocturia (83).

How much reduction in nocturia is needed to be clinically important has not been answered. As nocturia is associated with other factors that may affect bother and quality of life (comorbid conditions, lifestyle factors), not all bother is explained by number of voiding episodes. Hence, treatment for nocturia episodes may not relieve all impairment among subjects with nocturia (19).

## 3.4.4  Impact of nocturia: falls, fractures, mortality, and productivity

Sleep disturbance has been associated not only with increased bother and impaired quality of life, but also with increased morbidity and mortality (84–86). Sleep loss alters carbohydrate metabolism and endocrine function, and has been associated with incident diabetes (87,88). Additionally, falls constitute the greatest risk factor for fractures among the elderly (89). Nocturia is associated with an increased risk for both falls and fractures (90–96). Increased risk for mortality has been reported not only in the elderly, but also among younger men and women (33,93,97,98). In a Japanese study among the elderly, at least 2 voids per night was associated with a doubled risk for fractures and mortality (96).

Results of a US study among older men and women show a more modest association of nocturia (defined as ≥3 voids/night) with increased risk for falls (95). Data from the Third National Health and Nutrition Examination Survey (NHANES III) showed nocturia (≥2 voids/night) was associated with increased mortality risk in younger men and women (<65 years) rather than in the elderly, and among those without comorbid conditions (heart disease, diabetes) (33). Data from the Krimpen study among older men (55–84 years of age) showed no association of nocturia with increased mortality risk after accounting for confounding factors (99). In contrast, results of the Olmsted County Study in men 60 years and older showed an almost 50% increase in mortality risk after multivariate analyses (100). Increased mortality risk with nocturia among the elderly may be due to increased

risk for falls and fractures associated with nighttime voiding episodes. Alternatively, nocturia may be an indicator of frailty. Increased risk for morbidity and mortality among younger age groups and among those without prevalent comorbid conditions may indicate nocturia as a marker for impending morbidity (e.g. cardiovascular disease or diabetes), as an association of nocturia with chronic illnesses has been reported (101,102).

Although no research articles have been published on economic impact of nocturia, a few studies have investigated the impact of nocturia and associated sleep loss on work productivity. Nocturia has been associated with daytime fatigue and reduced vitality (19,69). A study of 203 working adults in Sweden has shown reduced work productivity with nocturia. Compared with age- and gender-matched controls, those with ≥1 voids per night had significant work productivity and activity impairment, impairment in non-work activities, and reduced vitality and quality of life (103).

## 3.4.5  Conclusions

Nocturia is one of the most common LUTS, with similar overall prevalence in both genders.

The prevalence of nocturia is higher among young women than young men, but the prevalence increases more markedly with age in men.

The literature on the incidence of nocturia remains relatively sparse. Incidence of nocturia increases with age, but significant short-term fluctuation in nocturia severity in individuals makes studies on incidence challenging.

Two or more episodes of nocturia per night constitutes clinically meaningful nocturia severity in the general population, affecting quality of life and perceived health, while a single episode usually does not.

Nocturia has been suggested to increase risk for falls, fractures, death, and impaired productivity.

## 3.4.6  Recommendations

Epidemiological studies need to employ strictly defined and clearly stated criteria of terminology and assessment.

Approaches to identify intra-individual variation and other confounding influences need to be considered.

Longitudinal studies using high-quality methodology remain *a priori*ty requirement.

Nocturia of twice or more per night may be a threshold of clinical significance in the general population. However, this threshold is not irrefutably established, and should not be extracted to sub-populations. Research into all grades of nocturia severity may yield information of clinical relevance.

# 3.5 **Pathophysiology**

Our knowledge of the pathophysiology of nocturia has really not changed over the last decade. What has changed is the knowledge that nocturia has multi-factorial etiology, which is not always urological in origin.

In normal adult urinary physiology, the amount of urine made at night is less than the functional bladder capacity during the daytime, and hence adults void more during the daytime and can sleep at night without having to wake up to void. This underpins the Ni, calculated as nocturnal urine volume divided by maximum voided volume (MVV; functional bladder capacity). It is positive if greater than 1. The normal pattern of voiding is established early in childhood and should, in theory, be maintained throughout adult life, and is based on the arginine vasopressin (AVP) control mechanism (104). Therefore, urine production and storage at night is based on two simple physiological events: the first is that the person needs to go to sleep and the second is that urine needs to be produced and stored in the bladder. If, for whatever reason, one or both of these two mechanisms are disturbed, then nocturia will result. Hence, by understanding this basic principle, it is possible to predict the pathophysiology of nocturia, which can be divided into two broad groups of non-pathological or pathological nocturia.

Non-pathological nocturia essentially means waking up for a reason other than the need to pass urine and feeling the desire to pass urine once awake (105), resulting in a "convenience" void (106). This may be due to, for example, noises outside the house, partner snoring, baby crying, light in the room being switched on, etc. Therefore, by definition, these are external factors and non-pathological.

Pathological nocturia, on the other hand, results from medical factors affecting either the sleep pattern, or production and storage of urine. It can be divided into five broad categories (107):

1. Reduced voided volume (indicating a reduced capacity of the bladder to store urine) throughout the 24-hour period, or exclusively during the hours of sleep (low nocturnal bladder capacity). This may be due to a variety of urological conditions, such as infravesical outflow obstruction, radiation cystitis, overactive bladder (OAB) syndrome, bladder calculi, or other primary bladder pathology causing a reduction in the anatomical capacity. Alternatively, the reduction in capacity may result from extrinsic compression by pelvic masses or urogenital prolapse (108).

2. 24-Hour (global) polyuria, characterized by excessive urine production during both day and night (indicating polyuria where 24-hour urine volume exceeds 40 mL/kg). This may be due to untreated diabetes mellitus (DM), diabetes insipidus (DI; central or nephrogenic), polydipsia (dipsogenic or psychogenic), or hypercalcemia. Drugs including diuretics, selective serotonin reuptake inhibitors (SSRIs), calcium channel blockers, tetracycline, lithium, carbonic anhydrase inhibitors work by several diverse mechanisms relevant to nocturia, such as increased urine output by way of disturbance of AVP secretion, AVP receptor inhibition, aquaporin level modification, atrial

natriuretic peptide (ANP) increase or action on proximal tubules, effect on the central nervous system, and sleep disturbance (10,108).

3. Excessive urine production rate only at night, in the setting of a normal 24-hour urine output (i.e. NP). The recommendation of the ICS is to define NP as a nocturnal output exceeding 20% of total 24-hour output in the young (aged 21–35 years) and exceeding 33% of total 24-hour output in the elderly. This is known as the nocturnal polyuria index (NPi). Other definitions that have been used include nocturnal urine production exceeding 6.4 mL/kg, nocturnal urine output >0.9 mL/min, or nocturnal urine production >90 mL/hr of urine produced during sleep (108,109,110). It should be noted, however, that no studies assess the validity of these cut-off points in clinical practice. Nocturnal polyuria may be a result of peripheral edema and ANP secretion secondary to congestive heart failure, autonomic neuropathy, venous stasis, lymphostasis, hepatic failure, hypoalbuminemia/malnutrition, or nephrotic syndrome. It may also be caused by excessive evening fluid intake; nighttime drinking; circadian defect in the secretion of AVP (including central nervous system lesions of the hypothalamic-pituitary axis, Parkinson's disease, multiple sclerosis); drugs including diuretics, ethanol, and steroids; renal tubular dysfunction (including DM and albuminuria); and obstructive sleep apnea (OSA) (111).

4. Sleep disorders–including primary (insomnia, periodic leg movements, narcolepsy, arousal disorders such as sleepwalking and nightmares) and secondary (cardiac failure, chronic obstructive pulmonary disease (COPD), endocrine disorders)–can cause nocturia. Neurological conditions (Parkinson's disease, dementia, epilepsy); psychiatric conditions (depression, anxiety); chronic pain disorders; alcohol or drug use (consumption or withdrawal); and medications (corticosteroids, diuretics, βadrenergic antagonists, thyroid hormones, psychotropics, anti-epileptics) have all been implicated in causing nocturia (81,83,112).

5. Combinations of the above, resulting in mixed etiology requiring a multi-disciplinary approach to diagnosis and treatment.

### 3.5.1  Risk factors

#### Conditions

*Benign prostatic obstruction (BPO):* Overall, "LUTS suggestive of BPO" constitute a well-recognized risk factor for nocturia (102,113,114). In the FINNO Study (102), half of the subjects with physician-diagnosed benign prostatic enlargement (BPE) reported at least 2 voids per night; however, only a third of the men with nocturia had BPE. Indeed, the impact of BPE causing BPO may be overestimated (nocturic men probably are more likely to be diagnosed with BPO than men without nocturia, and women do not have substantially less nocturia despite not having prostates). Nocturia was the least-specific LUTS associated with BPO, and treatment to relieve BPO had less effect on nocturia than on other LUTS in Japanese studies (115,116). Furthermore, in a Veterans Affairs study on men with bothersome LUTS, those receiving doxazosin had very modest net reductions in nocturia, while finasteride had an effect indistinguishable from placebo (117). Furthermore, nocturia is one of the most persistent LUTS following prostate surgery (118,119), if not the single most persistent.

*Depression:* In a Swedish population-based study (81), subjects with major depression (assessed by the Major Depression Inventory) reported substantially more nocturia than those without. The association was especially strong among men (odds ratio (OR 6.5, 95% confidence interval, CI [2.6, 15.6]

for men; and OR 2.8, 95% CI [1.3, 6.3] for women, adjusted for age and somatic health). However, in a subsequent analysis from the same database (120), the authors reported that both major depression (OR 4.6, 95% CI [2.8, 7.5]) and taking an SSRI (OR 2.2, 95% CI [1.1, 4.5]) were associated with increased prevalence of nocturia (gender was deleted by the logistic regression model). In the TAMUS (83) cohort study (conducted among men aged 50 years and older), those with depressive symptoms at study entry were at 2.8 times higher risk (95% CI [1.5, 5.2]) for moderate or severe nocturia (defined as ≥3 voids/night) than those without depressive symptoms, but nocturia had no effect on depressive symptoms during the 5-year follow-up. In the FINNO Study (102), nocturia was associated with antidepressant use only in men (OR 3.2, 95% CI [1.3, 7.7]). Depression itself was not associated with nocturia after adjustment for other factors, despite associations in the age-adjusted analyses (OR 2.8, 95% CI [1.6, 5.0] for men; and OR 2.0, 95% CI [1.2, 3.3] for women). In the BACH Survey (121), nocturia was associated with both depression (defined as score of 5 or more on the Center for Epidemiological Studies Depression Scale) and use of antidepressants in both genders, particularly in younger age groups. While 10.1% of men and 15.6% of women reported depression among those without nocturia, corresponding figures were 15.6% and 30.0% for those with nocturia (80).

*Hypertension and coronary artery disease:* The connection between nocturia and hypertension is not clear. It has been suggested that essential hypertension and NP are part of the same pathophysiological process (122). In a Japanese study (123) and in a US (39,55) study, hypertension was associated with nocturia, although effect sizes were modest (ORs, 1.5–1.6). However, in studies conducted in Europe (102,124), neither NP nor nocturia was associated with hypertension. In a secondary analysis from the BACH Survey (125), nocturia was not generally associated with antihypertensive use. However, monotherapy with calcium channel blockers in women (OR 2.65, 95% CI [1.04, 6.74]), and combination therapy with loop diuretics in men was associated with nocturia (combination therapy OR 2.55, 95% CI [1.26, 5.14]) (125). No other significant associations for nocturia with angiotensin-converting enzyme inhibitors, beta blockers, calcium channel blockers, or loop and thiazide diuretics were found. While the treatment for hypertension may cause (10,125,126) or alleviate nocturia (127) in some cases, appropriate methods are of particular importance when assessing this relation.

Earlier studies in men (38,123,124) did not find a relation between nocturia and cardiac disease. However, in these studies, an association between cardiac symptoms or disease and nocturia was found in the preliminary analyses before multivariate models. In more recent studies (98,102,121,128), coronary disease has been shown to be associated with nocturia. In the FINNO Study, coronary artery disease was associated with nocturia in the age-adjusted analyses in both sexes; but after adjustment for other factors, the association persisted only for women (OR 3.1, 95% CI [1.5, 6.6]) (102).

*Neurological diseases:* Most patients with multiple sclerosis have bladder dysfunction, which may also lead to nocturia (129). In studies conducted among elderly people, nocturia was associated with stroke and cerebrovascular disease (128–130). Moreover, in a study among patients with Parkinson's disease, severity of disease was also associated with increased nocturia (mean number of nocturia episodes was 1.8 in the mild, and 2.9 in the severe Parkinson's groups) (131). A relationship of nocturia with restless legs syndrome (RLS) was found in the FINNO Study (102). Subjects of both sexes with RLS (compared with those without) had almost triple the risk of having nocturia. However, only 1

of 8 with nocturia had RLS. Increased risk for nocturia in patients with RLS may relate to disturbed sleep (132). Furthermore, patients with RLS use antidepressants, gastrointestinal medications, and asthma/allergy drugs more frequently than subjects free of them (133).

*Menopause and hormone therapy:* In the FINNO Study, the postmenopausal period was associated with increased nocturia (OR 2.3; compared with premenopausal women) (134), consistent with a population-based study conducted on middle-aged women in Denmark (OR 2.4) (135). Two other studies also reported increased nocturia in the postmenopausal period (136,137), whereas another attributed this to aging rather than to menopausal transition (138). The menopausal period is often associated with sleep disturbances for other reasons including hot flashes, mood disorders, and increased sleep disordered breathing (139); therefore, individuals reporting nocturia may be awakening due to non-bladder causes. There are few studies evaluating the effect of menopausal hormone replacement therapy on nocturia. In Finnish and Swedish population-based studies, there were indications for increased nocturia among women with menopausal hormone therapy, but the findings were statistically insignificant in the multivariate analysis (134,140). In a small, randomized trial (151), those with menopausal hormone therapy did not report less (or more) nocturia than those with placebo. This finding was confirmed in randomized, controlled trials of an estradiol vaginal ring (152) and vaginal estradiol on urinary storage symptoms after sling surgery (143).

*Nocturnal polyuria:* The ICS defines NP as an increased proportion of the 24-hour output of urine volume occurring at night (2). However, there is a paucity of studies providing reference values. In the Krimpen study, average nocturnal urine production was slightly more than 60 mL/hr. The authors suggested that nocturnal urine production exceeding 90 mL/hr is abnormal (144). However, the authors concluded that "nocturnal urine production as an explanatory variable for nocturnal voiding frequency is of little value." What is the fundamental pathogenesis of NP? Congestive heart failure, "third spacing" (venous insufficiency, nephrosis), or late-night diuretic administration are potential underlying causes. Using bioelectric impedance analysis, nocturnal urine volume has been shown to correlate with the difference in fluid volume in the legs ($r=0.53$; $p=0.002$) and extracellular fluid volume ($r=0.38$; $p=0.02$) between the morning and evening (145). This is indirectly supported by the results of a non-randomized study, where the number of nocturia episodes decreased significantly from 3.3 to 1.9 after 8 weeks of walking exercise in elderly men (146). Possible other pathways to nocturnal polyuria also include impaired renal concentrating capacity, diminished sodium conserving ability, dysfunction of antidiuretic hormone secretion, and increased secretion of ANP (e.g. due to sleep apnea), leading to increased nighttime urine production (147–149). The pathophysiology of NP merits further studies.

*Obesity and diabetes:* Several studies have shown the relation of being overweight or obese with nocturia. Obesity was associated with more than 3-fold risk for nocturia in a Swedish study among middle-aged women (150), and with more than 2-fold risk in the FINNO Study (151). Confirmatory findings have been reported (39,121,152,153). In the longitudinal TAMUS study among men aged 50 years and older (154), obese men were at higher risk for mild nocturia, and particularly for moderate or severe nocturia (relative risk [RR] 2.3, 95% CI [1.1, 4.7]), compared with normal-weight men. The frequency of nocturia at baseline did not increase the incidence for obesity at follow-up (154). An association between diabetes and nocturia has been reported in most (102,114,121,123,128,150,153, 155,156), but not all reports (38,132). In the BACH Survey (126) and in a Danish study that included

patients aged 60–80 years (164), nocturia was associated with a doubled risk for diabetes (OR 1.7 in the Boston and OR 2.0 in the Danish study). In these surveys, it remained unreported whether there were gender differences. In the FINNO Study (102), diabetes was associated with nocturia in the age-adjusted analyses in both sexes, but after adjustment for other factors, the association persisted only for women (OR 2.7, 95% CI [1.4, 5.2]).

*Overactive bladder and detrusor overactivity*: According to the ICS, OAB is a symptom-defined condition characterized by urinary urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia (2). Urinary urgency is commonly proposed as the primary driver of all symptoms of the OAB constellation, including increased nocturia (157). Recent evidence using nocturnal cystometrogram testing has confirmed a temporal relationship between nocturnal detrusor overactivity and nocturic voids in some patients with nocturia (158). Urinary urgency was a clear risk factor for nocturia in the FINNO Study (OR 7.4, 95% CI [4.5, 12] for men; and OR 4.9, 95% CI [3.2, 7.7] for women) (102). However, while half of subjects with urgency also reported at least 2 voids per night, only 1 in 3 with nocturia reported urgency (51). As most people with nocturia do not report frequent urgency, it is not surprising that the treatment for nocturia with bladder relaxants (antimuscarinics) is often unsuccessful (159).

*Pelvic surgery–hysterectomy and stress urinary incontinence (SUI) operations*: Results are inconsistent regarding nocturia and hysterectomy, with hysterectomy variously being associated with decreased (160–162) or increased prevalence for nocturia (135), or not associated with nocturia (163,164). In the FINNO Study, hysterectomized women had an OR of 1.8 for nocturia, with borderline statistical significance, whereas surgery for SUI was not associated with nocturia despite an association of urgency with SUI surgery (134). However, statistical power was limited regarding analyses on SUI surgery in this study.

*Prostate cancer:* Many men with LUTS express a fear for prostate cancer (165); however, whether LUTS (including nocturia) really are suggestive of prostate cancer is not well known (166). In the large substudy of the Nord-Trøndelag Health Study 1995–1997 (HUNT-2) (167), LUTS severity was positively associated with the subsequent diagnosis of localized prostate cancer but not with advanced or fatal disease. In the FINNO Study (102), more than 70% of men with physician-diagnosed prostate cancer reported at least 2 voids per night, while 7% of men with nocturia reported prostate cancer. Are men with nocturia more vulnerable to be diagnosed (due to use of prostate-specific antigen [PSA] among men with LUTS), or does prostate cancer really cause nocturia, or is nocturia a side effect of various prostate cancer treatments (19,168)? Following radical prostatectomy, more SUI and less obstructive symptoms have been reported, whereas the impact on nocturia has been neutral or negative (i.e. increased nocturia) (169,171).

## Lifestyle

*Coffee and alcohol:* Nocturia treatment guidelines usually recommend decreasing (bedtime) fluid intake, particularly coffee and alcohol. However, most studies have not demonstrated a relation between nocturia and consumption of alcohol (55,75,102,123,153,172) or coffee/caffeine (29,102,154,173). In some studies, moderate alcohol consumers had less nocturia than abstainers (128,154,174). These findings could be explained by a systematic misclassification error (people

decrease or cease alcohol intake due to ill health) (175,176) or residual confounding (moderate drinkers have many favouring social and lifestyle factors) (177,178), although there could theoretically be several biological factors behind this association.

*Smoking:* Most studies have not found an association between nocturia and smoking (98,102,153,154,172,173,179). Some conflicting results have also been reported: in a Swedish study (150), smoking was associated with increased nocturia, but in Austrian (180) and Japanese (123) studies, with decreased nocturia.

*Physical activity:* Physical activity has been reported to be protective against LUTS in men (181–183), and against nocturia specifically in women (150). In an Austrian health-screening study (75), no relation was found between physical activity and nocturia. However, as exercise programmes appear to improve nocturia (184), these effects deserve to be further explored.

### Race/ethnicity and socio-economic status

In several US studies, it is consistently noted that black men are approximately twice as likely to report nocturia as other ethnic groups (39–41). This effect persisted, although attenuated, after adjusting for comorbidities and socio-economic status. Similar effects were reported for women participating in the BACH Survey (121), and the Penn Ovarian study (44), with black women being almost twice as likely to report nocturia even after multivariable adjustment. In addition to these population-based studies, reports from secondary care populations (45,46) have also suggested in a population seeking care that black women commonly reported more nocturia. However, conflicting results were found in a Kaiser Permanente study (47). Less is known about the relationship between ethnicity and nocturia outside the US. In small studies in Taiwan (48,49) and Scotland (50), association of nocturia with ethnicity has been found. In the Scottish study, the prevalence for nocturnal polyuria was significantly higher in 200 Caucasian men compared with 93 Asian men. Overall, the underlying mechanisms for the possible association of nocturia with race/ethnicity remain unknown. In the previous studies, some of the risk factors for nocturia (such as sleep apnea) remained unmeasured.

## 3.5.2  Conclusions and recommendations

Pathophysiology of nocturia can be divided into five categories and associated with several risk factors (Level 2 evidence, Grade of Recommendation [GOR] B)

1. Bladder storage problems
2. Nocturnal polyuria
3. Global polyuria
4. Sleep disorders
5. Mixed mechanisms

Research into pathophysiology remains a priority:
- Mechanisms underlying nocturia are poorly understood.
- Establishing why some patients manifest nocturia and others don't with apparently similar predisposing factors.
- Basic research into age-related circadian rhythms.
- Effects on sleep quality, and the relationship between nocturia and restorative stages of sleep (107).

**TABLE 2** Potential causes or associated risk factors for nocturia (211)

| Bladder Storage Problems | Nocturnal Polyuria | Sleep Disturbance & Primary Sleep Disorders | Other Potential Factors |
|---|---|---|---|
| Reduced functional bladder capacity | Congestive heart failure | Insomnia | Medical disorders<br>- Cardiac failure<br>- COPD<br>- Endocrine disorders |
| Bladder pain syndrome | OSA | Sleep apnea | Psychiatric conditions<br>- Depression<br>- Anxiety |
| Bladder outlet obstruction (i.e. BPH, BPO) | Peripheral edema<br>- Venous stasis<br>- Hepatic failure | Periodic leg movements | Neurological conditions<br>- Parkinson's disease<br>- Dementia<br>- Epilepsy |
| Nocturnal detrusor overactivity | Excess evening fluid intake | Narcolepsy | Chronic pain disorders |
| Neurogenic bladder | Circadian defect in secretion/action of AVP | Arousal disorders<br>Sleepwalking<br>Nightmares | Alcohol/drug use (consumption or withdrawal) |
| Cancer of bladder, prostate, or urethra | | | Medications<br>- Corticosteroids<br>- Diuretics<br>- β-Adrenergic antagonists |
| Learned voiding dysfunction | 24-hour polyuria | | |
| Bladder or ureteric calculi | DM | | |
| DO/OAB (idiopathic or neurogenic) | DI | | |
| Voiding problems/ post-void residual | Primary polydipsia | | |
| Urogenital aging (estrogen deficiency) | | | |

# 3.6 **Assessment**

A summary algorithm is presented in **Figure 2**.

**FIGURE 2**

Assessment of nocturia
Dx: diagnosis; PM: after noon.
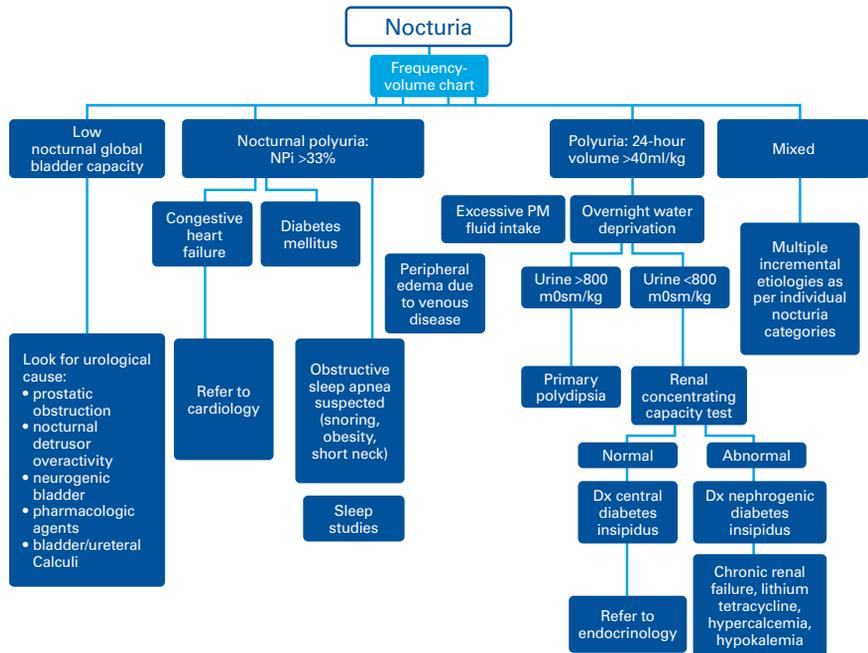


## 3.6.1 **Measures**

Measures for nocturia include questionnaires and urinary diaries. This paragraph focuses on the validation of nocturia questionnaires, including frequency-related questions and quality-of-life measures, and on the methodological aspects of urinary diaries.

### Questionnaires

Most generic LUTS-related questionnaires, such as the IPSS and the ICS Male questionnaire, include a question on nocturia. The ICS Male questionnaire included a validation of this question (212), whereas the IPSS did not (187). Subsequently, the Nocturia, Nocturnal Enuresis and Sleep-interruption Questionnaire (NNES-Q) has been validated as a symptom-specific questionnaire (105).

The main problem with the use of questionnaires, as well as history taking during consultation, is recall bias. This will be present particularly for patients who don't visit the physician with a specific symptom. Men with nocturia as the main symptom (or reason for the visit) may have registered their nocturnal frequency in a better manner, than those presenting with other (main) symptoms.

The (negative) impact of nocturia on quality of life can be estimated using specific questionnaires. The International Prostate Symptom Score – Quality of Life (IPSS-QoL) questionnaire is not appropriate for specific assessment of nocturia impact, as it reflects opinion on general LUTS-related QoL. Even in patients with a predominant complaint of nocturia, such an approach to QoL scoring may be confounded by other LUTS.

The Nocturia Quality-of-Life Questionnaire (N-QoL) has been validated as a symptom-specific QoL measure (70). It has been adopted as one of the International Consultation on Incontinence Questionnaire (ICIQ) modular tools (188) and is now known as ICIQ N-QoL. Linguistic validation for 16 languages has been performed (189), but currently it has yet to be validated for populations other than outpatient department patients.

It should be stressed that such specific questionnaires have a limited value for daily practice, as they can't be used for treatment decisions. These questionnaires bring detailed information important in research studies.

## Urinary charts and diaries

It is generally thought that collecting information from urinary diaries is not hampered by recall bias, as patients report actual data. Previous reports showed the large difference between FVC-derived nocturnal frequency and questionnaire-derived nocturnal frequency, both in patients referred to a urology outpatient department (190) and in men from the general population (38). This was thought to be the result of recall bias present in questionnaire data, but it may also reflect the differences in time frames used for either measure, or the presence of a fluctuation of nocturnal frequency. With questionnaires, patients report the average nocturnal frequency representative of the preceding week or month, whereas with FVCs they prospectively collect data. This was already noticed in the validation of the ICS Male questionnaire: allowing the discrepancy between questionnaire and FVC data with plus or minus one category increased the exact crude agreement from 68% to 97% (186).

Three approaches to recording micturition events have been categorized by the ICS (2):

1. Micturition charts, on which only the times of micturitions are recorded, day and night, for at least 24 hours.
2. Frequency volume charts, on which the volumes voided and the time of micturition are recorded, day and night, for at least 24 hours.
3. Bladder diaries (BDs), which combine the FVC data collection with any additional information required for the clinical context. For example, in people with incontinence this would include leakage episodes, pad usage, degree of urgency, degree of incontinence, and fluid intake.

The three approaches have their own premises. Micturition charts have limited value in clinical practice, as the collected data are restricted to frequency only, with no additional information. Frequency volume charts also provide information such as the volumes voided. For most patients with nocturia, this may be the appropriate approach to recording micturition events, as an FVC can ascertain the presence or absence of NP. Bladder diaries are more laborious for patients and will generally be applied where additional information is key to fully understanding the clinical situation, particularly in patients with urgency and incontinence symptoms. Also, in patients with nocturnal or global polyuria, the additional registration of fluid intake may be helpful.

The majority of experts involved in the ICIQ bladder diary validation process indicated volume of fluid intake to be an essential parameter (191). Surprisingly, registration of time of awakening and time of going to bed was considered essential only by a small minority, yet it is vital information in the analysis of nocturnal frequency and nocturnal urine production.

Recently, Bright *et al.* summarized the evidence for the development and validation of diary content, format, and duration (192). While a survey revealed numerous urinary diaries in use, none was formally validated. Accordingly, they performed a first phase of validation of an ICIQ urinary diary (191). In this phase, patient and clinician opinion on diary format, duration, and content was studied, using interviews and questionnaires. In addition, four draft diary formats were evaluated, and final consensus was reached on the single preferred format. The validity, reliability, and responsiveness of this diary will be further evaluated for contextual validation.

In various reviews of the literature, the best estimates for FVCs are presented, mainly focusing on the ideal duration (186,192). Charts of longer duration may increase reliability of nocturnal frequency estimates, but for patients it is more labour intensive and may impair patient compliance with accurate or complete recording. Shorter charts will generally achieve higher compliance, though this is dependent on the individuals completing the charts. Previous analyses on this topic were based on correlation coefficients between consecutive nights completed on the charts (193). High correlation coefficients were thought to reflect high reliability. This does not, however, take into account that nocturnal frequency may differ between nights, for a variety of reasons. In the analyses of short-duration FVCs, a difference between 2 nights is considered to be larger than a difference of 1 night compared with 4 or 5 other nights on a longer chart. It should be stressed that this only reflects a mathematical difference.

In the absence of an undisputed gold standard measurement, finding evidence for the correct duration of FVCs appears technically challenging. From the available literature, and based on logic, it seems that 3 or 4 consecutive days is the best compromise between information detail and patient compliance (Level of Evidence [LOE] 2) (186,192,194). This should include 2 or 3 complete nights, and allow for the need to identify normal variation in nocturnal frequency and voided volumes. Importantly, it must be clear what information should be collected by patients, both in daily practice and for research. Frequency volume charts should include volume of each single void, time of each single void, time of going to bed, and time of rising in the morning.

From this information, the following measures can be read or calculated:

- 24-Hour urine volume
- 24-Hour frequency, daytime, and nighttime frequency
- Maximum voided volume of a single void
- Nocturnal MVV
- Nocturnal voided volume (all voids during sleeping time, plus the first morning void)
- Nocturnal polyuria index

## 3.6.2 Clinical assessment

### Medical history taking

The clinician should document duration and severity of the nocturia. Other types of LUTS and the degree of bother due to nocturia should also be assessed. Several questionnaires on global LUTS, such as the IPSS (187), the ICIQ-Male Lower Urinary Tract Symptoms (ICIQ-MLUTS) Long Form, ICIQ-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) Long Form, and ICIQ-Overactive Bladder (ICIQ-OAB) (188), and the Overactive Bladder Symptom Score (OABSS) (195), can be used for assessment of nocturnal urinary frequency. The ICIQ-N (http://www.iciq.net/structure.html) is a simplified questionnaire for this purpose. Quality-of-life aspects regarding nocturia can be assessed by the ICIQ N-QoL (189).

Urological causes of low nocturnal and/or global functional bladder capacity (e.g. OAB, BPE, and neurogenic bladder dysfunction) are important, as nocturia induced by urological disorders may be treatable. For assessment of each LUTS, use of validated questionnaires facilitates capture of severity and bother. As excessive overall fluid intake or excessive intake at specific times can induce polyuria and/or NP (196), fluid intake habits should be inquired. History of recurrent urinary tract infections (UTIs), pelvic surgery, or radiotherapy should be taken.

There are several relevant medical disorders; some are known to induce nocturia, while others have an uncertain cause-and-effect relationship. For the former, successful treatment of the causative medical condition should result in improvement of nocturia, but for the latter nocturia might persist.

In the former group, OSA results from intermittent occlusion of the airway during sleep, leading to negative intrathoracic pressures. This negative pressure results in increased volume return and atrial stretch, which triggers the secretion of ANP, hence inducing NP (197). The association with nocturia has been confirmed by the finding that intervention for OSA, such as continuous positive airway pressure treatment, decreases nocturia episodes (198). As patients may not be able to report their state of breathing during the night, it is important to ask their bed-sharing partner as well as the patient about breathing interruptions, excessive snoring, or daytime sleepiness. Poorly uncontrolled DI (inadequate hypothalamic secretion of antidiuretic hormone [ADH] or renal insensitivity to ADH) and DM are well-known causes of global polyuria due to secondary polydipsia, where thirst results from excessive fluid loss. Psychiatric disorders, such as schizophrenia and anxiety disorder, are liable to primary polydipsia, leading to global polyuria and increase of nocturnal urinary frequency (199). These disorders generally accompany diurnal urinary frequency due to global polyuria as well as nocturia, and successful treatment can suppress urination frequency during day and night. Nocturia is one of the most prevalent symptoms in patients with cardiac failure or impaired cardiac function (200). Elevated plasma brain natriuretic peptide (BNP) level, which can occur with impaired cardiac function, is significantly associated with nocturia (201). Accumulation of fluid in

the third space of the body during daytime can return to the circulating volume when the patient is recumbent (156,202), and it is speculated that fluid accumulation in the third space can be induced by cardiac failure. However, there is little evidence that successful treatment for cardiac failure results in improvement of nocturia. Similarly, it is unclear that treatments for several disorders influence the degree of nocturia, such as hypertension, DM, stroke, and Parkinson's disease (203), although they are important as medical history for nocturic patients. Medications for several disorders are also important; diuretics, calcium channel blockers (204), and SSRIs (125) are modifiable drugs which alter fluid balance.

Situations where the cause-and-effect relationship with nocturia is uncertain include other sleep disorders such as insomnia, RLS, and periodic limb movement syndrome. It is important to enquire whether sensation of desire to void disturbs sleep or whether nocturnal voiding follows waking for any other cause. Several medications causing sleep disturbance as adverse events, such as central nervous system stimulants and psychotropics, can be theoretically associated with nocturia. However, there are few reports which show a direct association between those drugs and nocturia.

## Physical examination

Clinical examination should consider the possibility for occult neurological disease. Cardiovascular examination is needed, including edema in the lower extremities in the evening (156,202). Abdominal examination can detect an enlarged bladder (post voiding), suggesting chronic urinary retention, or other abdominal masses suggesting reduced functional bladder capacity. Digital rectal examination for assessment of the prostate should be performed.

## Investigations

*Frequency volume charts:* An FVC or BD is essential to exploring the underlying conditions. The assessed parameters are: minimum, maximum, and average bladder capacity during the daytime and nighttime; urine volume produced during daytime, nighttime, and 24 hours; urinary frequency during daytime and nighttime; and duration of time in bed. Based on these parameters, global or nocturnal polyuria, and global or nocturnal reduced bladder capacity can be judged. Long duration of time in bed is an important factor for nocturia (205).

*Urinalysis:* Despite lack of evidence on its usefulness for nocturia specifically, urinalysis is a key aspect of assessing LUTS. Its value is in detecting blood, protein, sugar, leucocytes, or nitrites, indicating the possibility for UTIs, malignant diseases, inflammatory problems, or unrecognized poorly controlled DM.

*Post-void residual (PVR):* Theoretically, incomplete bladder emptying on voiding results in frequent urination during day and night, and thereby can increase the likelihood for nocturia. If there is large PVR volume, treatment should decrease the number of nocturnal voiding episodes, though there is no reported evidence that routine measurement of PVR is beneficial for evaluation of nocturia.

*Uroflowmetry:* Flow rate testing is not considered to be essential for nocturia as an isolated symptom, but it is included in routine assessment of LUTS.

*Transabdominal ultrasonography:* Ultrasound can evaluate the size and configuration of the prostate in men, hydronephrosis, thickness of the bladder wall, bladder trabeculations, diverticula, stones, and tumours. These evaluations rarely contribute to the treatment strategy for nocturia except for assessment of the prostate, and may not be essential. However, ultrasonography is a non-invasive examination, and urologists may use this tool for routine assessment of LUTS including nocturia.

*Invasive urodynamics:* Routine use of invasive urodynamics, such as filling cystometry and pressure flow study, is not recommended.

*Blood chemistry examination:* Chronic kidney disease can be detected by serum creatinine, and unrecognized DM can be detected by appropriate serum glucose. Prostate-specific antigen should be considered in the context of diagnostic recommendations for prostate cancer. Low level of AVP, during nighttime or throughout the day, may be associated with nocturia (206,207), and it is the theoretical basis for treatment with desmopressin. However, there is no clear association between serum ADH level and therapeutic efficacy of desmopressin (208). While high levels of natriuretic peptides, such as ANP and BNP, are also speculated to be associated with nocturia, the significance of measurement of these peptides for detection of nocturnal polyuria or for management of nocturia is currently unknown (209,210).

*Radiological examinations,* such as retrograde urethrography, cystography, intravenous pyelography, and abdominal computed tomography, are not routinely used in assessment of nocturia. They should only be used where indicated by the medical context, such as suspected malignant disease or neurogenic bladder dysfunction.

*Cystoscopy* is not routinely used in assessment of nocturia. It should only be used where indicated by the medical context, such as suspected malignant disease or inflammatory bladder conditions.

### 3.6.3   Recommendations in guidelines

There are relatively few guidelines specific to nocturia. The European Association of Urology (EAU) guidelines on Non-neurogenic Male LUTS (2012), the EAU Guidelines on Urinary Incontinence (2012) (211), the U.K. National Institute for Health and Clinical Excellence (NICE) guidelines on Lower Urinary Tract Symptoms (2010), and the NICE Guidelines on Urinary Incontinence (2006) make no specific comment on assessment of nocturia. The guideline for "diagnosis and treatment of overactive bladder (non-neurogenic) in adults" by the American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) (2012) mention nocturia as one symptom of OAB. They simply describe the differential of nocturia (i.e. NP, low nocturnal bladder capacity, or both) and that sleep disturbances, vascular and/or cardiac disease, and other medical conditions are often associated with NP.

The draft New Zealand guideline for "nocturia in adults" (212) describes several points regarding assessment of nocturia. For history taking, the following are listed: aging; other LUTS; hematuria; sleep-disordered breathing; pregnancy; menopause; congestive heart failure; peripheral edema; chronic renal disease; sleep disorders; pelvic pathology, such as pelvic organ prolapse, DM, DI, hypercalcemia; and medication and other ingested substances. Recommended physical examinations

include assessment of peripheral edema, abdominal examination, plantar reflexes, pelvic examination for women, and digital rectal examination for men. Urinalysis, simple blood tests, and BD are listed as recommended investigations. While this guideline mentions global polyuria, NP, and reduced functional bladder capacity like others, the distinction between water and solute diuresis as a cause of global polyuria is also explained.

The Japanese clinical guideline for nocturia (213) recommends the classification of nocturia into three categories: i.e. (1) nocturia only; (2) nocturia and diurnal frequency without other LUTS; and (3) nocturia and diurnal frequency accompanying other LUTS. In addition, it mentions that categories (1) and (2) are generally treated by primary care physicians or internists but that category (3) will require treatment by a urologist.

## Conclusions and recommendations

Validated symptom questionnaires are recommended as tools for initial and treatment response evaluation in the clinical setting (GOR C).

Questionnaires are unsuitable for the estimation of nocturnal voiding frequency (LOE 4, GOR C).

Nocturia-specific quality-of-life questionnaires can be used to determine impact of nocturia on quality of life (LOE 4, GOR C).

Urinary diaries are essential in the analysis of nocturia (LOE 4, GOR C).

The ICIQ BD has been developed according to methodological requirements for assessment tools, and it is proceeding through contextual validations (LOE 2, GOR B).

Medication review is an important part of nocturia clinical assessment (GOR A).

Physical examination, flow rate testing, and urinalysis are relevant to assessment of LUTS and help identify potential contributory mechanisms in some cases of nocturia (GOR C).

Post-void residual measurement is directly relevant to nocturia (GOR C).

Routine use of invasive urodynamics, such as filling cystometry and pressure flow study, is not recommended (GOR D).

Blood chemistry examination is optional (GORs C, D).

Radiological examinations or cystoscopy should only be used where indicated by the medical context, such as suspected malignant disease (GOR D).

# 3.7 **Treatment**

## 3.7.1 **Conservative management**

Nocturia can sometimes be managed with conservative lifestyle and behaviour modifications such as:

- Fluid restriction 2–6 hours prior to bedtime
- Voiding immediately prior to bedtime
- Avoidance of caffeinated and alcoholic beverages
- Leg elevation to help mobilize third-spaced fluids (prior to going to bed)
- Taking diuretics in the mid-afternoon instead of just after rising
- Using natural sleep aids (chamomile, lemon balm, passion flower)/medications
- Wearing protective undergarments

### Behavioural modification with biofeedback

A prospective, randomized clinical trial of 131 incontinent women with nocturia (aged 55–92 years) was performed to determine whether behavioural modification or pharmacotherapy is more effective at reducing the number of episodes of nocturia. Women were randomized to receive behavioural therapy (four sessions of biofeedback-assisted pelvic floor muscle exercises); drug treatment (oxybutynin immediate release [IR] 2.5 mg titrated to 5 mg three times per day); or placebo. Participants completed BDs to calculate changes in nocturia. After 8 weeks of treatment, investigators found that behavioural training reduced nocturia by a median of 0.50 episodes per night versus pharmacotherapy (median reduction of 0.30 episodes per night; $p=0.03$) and versus placebo (median reduction of 0.0 episodes per night; $p<0.001$) (LOE 3) (214).

A prospective, randomized trial was performed to determine the effectiveness of behavioural treatment versus antimuscarinic therapy in 143 men with bladder outlet obstruction (BOO) who had persistent OAB symptoms despite alpha-blocker therapy. The study was composed of men (aged 42–88 years) who had persistent urgency and more than 8 voids per day with/without incontinence after a 4-week alpha-blocker run in. Participants were randomly chosen to receive 8 weeks of behavioural treatment (pelvic floor muscle exercises, urge suppression, and delayed voiding techniques) or drug therapy (individually titrated oxybutynin extended release [ER] 5–30 mg/day). A 7-day BD and validated urgency scale were used to calculate 24-hour voiding frequency, nocturia, urgency, and incontinence. The reduction of nocturia episodes was greater for behavioural treatment versus drug therapy (−0.7 vs. −0.32; $p=0.05$) (LOE 3) (215).

A prospective US Veterans Administration pilot study assessed the feasibility and efficacy of using a multicomponent intervention to reduce severity and bother of nocturia. Fifty-five men (mean age, 67 years) who completed BDs and the AUA symptom index then underwent a treatment protocol of behavioural therapy and targeted drug therapy. The multicomponent intervention was individualized for each participant based on his specific combination of risk factors for nocturia. All participants underwent the following behavioural modifications: reduction of caffeine and alcohol, limiting nighttime fluids, and improving sleep hygiene (moderate exercise, paying attention to room light, noise, and temperature). After 4 weeks, the subjects completed BDs and the AUA symptom index. These results were compared with the pretreatment BDs and the AUA symptom index. The mean

number of nocturia episodes decreased from 2.6 to 1.9 ($p<0.001$) in 50 of 55 men who completed diaries before and after treatment and the bother score was reduced from 3.1 to 1.1 ($p<0.001$) in 53 of 55 men who completed the AUA symptom index before and after treatment (LOE 3) (216).

A prospective, randomized study compared the effects of bladder training, tolterodine, and a combination of bladder training and tolterodine on OAB in women aged 18 years and older. Patients who received bladder training (either alone or in combination with tolterodine) were educated about pelvic floor and bladder anatomy and then instructed to look at their FVC. Their goal was to gradually increase their ability to hold urine by extending the interval between voids by 15 minutes until they reached an interval of 3–4 hours and a voided volume of 300–400 mL. Patients who received tolterodine (either alone or in combination with bladder training) received 2 mg by mouth (PO) twice daily. After 12 weeks of treatment, the patients completed FVCs and compared them with the pretreatment FVCs. Nocturia decreased in all treatment groups by 56.1% (bladder training group); 65.4% (tolterodine group); and 66.3% (combination group); $p<0.05$ for each. Tolterodine may be implemented as a first-line medication for treatment of OAB symptoms such as nocturia but may be more effective if used in combination with bladder training (LOE 3) (217).

A prospective, non-randomized, non-placebo–controlled evaluation of 56 patients was conducted to study whether non-drug lifestyle modifications has an impact on nocturia. The 56 patients were instructed to do the following: 1) restrict fluid intake; 2) exercise daily; 3) keep warm in bed; and 4) avoid excessive sleep. Patients were evaluated before and 4 weeks after the treatment using the FVC, IPSS, and Pittsburgh Sleep Quality Index (PSQI). Mean nocturnal urine volume decreased from 923 mL to 768 mL ($p=0.0005$) and mean number of nocturnal voids decreased from 3.6 to 2.7 ($p<0.0001$). Twenty-six (53.1%) of 56 patients showed an improvement of more than one episode per night. Therefore, non-drug therapy is effective at decreasing both nocturnal urine volume and episodes of nocturia (LOE 3) (201), but clinical significance of the magnitude of change is debatable.

## Conclusions

Lifestyle changes and behavioural modification are non-invasive, conservative methods that can successfully reduce the number of nocturia episodes (LOE 3).

Behavioural modification in conjunction with antimuscarinic pharmacotherapy is more effective at reducing nocturia episodes than either method alone (LOE 3).

## Recommendations

Lifestyle changes, such as reducing intake of caffeine and alcohol, limiting nighttime fluid intake, and improving sleep hygiene, are effective methods that help reduce nocturnal urine volume and episodes of nocturia (GOR C).

Consider using bladder training in conjunction with antimuscarinic medication (GOR C).

### 3.7.2 **Pharmacotherapy**

#### 5-alpha reductase inhibitors

Men with LUTS associated with BPE often present with voiding and storage symptoms including weak stream, incomplete emptying, frequency, urgency, and nocturia. 5-alpha reductase inhibitors (5ARIs) are thought to function by reducing prostate volume and decreasing prostatic urethral resistance. Finasteride was initially thought to reduce the overall risk for prostate cancer, but it may actually place its users at higher risk of developing high-grade prostate cancer. Subsequent analysis of the Prostate Cancer Prevention Trial (PCPT) found that finasteride improves the accuracy of prostate biopsy, but it does not significantly increase the risk of developing high-grade cancer. There was a 14% increase in high-grade cancer in the unadjusted model (RR, 1.14; 95% CI, 0.96–1.35; $p=0.12$) (218). Possibility for impotence, decreased libido, or ejaculatory dysfunction needs to be considered.

#### Evidence

A recent systematic review of 23 randomized, placebo-controlled trials involving 21,945 men was performed to evaluate the clinical effectiveness and harms of finasteride versus placebo for treatment of LUTS associated with BPE. The primary outcome was a meaningful change in AUA Symptom Score (SS)/IPSS (by at least 4 points). Outcomes were categorized as short term (<1 year) and long term (>1 year). Finasteride consistently improved urinary symptom scores and decreased the rate of BPE symptomatic progression (urinary retention, surgical intervention, or increase of the AUASS/IPSS by 4 or more points) more than placebo over 1 year. Finasteride did not show a significant improvement in nocturia, either in the short term (three trials) or long term (one trial). However, in men aged ≥70 years, finasteride ($n=126$) did show a significant reduction in episodes of nocturia over placebo ($n=127$) (–0.29 and –0.11, respectively; $p<0.05$) in short-term follow-up (one trial). Finasteride did show an increased risk for ejaculatory disorder, lower libido, and impotence over placebo (219).

#### Conclusion and recommendation

Finasteride does not reduce nocturia episodes in men, though some men over the age 70 years with LUTS may see a reduction in nocturia (LOE 1).

Finasteride may be effective at improving nocturia in men with LUTS aged 70 years and older (GOR C).

### 3.7.3 **Selective alpha-1 adrenergic antagonists**

Selective alpha-1 adrenergic blockers aid in relaxation of smooth muscle in the bladder neck and prostatic urethra and, accordingly, reduce BOO (220). These drugs may cause orthostatic hypotension, dizziness, or retrograde ejaculation. There are many, similarly effective choices when selecting an alpha-1 antagonist, and choice requires consideration of the patient's medical and financial needs.

## Evidence

A pooled analysis of three randomized, controlled trials looked at 955 patients with BPE who received alfuzosin (473) or placebo (482) for 84 days. The analysis showed a significant net decrease in nocturia episodes of 0.3 voids per night over placebo (LOE 1) (221).

A prospective, multicentre, open, randomized, parallel study of 189 Chinese men (aged 50–84 years) compared the effect of doxazosin gastrointestinal therapeutic system (GITS) 4 mg with tamsulosin 0.2 mg on nocturia. Ninety-four patients received doxazosin GITS and 95 received tamsulosin. Nocturia was assessed by question 7 on the IPSS and an FVC. Self-reported quality of life and quality of sleep were also analyzed. The reduction from baseline nocturia was greater with doxazosin GITS versus tamsulosin by the IPSS question 7 (1.5 vs. 1.1 at 4 weeks; $p=0.001$; 2.0 vs. 1.6 at 8 weeks; $p<0.001$) and by the FVC (1.7 vs. 1.3 at week 4; 2.1 vs. 1.7 at week 8; both $p=0.001$). Patients taking doxazosin GITS also reported improved quality of sleep over those taking tamsulosin (43.6% vs. 27.4% at 4 weeks; $p=0.020$; 81.9% vs. 67.4% at 8 weeks; $p=0.022$). Patients taking doxazosin GITS also reported improved quality of life according to the QoL question on the IPSS over those taking tamsulosin (2.5 vs. 2.8 at 4 weeks; $p=0.001$; 2.1 vs. 2.5 at 8 weeks; $p<.0001$). Therefore, doxazosin GITS is better than tamsulosin 0.2 mg (a standard dose in Asia) at improving nocturia, sleep quality, and quality of life in Chinese patients with LUTS/BPE (LOE 3) (222), but further work is needed to ascertain whether equivalent doses were compared.

A prospective, randomized trial of 2,583 men with one or more episodes of nocturia at baseline were treated with doxazosin, finasteride, combination therapy (doxazosin and finasteride), or placebo. Treatment efficacy was measured by self-reported number of nocturia episodes at 1 and 4 years post-treatment. After 1 year, mean nocturia was reduced by 0.35, 0.40, 0.54, and 0.58 in the placebo, finasteride, doxazosin, and combination groups, respectively. Reductions with combination therapy and with doxazosin were statistically greater than with placebo ($p<0.05$). After 4 years, the number of nocturia episodes was also significantly reduced in patients treated with doxazosin and combination therapy versus placebo ($p<0.05$). In a subgroup of men older than 70 years (495), all of the drugs significantly reduced nocturia at 1 year (finasteride 0.29, doxazosin 0.46, and combination 0.42) compared with placebo (0.11; $p<0.05$) (LOE 1) (223).

A prospective, 3-year, open-label study of 689 European men (mean age, 67.6 years) was performed to test the efficacy of alfuzosin 10 mg once daily. The men were asked to complete the IPSS before and after treatment. Post-treatment results were compared with baseline results. Overall IPSS improved with alfuzosin by 6.4 points (–33.4%) from baseline ($p<0.001$). There was also significant improvement from baseline in nocturia (–0.8, –25.5%; $p<0.001$) (LOE 2) (224).

A secondary analysis of the Department of Veterans Affairs Cooperative Study Trial studied the changes in nocturia in a cohort of 1,078 men with BPE who were randomly assigned to receive terazosin, finasteride, combination, or placebo. Overall, episodes of nocturia decreased from a baseline mean of 2.5 to 1.8, 2.1, 2.0, and 2.1 episodes in the terazosin, finasteride, combination, and placebo groups, respectively. Mean reduction of nocturia episodes from treatment with terazosin was significantly different than that from treatment with combination therapy ($p=0.03$), finasteride ($p=0.0001$), and placebo ($p=0.0001$). The results from combination treatment were significantly different than those

from treatment with finasteride ($p$=0.04) and placebo ($p$=0.03). Terazosin and combination therapy reduced the number of nocturia episodes in men with BPE although the advantage of terazosin over placebo was only a net reduction of 0.3 episodes (LOE 1) (225).

A multicentre, double-blind, placebo- and active-controlled parallel group study of 955 patients (aged ≥50 years with an IPSS ≥13 and a urine maximum flow rate ($Q_{max}$) >4 and ≤15 mL/s) were randomized to receive silodosin 8 mg ($n$=381), tamsulosin 0.4 mg ($n$=384), or placebo ($n$=190) once daily for 12 weeks. Baseline IPSS and $Q_{max}$ were compared with the same parameters post-treatment. Only silodosin significantly reduced nocturia versus placebo (the change from baseline was −0.9, −0.8, and −0.7 for silodosin, tamsulosin, and placebo, respectively; $p$=0.013 for silodosin vs. placebo) (LOE 1) (226).

A systematic review of eight trials with 744 participants (men with BPE) studied the effects of naftopidil on LUTS. There was not one trial that compared naftopidil with placebo. In five trials ($n$=419), naftopidil in doses 25 mg to 75 mg per day was found to have similar efficacy to low-dose tamsulosin (0.2 mg/day) with a mean IPSS improvement of 8.4 versus 8.9 points. In comparing naftopidil with a phytotherapy preparation (eviprostat), naftopidil significantly improved overall IPSS (−5.9 vs. 0.4; $p$<0.0002). Naftopidil was generally well tolerated and had similar efficacy in improving BPE symptoms as measured by the IPSS, compared with low-dose tamsulosin (LOE 3) (227).

In a randomized, non-placebo, cross-over study, 34 patients (mean age, 72.4 years) with LUTS (IPSS >8) secondary to BPE were enrolled. Seventeen patients were prescribed naftopidil 50 mg for 4 weeks followed by a 1-week washout period and then prescribed tamsulosin 0.2 mg (standard dosage of this drug for Japanese men) for 4 weeks (group A). Group B was prescribed tamsulosin 0.2 mg for 4 weeks followed by a 1-week washout period and then prescribed naftopidil 50 mg for 4 weeks. Improvement of nocturia was evaluated pre- and post-treatment with the IPSS. The IPSS (for nocturia) was significantly lower in the naftopidil group compared with the tamsulosin group. Pretreatment overall baseline IPSS for nocturia was 3.4 (standard deviation [SD], 1.0); after tamsulosin the IPSS was 3.1 (1.2) and after naftopidil 2.3 (1.3) $p$<0.001. This study showed that naftopidil was more effective than tamsulosin in treating nocturia, suggesting that an alpha 1-d adrenergic receptor antagonist may be more efficacious than an alpha 1-a adrenergic receptor antagonist in improving nocturia (LOE 3) (228), but further work is needed to ascertain whether equivalent doses were compared.

In a multicentre, prospective, randomized, controlled study of 59 patients with LUTS, 31 men received naftopidil 50 mg and 28 received tamsulosin 0.2 mg for 6–8 weeks. Nocturia severity was evaluated with the IPSS at baseline and then after 2 weeks and again after 6–8 weeks. After 2 weeks, the nocturia score of the naftopidil group improved from 3.5 to 2.2 ($p$=0.0004), but the tamsulosin group did not see a significant improvement in nocturia (3.4 to 2.7; $p$=0.1). At the end of the 6–8 week course, both naftopidil and tamsulosin groups saw a significant improvement in nocturia; for naftopidil the score decreased from 3.5 to 1.6 ($p$<0.0001) and for tamsulosin from 3.4 to 1.7 ($p$<0.0001). This study indicates that naftopidil may improve nocturia symptoms faster than tamsulosin (LOE 3) (229), but further work is needed to ascertain whether equivalent doses were compared.

A prospective, non-randomized trial of 51 patients over age 40 years with LUTS examined the efficacy of tamsulosin OCAS (oral controlled absorption system) over the course of 8 weeks. All enrolled patients received 0.4 mg tamsulosin OCAS and were followed up at 2, 4, and 8 weeks post-treatment.

Patients were assessed at each visit using the IPSS-QoL and the N-QoL. Total IPSS decreased from a baseline of 19.52 to 6.08 at week 8 ($p<0.001$). N-QoL also improved from a baseline of 32.10 to 42.89 at week 8 ($p<0.001$). Therefore, tamsulosin OCAS may be effective at improving LUTS and nocturia (LOE 3) (230).

A prospective, non-randomized trial of 160 patients with LUTS/BPE and nocturia (≥2 voids/night) were treated with tamsulosin hydrochloride 0.2 mg PO daily for 8 weeks. FVC, QoL index, IPSS, PVR volume, and uroflowmetry were recorded before and after treatment. Of the 160 patients, 97 were "responders." The FVC and IPSS significantly improved in regard to both nocturnal frequency and hours of undisturbed sleep (HUS). The mean IPSS nocturia score improved from 3.1 (±1.1) before treatment to 1.8 (±0.8) after treatment ($p<0.0001$). The FVC nocturia voiding frequency improved from 3.1 (±1.0) before treatment to 1.7 (±1.0) after treatment ($p<0.0001$). The HUS also improved from 2.1 (±1.0) before treatment to 3.5 (±1.5) after treatment ($p<0.0001$). Therefore, tamsulosin significantly lowered nocturnal frequency and increased HUS in patients with LUTS/BPE and nocturia (LOE 3) (231).

In a prospective, non-randomized trial, 93 men with BPH (mean age, 70 years) were treated with 0.2 mg tamsulosin for 4 weeks. The IPSS, QoL index, and bother score for each symptom of the IPSS were assessed before and after treatment to ascertain whether there is a correlation between QoL and LUTS. Bother scores were high for slow stream, nocturia, and daytime frequency. The most predictable symptom for improvement of QoL after treatment was the improvement of the bother score for nocturia (F test; $p<0.01$) (LOE 3) (232).

In men aged over 50 years with BPE, silodosin 8 mg once daily was significantly more effective than placebo and tamsulosin in simultaneously improving nocturia, frequency, and emptying according to a post-hoc analysis (LOE 1) (233).

Naftopidil 75 mg daily showed significant improvements in daytime and nighttime frequency, IPSS, and QoL index after treatment for 6 weeks in patients with BPH who were previously treated with tamsulosin. Nighttime frequency decreased from 3.1 (±0.6) episodes per night to 1.2 (±0.8) episodes per night ($p<0.0001$) after treatment (LOE 3) (234).

## Conclusions

Most studies were undertaken in the context of men with LUTS and presumed BPE, and assessment employed the IPSS, which has limitations in regard to evaluation of nocturia.

Alfuzosin, doxazosin, naftopidil, silodosin, tamsulosin, and terazosin are more effective than placebo at reducing the number of nocturia episodes in patients with BPE (LOE 1).

A second alpha-adrenergic antagonist may achieve improvement where nocturia has failed to improve sufficiently (LOE 3).

Studies comparing efficacy between agents need to take into account dose equivalence and population studied (LOE 3).

Improving nocturia is the most heavily weighted factor at improving overall QoL (LOE 3).

## Recommendations

Alpha-adrenergic antagonists may be offered to men with nocturia in association with LUTS and BPE (GOR A).

In the event of insufficient response to an alpha-adrenergic antagonist, another may be offered to men with nocturia in association with LUTS and BPE (GOR C).

### 3.7.4 Combination therapy

#### 3.7.4.1 5ARI + selective alpha-1 adrenergic antagonist

A randomized, controlled trial of 3,047 men with LUTS/BPE (enrolled in the Medical Therapy of Prostatic Symptoms [MTOPS] trial) were randomly assigned to receive doxazosin, finasteride, combination of the two, or placebo. Of the enrolled cohort, 2,583 men reported one or more episodes of nocturia and completed 12 months or more of follow-up. The mean number of nocturia episodes was reduced by 0.54, 0.40, 0.58, and 0.35 in the doxazosin, finasteride, combination, and placebo groups, respectively, after 1 year. Reductions with doxazosin and combination therapy were significantly greater than with placebo alone ($p<0.05$) (LOE 1) (223).

#### 3.7.4.2 Antimuscarinic and alpha-1 adrenergic antagonist

A randomized, double-blind, placebo-controlled study assigned patients to one of four groups for 12 weeks: placebo ($n=222$), 4 mg tolterodine extended release (Tolt ER, $n=217$), 0.4 mg tamsulosin ($n=215$), and combination Tolt ER plus tamsulosin ($n=225$). The combination of Tolt ER and tamsulosin significantly reduced the number of micturitions per night compared with placebo (–0.59 vs. –0.39; $p=0.02$) (LOE 1) (235).

In a randomized trial of 69 patients with LUTS, patients received either terazosin 2 mg once daily for 6 weeks ($n$=36) or both terazosin 2 mg once daily and tolterodine 2 mg twice daily ($n$=33) for 6 weeks. IPSS reduction in the combination group was significantly greater compared with the terazosin group. In the terazosin group, the pretreatment IPSS was 18.5 (±3.2) and the post-treatment IPSS was 17.3 (±4.1) ($p$=0.033). In the combination group, the pretreatment IPSS was 19.0 (±3.0) and the post-treatment IPSS was 14.0 (±4.2) ($p$<0.001). The main contributory factors in reducing the IPSS were decreases in urgency, frequency, and nocturia. This was determined by looking specifically at the storage IPSS questions 1, 2, 4, and 7 (StIPSS). The outcomes for these four questions were looked at collectively, but not individually. In the terazosin group, the pretreatment StIPSS was 12.7 (±3.1) and the post-treatment StIPSS was 11.7 (±3.0) ($p$=0.001). In the combination group, the pretreatment StIPSS was 13.2 (±3.2) and the post-treatment StIPSS was 9.2 (±2.9) ($p$<0.001) (LOE 3) (236).

### 3.7.4.3 Alpha-1 adrenergic antagonist and phosphodiesterase type 5 (PDE5) inhibitor

Another study looked at the effect of alfuzosin and sildenafil on IPSS. Patients treated with combination therapy showed the greatest improvement in the IPSS after 12 weeks (–24.1%) compared with alfuzosin alone (–15.6%) and sildenafil alone (–11.8%) ($p$<0.03). Frequency, nocturia, PVR, and $Q_{max}$ were significantly improved with alfuzosin only and the combination (LOE 3) (237).

## Conclusions

Alpha adrenergic antagonists can be used in conjunction with 5ARIs. Combination therapy may be more effective than either drug used separately (LOE 1).

A combination of an antimuscarinic and an alpha-1 adrenergic blocker significantly reduces the number of nocturnal micturitions over placebo (LOE 1).

A combination of an antimuscarinic and an alpha-1 adrenergic blocker can improve urgency, frequency, and nocturia severity over alpha-1 adrenergic blockade alone (LOE 3).

Alpha-1 adrenergic blockers may be more effective at improving nocturia when given with a PDE5 inhibitor (LOE 3).

## Recommendations

Alpha adrenergic antagonists in conjunction with 5ARIs may be offered to men with nocturia in association with LUTS and BPE (GOR A).

Alpha adrenergic antagonists in conjunction with antimuscarinic drugs may be offered to men with nocturia in association with storage LUTS (GOR A).

Alpha adrenergic antagonists in conjunction with PDE5 inhibitors may be offered to men with nocturia (GOR C).

## 3.7.5   **Anticholinergics/antimuscarinics**

Anticholinergics/antimuscarinics are used to treat OAB defined as "urgency with or without urge incontinence, usually with frequency and nocturia, in the absence of other causes of similar symptoms" (2). Antimuscarinics improve urgency, urgency incontinence, and detrusor overactivity (238). Antimuscarinics are not thought to affect nocturnal urine production through any well-understood mechanism. They may cause dizziness, dry mouth, or constipation. They are contraindicated in patients with urinary retention, or narrow (closed)-angle glaucoma.

### Evidence

In a post-hoc analysis of data from two 12-week, double-blind, placebo-controlled trials of nighttime (<4 hours before bedtime) Tolt ER (4 mg daily) dosing, 745 men (mean age, 64 years) were randomized to receive placebo ($n$=374) or Tolt ER ($n$=371). Patients used 7-day diaries to record urinary urgency for each void on a 5-point urgency rating scale (1, none; 2, mild; 3, moderate; 4, severe; 5, urgency urinary incontinence). Micturitions were analyzed *post hoc* by urgency rating categories: total (1 to 5); non-OAB (1 to 2); OAB (3 to 5); and severe OAB (4 to 5). At week 12, the reductions in the mean urgency ratings for the nighttime (−0.17 Tolt ER, −0.03 placebo), daytime (−0.09 Tolt ER, −0.02 placebo), and 24-hour (−0.12 Tolt ER, −0.03 placebo) intervals were significantly larger for Tolt ER–treated men compared with placebo-treated men (all $p \leq 0.01$). In terms of nocturnal frequency specifically, only patients with severe OAB manifested a significant reduction in nocturnal frequency (−50% for placebo vs. −77% for Tolt ER; $p \leq 0.01$) (LOE 1) (239).

Data was pooled from four 3-month, phase III, randomized, controlled trials where 2,534 of 3,032 patients reported nocturia at baseline (62% of these patients were classified as having nocturnal polyuria). These patients were randomized to receive solifenacin 5 mg or 10 mg or placebo. In patients without NP, there was a significant reduction in nocturia: −0.18 episode reduction advantage for 5 mg versus placebo and 0.08 episode reduction advantage for 10 mg versus placebo. Nocturia episode reduction in patients with NP was not significant. However, failure to achieve statistically significantly decreased nocturia between drug and placebo in the NP group appeared to be due to the unexpectedly high performance of the placebo in the latter arm (LOE 1) (240).

In a randomized, controlled trial, 658 patients at 52 sites were given either placebo or trospium chloride 20 mg twice daily in a 12-week, multicentre, parallel, double-blind, placebo-controlled study. After 12 weeks, there was a significant decrease in the mean number of nocturia episodes: −0.29 episodes for placebo versus 0.57 episodes for drug (baseline, 2 episodes/night) (LOE 1) (241).

An open-label, flexible-dose study of 516 adults with OAB (≥8 micturitions and ≥3 urgency episodes/24 hr) given fesoterodine was performed over a 12-week period. All subjects initially received 4 mg of fesoterodine once daily. About 50% of subjects opted for an increase in dosage at week 4. By week 12, there was a significant reduction in number of nocturnal voids compared with baseline, 2.6 versus 1.8 (31% reduction) (LOE 1) (242).

In a 12-week randomized, controlled study, 850 patients were given 4 mg Tolt ER or placebo once daily 4 hours prior to going to bed. All subjects had 8 or more micturitions per 24 hours, with or without urgency incontinence, and nocturia (mean, 2.5 episodes/night). Tolt ER did not significantly

reduce the total number of nocturnal micturitions; however, it did significantly reduce OAB-related and severe OAB-related nocturnal micturitions versus placebo. Tolt ER did not affect non-OAB nocturnal micturitions (LOE 1) (243).

Although flexible-dose fesoterodine does lead to a significant reduction in OAB symptoms, it does not lead to a significant reduction in the number of nocturnal micturitions. In a multicentre, randomized, double-blind, placebo- and active-controlled trial, 1,135 patients with OAB symptoms randomly received placebo, fesoterodine 4 mg, fesoterodine 8 mg, or Tolt ER 4 mg for 12 weeks. The median percent change in the number of nocturnal micturitions was as follows: placebo (−26.8%); Tolt ER 4 mg (−25%, $p$=0.815); fesoterodine 4 mg (−28.6%, $p$=0.982); and fesoterodine 8 mg (−23.1%, $p$=0.896) (LOE 1) (244). Several additional studies similarly reported lack of efficacy of fesoterodine in the treatment for nocturia (245–247).

In a 12-week, multicentre, parallel, double-blind, placebo-controlled trial, 523 patients from 51 sites were randomized to receive 20 mg trospium chloride twice daily or placebo. Trospium decreased the number of voids, urgency incontinence episodes, total daily micturitions, urgency severity, and increased the volume per void. It also significantly decreased nocturia severity by the end of weeks 4 and 12. At the end of week 4, trospium reduced the number of nocturia episodes: −0.43 vs. placebo −0.17 ($p$≤0.001). At the end of week 12, trospium reduced the number of nocturia episodes: −0.47 vs. placebo −0.29 ($p$≤0.05) (LOE 1) (248).

Once daily trospium chloride ER showed a significant reduction in the number of nocturnal voids compared with placebo (mean reduction in nocturic episodes, −0.8 vs. −0.6; $p$=0.006; mean percentage reduction, −27.1% vs. −22.6%; $p$=0.041) (249).

## Conclusions

Antimuscarinic drugs can significantly reduce the number of nocturnal micturitions versus placebo (LOE 1).

Antimuscarinic drugs are more effective than placebo at reducing OAB-related, but not non-OAB, nocturnal micturitions (LOE 1).

Antimuscarinic drugs are not effective at reducing nocturia in NP (LOE 1).

## Recommendations

Antimuscarinic drugs can be offered to men with OAB-related and severe OAB-related nocturnal micturitions with suitable counselling in regard to potential adverse effects, including urinary retention (GOR A).

Antimuscarinic drugs should not be offered to men with NP and no urinary urgency symptoms (GOR B).

## 3.7.6 **Antidiuretic pharmacotherapy**

Controlling nocturnal urine production is a rational therapeutic target in patients whose nocturia is caused by NP [40]. Desmopressin, a synthetic analog of the antidiuretic hormone AVP, is the only antidiuretic drug currently approved worldwide. It has previously been used to treat central DI and primary nocturnal enuresis. It is currently being utilized to decrease nocturnal urine production in patients with NP in about 80 countries globally (250). Desmopressin may cause hyponatremia, particularly in patients aged over 65 years.

Dosing:
- Desmopressin tablet 0.1 mg PO in the evening (may be titrated up to 0.4 mg PO for desired effect).
- Desmopressin lyophilisate (MELT) 60 µg sublingual in the evening (may titrate up to 240 µg PO for desired effect); 25–100 µg MELT preparation currently under investigation.

### Evidence

A meta-analysis of five studies with 619 participants and eight randomized, controlled trials with cross-over design were also included for systematic review. The analysis showed that desmopressin can potentially extend duration of the first sleep period and improve sleep quality by safely decreasing the frequency of nocturnal voids and nocturnal diuresis (LOE 1) (251).

The Noctopus trials were three short-term, randomized, controlled trials that studied the safety and efficacy of desmopressin in treating nocturia. There were 1,003 patients (519 men and 484 women) who underwent screening. A total of 157 patients were eliminated due to incomplete FVCs. Of the 846 patients who met inclusion criteria, 641 (76%) had nocturnal polyuria. The proportion of subjects having nocturnal polyuria was 66% in those <65 years versus 90% in those ≥65 years. In the short-term 3-week trials, 33% of men and 46% of women showed a significant (>50%) reduction in the mean number of nocturnal voids versus placebo. By 12 months, 67% of men and 67% of women who entered the extension study showed a significant reduction in the mean number of nocturnal voids versus placebo (LOE 1) (250).

A 4-week, randomized, double-blind, controlled trial was conducted in 757 nocturia patients who received 10, 25, 50, or 100 µg of sublingual desmopressin versus placebo. Reductions in the mean number of nocturnal voids were significant for 50 and 100 µg of sublingual desmopressin over placebo (−0.32; $p=0.02$; and −0.57; $p<0.0001$), respectively. Clinically significant hyponatremia (serum Na <125 mmol/L) occurred in 4 women and 3 men >65 years. This small but clinically significant risk for hyponatremia indicates that desmopressin is generally well tolerated, but must be carefully dosed and monitored in patients aged over 65 years (LOE 1) (252).

## Conclusions and recommendations

Desmopressin can decrease the frequency of nocturnal voids and decrease nocturnal diuresis (LOE 1).

Clinically significant hyponatremia (serum Na <125 mmol/L) is a rare but serious event; patients aged over 65 years are at greater risk (LOE 1).

Desmopressin can be prescribed to decrease nocturnal diuresis and nighttime frequency in men (GOR A).

Due to the risk for hyponatremia, serum sodium testing is essential when starting desmopressin to exclude low sodium levels, particularly in patients aged over 65 years (GOR A).

### 3.7.7 Diuretic pharmacotherapy

#### 3.7.7.1 Evidence

Diuretic pharmacotherapy has been viewed as both a cause and a treatment for nocturia. In a small, randomized, double-blind, placebo-controlled trial, 49 men (age >50 years) with NP were randomized to receive 40 mg of furosemide 6 hours prior to sleep or placebo. Among the 43 men who completed the study, the reduction in nocturia episodes was by 0.5 versus 0.0 (furosemide vs. placebo; $p$=0.014). There was also a significant reduction in percentage of nighttime voided volume (–18% for furosemide vs. 0% for placebo; $p$<0.001). Therefore, men with nocturnal polyuria may benefit from diuretic therapy 6 hours prior to sleep (LOE 2) (135).

In a randomized, double-blind, cross-over study, the efficacy of late-afternoon bumetanide 1 mg was compared with placebo. A cohort of 28 patients (15 men and 13 women) with nocturia (individuals with ≥2 episodes/night) completed two 2-week treatment periods. This group of patients had a baseline of 13.8 episodes of nocturia per week, which was reduced by 28% (–3.8 episodes) with bumetanide. Treatment with bumetanide was not beneficial in the 10 men with history of BPH. When excluding the 10 men with BPH, the remaining 18 patients reported that their weekly number of nocturic episodes was reduced by 4 compared with placebo (LOE 3) (253).

## Conclusions and recommendations

Men with NP may benefit from diuretic therapy with furosemide 6 hours prior to sleep (LOE 2) (GOR B).

Bumetanide may reduce the number of nocturnal micturitions, but it is not beneficial in men with BPE (288) (LOE 3) (GOR C).

### 3.7.8 Botulinum toxin

Evidence is limited. Ten patients with LUTS suggestive of BPE were included in one study. They were previously unsuccessfully treated with medical therapy (for at least 6 months) and were not surgical candidates. They received varying doses of botulinum toxin based on their prostate volume. The mean number of nocturia events decreased from $4.1\pm0.87$ pre-injection to $2.4\pm0.84$ post-injection ($p<0.001$) (LOE 3) (254).

## Conclusion and recommendation

Botulinum toxin can significantly reduce the number of nocturnal micturitions in patients who fail oral medical therapy and who are not surgical candidates (LOE 3).

Botulinum toxin may be offered as a treatment option for nocturia in patients who fail oral medical therapy and who are not surgical candidates. Due counselling related to unlicensed use and potential need for self-catheterization is mandatory (GOR C).

### 3.7.9 Nonsteroidal anti-inflammatory agents (NSAIDS)

The effect of loxoprofen sodium, an NSAID, on nocturia was studied as follows. Patients were divided into two groups: group 1 received an alpha blocker, a 5ARI, and 60 mg of loxoprofen sodium before sleep for 12 months; group 2 received an alpha blocker and a 5ARI before sleep for 12 months. Patients were evaluated at 3, 6, and 12 months. After 3 months, the number of nocturia episodes decreased significantly from baseline in both groups, but group 1 showed a greater decrease than group 2 ($-1.5\pm0.9$ vs. $-1.1\pm0.9$; $p=0.034$). At 6 and 12 months, for both groups, nocturia was significantly reduced from baseline, but did not significantly differ between the groups. However, patients in group 1 did experience gastric discomfort (12.5%), leg edema (7.5%), and decreased urine volume (2.5%). Therefore, loxoprofen may be used to treat nocturia for up to 3 months, but it should not be continued long term, as it adversely affected 22.5% of the participants in group 1 of this study; furthermore, the benefit of this NSAID seemed to disappear by 6 months of therapy (LOE 3) (255).

A prospective, randomized, double-blind, placebo-controlled study was performed to assess the efficacy of celecoxib for treatment of nocturia in men with BPE. Eighty men with LUTS were randomized to receive celecoxib 100 mg at 9 pm or placebo for 1 month. In the celecoxib group ($n=40$), nocturnal frequency ($\pm$SD) decreased from $5.17\pm2.1$ to $2.5\pm1.9$ ($p<0.0001$), and IPSS ($\pm$SD) decreased from $18.2\pm3.4$ to $15.5\pm4.2$ ($p<0.0001$), versus the control group ($n=40$), in which nocturnal frequency ($\pm$SD) decreased from $5.30\pm2.4$ to $5.12\pm1.9$ ($p>0.05$), and IPSS ($\pm$SD) decreased from $18.4\pm3.1$ to $18\pm3.9$ ($p>0.05$). There was a statistically significant difference found between the two groups ($p<0.0001$) (LOE 3) (256).

Side effects are a particular consideration in NSAID therapy, including the potential impact on renal function. Accordingly, more evidence is needed before such an approach can be considered mainstream practice.

## Conclusions and recommendations

Loxoprofen sodium may reduce nocturia for up to 3 months, but it should not be continued over the long term due to potential adverse effects (LOE 3).

Celecoxib may reduce nocturia in men with BPE (LOE 3).

More evidence is needed before NSAID therapy can be recommended for therapy of nocturia (GOR C).

### 3.7.10 Surgical interventions for benign prostatic enlargement

- Transurethral resection of prostate (TURP)
- Transurethral needle ablation (TUNA)
- High-intensity focused ultrasound (HIFU)
- Visual laser ablation (VLAP)
- Transurethral electrosurgical vaporization of the prostate (TUVP)
- Transurethral microwave therapy (TUMT)

Although there are several surgical options that address BPE (TURP, TUNA, HIFU, VLAP, TUVP, and TUMT), there have been few studies that have looked specifically at the effect on nocturia. One rationale for performing a procedure to reduce BOO is to lower the PVR volume. This might increase the amount of time taken to reach a volume at which the patient feels a need to pass urine (257).

In a retrospective analysis of 1,258 men, improvement in nocturia related to health-related quality of life (HRQL) was studied following various forms of treatment for BPE including: watchful waiting, alpha blockers, TURP, and TUMT. After 6–12 months, watchful waiting, alpha blockers, TURP, and TUMT yielded reduction in nocturia episodes by 7%, 17%, 75%, and 32%, respectively (LOE 3) (258).

Between 1994 and 1996, a prospective, non-randomized trial evaluated 95 men before and 6 weeks after surgical management for symptomatic BPE with TURP and four minimally invasive treatment alternatives (TUNA, HIFU, VLAP, and TUVP). The degree of nocturia did not improve significantly after VLAP (mean baseline 4.2 to 3.6 at the end of the study). The other four procedures did yield significant improvement in nocturia: 3.8 to 1.2 for TURP, 2.5 to 1.3 for HIFU, 2.6 to 1.2 for TUNA, and 3.8 to 1.3 for TUVP (LOE 3) (259).

In a single-centre study, 66 men with LUTS (mean age, 68.9 years) were randomized to receive TURP or tamsulosin 0.4 mg PO at bedtime (QHS) for management of nocturia (LOE 3) (260). Nocturia severity was assessed at baseline, 3 months, and 1 year. TURP was associated with a significant improvement compared with tamsulosin in the number of nocturnal awakenings, IPSS, ICIQ-N, and ICIQ N-QoL scores. The HUS increased in both groups, but was not statistically different.

## Conclusions

BPP-reducing procedures including TURP, TUMT, HIFU, TUNA, and TUVP can effectively reduce the number of nocturnal micturitions (LOE 3).

TURP is more effective than tamsulosin for treatment of BPH-related nocturia (LOE 3) (295).

## Recommendations

BOO-reducing procedures may improve nocturia in some patients with voiding LUTS and BOO who fail medical therapy and who are good surgical candidates (GOR C) (258–260).

Surgery for relief of BOO is not indicated for the management of patients whose primary complaint is nocturia (GOR C).

Comprehensive evaluation of the cause(s) of nocturia is essential before contemplating a surgical approach (GOR C).

Patients must be warned of the potential non-response and the risks associated with surgery for nocturia (GOR C).

### 3.7.11 Phytotherapy

There are many natural/herbal supplements that are marketed for treating BPE (296) including but not limited to:

- *Serenoa repens* (Sabal serrulata American dwarf palm/saw palmetto berry)
- *Pygeum africanum* (African plum tree)
- *Hypoxi rooperi* (South African star grass)
- *Urtica dioica* (stinging nettle)
- *Secale cerale* (rye pollen)
- *Cucurbita pepo* (pumpkin seed)

There are roughly 30 various phytotherapeutic compounds available for the treatment of BPE. The most common supplement is the American dwarf palm or saw palmetto berry (261). Although there are several theoretical explanations for the mechanism of saw palmetto, the actual mechanism is unknown.

A systematic review of 5,222 men from 30 randomized, controlled trials examined the effect of *Serenoa repens* on various LUTS, including nocturia, compared with other forms of pharmacotherapy and placebo. Although well tolerated, there was no significant difference in nocturnal voids in those treated with *Serenoa repens* versus placebo (weighted mean difference, 0.31; $p>0.05$; 1 trial). In addition, there was no significant advantage of *Serenoa repens* over finasteride (mean difference, –0.05; $p>0.05$) or tamsulosin (percent improvement of risk ratio, 0.91; $p>0.05$; 1 trial) (LOE 1) (261).

A systematic review of 1,562 men from 18 randomized, controlled trials examined the effect of *Pygeum africanum*. There was no comparison of *Pygeum africanum* to other pharmacologic treatments, such as alpha blockers and 5ARIs. Compared with placebo, men taking *Pygeum africanum* reported a 19% reduction in nocturia (weighted mean difference, −0.9 times per evening; $p>0.05$) (LOE 1) (262).

In a randomized, double-blind, multicentre, placebo-controlled trial, 369 men (aged 45 years and older) with a peak uroflow rate of at least 4 mL/s and an AUA Symptom Index score of 8–24 received 1, 2, then 3 doses of saw palmetto extract or placebo. Dose increases were done at 24 and 48 weeks. There was no difference in nocturia when comparing saw palmetto with placebo (LOE 1) (263).

Cernilton is prepared from the rye-grass pollen *Secale cereale*. A systematic review was conducted to assess the efficacy of Cernilton on urinary symptoms in men with BPH. Cernilton reduced nocturia compared with placebo and Paraprost. Versus placebo, the weighted risk ratio for improvement of nocturia was 2.05 (95% CI, 1.41 to 3.00); thus, those taking Cernilton are about 2 times more likely to have their nocturia improve over those taking placebo. Versus Paraprost, the weighted mean difference was −0.40 nocturia episodes per evening (95% CI, −0.73 to −0.07). Data was collected from a self-rated urinary symptom survey. The limitations of these trials were short duration, limited number of enrollees, gaps in reported outcomes, quality of preparations, and lack of a proven active control (LOE 1) (264).

## Conclusions and recommendations

*Serenoa repens* does not reduce the number of nocturnal micturitions compared with placebo (LOE 1).

*Pygeum africanum* and *Cernilton* reduce the number of nocturnal micturitions compared with placebo (LOE 1).

*Serenoa repens* should not be prescribed for treatment of nocturia (GOR A).

*Pygeum africanum* and *Cernilton* can be offered as an option for treating nocturia (GOR A).

## 3.7.12  Agents to promote sleep

The benzodiazepine oxazepam reduces severity of nocturia by 63%, but does not reduce nocturnal urine volume (LOE 3) (265). Overall, the influence of sedative agents in nocturia may be in improving return to sleep after each episode, rather than in improving nocturnal frequency (248); nitrazepam appeared to be better in this regard than triazolam (LOE 3) (266). Hypnotics can be associated with important adverse effects, such as morning drowsiness and confusion, which need to be considered carefully before prescription.

An alternative approach uses melatonin, which has lower risk for adverse effects than hypnotics. Melatonin is an endogenous hormone, which is secreted during nocturnal hours and is a determinant of circadian rhythm. Melatonin given at bedtime has been used for treatment of nocturia in men with BPE (LOE 1) (267). Changes versus placebo were not significant in the overall study group, but benefits were seen in a "responder group," in whom nocturnal frequency fell by more than 1 void per night. Melatonin has been compared with the hypnotic agent rilmafazone in elderly patients, with both groups showing a reduction in number of nocturnal voids (268).

## Conclusions and recommendations

Hypnotics do not appear to influence nocturia directly, but may be used to aid return to sleep (LOE 3, GOR C).

Melatonin may reduce number of nocturnal voids (LOE 1, GOR B).

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C4

# Male Lower Urinary Tract Symptoms and Sexual Dysfunction

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# CONTENTS

## Male Lower Urinary Tract Symptoms and Sexual Dysfunction

# 4.1 **Introduction**

The relationship between lower urinary tract symptoms (LUTS) and sexual dysfunction has been a focus of interest for many clinicians. The relationship between LUTS and erectile dysfunction (ED) has received increased attention recently because both diseases are highly prevalent, frequently co-associated in the same aging male group, and contribute significantly to overall quality of life (QOL).

Traditionally, the now well-accepted relationship was attributed to the coincidently high prevalence of both conditions in aged men. In recent years, the association between LUTS and sexual dysfunction has been emerging more clearly, as the level of concern of patients, government agencies, investigators, and health care providers grows. It is well established that both LUTS and ED independently reduce QOL. In combination, these two clinical entities logically compound life distress. The association between these two diseases has also garnered attention because investigators have hypothesized a common pathophysiology to explain the idea that they are causally linked. This common theme hypothesis has taken on a life of its own as pharmaceutical companies have expanded the indications for their drugs for both diseases.

Lifestyle factors–such as exercise, weight gain, and obesity–also appear to have an impact on LUTS. We expect these concerns to increase in importance in many parts of the world as the population ages and the obesity epidemic spreads. Because prevalence increases with age, the burden and the number of men complaining of LUTS will rise with the increasing life expectancy and growth of our elderly population. This will place increased demands on services for treatment, and necessitate the incorporation of evidence-based medicine.

New data have emerged that indicate potential links in epidemiological, physiological, pathophysiological, and treatment aspects of male LUTS (MLUTS) and various aspects of sexual dysfunction. If the relationships between MLUTS and sexual dysfunction are more than coincidental, there may be relevant clinical management questions and guideline implications related to the association. For example, the treatment of one condition (e.g. LUTS) may impact on the other (e.g. sexual dysfunction). It is also important for physicians to understand the link between ED and LUTS because the treatment of one disease may adversely affect the other. Almost all accepted therapies for LUTS (surgical or medical) can affect some aspect of sexual health, making it imperative that health care professionals understand their patients' concerns and motivations in these two linked diseases.

This relationship is important because: (1) additional information on risk factors for either disease could be important for patient screening; (2) many currently available LUTS treatments (medical and surgical) affect sexual function; (3) sexual problems related to LUTS are not necessarily limited to ED; (4) there is an increasing pool of affected men given the age demographics in many countries; and (5) knowing this relationship and the mechanism therein may open new avenues for the treatment of sexual dysfunction, ED, and LUTS. There is hope that this document will be a step in identifying the impact of MLUTS on the components of male sexual function, including ED and ejaculatory dysfunction (EjD), maintaining that appropriate direction.

In the management of bothersome LUTS, it is important that health care providers recognize the complex interactions between the bladder, bladder neck, prostate, and urethra, and that symptoms may result from interactions of these organs as well as the central nervous system. Men are remaining sexually active later in life, and the percentage of men who rated sex as being very important or extremely important was found to be over 60% in several countries in a worldwide study of 27,500 adults aged 40–80 years (1).

## 4.1.1 Outcomes assessments

Comparisons of treatments and their impact on sexual function must be based on standardized, reproducible, and relatively objective measures. Outcomes of interventions for MLUTS on sexual function can be categorized as either beneficial (benefits) or harmful (harms). They may be dichotomous (e.g. having a usable erection or not), categorical (e.g. having mild ED change to moderate ED), or continuous (e.g. experiencing an improvement in a symptom score of a certain number of points).

The impacts of many traditional therapies–e.g. trans-urethral needle ablation of the prostate (TUNA), trans-urethral microwave thermotherapy (TUMT), and trans-urethral resection of the prostate (TURP)–on ED and EjD have not been well elucidated. With medical therapies, most reports of changes in sexual function come from adverse event reporting. This is in part because some of the metrics commonly used today, such as the International Index of Erectile Function (IIEF), were not used during the regulatory trials of most drugs. Unfortunately, most reports of sexual function are poorly described or self-reported. Additionally, changes in sexual function among the proportion of men who were sexually active at baseline are nearly always ignored, thus the effects of treatment are muted, since data is generally reported as a mean for the entire group, which includes those men whose sexual function cannot decrease any further.

It is therefore important to review some of the issues affecting the reporting of sexual function scores (and other continuous scales) in the literature:

- These scales are not usually open ended, i.e. there is a worst or most severe score. Scores that start off very low at baseline can therefore not get much worse, or can only do so to a limited degree. This affects the ability to study the worsening of symptoms over time.
- Improvement (and worsening) can be expressed as an absolute value or a percentage. The absolute value of a point change on a given scale may impact a patient differently depending on the starting and ending scores. Some experts therefore advocate the use of percentage change values, thinking this will better reflect the impact of change on a scale. But reporting symptom improvement and worsening using percentages may over-emphasize worsening vs. improvement. For example, an increase in score from 6 to 18 represents a 50% worsening, but a decrease from 18 to 6 is only a 33% improvement.
- Treatment effect size is also of great importance. A large study with thousands of participants may show that a difference of 1 point ± a standard deviation of 5 points is significant, but this difference is unlikely to be of clinical relevance.
- The apparent incidence of these events depends on whether reports were elicited from patients by letting them report observed adverse drugs events/reactions spontaneously or by prompting them with a list of possible side effects, with this latter strategy resulting in higher reported incidence.

## 4.1.2 Levels of evidence

It is important to be transparent as to the strength of the recommendations made in a report of this nature, and there are several systems of determining and categorizing the levels of evidence in widespread use.

The International Consultation on Urological Diseases (ICUD) has published a document outlining the main steps for developing and grading guideline recommendations (2).

The ICUD follows the Oxford criteria for grading levels of evidence. These levels of evidence were published in 2009 and updated in 2011 (**Tables 1** and **2**).

**TABLE 1A**  The ICUD/Oxford criteria for grading levels of evidence, March 2009 (3).

| Level | Therapy/ Prevention Etiology/Harm | Prognosis | Diagnosis | Differential Diagnosis/ Symptom Prevalence Study | Economic and Decision Analyses |
|---|---|---|---|---|---|
| 1a | SR (with homogeneity) of RCTs | SR (with homogeneity) of inception cohort studies; CDR validated in different populations | SR (with homogeneity) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centres | SR (with homogeneity) of prospective cohort studies | SR (with homogeneity) of Level 1 economic studies |
| 1b | Individual RCT (with narrow CI) | Individual inception cohort study with >80% follow-up; CDR validated in a single population | Validating cohort study with good reference standards; or CDR tested within one clinical centre | Prospective cohort study with good follow-up | Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses |
| 1c | All or none | All or none case-series | Absolute SpPins and SnNouts | All or none case-series | Absolute better-value or worse-value analyses |
| 2a | SR (with homogeneity) of cohort studies | SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs | SR (with homogeneity) of Level >2 diagnostic studies | SR (with homogeneity) of Level 2b and better studies | SR (with homogeneity) of Level >2 economic studies |

CDR: clinical decision rule; CI: confidence interval; RCT: randomized controlled trial; SnNout: a diagnostic finding whose sensitivity is so high that a negative result rules out the diagnosis; SpPin: a diagnostic finding whose specificity is so high that a positive result rules in the diagnosis; SR: systematic review.

**TABLE 1A**  The ICUD/Oxford criteria for grading levels of evidence, March 2009 (3), *Cont'd*

| Level | Therapy/ Prevention Etiology/Harm | Prognosis | Diagnosis | Differential Diagnosis/ Symptom Prevalence Study | Economic and Decision Analyses |
|---|---|---|---|---|---|
| 2b | Individual cohort study (including low-quality RCT; e.g. <80% follow-up) | Retrospective cohort study or follow-up of untreated control patients in an RCT; derivation of CDR or validated on split-sample only | Exploratory cohort study with good reference standards; CDR after derivation, or validated only on split-sample or databases | Retrospective cohort study, or poor follow-up | Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses |
| 2c | Outcomes research; ecological studies | Outcomes research | | Ecological studies | Audit or outcomes research |
| 3a | SR (with homogeneity) of case-control studies | | SR (with homogeneity) of Level 3b and better studies | SR (with homogeneity) of Level 3b and better studies | SR (with homogeneity) of Level 3b and better studies |
| 3b | Individual case-control study | | Non-consecutive study; or without consistently applied reference standards | Non-consecutive cohort study, or very limited population | Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations |
| 4 | Case-series (and poor-quality cohort and case-control studies) | Case-series (and poor-quality prognostic cohort studies) | Case-control study, poor or non-independent reference standard | Case-series or superseded reference standards | Analysis with no sensitivity analysis |
| 5 | Expert opinion without explicit critical appraisal; or based on physiology, bench research, or first principles | Expert opinion without explicit critical appraisal; or based on physiology, bench research, or first principles | Expert opinion without explicit critical appraisal; or based on physiology, bench research, or first principles | Expert opinion without explicit critical appraisal; or based on physiology, bench research, or first principles | Expert opinion without explicit critical appraisal; or based on economic theory or first principles |

CDR: clinical decision rule; CI: confidence interval; RCT: randomized controlled trial; SnNout: a diagnostic finding whose sensitivity is so high that a negative result rules out the diagnosis; SpPin: a diagnostic finding whose specificity is so high that a positive result rules in the diagnosis; SR: systematic review.

**TABLE 1B** The ICUD/Oxford criteria for grades of recommendation, March 2009 (3).

| | |
|---|---|
| A | Consistent Level 1 studies |
| B | Consistent Level 2 or 3 studies or extrapolations from Level 1 studies |
| C | Level 4 studies or extrapolations from Level 2 or 3 studies |
| D | Level 5 evidence or troublingly inconsistent or inconclusive studies of any level |

**TABLE 2** The Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (4).

| Question | Step 1 (Level 1*) | Step 2 (Level 2*) | Step 3 (Level 3*) | Step 4 (Level 4*) | Step 5 (Level 5) |
|---|---|---|---|---|---|
| How common is the problem? | Local and current random sample surveys (or censuses) | Systematic review of surveys that allow matching to local circumstances** | Local non-random sample** | Case-series** | N/A |
| Is this diagnostic or monitoring test accurate? (Diagnosis) | Systematic review of cross-sectional studies with consistently applied reference standard and blinding | Individual cross-sectional studies with consistently applied reference standard and blinding | Non-consecutive studies, or studies without consistently applied reference standards** | Case-control studies, or "poor or non-independent reference standard"** | Mechanism-based reasoning |
| What will happen if we do not add a therapy? (Prognosis) | Systematic review of inception cohort studies | Inception cohort studies | Cohort study or control arm of randomized trial* | Case-series or case-control studies, or poor-quality prognostic cohort study** | N/A |
| Does this intervention help? (Treatment Benefits) | Systematic review of randomized trials or n-of-1 trials | Randomized trial or observational study with dramatic effect | Non-randomized controlled cohort/follow-up study** | Case-series, case-control studies, or historically controlled studies** | Mechanism-based reasoning |

  \* Level may be graded down on the basis of study quality, imprecision, indirectness, because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.
\** As always, a systematic review is generally better than an individual study.
N/A: not applicable.

| Question | Step 1 (Level 1*) | Step 2 (Level 2*) | Step 3 (Level 3*) | Step 4 (Level 4*) | Step 5 (Level 5) |
|---|---|---|---|---|---|
| What are the common harms? (Treatment Harms) | Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect | Individual randomized trial or (exceptionally) observational study with dramatic effect | Non-randomized controlled cohort/ follow-up study (post-marketing surveillance), provided there are sufficient numbers to rule out a common harm (for long-term harms, the duration of follow-up must be sufficient)** | Case-series, case-control, or historically controlled studies** | Mechanism-based reasoning |
| What are the rare harms? (Treatment Harms) | Systematic review of randomized trials or n-of-1 trial | Randomized trial or (exceptionally) observational study with dramatic effect | | | |
| Is this (early detection) test worthwhile? (Screening) | Systematic review of randomized trials | Randomized trial | Non-randomized controlled cohort/ follow-up study** | Case-series, case-control, or historically controlled studies** | Mechanism-based reasoning |

  * Level may be graded down on the basis of study quality, imprecision, indirectness, because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.
** As always, a systematic review is generally better than an individual study.
N/A: not applicable.

## 4.2 Epidemiology/Risk Factors: Epidemiological Evidence of Causality between Lower Urinary Tract Symptoms and Erectile Dysfunction

A large body of epidemiological data supports a causal relationship between LUTS and ED (5). The first large-scale study reporting on an age-independent association between LUTS and male sexual dysfunction was presented by Macfarlane *et al.* (6). Based on data from a study of 5,849 men who underwent a 1-year observational trial with alfuzosin, baseline LUTS were strongly correlated with different aspects of sexual dysfunction, despite the absence in the study of a validated

questionnaire to assess ED. Additional studies were published in the last decade, included in which were more than 35,000 men who contributed data on ED and LUTS. Based on these results, there is on average an increase of approximately 100% in ED rates in men with concomitant moderate or severe LUTS. The results are consistent overall across studies (7).

The largest and most widely cited study to date is the multinational survey of the aging male (MSAM-7) by Rosen *et al.* (8), in which the relationship between LUTS and both ED and EjD, as measured by the IIEF, International Prostate Symptom Score (IPSS), and Danish Prostatic Symptom Score (DAN-PSS)–a validated measure of ejaculation, low desire, and ejaculation-related bother in aging men (9). Data from 12,815 men aged 50–80 years from the US and six European countries were analyzed. Thirty-one percent of respondents had moderate-to-severe LUTS and 48.7% reported difficulties achieving an erection, with 10% reporting a complete absence of erection. Within each age category, the frequency of ED was strongly related to the severity of LUTS, with relative risk (RR) increasing from 3.1 (moderate LUTS) to 5.9 (severe LUTS), regardless of the coexistence of comorbid conditions, such as diabetes, hypertension, cardiac disease, or hyperlipidemia.

Recently, the impact of LUTS on men's sexual health was evaluated as part of a cross-sectional epidemiological study to assess the prevalence LUTS among men and women aged 40 years or older in the US, the UK, and Sweden (10). The analysis included 11,834 men with a mean age of 56.1 years, 71% of whom reported being currently sexually active. Twenty-six percent had mild-to-severe ED, 7% had EjD, and 16% had premature ejaculation. This problem (premature ejaculation) had not previously been assessed. However, a strong dose-related relationship between LUTS and male sexual dysfunction was again observed. Men with multiple LUTS had more severe ED, and more frequent EjD and premature ejaculation. In the logistic regression analysis, greater age, hypertension, diabetes, depression, urgency with fear of leaking, and leaking during sexual activity were significantly associated with ED. More frequent LUTS were associated with most of the common sexual dysfunctions in men, highlighting the importance of assessing the sexual health of all men presenting with LUTS.

In summary, the major epidemiological findings to date include: (1) a consistent dose-response association between increased frequency of LUTS and ED; (2) a significantly higher prevalence of LUTS in men suffering from ED as compared with men with normal erections; and (3) a statistically significant increase in the risk of ED for increasing urinary complaints in logistic regression models after controlling for age and comorbidities.

According to these reproducible and robust data, considering strength of association, internal consistency, and dose-response effects, a causal link between LUTS and ED is strongly supported (11). Moreover, the association between ED and LUTS has biological plausibility, given the interrelationships of the known pathophysiological mechanisms of these disease states.

# 4.3 Pathogenic Mechanisms

## 4.3.1 Pathogenic mechanisms of the relationship between male lower urinary tract symptoms and erectile dysfunction

The pathogenic mechanisms underlying the relationship between LUTS and ED are still not completely understood. However, in the last decade, several data have supported the involvement of different contributing factors (12). Proposed theories of how these disorders interrelate include: (1) alteration of the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway; (2) enhancement of RhoA/Rho-kinase (ROCK) signalling; (3) autonomic hyperactivity (AH); and (4) pelvic atherosclerosis (**Figure 1**).

**FIGURE 1**

Pathogenic mechanisms of the relationship between MLUTS and ED (12).
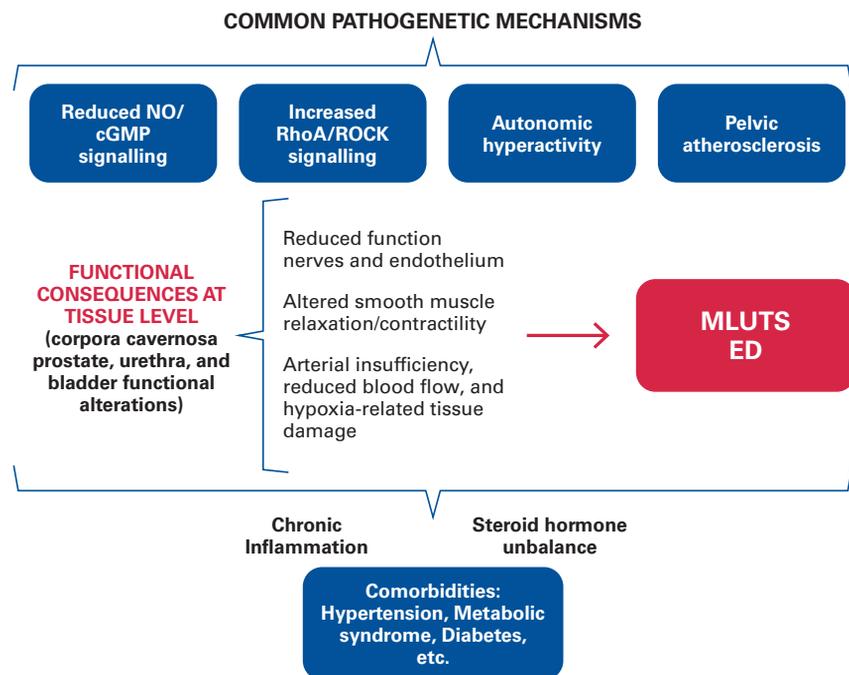


## 4.3.1.1 Alteration in NO levels: the NO/cGMP pathway

The role of the NO/cGMP pathway in the regulation of penile smooth muscle relaxation and erection has been well characterized. Several pieces of data indicate a role of NO in the regulation of smooth muscle tone of bladder, prostate, and urethra (12). Following NO release, catalyzed by the enzyme NO synthase (NOS), cGMP formation elicits smooth muscle relaxation involving a decrease in intracellular calcium levels and the activity of downstream proteins, such as cGMP-specific protein kinase.

Nitric oxide synthase activity has been identified in the urothelium, smooth muscle, blood vessels, and nerves of the bladder, being higher in the outlet region (13). Others have demonstrated that stimulation with an NO donor potentiates cGMP-dependent currents in isolated detrusor muscle strips, suggesting that the NO/cGMP pathway might be involved in regulating tonic bladder contractions (14).

The demonstration of antiproliferative and pro-apoptotic effects of NO donors on cultured bladder, prostate, and urethra smooth muscle cells further suggests a role for the nitrergic pathway in MLUTS. These findings explain why pathological conditions characterized by the deterioration of nerves and endothelium with impairment of NO production, such as hypertension or metabolic syndrome, are associated with ED and LUTS. Finally, phosphodiesterases (PDEs), enzymes that metabolize cGMP, thus limiting the intracellular signalling initiated by NO, participate as crucial modulators of the nitrergic pathway not only in the penis but also in the lower urinary tract (LUT), as recently shown (15).

### 4.3.1.2 RhoA/ROCK calcium-sensitizing pathway

Smooth muscle tone is also mediated through the activity of the RhoA/ROCK calcium-sensitizing pathway. The RhoA/ROCK pathway mediates α-adrenergic and endothelin-1 (ET-1)–triggered smooth muscle contraction. Hence, an up-regulated RhoA/ROCK pathway could impair smooth muscle relaxation, causing ED and LUTS. Accordingly, penile RhoA/ROCK signalling is increased in pathological conditions associated with ED, such as diabetes, and involuntary bladder contractions are associated with an increased signalling of the muscarinic receptor-activated RhoA/ROCK pathway (16). Up-regulated RhoA/ROCK signalling was also demonstrated in the corpora cavernosa and bladder of spontaneously hypertensive rats (SHR) (17). Rho-kinase inhibition limits bladder hyperactivity, reduces contractions in bladder strips from SHR, and improves erectile function.

### 4.3.1.3 Autonomic nervous system hyperactivity

Autonomic hyperactivity, a component of the metabolic syndrome, is a dysregulation of sympathetic and parasympathetic tone. Increased sympathetic tone results in penile flaccidity and antagonizes penile erection. Several epidemiological studies that did not account for confounding showed increased risk for LUTS with components of metabolic syndrome and AH, including type II diabetes, beta-blocker requirements, sedentary lifestyle, hypertension, and obesity (18,19).

Autonomic hyperactivity has been shown to lead to LUTS and subjective dysfunctional voiding (20). In this study, increased American Urological Association (AUA) symptom scores, benign prostatic hyperplasia (BPH) impact index scores, and even prostate size significantly correlated with markers for AH, such as increased serum norepinephrine levels and abnormal hypertensive response to tilt table testing. This relation remained significant after controlling for confounders–body mass index (BMI), insulin level, physical inactivity, and age.

Rat models have demonstrated an effect on prostatic growth and differentiation through manipulation of autonomic activity. Spontaneously hypertensive rats develop increased autonomic activity, prostate hyperplasia, and ED, and show improvement in their ED after brief aggressive treatment of their hypertension (21). In a different model, hyperlipidemic rats developed simultaneous prostatic enlargement, bladder over-activity, and ED after being fed a high-fat diet. It remains unclear whether

the increase in LUTS or ED is a consequence of an alteration in the function of the bladder/penis itself that generates increased central activation, or is the result of a central increase in sensitivity to peripheral signals.

Studies using SHR, which have been shown to develop increased autonomic activity, prostatic hyperplasia, LUTS, and ED, further support a significant role of the autonomic nervous system in promoting the common pathophysiology of these disorders. Spontaneously hypertensive rats had an overabundance of sympathetic fibres innervating the bladder, prostate, and penis, and showed improvement in erectile function after antihypertensive therapy.

### 4.3.1.4 Pelvic ischemia

Atherosclerosis of the prostate, penis, and bladder is regarded as the mechanism that ties together all the previously described theories, since pelvic atherosclerosis reduces NO signalling, up-regulates the RhoA-ROCK pathway, and is a component of the metabolic syndrome/AH. Known risks for ED and atherosclerosis, such as hypertension and diabetes, also affect LUTS (22).

Diffuse atherosclerosis of the prostate, penis, and bladder also ties in with an additional hypothesis linking LUTS with ED. The theory asserts that known risks for ED (hypertension, smoking, hyper-cholesterolemia, and diabetes mellitus) also impacts LUTS. A recent epidemiological study supports this notion. In it, both men and women who had two of four risk factors for atherosclerosis (diabetes mellitus, hypertension, hyperlipidemia, and nicotine use) had a statistically significantly higher IPSS score compared with subjects with one or no risk factors.

Smooth muscle alterations in the bladder, prostate, and penis of animal models of hypercholesterol-emia and pelvic ischemia show similarities (23). Hypoxia-induced over-expression of transforming growth factor, beta 1 (TGFb1) and altered prostanoid production have been proposed as potential mechanisms. Penile ischemia leads to smooth muscle loss in the penis, resulting in ED. Loss of smooth muscle in the bladder decreases compliance and worsens LUTS.

Similarly, bladder ischemia from either bladder outlet obstruction (BOO) or pelvic vascular disease can induce bladder smooth muscle loss with resultant replacement of collagen deposition and fibro-sis, as well as loss of compliance, hyperactivity, and impaired contractility. Loss of smooth muscle in the prostate results in a less distensible urethra, increased flow resistance, decreased urinary flow rate, and worsening of LUTS (24). Pelvic atherosclerosis ties in elegantly with all of the previously described theories, as pelvic ischemia/atherosclerosis is a component of the metabolic syndrome/AH, it up-regulates ROCK activity, and reduces NOS expression.

## 4.3.2 Pathogenic mechanisms of the relationship between male lower urinary tract symptoms and ejaculatory dysfunction

Ejaculation in the male sexual response cycle represents a reflex encompassing sensory stimuli, cere-bral and spinal control centres, and efferent nerve pathways (25). Ejaculation requires a complex interplay among somatic, sympathetic, and parasympathetic pathways, involving predominantly central dopaminergic and serotonergic neurons.

Ejaculatory dysfunction, broadly defined as any disturbance in ejaculation, can be considered to include premature ejaculation, delayed ejaculation, retrograde ejaculation, anejaculation (complete loss of ejaculation), and painful ejaculation (26). Anejaculation or decreased amount of ejaculate may be related to decreased force of LUT smooth muscle contraction, and/or decreased secretion from the prostate gland, seminal vesicle, testis, or epididymis. The condition might more likely relate to autonomic dysfunction, pelvic atherosclerosis, and hormonal imbalance, all of which have been linked with MLUTS. Aberrant sensation and inflammation of the prostate may cause painful ejaculation as well as MLUTS.

The pathophysiology underlying the relationship between LUTS and EjD is not yet completely understood. The topic of EjD is most often discussed in association with MLUTS and ED. It has been suggested that the common basics of LUTS and ED/EjD are: (1) endothelial (NOS/NO) dysfunction; (2) enhancement of RhoA/ROCK contractile signalling; (3) autonomic adrenergic hyperactivity/increased sympathetic tone; (4) pelvic atherosclerosis–induced pelvic ischemia; and (5) age-related hormonal imbalances. Taken together, aberrant functions of these factors may contribute to malfunction of LUT organs, and induce LUTS as well as EjD.

## 4.4 Impact of Therapies for Lower Urinary Tract Symptoms/ Benign Prostatic Hyperplasia on Sexual Activity

As mentioned above, many of the accepted medical therapies for LUTS can affect aspects of sexual health, making it imperative that health care professionals understand their patients' concerns and motivations in these two linked diseases.

### 4.4.1 Active surveillance

The primary goal of treating MLUTS is to improve symptoms and reduce bother. Both medical and surgical treatments have been reported to have a significant impact on sexual function compared with watchful waiting. Therefore, men with minor LUTS and minimal bother are candidates for active surveillance (27).

In a study of 234 men with LUTS, after 9 months of watchful waiting, 10% and 6% reported an increase or a decrease, respectively, in the frequency of sexual activity (28). In the same study, an improvement or a reduction of penile rigidity was reported by 11% and 6% of men, respectively.

In the Prostate Cancer Prevention Trial at 221 US centres, men aged 55 years or older who were randomized to the placebo group (*n*=9,457) were evaluated every 3 months for cardiovascular disease and ED between 1994 and 2003 (29). Of the 9,457 men randomized to placebo, 3,816 (47%) had ED at study entry. Among the 4,247 men without ED at study entry, 2,420 men (57%) reported incident ED after 5 years, and this increased to 65% at 7 years.

Other investigators reviewed the effect of finasteride on sexual function and found that in the placebo group, the incidences of impotence, ejaculation disorders, and decreased libido were 3.3%, 0.8%, and 1.4%, respectively, in the Medical Therapy of Prostatic Symptoms (MTOPS) study (4.5 years' follow-up) (30,31), and 5.1%, 0.1%, and 2.6%, respectively, in the Proscar Long-Term Efficacy and Safety Study (PLESS) (4 years' follow-up) (32).

Taken together, these studies show that the effect of active surveillance on ED in men with LUTS is variable during a short period, with some men finding that their sexual function improves and others finding that it deteriorates. However, in the long run, sexual function tends to deteriorate.

## Recommendation

The effect of active surveillance on ED in men with LUTS is variable during a short period, with some men finding that their sexual function improves and others finding that it deteriorates. However, in the long run, sexual function tends to deteriorate (Level 1a, Grade A).

## 4.4.2 Alpha-blockers

Alpha-blockers can affect ejaculation, orgasm, and penile erection, but they have no effect on sexual desire. The effects are reversible and disappear upon cessation of the medication.

Of the agents that are currently available for BPH therapy, tamsulosin and silodosin have the greatest effect on ejaculation, suggesting a mechanism mediated via the alpha-1A receptor (33). The frequency of EjD depends on the dose of the drug. The mechanism was initially thought to be retrograde ejaculation, but it appears that there is failure of emission and ejaculation (24).

According to a meta-analysis undertaken by the AUA, the frequency of EjD is as shown in **Table 3**, which demonstrates that tamsulosin is associated with a much higher incidence of EjD than are other alpha-blockers (27). Silodosin was not available at the time of that meta-analysis, but a recent randomized, placebo-controlled trial comparing tamsulosin 0.4 mg and silodosin 0.8 mg reported a 14.2% incidence of EjD with silodosin compared with 2.2% with tamsulosin and 1.1% with placebo (34).

**TABLE 3** AUA meta-analysis of sexual side effects of alpha-blockers (27).

| Agent | Incidence of EjD | Incidence of ED | Incidence of Changes in Libido |
|---|---|---|---|
| Placebo | 1% | 3% | 4% |
| Alfuzosin | – | 3% | 1% |
| Doxazosin | 0% | 4% | 3% |
| Tamsulosin | 10% | 4% | – |
| Terazosin | 1% | 5% | 5% |

There may be several mechanisms involved in the pathophysiology of EjD. These include relaxation of the smooth muscle of the bladder neck (resulting in retrograde ejaculation), a direct effect on the seminal vesicles, and a central effect (33). There is evidence for the former hypothesis, given that the efficacy of silodosin in the treatment of LUTS is associated with the development of EjD (35,36). However, clinical studies strongly suggest that retrograde ejaculation does not happen, as evidenced by the absence of sperm in the urine (37). The overwhelming evidence instead seems to suggest that the primary effect of these drugs on ejaculation is in fact to cause an ejaculation (38,39), and that this effect is mediated via alpha-1A receptors (40).

The effect on ED is more subtle, but generally, this class of drugs probably improves erectile function. The alpha-blocker phentolamine has actually been used as an intracavernosal agent and as an oral agent to treat ED (41), and there are data from a number of placebo-controlled trials suggesting that alpha-blockers used to treat BPH-related LUTS can also have a positive effect on penile erection (42).

However, a recent study comparing tadalafil and tamsulosin in the treatment of men with MLUTS also reported the results of IIEF measures (43). In comparison with placebo, tadalafil improved the IIEF domain score significantly, by 4.0 points, while there was no significant change in the score among the men taking tamsulosin (least squares mean change: −0.4). This emphasizes the marginal effect of alpha-blockers on erectile function. The presumed mechanism of action (MOA) is via a direct effect on penile smooth muscle by inhibition of the adrenergic contractile (anti-erectile) response.

## Recommendations

The effect of alpha-blockers on ED in men with LUTS is variable during a short period, with men reporting either no change or a modest improvement of unknown significance (Level 1a, Grade A).

Ejaculatory dysfunction in men with LUTS is significantly affected by two alpha-blockers: tamsulosin and silodosin. Other alpha-blockers have little or no impact on EjD (Level 1a, Grade A).

## 4.4.3　5-alpha-reductase inhibitors

The 5-alpha-reductase inhibitors (5-ARIs) have multiple effects on sexual function. Randomized, placebo-controlled clinical trials have shown that there is a potential effect on penile erection, ejaculation, and sexual desire. There is also occasional gynecomastia. The frequency of side effects in placebo-controlled trials is shown in **Table 4**. There seems to be no significant difference between the two agents that are currently available (finasteride and dutasteride).

In a non–direct comparative trial, the incidence of ED was 7% with dutasteride vs. 8% with finasteride; the incidence of decreased libido was 5% with dutasteride vs. 6% with finasteride; the incidence of EjD was 1% with dutasteride vs. 1% with finasteride; and the incidence of gynecomastia was 1% with dutasteride vs. 1% with finasteride (44).

**TABLE 4**　Sexual side effects with 5-ARIs

| Agent | ED | | EjD | | Loss or Reduction of Libido | |
|---|---|---|---|---|---|---|
| | 5-ARI | Placebo | 5-ARI | Placebo | 5-ARI | Placebo |
| Finasteride (27) | 8% | 4% | 4% | 1% | 5% | 3% |
| Dutasteride (45) | 7.3% | 4.0% | 2.2% | 0.8% | 4.2% | 2.1% |

The proposed MOAs include down-regulation of NOS within the penis (46) and possible effects on prostatic steroid metabolism (47).

While it was originally thought that the effects were fully reversible, there have been reports of persistence of sexual side effects following cessation of therapy when these drugs have been used to treat male pattern baldness (48). The veracity of this finding is still unclear, but it has been proposed that the mechanism may involve changes to steroid biochemistry in the central nervous system and within the prostate (47).

## Recommendations

The effect of 5-ARIs on sexual function in men with LUTS is modest but global, with effects on penile erection, ejaculation, and sexual desire. There seems to be no significant difference between the two agents that are currently available (Level 1a, Grade A).

It was originally thought that the effects were fully reversible, but there have been reports of persistence of sexual side effects following cessation of therapy when these drugs have been used to treat male pattern baldness. The veracity of this finding is still unclear, and no recommendation can be made based on the literature (Level 4, Grade D).

### 4.4.4 Combination therapy: 5-alpha-reductase inhibitors and alpha-blockers

There have been a number of large trials combining 5-ARIs and alpha-blockers for the treatment of men with BPH. Broadly speaking, the sexual side effects of this combination are more than simply the additive effects of the two drugs separately. The trial protocols were different, and data from the MTOPS trial (31), which compared doxazosin, finasteride, the combination of both, and placebo, is shown in **Table 5**, while data from the Combination of Avodart and Tamsulosin (CombAT) trial (49), which compared tamsulosin, dutasteride, and the combination both, and did not have a placebo arm, is shown in **Table 6**.

**TABLE 5** Sexual side effects in the MTOPS trial (31).

| Side Effect | Placebo | Doxazosin | Finasteride | Combination |
|---|---|---|---|---|
| ED | 3.32 | 3.56 | 4.53* | 5.11* |
| EjD | 0.83 | 1.10 | 1.78* | 3.05* |
| Diminution of libido | 1.4 | 1.56 | 2.36* | 2.51* |

*$p<0.05$ for comparison with placebo group.

**TABLE 6** Sexual side effects in the CombAT trial (49).

| Side Effect | Tamsulosin | Dutasteride | Combination |
|---|---|---|---|
| ED | 5% | 7% | 9% |
| Decreased semen volume | <1% | <1% | 2% |
| Retrograde ejaculation | 1% | <1% | 4% |
| Diminution of libido | 2% | 3% | 4% |

## Recommendation

The effect of 5-ARIs on sexual function in men with LUTS is modest but global, with effects on penile erection, ejaculation, and sexual desire. When adding select alpha-blockers, the sexual side effects on EjD are additive (Level 1a, Grade A).

## 4.4.5 Combination therapy: alpha-blockers and phosphodiesterase type 5 enzyme inhibitors

There are no large trials reporting the effects of combination phosphodiesterase type 5 enzyme (PDE5) inhibitors and alpha-blockers. However, a number of small studies have been reported, and they show varying effects on sexual function, as shown in **Table 7**. The primary purpose of these trials was to assess the effect on MLUTS. Overall, there is no evidence that combinations of alpha-blockers and PDE5 inhibitors (PDE5-Is) have a greater beneficial effect on erectile function compared with PDE5-Is alone.

**TABLE 7** Sexual side effects with PDE5-I/alpha-blocker combinations.

| Study Treatments | Alpha-Blockers | | PDE5-Is | | Combination | |
|---|---|---|---|---|---|---|
| | Patients (N) | Change in IIEF-EF | Patients (N) | Change in IIEF-EF | Patients (N) | Change in IIEF-EF |
| Sildenafil 25 mg + alfuzosin 10 mg (50) | 20 | + 2.9 | 21 | + 7.1 | 21 | + 9.5 |
| Tamsulosin 0.4 mg vs. tamsulosin 0.4 mg + tadalafil 20 mg/day (51) | 27 | + 1.9 | N/A | N/A | 27 | + 8.2 |
| Tadalafil 20 mg every other day + alfuzosin 10 mg/day (52) | 22 | +15% | 21 | +36.3% | 23 | + 37.6% |
| Sildenafil 25 mg 4x/day + tamsulosin 0.4 mg (53) | 20 | +12.4% | 20 | + 65% | 20 | +67.5% |
| Tamsulosin 0.4 mg vs. vardenafil 20 mg/day + tamsulosin 0.4 mg/day (54) | 29 | + 0.1 | N/A | N/A | 30 | + 2.6 |

IIEF-EF: International Index of Erectile Function – Erectile Function domain
N/A: not applicable.

## Recommendation

There is no evidence that combinations of alpha-blockers and PDE5-Is have a greater beneficial effect on erectile function compared with PDE5-Is alone (Level 4, Grade C).

### 4.4.6  Anticholinergics

Antimuscarinics have been widely used in the treatment of overactive bladder (OAB) in MLUTS. Five subtypes of muscarinic receptors (M1, M2, M3, M4, and M5) have been identified, and are distributed throughout the LUT and other systemic organs (55).

In the human urinary bladder, M2 and M3 are the main receptors responsible for detrusor contraction. Adverse effects associated with antimuscarinics include dry eyes, blurred vision, dry mouth, confusion, tachycardia, urinary retention, and constipation (56). Cholinergic receptors are widely distributed throughout the LUT and might impact sexual function. However, the effect of anticholinergics on sexual activity is unclear, with few data reported in the literature.

Cholinergic innervation of the prostate gland has an important role in the regulation of growth and secretion of the prostate epithelium (57–59). Muscarinic receptors have been found to be localized exclusively in the glandular epithelium of the human prostate, consistent with the lack of contractile effects of muscarinic receptor–active drugs on human prostate preparations (60). Muscarinic receptors in the prostate appear to be involved in processes other than control of smooth muscle contraction. Evidence of the clinical effects of anticholinergics on prostate secretion and sexual function is lacking.

The influence of the parasympathetic nerve on the contraction of the seminal vesicle has seldom been investigated. In animal models, the M3 subtype has been found to be involved in seminal vesicle contraction (61). Other models have demonstrated that sympathetic and parasympathetic innervations both trigger contraction of the seminal vesicle and work independently (62). They also found that the M3 subtype is the dominant muscarinic receptor responsible for the effects of parasympathetic stimulation on the seminal vesicle in rats. Evidence of the clinical effects of antimuscarinics on the function of the seminal vesicle is incomplete.

In the human vas deferens, the effect of exogenous acetylcholine (Ach) is a dose-dependent sudden increase in the basal tension of the vasa (63). The Ach-induced contractile response of the human vas deferens is antagonized by prazosin, a selective alpha-1 adrenergic antagonist. This suggests that Ach acts at the presynaptic level, stimulating the release of norepinephrine from adrenergic neurons. Therefore, an anticholinergic might decrease the contractile force of the vas deferens and impair ejaculatory function. Unfortunately, clinical data are lacking.

In the human corpus cavernosum, relaxation of the smooth muscle is necessary for penile erection, which is under the control of neurotransmitters and vasoactive agents. Investigators have reported that the human corpus cavernosum expresses four subtypes of muscarinic receptors (M1, M2, M3, and M4) (64). However, in cultured human corpus cavernosum, smooth muscle cells only express the M2 and M4 subtypes. The M2 and M4 receptors are thought to inhibit adenylate cyclase, leading to increased levels of cyclic adenosine monophosphate (cAMP). This suggests a potential role of M2 and M4 in maintaining smooth muscle tone and treating ED.

In a recent study, investigators reported that low-dose neostigmine (0.02 mg/kg) reduced the intra-cavernosal pressure/mean arterial pressure (ICP/MAP) increase with cavernous nerve stimulation, but that high doses (0.06 and 0.4 mg/kg) potentiated ICP/MAP rise (65). This study demonstrated that muscarinic receptors may modulate NO synthesis in nitrergic nerves and that a high level of cholinergic stimulation may promote erection by increasing NO synthesis.

One group of investigators reported that the impact of OAB is evident across domains of sexual health in both men and women (66). Another study showed that the presence of OAB wet increased the risk and severity of ED (67). Therefore, treatment of OAB with an anticholinergic may improve sexual function. A supportive multicentre study of trans-dermal oxybutynin therapy was conducted in 2,878 subjects with OAB (12.8% male), treated with trans-dermal oxybutynin for 6 months or less (68). The effects of OAB on subjects' sex lives improved in 19.1% and worsened in 11.2%. The effect on relationships with partners improved in 19.6% and worsened in 11.9%. The effects on sexual function may secondly relate to improvement in OAB.

Clearly, additional research is needed to determine whether antimuscarinics have a clinically significant effect on the function of the prostate, the cavernous tissue, or ejaculatory processes in humans, and their overall impact on sexual function.

## Recommendation

There is sparse evidence that treatment with anticholinergics may improve sexual function. This is reflective of the small number of studies investigating this ignored topic, rather than poorly designed studies. A specific recommendation about the overall impact of anticholinergics on sexual activity cannot be made (Level 1b, Grade B).

## 4.4.7 Phosphodiesterase type 5 enzyme inhibitors

Although the underlying mechanisms of the relationship between MLUTS and ED are not yet fully elucidated, common pathogenic pathways can be potential targets for PDE5-Is. Both PDE messenger ribonucleic acid (mRNA) and protein have been identified throughout the human lower urogenital tract, with varying concentrations and expression, providing evidence of a significant role of the NO/cGMP pathway in the regulation of smooth muscle contraction in the human bladder and prostate.

The presence of cGMP-dependent protein kinase-1 (cGKI) isoforms alpha and beta was identified in the prostate, providing further evidence of a significant role of the NO/cGMP pathway in the regulation of smooth muscle contractility in the human prostate (69). Among all tissues of the LUT, PDE5 was localized in blood vessels and muscular fibres, and PDE5 expression and activity was higher in the bladder neck, even when consistent PDE5 expression and activity was also found in the prostatic urethra (70).

Several trials have demonstrated that sildenafil, vardenafil, and tadalafil can significantly improve overall erectile function in men with co-morbid LUTS/BPH and ED (50–54,71–77). Differences between the trial results may be due to different populations, designs, dosage, and treatment durations (78). In the current literature, there are no data about ejaculation or global sexuality improvement that are useful in the context of MLUTS with or without sexual (including ejaculatory) dysfunction.

In the first prospective, randomized, double-blind, placebo-controlled trial in men with a history of LUTS/BPH, regardless of their erectile function, McVary reported a significant improvement in both urinary and erectile function from baseline at 6 and 12 weeks with once-daily 5 mg tadalafil, followed by dose escalation to 20 mg tadalafil, compared with placebo, demonstrating a dose-dependent effect on both urinary and sexual function, and a direct correlation between improvement in sexual function and urinary function (IIEF: +6.0 and IPSS: −2.8; IIEF: +7.7 and IPSS: −3.8, with 5 mg and 20 mg tadalafil, respectively) (72).

Other investigators, in a post-hoc analysis of a phase 2/3 randomized controlled trial (RCT) of men with ED and moderate-to-severe LUTS, reported that the improvement in erectile function with daily administration of tadalafil can be achieved regardless of baseline age, BMI, LUTS severity, or prior ED therapies, demonstrating a strong efficacy of PDE5-Is in treating a broad group with MLUTS (74).

After a median of 12 weeks of treatment with any PDE5-I for MLUTS, the mean improvement from baseline in IIEF score was above 3 points (mean: 5.5, range: 2.8–7.6) (see **Figures 2** and **3** and **Table 8**). Moreover, as noted in a recent meta-analysis, the combination of a PDE5-I plus an alpha-blocker was consistently superior to alpha-blockers alone in the improvement of sexual function of men with LUTS (IIEF score +3.6, range: +3.1 to +4.1) (78). Unfortunately, there is no evidence that PDE5-Is could limit or restore the impact of other therapies for MLUTS on sexual function.

## FIGURE 2

PDE5-Is for MLUTS: Mean improvement from baseline IIEF score–Weighted differences (with 95% CI) of IIEF score for the studies on PDE5-Is vs. placebo. Modified from (78).

**IIEF mean differences**

| Source | Diff. In means | LL, 95% CI | UL, 95% CI |
|---|---|---|---|
| McVary, 2007 @ | 7.600 | 6.171 | 9.029 |
| McVary, 2007 @@ | 6.800 | 4.306 | 9.294 |
| Stief, 2008 ^ | 6.000 | 3.494 | 8.506 |
| Porst, 2009 ^^ | 3.600 | 1.225 | 5.975 |
| Porst, 2009* | 2.800 | 0.471 | 5.129 |
| Porst, 2009** | 5.800 | 3.445 | 8.155 |
| Porst, 2009*** | 5.200 | 2.866 | 7.534 |
| **OVERALL** | **5.487** | **4.097** | **6.877** |

Placebo ← | → PDE5-Is
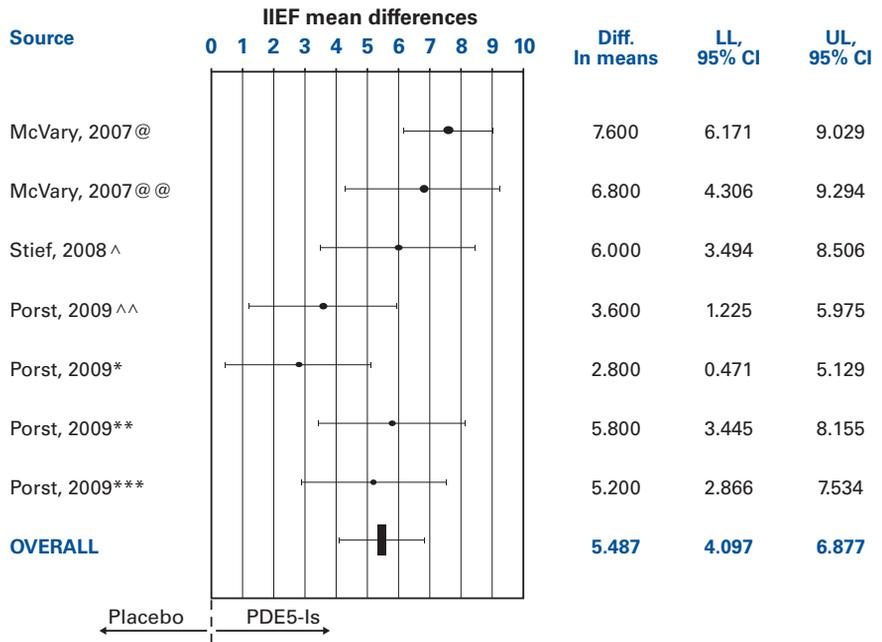
@ (79); @@ (72); ^ (76); ^^ (74)

## FIGURE 3

Mean improvement of PDE5-Is + alpha-blockers vs. alpha-blockers alone–Weighted differences (with 95% CI) of IIEF score for the studies on PDE5-I + alpha-blocker vs. alpha-blocker alone. Modified from (78).

**IIEF mean differences**

| Source | Diff. In means | LL, 95% CI | UL, 95% CI |
|---|---|---|---|
| Kaplan, 2007* | 5.40 | 2.31 | 8.49 |
| Bechara, 2008** | 6.30 | 0.89 | 11.71 |
| Liguori, 2009*** | 3.90 | 1.15 | 6.65 |
| Gacci, 2011 @ | 3.50 | 2.95 | 4.05 |
| **OVERALL** | **3.60** | **3.07** | **4.12** |

α-Blocker alone ← | → α-Blocker + PDE5-Is
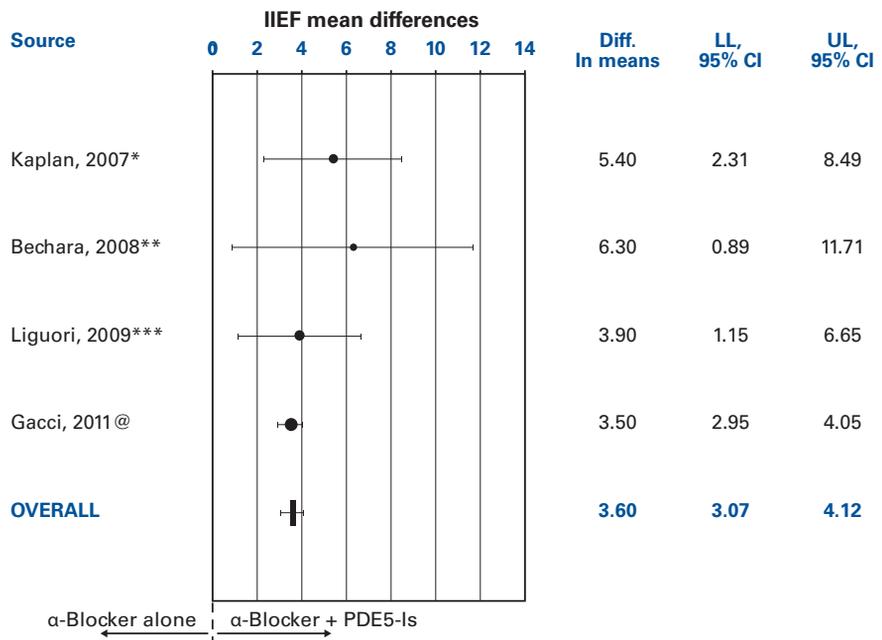
* (50); ** (51); *** (52); @ (54)

LL = lower limit
UL = upper limit
*       P≤0.05
**      P≤0.01
***     P≤0.001

**TABLE 8** Clinical evidence of PDE5-Is alone or with alpha-blockers and LUTS derived from clinical trials.

| Study | Baseline Characteristics | | | Treatment | | | Study Design | | |
|---|---|---|---|---|---|---|---|---|---|
| | Age | BMI | IPSS | Drug | Dosage (mg) | Pills/Week | Number of Patients Completed | Study Duration (Weeks) | Jadad Score |
| McVary, J Urol 2007 (79) | 60 | – | – | Sildenafil | 50 (2 wks) 100 | 7 | 323 | 12 | 4 |
| McVary, J Urol 2007 (72) | 61.5 | – | 17.9 | Tadalafil | 20 (2 wks) 100 | 7 | 251 | 12 | 3 |
| Stief, Eur Urol 2008 (76) | 55.9 | 27.3 | 16.8 | Vardenafil | 10 | 14 | 215 | 8 | 3 |
| Roehrborn, J Urol 2008 (75) | 62.0 | 28.5 | 17.2 | Tadalafil | 2.5; 5; 10; 20 | 7 | 886 | 12 | 3 |
| Porst, Eur Urol 2009 (74) | 61.9 | 28.3 | 16.1 | Tadalafil | 2.5; 5; 10; 20 | 7 | 491 | 12 | 3 |
| Tamimi, BJU Int 2010 (77) | 60.9 | 26.9 | 19.0 | UK-369,003 | 10; 25; 50; 100 | 7 | 283 | 12 | 3 |
| Porst, Eur Urol 2011 (73) | 64.8 | 27.8 | 16.8 | Tadalafil | 5 | 7 | 300 | 12 | 4 |
| Egerdie, J Sex Med 2012 (71) | 62.3 | 28.1 | – | Tadalafil | 2.5 or 5 | 7 | 526 | 12 | 4 |
| Kaplan, Eur Urol 2007 (50) | 63.4 | 25.4 | 17.3 | Sildenafil + alfuzosin | 25 | 7 | 37 | 12 | 3 |
| Bechara, J Sex Med 2008 (51) | 63.7 | – | 19.4 | Tadalafil + tamsulosin | 20 | 7 | 27 | 12 | 3 |
| Liguori, J Sex Med 2009 (52) | 61.3 | – | 15 | Tadalafil + alfuzosin | 20 | 7 | 39 | 12 | 3 |
| Tuncel, Word J Urol 2010 (53) | 58.8 | – | 15.4 | Sildenafil + tamsulosin | 25 | 4 | 40 | 8 | 2 |
| Gacci, J Sex Med 2012 (54) | 68.0 | 25.7 | 19.6 | Vardenafil + tamsulosin | 10 | 7 | 59 | 12 | 3 |

## Recommendation

There is strong evidence of improvement in LUTS with PDE5-Is, either alone or in combination with alpha-blockers. Since the prevalence of co-morbid LUTS and ED in men with BPH is high, especially in elderly men, the possibility of a single therapy approved to treat both conditions could be of clinical interest (Level 1a, Grade A).

### 4.4.8   Botanicals/Phytotherapies

In many parts of the world, the use of phytotherapeutic agents has markedly increased. At least one-third of men choosing non-surgical treatment for BPH are treated with herbal preparations alone or in combination with conventional therapies (80). The phytotherapeutic products commonly used for MLUTS are extracts derived from the roots, seeds, bark, or fruits of various plants (**Table 9**).

**TABLE 9**   Phytotherapeutic agents used in MLUTS.

| Scientific Name | Alternative or Common Name | Proposed MOA(s)* |
|---|---|---|
| *Serenoa repens* | Saw palmetto | - Anti-inflammatory<br>- Anti-androgenic<br>- Pro-apoptotic |
| *Secale cereale* | Rye pollen | - Anti-androgenic<br>- Smooth muscle relaxation<br>- Inhibition of prostatic growth |
| *Pygeum africanum* | African plum | - Anti-inflammatory<br>- Anti-androgenic<br>- Pro-apoptotic<br>- Anti-FGF beta |
| *Urtica dioica* | Stinging nettle | - Anti-androgenic |
| *Pinus pinaster* | Pycnogenol | - Anti-inflammatory |
| *Hypoxis rooperi* | South African star grass | - Anti-inflammatory<br>- Anti-androgenic<br>- Anti-estrogenic |
| *Cucurbita pepo* | Pumpkin seed | - Anti-androgenic |

*Proposed MOA does not infer any valid adequate evidence.

Although mono-preparations (from a single plant species) are available, many companies produce combination compounds (extracts of >2 species) in an attempt to provide supposedly enhanced efficacy and to create a unique product that can be registered, since these products have no patent protection.

The composition of plant extracts is very complex. They contain a wide variety of chemical compounds, including phytosterols, plant oils, fatty acids, and phytoestrogens. It is often unclear which of these compounds is the active component.

Although phytotherapies generally are less expensive, are better tolerated, and have milder and less frequent adverse events than do conventional medical treatments for LUTS, only a few trials have extensively investigated the overall impact of botanicals on sexual activity. These studies have mostly focused on *Serenoa repens* (81).

In a randomized equivalent study in 1,098 patients, patients who received *Serenoa repens* fared better than those who received finasteride on a sexual function questionnaire, and *Serenoa repens* gave rise to fewer complaints of decreased libido and impotence (82). In another trial, in 811 men with symptomatic BPH recruited in 11 European countries and randomized to *Serenoa repens* or tamsulosin for 12 months, the adjusted mean change from baseline in overall sexual activity was equivalent in both treatment arms. However, a significantly lower incidence of EjD was reported with *Serenoa repens* than with tamsulosin (0.6% vs. 4.2%, respectively) (83).

In a study encompassing patients from the main double-blind, randomized studies (*Serenoa repens* vs. finasteride, *Serenoa repens* vs. tamsulosin, and *Serenoa repens* 160 mg vs. 320 mg), in a total of 2,511 patients, a slight increase in sexual disorders–based on the Male Sexual Function 4-item (MSF-4) questionnaire (Evaluating the patient's interest in sex, quality of erection, achievement of orgasm, and ejaculation)–was reported with tamsulosin (+0.3) and finasteride (+0.8), while a slight improvement was reported with *Serenoa repens* (−0.2). Ejaculatory dysfunction was the most frequently reported side effect with tamsulosin and finasteride (both +0.2 on the specific MSF-4 question 4). The investigators concluded that in contrast to the impact on sexual function of both finasteride and tamsulosin, *Serenoa repens* has no negative impact on global sexual function, or on libido, erection, orgasm, and ejaculation (84).

In a systematic review of the adverse events associated with *Serenoa repens*, encompassing 40 articles, the authors confirmed that the adverse events, which are typically mild, infrequent, and reversible, include abdominal pain, diarrhea, nausea, fatigue, headache, rhinitis, and decreased libido, with an incidence similar to that seen with placebo (85). This correspondence of the safety profiles of *Serenoa repens* and placebo was confirmed by a recent Cochrane systematic review (86).

The overall safety and efficacy profile of a preparation of rye pollen (*Secale cereale*) was evaluated in 444 men enrolled in two placebo-controlled and two comparative trials, demonstrating a low incidence of adverse events of mild severity, and a withdrawal rate comparable to that of placebo (4.8% vs. 2.7%, respectively) (87).

Another Cochrane systematic review of a total of 18 RCTs involving 1,562 men treated with *Pygeum africanum* for MLUTS demonstrated the good safety profile of this compound, with mile adverse events and a low incidence of drop-out (12%), comparable to placebo (88).

Several other phytotherapeutic agents, such as *Urtica dioica* and *Pinus pinaster,* have also been evaluated in association with *Serenoa repens* (89).

## Recommendation

Several meta-analyses on the use of phytotherapies for MLUTS suggest a good safety profile, with incidences and severities of sexual adverse events similar to those associated with placebo. A specific recommendation about the overall impact of all combinations of phytotherapeutic agents on sexual activity cannot be made, due to the heterogeneity of the compounds and the methods used in the RCTs (Level 1a, Grade B)

## 4.5 Impact of Minimally Invasive Therapies for Lower Urinary Tract Symptoms/Benign Prostatic Hyperplasia on Sexual Activity

Although minimally invasive surgical therapies (MISTs) for MLUTS have been touted as safe and effective, their impact on sexual function has been less well described. Specifically, the effects on ED and EjD have not yet been well elucidated for two specific MIST options: TUMT and TUNA. In large part, this is because the metrics commonly used today, such as the IIEF, were not in use during the regulatory trials for these procedures. Unfortunately, most reports of sexual function are poorly described or self-reported.

### 4.5.1 Trans-urethral needle ablation of the prostate and trans-urethral microwave thermotherapy

#### 4.5.1.1 Trans-urethral needle ablation of the prostate

In a review of 35 studies using TUNA, the incidence of sexual side effects was sparsely reported (90). The incidence of ED in comparative studies with TURP was 20%, and the incidence of EjD was 14%.

Frieben *et al.* reported on three RCTs and one cohort study that compared TUNA (198 patients) with TURP (200 patients) (91–94). These studies suggested that TUNA resulted in fewer adverse effects on sexual function, with 5.8% of patients reporting decreased erectile function and 5.6% of patients reporting EjD, compared with TURP, with which 18.2% of patients reported ED and 39.7% reported EjD. As with TUMT, 7.9% of patients reported increased erectile function after TUNA.

## Recommendation

Erectile dysfunction and EjD have not been well elucidated with TUNA. In large part, this is because the metrics commonly used today, such as the IIEF, were not in use during the regulatory trials for the procedure. Unfortunately, most reports of sexual function are poorly described or self-reported. A specific recommendation about the overall impact of TUNA on sexual activity cannot be made (Level 3b, Grade D).

#### 4.5.1.2 Trans-urethral microwave thermotherapy

In a recently published Cochrane review, sexually active participants undergoing TUMT were significantly less likely to experience retrograde ejaculation (RR: 0.39; 95% CI: 0.21 to 0.75; risk difference: 0.34; 95% CI: $-0.55$ to $-0.13$) (95).

There are a number of studies suggesting advantages with TUMT in comparison with TURP (96–98). The authors of one systematic review of four studies (encompassing 190 patients who underwent TUMT and 148 who underwent TURP) noted that TUMT was collectively associated with less ED (8.7%) and EjD (17.8%) vs. TURP (19.3% and 42.7%, respectively) (91). A number of men (15.2% and 20.4%) actually noted improved erectile function after TUMT and TURP, respectively.

Collectively, both TUMT and TUNA, which are widely thought to be less effective than TURP, have been shown to be associated with fewer sexual adverse events than TURP. However, a definitive correlation between efficacy and sexual side effects cannot be absolutely stated. Studies have not consistently reported on or defined peri-operative adverse events such as sexual dysfunction, and estimates of these complications may be unreliable.

## Recommendation

Erectile dysfunction and EjD have not been well elucidated with TUMT. In large part, this is because the metrics commonly used today, such as the IIEF, were not in use during the regulatory trials for the procedure. Unfortunately, most reports of sexual function are poorly described or self-reported. A specific recommendation about the overall impact of TUMT on sexual activity cannot be made (Level 3b, Grade D).

## 4.5.2 Urethral compression/prostatic urethral lift system (Urolift®)

The UroLift® System is a new non-ablative approach to treat MLUTS. The system uses sutures that are delivered trans-urethrally to mechanically open the prostatic urethra without ablation or resection, assuming that bladder BOO is the etiology of the bothersome symptoms. During the procedure, a handheld delivery device is inserted through a cystoscope and deploys a spring-actuated implant that compresses the lumen of the prostatic urethra towards the prostatic capsule, thus stenting open the urethra and putatively relieving the obstruction.

In the single reported study with the system, 64 men aged 55 years or older, with symptomatic BOO, were recruited from a single centre. Treatment by urethral compression did not compromise sexual function in the 50% (*n*=32) of patients in whom sexual function was prospectively measured. Erectile function, as measured by the IIEF–Erectile Function domain, was stable or slightly increased at all time points as compared to baseline (**Table 10**).

Ejaculatory function, as measured by the Male Sexual Health Questionnaire (MSHQ)–EjD domain, was preserved throughout the follow-up period. Similar to the results for erectile function, ejaculatory function did not degrade in the initial 6 weeks post-procedure.

The MSHQ bother score also showed a modest but statistically significant decrease at most time points, indicating that the bother associated with ejaculatory function was not adversely affected by this LUTS/BPH therapy.

TABLE 10    Sexual Health Inventory for Men (SHIM), IIEF–Erectile Function domain and MSHQ values from 6 weeks through 12 months; the *p* values shown are for follow-up compared to baseline using a paired t test.

|  | 6 Weeks | 3 Months | 6 Months | 12 Months |
|---|---|---|---|---|
| **SHIM** | | | | |
| n (paired values) | 29 | 32 | 30 | 26 |
| Baseline | 18.3 ± 5.0 | 17.7 ± 5.7 | 17.4 ± 5.8 | 17.7 ± 5.9 |
| Follow-Up | 20.4 ± 4.8 | 20.3 ± 4.4 | 19.1 ± 5.3 | 19.5 ± 5.4 |
| Change | 2.1 | 2.7 | 1.7 | 1.8 |
| % Change | 11% | 15% | 10% | 10% |
| *p* value | | | | |
| **IIEF–Erectile Function Domain** | | | | |
| n (paired values) | 29 | 32 | 30 | 26 |
| Baseline | 23.0 ± 6.0 | 22.3 ± 6.7 | 22.2 ± 6.6 | 22.3 ± 6.8 |
| Follow-Up | 25.2 ± 5.7 | 24.8 ± 5.4 | 23.9 ± 6.1 | 23.9 ± 6.2 |
| Change | 2.1 | 2.6 | 1.7 | 1.6 |
| % Change | 9% | 12% | 8% | 7% |
| *p* value | 0.06 | 0.008 | 0.04 | 0.1 |
| **MSHQ** | | | | |
| n (paired values) | 31 | 33 | 30 | 26 |
| Baseline | 11.4 ± 2.4 | 11.4 ± 2.7 | 11.9 ± 2.8 | 11.6 ± 2.4 |
| Follow-Up | 12.5 ± 2.9 | 12.6 ± 3.1 | 11.6 ± 3.3 | 11.5 ± 2.8 |
| Change | 1.1 | 1.2 | -0.3 | -0.1 |
| % Change | 10% | 10% | -3% | -1% |
| *p* value | 0.01 | 0.008 | 0.6 | 0.9 |

## Recommendation

Although urethral compression–based treatment may improve the IPSS without impacting sexual function, this therapy is quite novel, with a small patient population, single-centre study, and short-term follow-up. For this reason, a specific recommendation about the overall impact of all combinations of urethral compression on sexual activity cannot be made. Longer follow-up, with larger patient populations is needed (Level 4, Grade C).

# 4.6 Impact of Trans-Urethral Resection of the Prostate (Bipolar/Monopolar) on Sexual Activity

The surgical management of MLUTS related to BOO continues to evolve towards less invasive, endoscopic procedures that are viable alternatives to open prostatectomy. In addition to open prostatectomy and TURP, newer surgical options include bipolar TURP, various laser trans-urethral approaches, trans-urethral electrovaporization of the prostate (TUVP), and robotic prostatectomy.

Trans-urethral resection of the prostate, in its various forms, is still regarded as the gold standard for the treatment of MLUTS secondary to benign prostatic obstruction (BPO) in those with moderate prostate volume, and it has invariably been touted as safe and effective.

Unfortunately, the impact of TURP on sexual function has been less well described. Specifically, the effects on ED and EjD have not yet been well elucidated, largely because the sexual function metrics used today are often not used in a comprehensive fashion. Unfortunately, most reports of sexual function are poorly described or self-reported.

The only RCT that compared TURP with a wait-and-see approach, with a follow-up of 2.8 years, reported similar rates of ED in both arms (19% and 21%, respectively) (99).

In an analysis of 29 RCTs, the incidence of ED following TURP was 6.5% (100). The incidence of newly diagnosed post-operative ED in patients treated with TURP has been reported to be between 0% and 32.5% (101).

Arai *et al*. compared cohorts undergoing TURP, TUMT, and TUNA (total with evaluable data: *n*=173) (97). A mild decrease in erectile function was reported in 18% to 25% of subjects in the treatment groups, with no significant differences between groups.

The reported increase in frequency of ED after TURP has been attributed by some to confounding ED risk factors (e.g. age), rather than being a direct consequence of TURP. Comorbidities such as diabetes mellitus and capsular perforation were reported as etiological risks factors for newly developed ED (102). In this rather large single-cohort study, and consistent with the lower risk estimates, 7.7% (range: 0% to 17%) of patients reported decreased erectile function after TURP. Interestingly, in one report, 6.2% (range: 0% to 19%) of patients actually reported increased erectile function after TURP (91).

There was no significant difference between the impact of bipolar and monopolar TURP on sexual function. With both, post-operative ED was found in 14% of patients (103). In an RCT comparing bipolar and monopolar TURP, there was no significant difference in the changes in IIEF scores during the follow-up period, and when the IIEF scores of all patients in both groups were compared, ED was found to have worsened in 17.0%, improved in 28.2%, and remained unchanged in 54.8% (104).

Ejaculatory dysfunction, the most common sexually related adverse event following surgery, putatively results from resection/destruction of the bladder neck, and is reported by 65%–70% of patients after TURP (27).

In a single-centre study, Arai *et al.* compared cohorts undergoing TURP, TUMT, TUNA and interstitial laser coagulation (total with evaluable data: *n*=173) (97). A severe decrease in ejaculate volume was noted in 49% of the men after TURP, compared with 29% after both TUMT and TUNA. This was also noted in another single-centre trial, in which investigators examined 212 men who had been randomized to undergo TURP, TUVP, or TUNA (105). Retrograde ejaculation occurred after TURP (100%) and TUVP (92.3%), but not after TUNA.

## Recommendation

Although TURP and its numerous variations have been performed for decades, there is poor reporting of their impact on sexual function. The literature primarily contains underpowered, uncontrolled, single-centre cohort studies of poor quality. Nearly all of these reports estimate ED and EjD based on adverse events reporting rather than prospective assessment. Additionally, changes in sexual function among the proportion of men who are sexually active pre-operatively are nearly always ignored, further muting the effects of treatment. For these reasons, a specific recommendation about the overall impact of all combinations of TURP on sexual activity cannot be made. Longer follow-up with larger patient populations is needed (Level 4, Grade D).

# 4.7 Impact of Laser Resection/Ablation/Enucleation on Sexual Activity

Laser interventions have the capacity to induce sexual dysfunction in the form of ED or in the form of retrograde or absent ejaculation. As with traditional TURP, there is poor reporting of the impact on sexual function of laser TURP. Trans-urethral laser procedures, in their various manifestations, have invariably been touted as safe and effective. Unfortunately, their impact on sexual function has been less well described. Specifically, the effects on ED and EjD have not yet been well elucidated, largely because the sexual function metrics used today are often not used in a comprehensive fashion. Unfortunately, most reports of sexual function are poorly described or self-reported.

Randomized controlled studies indicate that both holmium laser enucleation of the prostate (HoLEP) and TURP increase the risk of ED to a similar degree (27).

Regarding ED, there remains considerable controversy surrounding post-operative photoselective vaporization of the prostate (PVP). One group reported improvement in erectile function after PVP, compared to baseline, in all the IIEF domains at 6 months (106). But this report has numerous design problems, including a lack of focus on those changes in sexual function among the proportion of men who were sexually active pre-operatively.

Other investigators have shown that a major decline in erectile function was seen in 12.4% and 24% of men at 3 and 12 months, respectively. They reported a major improvement in erectile function in only 8.3% and 6% at 3 and 12 months, respectively (107). Similarly, others demonstrated that a decline in erectile function was experienced in 11.3%, while 3.2% experienced improved erectile function after PVP (108).

In contrast to most study designs, one group of investigators stratified the effect on ED by baseline function, which led to results suggesting a sustained impact on ED in those men with normal pre-operative erectile function (109).

Ejaculatory disorders were common after HoLEP, and their rate of occurrence was not significantly different from their rate after TURP (27). Single-cohort studies with holmium laser resection of the prostate also reported similarly high rates of ejaculatory disorders following treatment. The frequency of EjD, including retrograde ejaculation, has been reported to be 70%–80% following HoLEP or holmium laser ablation of the prostate (110–112). With PVP, loss of emission was reported in 65% of patients (107,113–116).

## Recommendation

Although laser TURP and its numerous variations have been performed for at least a decade, there is poor reporting of their impact on sexual function. The literature primarily contains underpowered, uncontrolled, single-centre cohort studies of poor quality. Nearly all of these reports estimate ED and EjD based on adverse events reporting rather than prospective assessment. Additionally, changes in sexual function among the proportion of men who are sexually active pre-operatively are nearly always ignored, further muting the effects of treatment. For these reasons, a specific recommendation about the overall impact of all combinations of laser TURP on sexual activity cannot be made. Longer follow-up with larger patient populations is needed (Level 4, Grade D).

# 4.8 Impact of Open Simple Prostatectomy on Sexual Activity

Open prostatectomy is the oldest surgical treatment modality for LUTS secondary to BPO. Open prostatectomy is the most invasive–but also the most effective and durable–procedure for the treatment of LUTS secondary to BPO. The incidence rate of post-operative ED after prostatectomy was 12.5% (117). Erectile dysfunction risk factors included hypertension, diabetes mellitus, higher transfusion rates, higher cardiac risk index, and an older age. The frequency of EjD is estimated to be 80% with open surgery (111).

## Recommendation

Although open simple prostatectomies have been performed for over 100 years, there is poor reporting of the impact on sexual function. The few reports contained in the literature suffer from numerous deficits. Nearly all them estimate ED and EjD based on adverse events reporting rather than prospective assessment. Additionally, changes in sexual function among the proportion of men who are sexually active pre-operatively are nearly always ignored, further muting the effects of treatment. For these reasons, a specific recommendation about the overall impact of open simple prostatectomy on sexual activity cannot be expressed. Longer follow-up with larger patient populations is needed (Level 4, Grade D).

# 4.9 **Conclusions/Summary**

1. The relationship between LUTS and sexual dysfunction has received increased attention recently because both conditions are highly prevalent, are frequently co-associated in the same aging male group, and significantly impact overall QOL.

2. The pathogenic mechanisms underlying the relationship between LUTS and ED are still not completely understood. However, in the last decade, evidence has begun to emerge that supports the involvement of various contributing factors.

3. The pathogenic mechanisms underlying the relationship between LUTS and EjD remained largely unexplored. This is an unmet need.

4. The effect of active surveillance on ED in men with LUTS is variable during a short period, with some men finding that their sexual function improves and others finding that it deteriorates.

5. The effect of alpha-blockers on ED in men with LUTS is variable during a short period, with men reporting either no change or a modest improvement of unknown significance.

6. Ejaculatory dysfunction in men with LUTS is significantly affected by two alpha-blockers: tamsulosin and silodosin. Other alpha-blockers have little or no impact on EjD.

7. The effect of 5-ARIs on sexual function in men with LUTS is modest but global, with effects on penile erection, ejaculation, and sexual desire. There seems to be no significant difference between the two agents that are currently available.

8. The veracity of reports of persistence of sexual side effects following cessation of 5-ARIs used to treat male pattern baldness is unclear. This is an unmet need.

9. There is sparse evidence that treatment with anticholinergics may improve sexual function. A specific recommendation about the overall impact of anticholinergics on sexual activity cannot be made. This is an unmet need.

10. There is strong evidence of improvement in LUTS with PDE5-Is, either alone or in combination with alpha-blockers. The impact of combination therapy (PDE5-I/alpha-blocker) is unclear. This is an unmet need.

11. A specific recommendation about the overall impact of all combinations of phytotherapeutic agents on sexual function cannot be made, due to the heterogeneity of the compounds and the methods used for the associated RCTs. However, this is not an unmet need.

12. The effects of TUNA, TUMT, TURP, laser TURP, and open simple prostatectomy on ED and EjD have not been well elucidated. In large part, this is because the metrics commonly used today, such as the IIEF, have not been applied to the evaluation of these procedures. Unfortunately, most reports of sexual function are poorly described or self-reported. Specific recommendations about the overall impact of these therapies on sexual activity cannot be made. This is an unmet need.

13. The effects of urethral compression on ED and EjD have been rather well elucidated in a single study. Given the limited population this study enrolled, no recommendation can be made. However, the prospective approach is endorsed.

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# C5

# Surgical Therapies and New Treatments

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# CONTENTS

## Surgical Therapies and New Treatments

# 5.1 **Introduction**

The previous (6th) International Consultation was published in 2006. Committee 7 was charged with reviewing "New Minimally Invasive and Surgical Developments in the Management of BPO" at that time. Since that report, further changes in the mix of treatments have occurred (**Figure 1**) (1). There has been a further decline in transurethral resection of the prostate (TURP), constituting only 39% of benign prostatic hyperplasia (BPH) procedures in the US Medicare population in 2005 (2). A 47.6% decline in TURP occurred between 2000 and 2008 in this patient group. Bipolar TURP (B-TURP) has become more common and the evolution of laser has continued. Visual laser ablation of the prostate (VLAP) and interstitial laser coagulation (ILC) featured prominently in the last report, but they have now all but disappeared as has contact laser vaporization using a sapphire tip.

**FIGURE 1**

US Medicare data for BPH procedures. From Malaeb BS, Yu X, McBean AM, *et al.* National trends in surgical therapy for benign prostatic hyperplasia in the United States (2000–2008). Urology. 2012;79(5):1111–1116. (1)
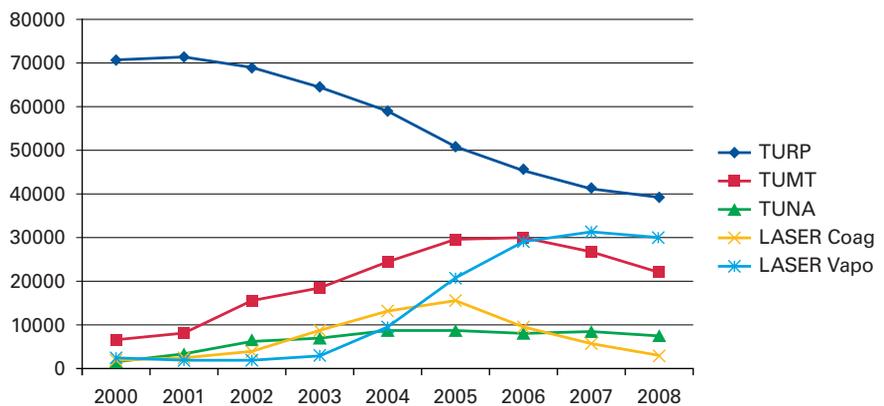


In contrast, 532-nm laser vaporization and holmium laser prostatectomy have continued expanding worldwide (3). Microwave thermotherapy has decreased in usage and transurethral needle ablation (TUNA) and water-induced thermotherapy (WIT) have largely been abandoned.

As the choice of therapeutic options for the treatment of BPH continues to widen, the technology continues to evolve and progress. Increased choice creates the increased need for different treatments to be firmly based on the evidence of superior clinical outcomes, morbidity, and technical improvement of these new technologies.

At present, the leading treatment option for male lower urinary tract symptoms (LUTS) is conservative or medical treatment (4). If the treatment is not effective, if the patient prefers a (more effective) surgical treatment, or if the patient has absolute indications for de-obstruction, an instrumental treatment is recommended. Transurethral resection of the prostate has been considered the "gold standard" for surgical treatment in terms of efficacy and re-treatment rate. Scientific and technological progress during recent years, however, has challenged the traditional surgical treatment patterns regarding LUTS. The driving force behind the development of these minimally invasive procedures was the ongoing morbidity of TURP in terms of early (bleeding, TUR syndrome) and late complications, as well as the need for anesthesia and hospitalization. Various minimally invasive treatments (MITs) have been developed using new techniques including thermal-based therapies,

laser therapy, and other treatment modalities such as prostatic ethanol injection. These alternative treatments have been evaluated and compared with TURP, leading to their inclusion in national and international guidelines.

## 5.1.1 BPH guidelines

Clinical practice guidelines have been developed to assist practitioners and patients to choose appropriate health care for specific clinical circumstances. These guidelines are developed based on the highest evidence available, including data from case series, registries, and preferably randomized controlled trials (RCTs).

It is unfortunate that high-quality RCTs in urology are scarce in many areas, including the surgical management of LUTS secondary to benign prostatic obstruction (BPO). The majority of studies in the urological literature provide low-level evidence that may not be adequate to guide clinical decisions. The flaws are many, including problems with design, conduct, and reporting.

Several initiatives have been undertaken to improve the data quality we base our recommendations upon. These initiatives, among others, include the Idea, Development, Exploration, Assessment, Long-term study (IDEAL) framework and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (5,6). With the establishment of IDEAL, specific schemes were recommended for appropriate study design to improve evidence collection before incorporating innovations into surgical practice. The IDEAL recommendations are expected to solve the problem by serving as guidelines for tailored surgical research, a platform for systematic data generation from well-designed, conducted, and reported studies, and a regulatory structure to protect patients from potential harms of novel procedures. Accurate Level of Evidence (LOE) grading is another crucial issue. Systematic reviews provide a transparent and robust summary of existing research, but the information may be inadequate for making well-informed decisions unless a systematic and explicit approach to making judgments on LOE is implemented. Unfortunately, a variety of grading systems are used, potentially resulting in miscommunication. The GRADE system provides a concise and precise information framework.

The European Association of Urology (EAU) and the American Urological Association (AUA) recently updated their guidelines (7,8). Conceptually, the committees responsible followed a similar strategy: the literature was searched following MESH terms and both aim to identify the best evidence for management of the index patient who is consulting the urologist for LUTS. Studies were selected and stratified by design, comparator, follow-up interval, and outcome of treatment. The studies varied in terms of patient selection, randomization, patient demographics, comorbidities, symptoms, consistency and intervals of follow-up, trial duration and timing, and technique of outcomes measurement.

It was concluded that transurethral resection is still the gold standard, but when available, new therapies could be considered. The choice of treatment depends on findings of the initial evaluation, ability of the treatment to change assessed findings, treatment preferences of the individual patient, as well as expectations to be met in terms of speed of onset, efficacy, side effects, quality of life, and disease progression. The choice of the surgical technique depends on prostate size, patient

comorbidities, ability to have anesthesia, patients' preferences, willingness to accept the respective surgery-dependent side effects, availability of each treatment, and experience of the surgeon with these operative techniques. The best evidence available, based on RCTs, is for (bipolar) TURP, holmium laser enucleation of the prostate (HoLEP) and GreenLight laser treatment. Unfortunately, most of this information is not included in the recently published guidelines (9–11). This underscores the need for the regular updating of the guidelines and for sending a strong message to encourage the urological community to perform more high-quality studies.

## 5.2 Electrosurgery

### 5.2.1 Introduction

Monopolar transurethral resection of the prostate (M-TURP) has long been the benchmark therapy for BPH. This is partly due to the available long-term outcomes, as several reports provide durable follow-up of up to 25 years. Similar data on durability do not exist for any other surgical BPH treatment option. Moreover, efficacy of M-TURP in improvement of subjective and objective urinary symptoms, often assessed by extensive urodynamic investigations, has been proven beyond doubt (7,12–23).

A substantial number of studies with data mostly provided by health authorities show an overall incidence of a secondary procedure after initial M-TURP, including secondary TURP, urethrotomy, and bladder neck incision (BNI), of 5.8%, 12.3%, and 14.7% at 1, 5, and 8 years of follow-up (15,17,20,23,24).

Improvements in subjective and objective micturition parameters after 12 months have been confirmed in systematic meta-analyses and described in the various guidelines. The International Prostate Symptom Score (IPSS) decreased by 15 to 20 (12,14), an average reduction of 72%, in an analysis of 29 RCTs (16). The AUA guidelines document an average improvement in quality-of-life (QOL) score of 3.3 after 12 months (range, 0–6) (12).

Maximum flow rate ($Q_{max}$) improves by 10–11 mL/s within the same follow-up period (12,14,15,17–21,23,24), or relatively by 120% (16). Despite its controversial significance in LUTS, a post-void residual (PVR) can be reduced by 70% with M-TURP (16).

The outstanding long-term treatment efficacy of M-TURP is widely accepted; however, the associated morbidity led to the development of alternative therapy modalities. The main aspect in this regard is the complication of intra- and post-operative bleeding. Peri-operative transfusion rates of less than 1% have been reported in some small, single-centre series. In contrast, meta-analyses have shown average peri-operative transfusion rates of 8.6% for M-TURP (16). In a large-scale evaluation comprising 44 urological departments in Bavaria with data including more than 10,000 patients, the transfusion rate was 2.9% (25). However, transfusion rate and clinically relevant absorption syndrome increased dramatically in prostates larger than 60 g (**Table 1**) (25).

**TABLE 1**  Influence of Resection Weight on Morbidity and Mortality

| Resected Weight (g) | Transfusion (%) | TUR Syndrome | Revision | Mortality |
|---|---|---|---|---|
| <30 g | | | | |
| (*n*=5,506) | 2.0 | 1.2 | 5.2 | 0.09 |
| 30–60 g | | | | |
| (*n*=3,130) | 3.4 | 1.4 | 6.2 | 0.06 |
| >60 g | | | | |
| (*n*=561) | 9.5 | 3.0 | 9.8 | 0.71 |

From Reich O, Gratzke C, Bachmann A, *et al.* Morbidity, mortality and early outcome of transurethral resection of the prostate: A prospective multicenter evaluation of 10,654 patients. J Urol. 2008;180(1):246–249. (25)

Alongside peri-operative bleeding, TUR syndrome (i.e. the absorption of irrigation fluid) is a rare, but potentially fatal complication of M-TURP. Depending on the detection mode, rates vary from 0% to 7% (15,17–21,23–25); however, a clinically relevant TUR syndrome needing intervention is very rare.

In addition, the AUA guidelines (7,12) document the following relevant complications of M-TURP (range, 95% confidence interval [CI]): PVR urine, 5% (4–8); urethral stricture/bladder neck contractures, 7% (5–8); cardiovascular adverse events, 2% (0–6); thromboembolic events, 2% (0–8); hematuria, 6% (5–8); urinary incontinence, 3% (2–5); urinary tract infections, 6% (5–9); irritative voiding symptoms, 15% (9–23); ejaculatory dysfunction, 65% (56–72); and sexual dysfunction, 10% (7–13).

While mortality was 2.5% 40 years ago, contemporary series show mortality rates of less than 0.10% to 0.25% (25–28). However, mortality rates with M-TURP are much higher in prostates larger than 60 g compared with prostates smaller than 60 g (**Table 1**) (25).

The complications of M-TURP and competing minimally invasive laser procedures have led to different modifications and innovations in transurethral high-frequency surgery. These consist of advances in high-frequency generators such as the so-called "coagulant intermittent cutting" (CIC), which have led to a reduction in the rates of transfusion and TUR syndrome. Similar modulations of the high-frequency generators such as dry-cut resection are already in clinical use (29).

 Changes in the electrode are another critical innovation. However, these cause changes in the high-frequency current. The techniques (bipolar resection in isotonic irrigation fluid with a bipolar resection device and plasma vaporization of the prostate) differ significantly from conventional M-TURP. Bleeding complications and TUR syndrome with conventional M-TURP have been the main reasons for the decline of TURP. The changes of the electrodes and the high-frequency generators described above have significantly contributed to improved hemostasis of modern TURP.

## 5.2.2　Bipolar TURP

In contrast to monopolar systems, B-TURP uses high-frequency electric current flowing between two electrodes within the surgical instrument. The major advantage of bipolar resection over the conventional monopolar technique, in which the current flows through the tissue, is the use of isotonic irrigation fluid, eliminating the possibility for TUR syndrome (hypotonic hyper-hydration with hyponatremia).

Contradictory data regarding comparisons of monopolar and bipolar TURP exist. Less bleeding complications and improved hemostasis have been repeatedly described for B-TURP in the literature (30–33). However, in the majority of studies, these observations are not supported by objective criteria, such as post-operative change in hemoglobin (Hb) level and transfusion rates (25,30,34).

Chen and colleagues presented 2-year follow-up data of 100 consecutive patients comparing B-TURP with monopolar TURP (M-TURP) (35). The authors found a greater decrease in serum sodium (Na+) and more absorption of irrigant in the M-TURP cohort, while the resection time was similar between the groups. The rates of blood transfusion and re-catheterization were lower in the B-TURP than in the M-TURP group. In both the M-TURP and B-TURP groups, there were significant improvements in IPSS (mean IPSS improved 6-fold at the 2-year follow-up) and maximum urinary flow rates (3 fold in both groups at the 2-year follow-up) (35). Fagerström *et al.* compared bipolar resection with the conventional monopolar TURP with respect to peri- and post-operative complications and long-term outcome up to 18 months after surgery (36). They found that the incidence of post-operative re-admissions was significantly reduced and the post-operative recovery was faster in bipolar versus monopolar TURP. No differences between the groups with respect to hospital stay and catheter duration were recorded. Bipolar and monopolar TURP both resulted in long-lasting improvement of symptoms associated with BPH (36). Most available studies were limited by the study group being too small to be subject to analyses of subgroups.

In a systematic meta-analysis of 16 RCTs, no clinically relevant differences in short-term efficacy (after 12 months) were found between monopolar and bipolar TURP (37). Furthermore, no differences were evident regarding operation time and rates of adverse events such as transfusions, retention after catheter removal, and urethral complications. However, B-TURP was found to be preferable due to a more favourable safety profile (lower TUR syndrome and clot retention rates) and shorter irrigation and catheterization duration. In their meta-analysis, Mamoulakis and colleagues pointed out the lack of well-designed international/multicentre RCTs and the low methodological quality of the existing trials. Results of the first international, multicentre, double-blind RTC on the peri-operative efficacy and safety of bipolar versus monopolar TURP fulfilling the suggested criteria (36) were recently published by the same authors (38). A total of 295 patients were enrolled and randomized in a 1:1 ratio to undergo M-TURP or B-TURP. Efficacy was quantified by $Q_{max}$, PVR, and IPSS improvement at 6 weeks after surgery. Safety was estimated by changes in Na+ and Hb levels immediately after surgery, and peri-operative complications were graded according to the modified Clavien classification system (39) as previously proposed for TURP procedures (40). Secondary outcomes included resection time, resection rate (resected tissue weight divided by resection time), capsular perforation, and catheterization time. In contrast to the previously available evidence, no clinical advantage for B-TURP was shown. Peri-operative efficacy, safety, and secondary outcomes

were comparable between both study arms. However, since the authors focused mainly on the perioperative results, a longer follow-up period and accrual of increased numbers of patients in future studies might change the presented results (38).

### 5.2.3 Bipolar vaporization

Bipolar plasma vaporization of the prostate was introduced in 2008 (41). This method was developed in an attempt to combine the benefits of vaporization techniques (good hemostasis, low morbidity, and low learning curve owing to easy handling) and bipolar resection. It derives from plasmakinetic bipolar resection of the prostate and utilizes well-known electro-surgical principles.

The instrument consists of a bipolar mushroom-like electrode (41). Plasma vaporization of the prostate is performed under direct visualization using the electrode in a near-contact technique ("hoovering" technique). Monopolar electrovaporization of the prostate, which was performed using a rollerball electrode, has largely been abandoned due to the disproportionate extent of coagulation (up to 10 mm) in the tissue treated, leading to mostly irritative side effects and stress incontinence.

In an initial, non-randomized, prospective, bi-centre study, Reich *et al.* presented the data of 30 men with a follow-up of 6 months (41). IPSS, bother score, $Q_{max}$, and PVR were evaluated at baseline and at the time of discharge, as well as at 1, 3, and 6 months after plasma vaporization. Mean pre-operative prostate volume was 59 mL (range, 30–170), and mean operating time was 61 minutes (range, 20–140 min). Apart from one re-operation (conventional transurethral resection) due to persistent obstruction, no major complication occurred either intra- or post-operatively and no blood transfusion was required. Catheterization time averaged 41 hours (range, 18–192). Transient mild-to-moderate dysuria was noted in four patients (13%). At 1, 3, and 6 months, $Q_{max}$ increased from 6.6 mL/s pre-operatively to 17.3 mL/s, 18.5 mL/s, and 18.1 mL/s, respectively. The IPSS decreased from 20.8 to 10.4, 8.2, and 8.1, respectively (41). These initial results are promising. Owing to the wide availability of bipolar high-frequency generators and a comparable low learning curve, this technique has found broad clinical use.

Recently, Geavlete *et al.* published their data of a prospective, long-term comparison between plasma vaporization, M-TURP, and B-TURP, with a follow-up of 18 months (42). A total of 510 patients (170 patients in each study arm) with BPH, $Q_{max}$ <10 mL/s, IPSS >19, and prostate volume between 30 and 80 mL were enrolled in the study and evaluated pre-operatively and at 1, 3, 6, 12, and 18 months after surgery. IPSS, QOL score, $Q_{max}$, and ultrasonography were employed. The intraoperative bleeding and capsular perforation rates, as well as the mean Hb level, were significantly decreased for plasma vaporization compared with B-TURP and M-TURP. Post-operative hematuria, blood transfusion, and clot retention rates were significantly higher in the M-TURP group. The catheterization period and hospital stay were significantly reduced for plasma vaporization, followed by B-TURP. While the rates of irritative symptoms and urethral strictures were similar in the three groups, the re-catheterization, bladder neck stenosis, and re-treatment rates were significantly lower in the plasma vaporization group. During the follow-up (up to 18 months), the plasma vaporization series showed significantly superior outcomes in terms of IPSS and $Q_{max}$ (42). Considering these data, the authors concluded that plasma vaporization represents a viable alternative for BPH treatment. It may be a significant addition to the bipolar electrosurgical approach (42).

## 5.2.4 Transurethral incision of the prostate

As opposed to other electrosurgical treatments for BPH, the transurethral incision of the prostate (TUIP) is an outpatient endoscopic procedure which is limited to the treatment of smaller prostates (<30 mL) and is usually recommended for young, sexually active men (13).

Several randomized trials have reported comparable efficacy of TUIP and TURP for this patient population (16). In a meta-analysis of six RCTs comparing TUIP with TURP with a follow-up of more than 6 months, Madersbacher and colleagues concluded that efficacy of TUIP in that subgroup is comparable or slightly inferior to TURP (16). Re-intervention rates clearly favoured TURP compared with TUIP (2.6% vs. 15.9%). Concerning morbidity though, TUIP had superior results in terms of blood transfusions (TUIP: 0.4% vs. TURP: 8.6%) and retrograde ejaculation (TUIP: 18.2% vs. TURP: 65.4%). Lourenco *et al.* provided a systematic review and meta-analysis of short- and long-term data from 10 RCTs (795 patients) comparing TUIP with TURP (43). The patients had mainly mild-to-moderate BPH. The authors did not find clear evidence of superiority on meta-analysis regarding the primary outcome of improvement in symptom score at 12 months. In contrast, TURP was clearly superior in terms of urodynamic improvement, with a consistent and statistically significant greater increase in peak urinary flow rate, while the rates of blood transfusion and TUR syndrome were higher after TURP (43). Urinary retention, urinary tract infection, strictures, and incontinence did not differ between the two approaches. As described previously, TUIP was associated with a shorter duration of operation and length of hospital stay, but a higher re-operation rate (43). However, high dropout rates and only two trials reporting data in a suitable format impaired this analysis (43). For the appropriate patient, TUIP is recommended as an appropriate and effective treatment alternative in men with moderate-to-severe LUTS (LOE 1) in both the EAU and AUA guidelines on BPH (12–14).

In summary, the efficacy of conventional M-TURP in improvement of subjective and objective micturition parameters has been proven beyond doubt. While the long-term treatment efficacy of M-TURP is widely accepted, it is the associated morbidity of M-TURP which has led to the development of alternative therapy modalities. Mortality rates with M-TURP are much higher in larger prostates (>60 g). Fewer bleeding complications and the lack of TUR syndrome have been repeatedly described for B-TURP. Recent studies have documented long-lasting improvement of symptoms associated to BPH for both bipolar and monopolar TURP. Bipolar plasma vaporization is a safe and effective treatment alternative for patients with LUTS due to bladder outlet obstruction (BOO).

# 5.3 **Open Prostatectomy**

## 5.3.1 **Overview**

If cutting for the stone defined our specialty in the middle ages, cutting for the prostate helped define modern urology at the end of the 19th century. The revolution started on both sides of the Atlantic when Eugene Fuller in New York and Peter Fryer in London pioneered the suprapubic removal of prostatic adenoma (44–46). The complications of the procedure were initially high, but the technique was gradually perfected to acceptable levels of complications (from 18% to 5.2% mortality) (47,48). It took nearly 50 years before the transvesical approach was standardized by S. H. Harris from Sydney, Australia, in 1927 and T. Hryntschack from Vienna, Austria, in 1951 (49). The retropubic route, pioneered by Stockum, Hildebrand, Maier, and Mermingas, was popularized by Terence Millin in 1947 (50). Recently, a modification of the current procedures was proposed by Madigan and co-workers with preservation of the prostatic urethra–this technique is apparently associated with decreased bleeding and maintenance of anterograde ejaculation, and can also be performed laparoscopically (51) (52,53).

The title of this section reflects a semantic issue caused by a paradigm shift in prostate surgery: both the Hryntschack and the Millin procedures can now be performed laparoscopically (whether robotically assisted or not) and such procedures can no longer be called "open."

The present paragraph is an update of the one published after the 5th International Consultation on BPH in 2001, as simple prostatectomy was not addressed in the 2005 one. Simple prostatectomy has been the gold standard treatment for benign prostatic enlargement/obstruction (BPE/BPO) for the first half of last century when it gradually gave its way to transurethral surgery. Large variations in the use of open surgery have been observed in different countries/areas, as the management of large prostates remains a challenge for the practicing urologist who tends to adopt the technique that works best in his hands. In general, once the outcome of a certain medical procedure/treatment has been optimized in daily practice, clinical research looks into novel treatments that aim to maintain the same level of performance while reducing the therapeutic burden for patients and the economic cost for payers. Simple prostatectomy did not become outdated because any of the new procedures produced better clinical outcomes, but because less invasive techniques achieved comparable results or even slightly lesser ones that were deemed sufficient to improve patients' quality of life with lower morbidity and costs.

The Medline and Embase databases were searched for Patient, Intervention, Comparison, and Outcome (PICO) terms including benign prostatic hyperplasia or BPH, open or simple prostatectomy; no comparator or transurethral resection of the prostate or TURP, holmium laser enucleation of the prostate or HoLEP, GreenLight vaporization of the prostate; outcome, failure. Relevant full-text papers were obtained and additional references found in papers' and books' reference lists. With minimal exceptions, this report is based on manuscripts available in the English language.

The Clinical Practice Guideline No. 8. (*AHCPR Pub. No. 94–0582: February 1994*), published in 1994, summarized the available evidence for treatments of BPH at that time point and can be considered as a background knowledge base. The following data for open prostatectomy were provided.

**TABLE 2**  Direct Treatment Outcomes of BPH Treatment

|  | Open | TURP |
|---|---|---|
| Chance for improvement of symptoms (90% CI) | 94–99.8% | 75–96% |
| Degree of symptom improvement (percent reduction in symptom score) | 79% | 85% |
| Morbidity/complications | 6.98–42.7% | 5.2–30.7% |
| Chance of dying with 30–90 days of treatment | 0.99–4.56% | 0.53–3.31% |
| Risk for total urinary incontinence (90% CI) | 0.34–0.74% | 0.68–1.4% |
| Need for operative treatment of surgical complication in future (90% CI) | 0.6–14.1% | 0.65–10.1% |
| Risk for impotence (90% CI) | 4.7–39.2% | 3.3–34.8% |
| Risk for retrograde ejaculation (percentage of patients) | 36–95% | 25–99% |
| Loss of work time (days) | 21–28 | 7–21 |
| Hospital stay (days) | 5–10 | 3–5 |

Modified from McConnell JD, Barry MJ, Bruskewitz RC, *et al. Benign prostatic hyperplasia: Diagnosis and treatment. Clinical practice guidelines, No. 8.* Rockville, MD: Agency for Health Care Policy and Research, Public health service, US department of Health and Human Services; 1994. AHPCR Publication No. 94–0582. (54)

**TABLE 3** Complications of Simple Prostatectomy (mean values, if not otherwise stated [90% CI])

| | Retropubic | Suprapubic | Any Open Method | TURP |
|---|---|---|---|---|
| Prostate weight (g) | | | 46.7 | 21.1 |
| Overall surgical complications | | | 24.5%* | 11.9%* |
| Bleeding intervention | | | 1.5%* | 2.2%* |
| Urethral stricture | 0.92% | 7.24% | 4.44% | 4.25% |
| Bladder neck contracture | 0.96% | 3.63% | 2.35% | 1.41% |
| Epididymitis | 2.45% (0.8–5.5) | 3.6%† (0.4–12.6) | 2.6%† (0.4–8.2) | 1.0%† (0.09–4.5) |
| UTI | 2.6% (0.1–12.9) | 12.5%† (5.0–24.3) | 13.4%† (2.13–31.6) | 15.5%† (3.4–38.3) |
| Probability of becoming impotent | 17.7% (4.9–39.3) | 16.2% (4.8–35.6) | | 13.6% (3.4–32.4) |
| Retrograde ejaculation | | | 77.2% (46.4–95.2) | 73.4% (30.4–96.9) |
| Urinary incontinence | 0.32%† (0.09–0.8) | 0.52%† (0.34–0.8) | 0.5%† (0.35–0.75) | 1.0%† (0.7–1.4) |
| 5-year projected failure rate | | | 2% (1–4) | 10% (9–11) |
| Mortality rate (≥days post-surgery) | | | 2.6%* (1.0–4.6) | 2.0%* (0.5–3.3) |

Modified from McConnell JD, Barry MJ, Bruskewitz RC, *et al. Benign prostatic hyperplasia: Diagnosis and treatment. Clinical practice guidelines, No. 8*. Rockville, MD: Agency for Health Care Policy and Research, Public health service, US department of Health and Human Services; 1994. AHPCR Publication No. 94–0582. (54)
*weighted average; †median

UTI = urinary tract infection

**TABLE 4** Average Individual Direct Costs of Treatment of BPH (USD)

| | Open Prostatectomy | TURP |
|---|---|---|
| Cost for primary treatment and 1-year follow-up | 12,788.00 | 8,606.00 |
| Cost for second year of treatment after primary treatment | 69.00 | 360.00 |

Modified from McConnell JD, Barry MJ, Bruskewitz RC, *et al. Benign prostatic hyperplasia: Diagnosis and treatment. Clinical practice guidelines, No. 8*. Rockville, MD: Agency for Health Care Policy and Research, Public health service, US department of Health and Human Services; 1994. AHPCR Publication No. 94–0582. (54)

These data clearly show the good short- and long-term clinical outcome of simple prostatectomy but highlight a complication rate higher than observed with TURP (24.5% vs. 11.9%) and a significantly higher cost (12,788.00 vs. 8,606.00 USD). A recent nationwide analysis performed in Austria showed a lower re-operation rate following open prostatectomy compared with TURP (**Table 4**).

**TABLE 5** Re-operation Rate, Myocardial Infarction, and Mortality Rate from an Austrian Nationwide Survey

|  | TURP | Open Prostatectomy |
|---|---|---|
| **Re-do TURP** | | |
| 1 year | 2.9% | 1.0% |
| 5 years | 5.8% | 2.7% |
| 8 years | 7.4% | 3.5% |
| Secondary endourological procedures | 14.7% | 9.5% |
| Myocardial infarction | 4.8% | 4.9% |
| **Mortality rates** | | |
| 90 days | 0.7% | 0.9% |
| 1 year | 2.8% | 2.7% |
| 5 years | 12.7% | 11.8% |
| 8 years | 20% | 20.9% |

Modified from Madersbacher S, Lackner J, Brossner C, *et al.* Reoperation, myocardial infarction and mortality after transurethral and open prostatectomy: A nation-wide, long-term analysis of 23,123 cases. Eur Urol. 2005;47:499–504. (55)

Direct comparisons of suprapubic and retropubic techniques are rare. A small randomized trial from Brazil suggests that the Millin procedure is associated with a lower risk for bleeding and transfusion (**Table 5**) (56).

**TABLE 6** Comparative Data of Retropubic Versus Transvesical Prostatectomy

|  | Surgical Procedure | | |
|---|---|---|---|
|  | Millin | Transvesical | *p* |
| Blood loss during surgery (mL) | | | |
| 362 (50–700) | 640 (200–1,500) | 0.07 | |
| Hb decrease from pre-operative to 1 day after surgery (g/dL) | 1.76 (0.31) | 3.15 (0.33) | <0.001 |
| Hb decrease from post-operative day 1 to day 3 (g/dL) | 0.15 (0.31) | 0.74 (0.33) | 0.031 |
| Blood transfusion (n) | 1/31 | 3/31 | |

Modified from Dall'Oglio MF, Srougi M, Antunes AA, *et al.* An improved technique for controlling bleeding during simple retropubic prostatectomy: A randomized controlled study. BJU Int. 2006;98:384–387. (56)
Hb = hemoglobin

Blood transfusion is one of the costly complications of this type of prostate surgery, and variable rates have been described ranging from 10% (56) up to 36% (57). Pre-operative Hb levels, comorbidities, surgical techniques, and local blood transfusion rules and regulations are considered to play a role, although it is difficult to make sense of the different published data. A large series (3,000 patients) from Iran describes an exceedingly low transfusion rate (3.3%), while series from Chicago (57) and Nairobi (58) suggest similarly high transfusion rates (36% and 36.8%, respectively), implying that the economic environment in which the surgery is performed is not necessarily a risk factor for such a complication.

Total prostate-specific antigen (PSA) levels <1 ng/mL have been described following open prostatectomy, suggesting that the largest part of the pre-operative PSA level is associated with the adenomatous tissue, with very little contribution of the peripheral zone of the prostate (57).

Reading the peer-reviewed literature, case series tend to mirror daily practice, while randomized trials may differ substantially. Analysis of 12 series (non-randomized vs. TURP or other procedures) shows a mean prostate volume for open surgery of >60 mL with a very wide range (37–92). Urodynamic outcome is usually excellent, with an observed increase in $Q_{max}$ from 8.2 mL/s to 22.2 mL/s (59) (60,61). Pressure-flow studies, performed before and after surgery, confirm complete relief of outlet resistance following surgery and a significant decrease in detrusor hypertrophy (62).

Some new evidence has been recently produced, but it hardly changes what we already know about the procedure. One point for discussion is the complication rate. An interesting review on TURP from Rassweiler *et al.* highlighted the effect of modern medicine on surgical procedures, with a significant decrease in some of the adverse events of transurethral surgery (63). We have enough new series on simple prostatectomy to test such a hypothesis, but the way complications are considered varies so much that comparison is difficult.

A recent series from the Bavaria region of Germany provides data from 868 patients in 55 different institutions (64). The average operative time was 80.8±34.2 minutes and mean prostate volume was 96.3±44.0 g. Hospital stay was 11.9±6.5 days, and mortality and transfusion rates were 0.2% and 17.3%, respectively. Urinary tract infections occurred in 5.1% of cases, and blood transfusion and surgical revision were required in 7.5% and 3.7% of patients, respectively (64).

The development of the Clavien classification system, introduced in 1992, helped to standardize the evaluation of complications in surgical clinical trials (65). Data on complications of simple prostatectomy according to the Clavien classification have been only recently available. Oranusi and co-workers report data from a retrospective analysis of a patient series operated on in Southeast Nigeria, with an overall complication rate of 40.1%. Complication rates for the different Clavien grades are summarized in **Table 7** (66).

Erectile dysfunction (ED) ranks sixth after symptomatic improvement, incontinence, immediate surgical complications, mortality, and complications requiring surgery (54). A recent analysis from Iran showed a 12.5% incidence rate of ED, with risk factors including hypertension, diabetes mellitus, higher transfusion rates, higher cardiac risk index, and an older age, suggesting that patients factors more than those related to the procedure play a role (67).

**TABLE 7** Complications of Open Prostatectomy According to the Clavien Classification

| | Management | Complication Grades | | | | |
|---|---|---|---|---|---|---|
| | | I | Id | II | IIIa | IIIB |
| Total: | 0.8% | 0.6% | 35.1% | 0.6% | 3.1% | |
| Intra-operative bleeding | Blood transfusion | | | 2.8% | | |
| Bleeding | Blood transfusion | | | 18.0% | | |
| Wound infection | Wound dressing/antibiotics | | | 6.9% | | |
| UTI | Antibiotics | 3 | | 3.3% | | |
| Epididymitis | Antibiotics | | | 4.1% | | |
| Vesico-cutaneous fistula | Extended urethral catheterization | 0.8% | | | | |
| Clot retention | Bladder exploration/ evacuation | | | | | 1.4% |
| Urethral stricture | Suprapubic cystotomy/delayed urethroplasty | | | | | 1.4% |
| Urinary incontinence | Kegel's exercise | | 0.6% | | | |
| Incisional hernia | Delayed herniorrhaphy | | | | | 0.3% |
| Bladder neck stenosis | Bourginage | | | | 0.6% | |

Modified from Oranusi CK, Nwofor A, Oranusi IO. Complication rates of open transvesical prostatectomy according to the Clavien-Dindo classification system. Niger J of Clin Pract. 2012;15:34–37. (66)

## 5.3.2 **Comparison with other techniques**

The most important question that remains to be answered is why open prostatectomy provides such an excellent outcome and how other less invasive procedures can be improved to achieve similar results. Evaluation of randomized trials shows that only transurethral enucleation of the prostate (such as HoLEP) is able to challenge open surgery, suggesting that complete removal of the hypertrophic tissue is required to maximize outcome. Whether such an outstanding improvement is really needed in our daily practice is an open question that goes beyond the scope of this discussion. The outcome of prostate vaporization with the GreenLight laser is undermined by post-operative values of PSA >1 ng/mL, suggesting incomplete removal of the adenomatous tissue.

Evaluation of randomized trials of open prostatectomy versus TURP is difficult and potentially unethical (68), as indications for the two procedures in daily practice differ and in the study from Meyhoff and Nordling, for example, an average prostate volume of 27 g was reported (59). A similar study from Iran showed a mean prostate volume of <50 g, showing the limitations inherent in the randomized design of the study (69). Recent cases series of open prostatectomy may offer a more reliable perspective of its clinical outcome in the current medical environment. A recent single-centre series from Turkey shows that open prostatectomy is now performed in larger prostates (mean prostate volume 73.6 g in the years 1995–2001 and 98.2 g in the years 2002–2007) (70), with a 31.2% incidence of complications, including a 12.7% transfusion rate and a mean hospital stay of 6.7 days

(range, 4–14). Open prostatectomy can still be considered a standard procedure for glands greater than 100 g (70). Consistent data were published from Japan where Takeuchi and co-workers compared the prostate volume of patients undergoing open prostatectomy in the period 1987–1990 and 1991–1994, showing an increase in the average prostate volume. In their opinion, subcapsular prostatectomy could be indicated in 18% of patients in contemporary series (71). Another recent series suggests that it is the surgeon's experience that makes the difference, and although the patient population is small, a recent paper from Korea shows that even large glands can be managed endoscopically with TURP, with results comparable to those of open surgery with shorter hospital stay (72).

New randomized trials have been published in which simple prostatectomy has been used as the benchmark against which novel surgical treatments for BPE/BPO, such as HoLEP and GreenLight vaporization, must be measured. Randomized trials of HoLEP versus open prostatectomy are consistent in showing a comparable clinical outcome of the two techniques, with open surgery having a shorter operative time but longer catheterization time, longer hospitalization, and higher costs (**Table 8**). Only one randomized trial of GreenLight vaporization of the prostate (80-W KTP side-firing laser -Laserscope®; GreenLight PVTM, San Jose, CA) versus open prostatectomy is available, showing a shorter operative time for open surgery but longer catheterization time and hospital stay, and a comparable clinical outcome in terms of post-operative PSA levels (**Table 9**). Some of the new less-invasive modifications proved to be as effective as open surgery, but simple prostatectomy itself cannot be ignored and remains a part of the urologist's armamentarium (70,73).

Laparoscopic and robot-assisted laparoscopic surgery has recently challenged open prostatectomy, and the feasibility of these approaches has been confirmed. A small series of very large prostates (mean volume, 163 mL) from Washington, DC, United States, suggests that the procedure is feasible, although the mean operative time was relatively long (179 min; range, 90–270 min), hospital stay was short (2.7 days; range, 1–8 days), but catheterization time was long (8.8 days; range, 5–14 days) (74). IPSS went down from 18.1 to 5.3, and $Q_{max}$ increased from 4.3 mL/s to 19.1 mL/s. This is clearly a preliminary series, and it is difficult to compare these data with those from other series, as operative time may decrease with increasing experience, although the long catheterization time remains difficult to explain. Another series from Italy confirms the feasibility of the procedure but also the long operative time (median, 180 min), the short hospital stay, and the long catheterization time (7.4 days).

Single-port procedures have also been described, showing that the technical challenges have been solved, although no patient series is available–only case reports (75).

The first task when a new procedure is proposed is its feasibility–that is, the possibility to complete the operation (without conversion to open surgery for laparoscopic procedures) with reasonable rates of peri-operative complications and good short- and mid-term clinical outcomes. Once feasibility is proven, other issues become important, such as operative time, hospital stay, and catheterization time (for simple prostatectomy).Where are we now with laparoscopic simple prostatectomy? Well, the technique is feasible, although operative time remains, on average, long. But the question remains, should surgeons be trained in open suprapubic or retropubic prostatectomy to be able to perform it laparoscopically, or can residents be trained directly with the robot? To be fair, robot-assisted laparoscopic simple prostatectomy should be compared with holmium enucleation rather than open simple prostatectomy, as HoLEP has already been proven to be equally effective and less invasive.

Interestingly, a recent evaluation of the Medicare database with reference to BPH surgery from the years 2000–2008 did not even include open prostatectomy in the analysis, although the procedure is coded (CPT 55801, 55821, 55831) and used in daily practice (1).

### 5.3.3  Discussion

The era of open prostatectomy is probably over in Western Europe, the United States, and other highly industrialized countries, but it remains a viable option in many other countries (76). Laser treatments, particularly HoLEP, have proven to be effective independent of prostate size and represent a real alternative whenever the technology and the expertise are available. Complete removal of the hyperplastic tissue seems to guarantee the best long-term clinical outcome in patients with large prostates. Training of our residents in the management of large prostates remains a priority and a challenge independent of surgical technique.

Current indications for open prostatectomy include large prostates for which the surgeon does not feel comfortable performing TURP and for which other techniques such as HoLEP are not available. The presence of coexisting conditions such as large bladder stones, inguinal hernias, and large bladder diverticula may dictate an open surgical approach. An interesting study from China suggests that large prostate volume (>85.2 mL) and intra-operative splitting of the prostatic capsule are major risk factors for conversion from TURP to open prostatectomy (77). Although most of us would never consider such a complication, the Chinese paper implies this is a possibility.

### 5.3.4  Conclusions

It is unlikely there will ever be a single solution for all patients with BPE, and simple prostatectomy for very large prostates, after more than a century, remains an important option.

**TABLE 8**  Summary Table of Trials on Laparoscopic and Robot-assisted Laparoscopic Simple Prostatectomy

| Author | N | Prostate Size (mL) | Operative Time (min) | Hospital Stay (days) | Catheterization Time (days) | IPSS | | $Q_{max}$ (mL/s) | | Blood Loss (mL) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | pre | post | pre | post | |
| Vora (74) | 13 | 163 | 179 | 2.8 | 8.9 | 18.1 | 5.3 | 4.3 | 19.1 | 219 |
| Matei (78) | 35 | 107 | 180 | 3.17 | 7.4 | 28 | 7 | 6.6 | 18.9 | 121 |
| Quan (53) | 16 | | 111.8 | | | | | | | 112.5 |
| Duffey (79) | | | | | | | | | | |
| Castillo (80) | 95 | 108.5 | 123 | 3.5 | 4.2 | | | | | 415 |
| Yun (81) | 11 | 109.3 | 191.9 | 6.5 | 5.6 | 25.3 | 4.2 | 4.5 | 15.5 | 390.9 |
| McCullough (82) | 96 | 11.3 | 95.1 | 6.3 | 5.2 | | | | | 350 |
| Mariano (83) | 60 | 144.5 | 138.48 | 3.46 | 4.6 | | | | | 330.98 |
| Baumert (84) | 30 | 121.8 | 115 | 5.1 | 4.0 | 22.4 | 5.7 | 8.1 | 24.6 | 367 |

**TABLE 9** Summary Table of Trials of HoLEP Versus Simple Prostatectomy

| | N | Prostate Volume (mL) | PSA Pre (ng/mL) | AUA/IPSS | | $Q_{max}$ (mL/s) | | Operative Time (min) | Catheterization Time (days) | Hospital Stay (days) | Costs* (€) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | pre | post | pre | post | | | | |
| Ahyai (85) | | | | | | | | | | | |
| HoLEP | 53 | 90.6 | 8.0 | 21.7 | | 3.6 | | 101.3 | | | |
| Open | 53 | 108.2 | 11.2 | 21.3 | | 3.4 | | 89.8 | | | |
| Kuntz (86) (87) | | | | | | | | | | | |
| HoLEP | 60 | 114.6 | | 22.1 | 3.0 | 3.8 | 27.7 | 136 | 1.3 | 2.9 | |
| Open | 60 | 113.0 | | 21 | 2.8 | 3.6 | 25.0 | 91 | 8.1 | 10.5 | |
| Naspro (88); Suardi (89); Salonia (90) | | | | | | | | | | | |
| HoLEP | 41 | 113.27 | 6.33 | 20.11 | 7.9 | 7.83 | 19.19 | 72.09 | 1.5 | 2.7 | 2,356.5 |
| Open | 39 | 124.21 | 6.99 | 21.6 | 8.1 | 8.32 | 20.11 | 58.31 | 4.1 | 5.4 | 2,868.9 |

*peri-operative

**TABLE 10** Summary Table of Trial of GreenLight Laser Vaporization Versus Simple Prostatectomy (18 months follow-up)

| Author | N | Prostate Volume (mL) | PSA (ng/mL) | | AUA/IPSS | | $Q_{max}$ (mL/s) | | Operative Time (min) | Catheterization Time (days) | Hospital Stay (days) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | pre | post | pre | post | pre | post | | | |
| Skolarikos (91) | | | | | | | | | | | |
| GreenLight | 65 | 93 | 6.2 | 2.4 | 21 | 8.5 | 8.6 | 16 | 80 | 1 | 2 |
| Open | 60 | 96 | 6.3 | 2 | 20 | 10 | 8 | 15.1 | 50 | 5 | 6 |

# 5.4 Laser Prostatectomy

## 5.4.1 The 532-nm wavelength laser

The high-power 532-nm laser system employs a high-powered green light visible wavelength utilizing laser systems also described as a KTP laser, lithium triborate (LBO) laser, and GreenLight laser system, and the technique is often called photoselective vaporization of the prostate (PVP).

The original 532-nm high-power laser for PVP was a potassium-titanyl-phosphate (KTP)–based laser system that contained a KTP crystal through which a 532-nm wavelength was generated. This had a different interaction with the prostate tissue compared with its parent, Nd-YAG (92). The 532-nm wavelength is selectively absorbed by Hb, which acts as an intracellular chromophore. 532-nm wavelength laser energy can be fully transmitted through aqueous irrigants into the cell, where it is absorbed by hemoglobin, which is then rapidly heated, leading to vaporization of prostate tissue. The short optical penetration that is associated with this wavelength confines its high-power laser energy to a superficial layer of prostatic tissue that is vaporized rapidly and hemostatically with only a 1 to 2 mm rim of coagulation. The thin coagulation zone arises as a result of the quasi-continuous emission characteristics of the 532-nm laser. Typically, continual irradiation of a single point causes heat to diffuse into deeper tissue layers, creating coagulation wherever there is enough convection thermal energy for protein denaturation but insufficient energy for vaporization. These selective characteristics led to the use of the 532-nm laser in prostatectomy being coined "Photoselective Vaporization of the Prostate" (PVP).

## 5.4.2 60-W data

Experiments with a higher-power 60-W KTP laser began with both *in vivo* canine studies as well as cadaveric canine and human trials (92). These studies proved the ability of the KTP laser to vaporize tissue while minimizing accompanying coagulation effects. The first human trials with the 60-W KTP laser were conducted in a series of 10 patients described by Malek *et al.* in 1998 (93). No patients suffered post-operative TUR syndrome or urinary retention; in fact, all patients were catheter free within 24 hours of the procedure. Patients experienced a significant improvement in $Q_{max}$ (142%) by 24 hours post-operatively.

These trials with the 60-W KTP laser were followed by a larger series of 55 patients in 2000 (94). The 2-year experience with the higher-powered KTP laser again corroborated initial findings. Patients experienced statistically significant enduring improvements in post-operative AUA symptom score (mean, 14; 82% improvement), $Q_{max}$ (mean, 29.1 mL/s; 278% improvement), and PVR (27 mL; 75% improvement) with 2 years of follow-up, comparing favourably with published results for conventional TURP. Mean operative time was 44 minutes. All patients in the series were catheter free 24 hours after the procedure; none required re-catheterization or experienced TUR syndrome. Hematuria was negligible despite the use of antiplatelet agents by many patients. These early results demonstrated level 4 evidence that prostatectomy with the prototype 60-W KTP laser was as effective as conventional TURP and, in fact, demonstrated post-operative complications comparable to TURP and even to other laser therapies, such as Holmium:YAG (Ho:YAG).

### 5.4.3 **80-W data**

Despite the effectiveness of the 60-W KTP laser in prostatectomy, its less-than-ideal speed of vaporization inherently limited the size of prostate that could be resected. The next logical improvement therefore lay in increasing laser power to improve tissue ablation and lead to the first clinically available 532-nm laser, which was a quasi-continuous 80-W KTP-based laser. Many important, early level 3 studies led to its popular use.

Hai and Malek presented the first human experience with 80-W KTP laser prostatectomy (95). Ten patients were followed for 1 year after their prostatectomy in a pilot study. Patients experienced statistically significant improvements in AUA symptom score (23.2 to 2.6), QOL scores (4.3 to 0.5), $Q_{max}$ (10.3 to 30.7 mL/s), and PVR (137.6 to 3 mL). The authors reported a 27% reduction in prostate volume. No patient experienced post-operative urinary retention, infection, incontinence, or ED; none subsequently developed bladder neck contractures or urethral stricture.

Te *et al.* presented the first large, multicentre series on the use of 80-W KTP laser in laser prostatectomy for 145 patients with long-term follow-up (96). This early study represented the initial PVP experience with these centres, testing ease of use. Significant and durable improvements in AUA Symptom Index (AUA SI) scores, QOL scores, $Q_{max}$, and PVR were demonstrated up to 12 months post-operatively. Mean AUA symptom scores declined from 24 to 1.8 at 12 months; mean QOL scores improved from 4.3 to 0.4, $Q_{max}$ from 7.7 mL/s to 22.8 mL/s, PVR volume from 114.2 mL to 7.2 mL. Mean prostate volume, as determined by ultrasound, decreased from 54.6 mL to 34.4 mL. Mean operative time was 36 minutes, and no patient required a blood transfusion. More than 30% of patients were sent home without a catheter; those with post-operative catheters had them removed in a mean of 14 hours. Reported morbidities were generally minor: 8% of patients experienced mild-to-moderate dysuria lasting more than 10 days, 8% had transient hematuria, and 3% had post-operative retention. Among the 56 men who were potent prior to the procedure, 27% experienced retrograde ejaculation, but none of them experienced impotence.

As a novel procedure, there are growing numbers of reports of long-term outcomes of 80-W KTP laser prostatectomy. Ruszat *et al.* published the largest series of 80-W KTP laser prostatectomies. At a single centre, 500 patients underwent PVP, including 45% taking oral anti-coagulation. After 3 years, 26.2% of patients had follow-up and mean AUS SI, PVR, and QOL scores were significantly improved compared with baseline. At 60 months, the re-treatment rate was 6.8% and the re-operation rate was 14.8%. Urethral and bladder neck strictures were observed in 4.4% and 3.6% of patients, comparable to the rate in TURP (97). Te *et al.* reported 3-year, multicentre, long-term follow-up in 139 patients who underwent 80-W KTP laser prostatectomy. At 3 years, 33.8% of patients had follow-up, and improvements in symptom relief and urinary flow rate were durable (98). The re-treatment rate was 4.3%.

The 80-W KTP/ 532-nm laser was also studied on larger glands, with reported good outcomes and an excellent safety profile. Sandhu *et al.* detailed large prostate volume resection with the 80-W KTP laser (98). A total of 64 men with BPH possessing prostates with volumes of at least 60 mL who had failed medical therapy were taken for vaporization with the 80-W KTP laser. The mean pre-operative prostate volume was 101 mL, with a mean operative time of 123 minutes. International Prostate

Symptom Score decreased from 18.4 to 6.7 at 12 months; $Q_{max}$ increased from 7.9 mL/s to 18.9 mL/s, while PVR decreased from 189 mL to 109 mL. No transfusions were required, nor was there evidence of post-operative hyponatremia. All 62 patients were discharged within 23 hours. This was the first evidence that the 80-W KTP laser could be used as a safe and effective means, with durable results for large-volume prostatectomy.

Pfitzenmaier *et al.* conducted a comparative study between vaporization of prostates greater than or equal to 80 mL and those smaller than 80 mL; 39 of 173 patients had prostates ≥80 mL. The authors found that PVP was safe and effective in prostates ≥80 mL, but the re-operation rate was higher (99). In another study, Rajbabu *et al.* assessed 54 consecutive patients with prostates >100 mL who underwent 80-W KTP laser prostatectomy. Another recent study of 150 consecutive patients with LUTS who underwent laser vaporization with 80-W KTP laser showed a decrease in storage and voiding symptoms by 81.8% and 90.9% at 12 months, respectively (100). Consistent with other published series, these studies further support the procedures' safety, efficacy, and durable improvements on IPSS and QOL score (101).

The safety of the 80-W KTP laser prostatectomy has been studied in patients at high cardiopulmonary risk, and demonstrated to be excellent due to the excellent hemostatic profile and peri-operative hemodynamic stability of the procedure. Reich *et al.* performed 80-W laser prostatectomy on 66 patients with an American Anesthesiology Score of 3 or greater (102). Of these patients, 29 were being treated with ongoing oral anti-coagulation or had a severe bleeding disorder. No major complications occurred during or following the procedure and no blood transfusions were required. Two patients required re-operation within 12 months due to recurrent urinary retention. Mean improvements in IPSS (20.2 to 6.5) and peak flow (6.7 to 21.6 mL/sec) were durable at 12 months.

One specific safety application of the 80-W KTP laser was its use in anti-coagulated patients at high risk for clinically significant bleeding. A series of 24 anti-coagulated patients with BPH treated with laser prostatectomy using the 80-W KTP laser was studied (103). Of these, eight were on warfarin, two on clopidogrel, and 14 on aspirin. Eight (33%) of these patients had a previous myocardial infarction, seven (29%) cerebrovascular disease, and seven (29%) peripheral vascular disease. No patients developed clinically significant hematuria post-operatively and none developed clot retention. No transfusions were required and there were no thromboembolic events. Follow-up revealed a decrease in IPSS from 18.7 to 9.5 as well as an increase in $Q_{max}$ from 9.0 mL/s to 20.1 mL/s at 12 months. PVR decreased from 134 mL to 69 mL at 1 month, but it was not statistically significant beyond that time point. All patients underwent PVP safely without any adverse thromboembolic or bleeding events. Significantly more energy and time was used for lasing per gland size in these patients (104).

The largest published series is a study by Chung *et al.* reporting on outcomes and complications after PVP in an anti-coagulated, high-risk cohort of 162 men on systemic anti-coagulation who underwent PVP (105). Mean age was 72 years, mean baseline prostate volume was 91 g, and mean PSA level was 4.1 ng/mL. Of the patients, 31 (19%) were on warfarin, 101 (62%) were on acetylsalicylic acid, 19 (12%) were on clopidogrel, and 11 (7%) were on two or more anticoagulants. Median American Society of Anesthesiologists (ASA) class was 3 and mean Charlson comorbidity index was 5. Median operative time was 105 minutes and mean energy use was 168 kJ. The immediate mean hematocrit decrease was 1.94%. One patient who received excessive intravenous fluids experienced heart failure.

Complications within 30 days included UTI in four patients (2.5%) and delayed bleeding in six (4%). Three of these patients (50%) required blood transfusion and one (17%) required re-operation. In 2 years of follow-up, three patients (2%) required repeat PVP. No incontinence or urethral stricture developed. Significant improvements occurred in IPSS, $Q_{max}$, and PVR urine. This series supports using 532-nm PVP in patients at high risk on systemic anti-coagulation, even those on two or more anti-coagulation agents and with a large prostate requiring longer operative time. Few complications developed and significant durable clinical improvement was seen in this high–surgical risk cohort treated with PVP.

There is a growing body of level 2 and 3 evidence comparing 80-W KTP laser prostatectomy with TURP. Ruszat *et al.* conducted a study with 396 patients randomized to receive either 80-W laser prostatectomy or TURP (106). Interim 24-month follow-up data found that the rate of intra-operative bleeding (3% vs. 11%), blood transfusion (0% vs. 5.5%), capsule perforations (0.4% vs. 6.3%), and early post-operative clot retention (0.4% vs. 3.9%) was significantly lower in the laser group. There was no significant difference in IPSS and PVR. After 12 months, size reduction was greater in the TURP group (66% vs. 44%) and the rate of repeat procedure was greater in the PVP group (6.9% vs. 3.9%; not significant). Bouchier-Hayes *et al.* reported data on 120 patients randomized to undergo TURP or 80-W laser PVP. At 12 months, equivalent improvements in IPSS and flow rates were demonstrated. Length of hospitalization, length of catheterization, and adverse events were lower in the laser group. In a non-randomized study, Bachmann *et al.* studied 101 patients who underwent either TURP or laser prostatectomy. Peri-operative morbidity and symptom improvement was equivalent in the groups at 6 months (107). Another randomized study has yielded divergent results. In this study, 76 patients with prostate size >70 mL were randomized to receive TURP and 80-W laser prostatectomy (108). Procedure time was shorter for the TURP group. Hospitalization stay and catheterization time were significantly shorter in the laser group. There was a significant difference in favour of TURP in terms of improvement in IPSS, PVR, and $Q_{max}$, as well as volume reduction in the TURP group. In addition, the re-operation rate was higher in the laser group (108). An Australian study had similar results when comparing patients randomized to receive either 80-W laser prostatectomy or TURP. Both groups showed a significant increase in mean urinary flow rate, improvement in IPSS, and no difference in sexual function with 1-year follow-up (109).

### 5.4.4 **120-W data**

The 80-W KTP laser system evolved to a higher-power system capable of delivering 80 W to 120 W to increase vaporization efficiency. This laser emits the same 532-nm wavelength, with the same hemostatic properties as the 80-W KTP (110), but it utilizes a different crystal. The 532-nm 80-W KTP laser is created by passing a 1064-nm Nd:YAG laser beam through a KTP crystal. In contrast, the 120-W HPS 532-nm wavelength is created by passing an Nd:YAG laser beam through an LBO crystal. The 532-nm LBO–based system also has a beam that is better collimated than the KTP-based beam.

Several animal studies have been performed with the 120-W 532-nm laser. Lee *et al.* investigated the use of the 120-W laser in five male beagles (111). Photoselective vaporization of the prostate was performed in antegrade fashion through a suprapubic cystotomy at 40, 80, and 120 W settings for 3 distinct firing periods (5,10, and 20 seconds) at unique locations in the prostate. 120-W HPS consistently vaporized more tissue per unit time while the depth of coagulation (1.2–2.5 mm) was decreased

compared with the lower-powered systems. Kang *et al.* compared the use of the 120-W HPS laser to the 80-W HPS laser and the 80-W KTP laser from 96 specimens of bovine prostate tissue (112). The 120-W HPS laser vaporized bovine prostate tissue more efficiently than the 80-W KTP laser, and coagulation was equivalent. Lee *et al.* advised caution with the higher-power setting, particularly at 120 W due to the potential higher risk for capsular perforation and bladder wall perforation. Moreover, the higher power provided more efficient vaporization with less hemostasis, and, as a result, utilization of a lower-power coagulation setting is important in achieving hemostasis.

Heinrich *et al.* used blood-perfused porcine kidney to determine the ablation capacity, hemostatic properties, and coagulation depth of a 120-W 532-nm laser compared with an 80 W (113). The 120-W LBO laser offered a significantly higher tissue ablation capacity compared with the conventional 80-W KTP laser. The increased efficacy of the 120-W laser device was accompanied by a higher bleeding rate and a slightly deeper coagulation zone.

Several level 2 and 3 studies confirm the PVP experience with 120-W laser for safety and efficacy, though the higher efficiency warranted the caveat of only using the energy needed to achieve vaporization efficiency, with care to prevent compromising hemostasis and causing unwanted coagulation necrosis.

A study by Al-Ansari *et al.* randomized 120 patients with BPH to receive TURP or 120-W 532-nm laser (114). A total of 55 and 54 patients completed 36 months of follow-up in the TURP and 532-nm laser groups, respectively. Baseline characteristics were comparable. Mean operative time was significantly shorter for TURP. Compared with pre-operative values, there was significant reduction in Hb and serum Na+ levels at the end of TURP only. In the PVP group, no major intra-operative complications were recorded, and none of the patients required blood transfusion. Among patients who received TURP, 12 (20%) required transfusion, three (5%) developed TUR syndrome, and capsule perforation was observed in 10 patients. There was dramatic improvement in $Q_{max}$, IPSS, and PVP compared with pre-operative values, and the degree of improvement was comparable in both groups at all time points of follow-up. Storage bladder symptoms were significantly higher in the PVP groups. A redo procedure was required in one patient in the TURP group and six patients in the PVP group ($p<0.05$). Two patients who received TURP and four patients who received PVP developed bladder neck contracture ($p>0.05$) treated by BNI; no patients in either group experienced urethral stricture or urinary incontinence.

Lukacs *et al.* assessed the non-inferiority of PVP compared with TURP on urinary symptoms and the superiority of PVP over TURP on length of hospital stay in a French, multicentre, RCT that was conducted on patients who underwent monopolar TURP or PVP with the GreenLight HPS 120-W laser (10). IPSS, the Euro-QOL questionnaire, uroflowmetry, Danish Prostate Symptom Score Sexual Function Questionnaire, sexual satisfaction, and adverse events were collected at 1, 3, 6, and 12 months. A total of 139 patients were randomized equally. Median IPSS at 12-month follow-up was five for TURP versus six for PVP. Similarly, non-inferiority could not be considered to have been demonstrated. Median length of stay was significantly shorter in the PVP group than in the TURP group, with a median of 1 versus 2.5 days, respectively ($p<0.0001$). Uroflowmetry parameters and complications were comparable in both groups. Sexual outcomes were slightly better in the PVP group without reaching statistical significance.

Several trials comparing TURP with PVP have been analyzed in a meta-analysis by Thangasamy *et al.* to provide a systematic review and meta-analysis of LOE 1 studies to determine the effectiveness of PVP versus TURP for surgical treatment of BPH (115). Outcomes reviewed included peri-operative data, complications, and functional outcomes. Biomedical databases from 2002 to 2012 and AUA and EAU conference proceedings from 2007 to 2011 were searched. Trials were included if they were RCTs and had PVP as the intervention and TURP as control. Meta-analysis was performed using a random effects model.

Evidence synthesis: Nine trials were identified with 448 patients undergoing PVP (80 W in five trials and 120 W in four trials) and 441 undergoing TURP. Catheterization time and length of stay were shorter in the PVP group by 1.91 days ($p<0.00001$) and 2.13 days ($p<0.00001$), respectively. Operative time was shorter in the TURP group by 19.64 minutes ($p=0.0003$). Blood transfusion was significantly less likely in the PVP group ($p=0.003$). There were no significant differences between PVP and TURP when comparing other complications. Regarding functional outcomes, six studies found no difference between PVP and TURP, two favoured TURP, and one favoured PVP. In summary, the authors found that peri-operative outcomes of catheterization time and length of hospital stay were shorter with PVP, whereas operative time was longer with PVP. Post-operative complications of blood transfusion and clot retention were significantly less likely with PVP; no difference was noted in other complications. Overall, no difference was noted in intermediate-term functional outcomes.

### 5.4.5 180-W data 532-nm laser

The current clinical popular advance PVP system is a 180 W–capable, 532-nm LBO–based laser system with a feedback mechanism to control energy with a water cooled re-designed high-power fibre. The modifications increase the potential vaporization efficiency of this laser. Another modification is an added coagulation power mode due to the intermittent pulsing and continuous flow of a room temperature irrigant over the tip.

Early level 4 evidence with the 180-W laser with the actively cooled fibre demonstrates it to be extremely efficient, and, in the hands of experienced users, it appears to have equal efficacy and safety (116). With the new aqueous cooled fibres and the 180-W laser system, power to 180 W can be utilized. However, at 120 W or greater, the higher efficiency seems to be obtained at the expense of hemostasis. This increased power and efficiency highlights a concern that if there was a misfire within the bladder at settings such as 180 W, there could be damage done to the bladder and ureteral orifices, as well as bladder perforation very quickly without recognition by the surgeon.

### 5.4.6 Complications

All reported studies have noted markedly less morbidity associated with laser prostatectomy compared with traditional surgical approaches. Bleeding is the main complication of traditional electrocautery TURP, often necessitating transfusion and causing associated problems such as clot retention, premature termination of the procedure, and inadequate relief of obstruction (117). Bleeding can also result in continuous catheter irrigation and complications such as strictures secondary to traction on the Foley catheter. Rarely, uncontrolled bleeding can even require open packing of the

prostatic fossa. Poor visibility because of bleeding is also thought to be a cause of sphincteric damage and incontinence resulting from TURP. The incidence of hemorrhage requiring blood transfusion is 3.9%, and increases 2-fold if the amount of resected tissue exceeds 45 mL or if the resection time is longer than 90 minutes. In contrast to transurethral electroresection, which cuts across the prostatic parenchyma and opens prostatic venous sinuses, laser prostatectomy seals blood vessels as it coagulates the transition zone and prevents both absorption of irrigating fluid and hemorrhage, and thus the hemostasis associated with laser prostatectomy is superior, with many studies of anti-coagulated patients undergoing laser treatment without bleeding complications (103,118,119).

Irrigant fluid absorption during electrocautery TURP results in a 2% incidence of TURP syndrome because of dilutional hyponatremia, glycine-induced ammonia intoxication, or the direct toxic effect of glycine (120). As with bleeding, fluid absorption increases with larger glands and longer resection times. Laser prostatectomy minimizes this complication again through its sealing effect on tissue, which prevents fluid absorption.

The incidence for urethral stricture after electrocautery TURP is 3.1%; if bladder neck contractures are included, this figure approaches 5% (119). Stricture formation is thought to be secondary to trauma induced by the large size of the resectoscope as well as the use of low-intensity, coagulating current, which penetrates more deeply into tissue than cutting current. As laser procedures do not use electrical current, the cystoscopes utilized are smaller in size, the overall operative time is usually shorter, and the incidence for stricture is lower following laser procedures (121,122). The incidence of re-operation for residual obstructive tissue is difficult to determine, as most published series of laser prostatectomy have documented initial experiences with this technology. Our experience with strictures and bladder neck contracture demonstrated that the incidence is higher in patients with bladder dysfunction, bladder diverticulum, or with long procedures utilizing larger-diametre scopes (123).

Post-operative infections may also occur after TURP. The incidence of UTI following TURP is 15.5% (median) while epididymitis occurs in 1.2% (120). Urinary tract infections have been reported in 1% to 20% of patients following laser prostatectomy and epididymitis in 5% to 7% of patients (124–128). The treatment for such infections may be more problematic in laser prostatectomies due to the residual necrotic prostate tissue that remains *in situ* for several weeks after laser coagulation. When this occurs, the most common manifestation is sub-acute prostatitis, characterized by significant and persistent irritative voiding symptoms, with mild prostatic and/or epididymal tenderness on examination, persistent pyuria, and positive urine cultures. Two cases of frank urosepsis have, in fact, been reported following laser prostatectomy, both requiring TURP to remove infected necrotic prostate tissue (129). Aggressive antibiotic therapy is therefore warranted in these patients.

Finally, retrograde ejaculation represents another potential side effect of electrocautery TURP, occurring in up to 90% of patients. 80-W KTP laser data shows that retrograde ejaculation also represents a potential problem in laser prostatectomy, with a 27% incidence of retrograde ejaculation (96). Similarly, the incidence for impotence following electrocautery TURP ranges from 4% to 13% (120). However, the overall incidence of impotence following all forms of laser prostatectomy is extremely low. While data are limited, available 80-W KTP data show no loss of potency in patients treated with laser prostatectomy (96).

### 5.4.7 Conclusion

Laser prostatectomy (532 nm) has proven to be a safe and efficacious surgical intervention to relieve symptomatic BOO based on a large body of level 1 to 4 evidence. Overall morbidity contrasts favourably with standard surgical approaches. Moreover, laser technology is generally accessible to the practicing urologist. The transurethral endoscopic approach and operative techniques are not complex. These attributes have positioned 532-nm laser prostatectomy as an accepted surgical treatment for BPH.

# 5.5 Holmium Laser Prostatectomy

Holmium:YAG is a multi-functional surgical laser that has multiple applications in urology such as incision of urethral and ureteral stricture (130), lithotripsy of urinary calculi (131), ablation of superficial urothelial tumours (132), BNI (133), and ablation, resection, and enucleation of the prostate (134). The excellent hemostatic properties of the holmium laser during soft-tissue applications results in a mostly bloodless field and a decrease or elimination of the need for bladder irrigation (135). The Ho:YAG laser works through thermal energy, which allows for use of physiologic irrigants, eliminating risks for dilutional hyponatremia and TUR syndrome (136).

### 5.5.1 Holmium laser incision and ablation

Application of the Ho:YAG laser for BPH includes BNI, prostate ablation (HoLAP), and enucleation (HoLEP).

1. Holmium laser BNI. The holmium laser can be used to perform BNI in a manner similar to TUIP (133). Cornford et al. reported the results of holmium laser incision of the bladder neck in 100 men with prostate glands <30 g. International Prostate Symptom Score decreased from 19.2 to 3.7 at 6 weeks and remained improved at 2 years. $Q_{max}$ increased from a mean of 9.79 mL/s to 19.23 mL/s and 18.27 mL/s at 6 weeks and 2 years, respectively. The authors confirm that the Ho:YAG laser allows TUIP to be performed without the need for post-operative catheterization and without significant peri-operative complications.

2. Holmium laser ablation of the prostate (HoLAP). Holmium laser ablation of the prostate is a simple procedure that is suitable for small-to-moderate–sized prostates, but it is not efficient and is tedious for treating larger prostate glands; it also generates no tissue specimen for histopathological analysis (137,138). 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 (SF) laser fibre to make a BNI at 5 and 7 o'clock, then the laser fibre is gently moved over the surface of the lateral lobes toward 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.* (139) (LOE 1) reported the results of a prospective RCT comparing HoLAP with 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 catheterization times without the need for any irrigation.

Tan *et al.* (140) reported the results of a 7-year follow-up of 34 patients who underwent HoLAP. There was an 83% improvement in $Q_{max}$ and 47% decrease in AUA score with a re-operation rate of 15% and re-catheterization 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 $Q_{max}$, a 51% decrease in IPSS, and a 67% decrease in PVR at 5 years compared with pre-operative values.

HoLAP is an easy technique with a short learning curve, but the procedure is rather slow (138).

## 5.5.2 Holmium laser enucleation of the prostate

Holmium laser enucleation of the prostate is now a well-established technique for the surgical management of BPH. Level 1 evidence has been published documenting the superiority of HoLEP over TURP for prostates of standard size and as an alternative to open simple prostatectomy for prostates of large size (86,141–147). The technique of HoLEP duplicates the complete adenectomy provided by open simple prostatectomy via either the suprapubic or retropubic approaches. The HoLEP technique involves identification and dissection in the surgical plane between the adenoma and surgical capsule much like it's done with open surgery. The technique can be accomplished in a variety of manners. The prostate can be enucleated in a two-lobe or three-lobe technique depending upon surgical anatomy and surgeon preference. Once the adenoma has been enucleated, the lobes are displaced into the bladder where a tissue morcellator is then used to retrieve the specimen. There is virtually no thermal effect on the tissue, making it ideally suited for histologic examination (148). Recently, newer morcellators have been introduced by the Richard Wolf and Karl Storz companies (149,150).

One advantage of HoLEP is that with experience, there is no practical size limitation for its application. Significant improvements in symptoms and flow rate regardless of the size of the prostate have been reported (151). Furthermore, the rate of blood transfusion, catheterization time, and hospital stay did not depend on prostate size (152,153). With experience, HoLEP now allows patients with a very large prostate who would traditionally be treated with open prostatectomy to be treated endoscopically (154,155).

Holmium laser enucleation of the prostate is the most rigorously studied of all surgical techniques for the management of BPH. A number of publications now document the long-term outcomes that can be expected with this technique. Gilling reported 38 patients with a mean follow-up of 6.1 years. Only one patient required re-operation. IPSS was 8.5 and $Q_{max}$ was 19 mL/s (156). Kuntz reported 5-year follow-up results of 42 patients treated with HoLEP compared with open prostatectomy as part of an RCT. The AUA symptom score was 3.0 and the mean $Q_{max}$ was 24.4 mL/s. Late complications comprising urethral strictures and bladder neck contractures occurred in 5% of patients.

No patient developed a recurrence of his BPH (87). Krambeck reported on 79 patients who had >5-year follow-up after HoLEP. Mean AUA symptom score was 5.1 and mean BPH index was 1.07. In this series of more than 1,000 patients, only two patients were unable to void following HoLEP and only one patient required re-operation for BPH re-growth. Urethral stricture and bladder neck contracture were also rare, occurring at some point in 2.3% and 1.5% of patients, respectively. At most recent follow-up, 0.8% and 0.6% of patients reported stress or urge incontinence, respectively. The mean PSA level in 83 patients with >5 years of follow-up was 0.95 mg/dl (157). Elmansy reported on 89 patients who had a minimum of 10 years follow-up after HoLEP. Mean IPSS was 3.6 and mean $Q_{max}$ was 26.9 mL/s. Re-operation due to residual or re-growth of BPH occurred in 0.7% of patients (158). In addition to producing superior outcomes compared with TURP and open prostatectomy, HoLEP is a cost-effective approach to the problem of BPH. Fraundorfer reported that nursing costs to manage bladder irrigation and clot retention were fewer in patients treated with HoLEP due to the reduced risk for bleeding following this procedure (159). Furthermore, the laser fibres and morcellator blades utilized during HoLEP are reusable, eliminating the costly disposals associated with most other surgical techniques for the treatment of BPH.

In summary, extensive short- and long-term data suggest that HoLEP remains the modern gold-standard alternative to TURP and open prostatectomy. Furthermore, outcomes are very consistent among reports from around the world, undoubtedly related to the salutory benefits of the complete removal of the transition zone, which HoLEP accomplishes.

# 5.6 Thulium and Diode Lasers

## 5.6.1 Thulium laser

Thulium laser emission is achieved by using a laser diode (the excitation source) to excite a thulium:YAG crystal (the active medium). This generates laser light at a wavelength tunable from 1750 to 2220 nm, but most commonly used at 2013 or 1940 nm. It is sometimes also referred to as the 2-micron laser. Thulium is usually emitted in continuous mode. Although the thulium wavelength is very similar to that of the Ho:YAG laser, their interaction with tissue is quite different, due to their differing modes of emission (Holmium is pulsed, while thulium continuous). The thulium laser heats tissue above the boiling point, vaporizing it, and allowing it to cut through tissue "like a hot knife through butter." It has a tendency toward carbonization and charring. In contrast, the high peak power of each holmium laser pulse creates a pulsatile steam bubble which mechanically separates the tissue rather than cutting it, with minimal or no charring.

The initial thulium laser generators offered 70 W of power. Subsequently, models capable of delivering 120 W and 200 W have become available.

Thulium can be used to perform each of the three main BPH techniques: vaporization, resection, and enucleation.

## 5.6.2   Thulium vaporization

Although vaporization was the first thulium BPH technique described, there are only four published studies relating to it. None of these is randomized however, and two relate to animal models. The acronyms assigned to thulium vaporization vary and include ThuVP and ThuVAP.

Thulium vaporization via an SF fibre was first reported by Fried in 2005 using *ex vivo* canine prostates (160,161). The conclusion was that high-powered thulium is capable of rapid vaporization and coagulation in the prostate model (ablation rate, 0.83±0.11 g/min) (160).

Level 3 evidence for ThuVAP is available in two papers: Mattioli *et al.* (162) report on 99 cases of ThuVAP for prostates <35 g and 101 cases of thulium vaporesection of the prostate (ThuVaRP) for prostates >35 g. The authors conclude that these techniques are both safe, with short learning curves, and suggest that ThuVAP might be better suited for prostates <35 g and ThuVaRP for prostates >35 g.

Another case series describes only 19 cases of ThuVAP, with mean prostate volume and laser time of 68.8 mL and 34.7 minutes, respectively (163). No blood transfusions were required and there were no significant changes in serum Hb and Na+. The only complication reported was post-operative urinary retention in one case. Follow-up was only reported at 1 month.

No firm conclusions on ThuVAP can be drawn from this sparse level 3 and 4 evidence with short follow-up.

## 5.6.3   Thulium resection

The thulium laser was initially marketed for resection of the prostate. The so-called "tangerine technique" was described by Xia (164). It is very similar to the technique of holmium laser resection of the prostate (HoLRP) and involves making radial incisions at 1, 3, 5, 6, 7, 9, 11, and 12 o'clock down to the capsule, then removing the segments off the capsule like segments of a tangerine. These segments are small enough to allow removal by Ellick evacuation or by using forceps, thereby avoiding the need for a morcellator. This technique has been termed thulium laser vaporesection of the prostate, or ThuVaRP. To avoid confusion, it is worth noting that several other acronyms have been used to refer to the same technique. These include TmLRP and TLVR.

In the single randomized trial published to date for ThuVaRP, Xia *et al.* randomized 100 consecutive patients to receive ThuVaRP at an average power of 50 W or M-TURP (165). Thulium vaporesection of the prostate was superior to M-TURP in terms of catheterization time (45.7 vs. 87.4 hours), hospital stay (115.1 vs. 161.1 hours), and change in Hb (0.92 vs. 1.46 g/dl). Blood was transfused in 4.2% of the TURP group compared with none in the ThuVaRP group, and while TUR syndrome occurred in 2.1% in the TURP group, it did not occur with ThuVaRP. There were no significant differences in operative time, IPSS, QOL score, $Q_{max}$, PVR, and late complications during 12 months of follow-up.

A Chinese-language paper compares ThuVaRP (36 patients) with GreenLight PVP (82 patients) for men with prostates >80 g (166). It is unclear from the abstract whether this study is randomized. The mean operating time, post-operative bladder irrigation time, and cost were significantly less for ThuVaRP. No blood transfusions or serious complications were reported. There were no significant differences in improvement in IPSS, QOL score, $Q_{max}$, and PVR between the groups.

A number of case series have been published for ThuVaRP.

In a series of 72 patients with mean prostate volume of 65.8 g (range, 36–108 g) who had ThuVaRP at 70 W, the mean operating time was 56 minutes (range, 45–110 min) (167). Mean catheterization time and hospital stay were 1.7 days and 2.8 days, respectively. There were no blood transfusions and TUR syndrome. Percentage improvements in mean IPSS, QOL score, $Q_{max}$, and PVR at 12 months were 72%, 71%, 264%, and 66%, respectively. Within the first 2–4 weeks, dysuria occurred in 8% and irritative urinary symptoms in 30%.

Pal *et al.* reported on their first 60 consecutive patients (168). One developed urosepsis and one a UTI. Hematuria requiring irrigation occurred in one patient, but none of the patients required transfusion. There were significant improvements in mean IPSS, $Q_{max}$, and PVR at mean follow-up of 19 months (15–28 months).

Szlauer *et al.* retrospectively evaluated 56 patients with mean TRUS volume of 50 mL who had ThuVaRP at 70 W (169). Median operation time was 60 minutes (range, 25–171 min). Resected weight was very small, suggesting either a significant vaporization component and/or incomplete resection (mean, 7 g; range, 1–23 g). There was modest PSA reduction of 56% and a re-operation rate for persistent/recurrent BPH of 7% after a median follow-up of 9 months. Post-operative irrigation was used in 34%, and 2 of 56 patients received blood transfusions.

In a recent *ex vivo* study, the speeds of resection of the thulium laser at 70 and 120 W were compared (170). 120-W resection was twice as fast as 70-W resection (10.39 g/5 min vs. 5.21 g/5 min, respectively), without a significant increase in the depth of the necrotic tissue layer (0.99 mm vs. 0.98 mm).

Yee *et al.* investigated the sexual side effects of ThuVaRP at 70 W in a cohort of 113 consecutive patients (171). Only 54 patients who were able to sustain an erection satisfactory for intercourse pre-operatively were assessed for ED and retrograde ejaculation post-operatively. No validated sexual function questionnaires were used. Patients were simply asked if they experienced ED and to comment on the quantity of their ejaculate compared to their ability pre-operatively; 20% reported ED and 6% an improvement in erectile function. A total of 56% had either reduced or absent ejaculate, while 7% described improved ejaculation. The lack of a validated questionnaire and the relatively small number of patients assessed weaken this study.

## 5.6.4 Thulium laser enucleation

The thulium laser was first used for enucleation at a conference in Paris by Aho in 2007. The technique employed was identical to that used for HoLEP (172), and this technique has subsequently become known as ThuLEP. It was noted at the time that although the thulium laser could be used

for anatomical enucleation, it was not as well suited to the technique as the holmium laser for several reasons. Firstly, due to its ability to cut like a hot knife through butter, the thulium laser tends to cut in and out of the enucleation plane, rather than following it as the finger does in an open simple prostatectomy. Secondly, the thulium laser causes significantly more tissue carbonization than holmium and also produces a stream of bubbles at the fibre tip (unlike holmium). These characteristics can interfere with the view of the enucleation plane.

Nonetheless, thulium continues to be used by some surgeons as an energy source for enucleation, and the procedure referred to as ThuLEP has been adapted with time to involve less laser energy and a more blunt dissection and vaporization (173).

A different "enucleation" technique known as thulium laser vapo-enucleation of the prostate (ThuVEP) has evolved. This involves a relatively non-anatomical enucleation which combines resection of the lateral lobes in large pieces with vaporization to "tidy up" the cavity. The true enucleation plane is not followed in this technique, and hence it can be regarded as a version of resection.

In a randomized trial of 133 patients comparing ThuLEP (70 W) with HoLEP (90 W), ThuLEP had a longer operating time (72.4 min vs. 61.5 min) (174). The authors commented on the aforementioned differing laser-tissue interactions of thulium and holmium. In contrast to the "scar-free" effect of holmium on the tissue surface, and its precise incision and dissection capabilities which allow the prostatic lobes to "burst from the plane making enucleation easier," they proposed that the "Eschar-like" effect of thulium on the tissue surface and the subsequent use of mainly blunt dissection to free the prostate lobes during ThuLEP might explain its longer operating time. Thulium laser enucleation of the prostate caused less blood loss than HoLEP (130.0 mL vs. 166.6 mL, respectively), but there was no difference between the groups in terms of change in serum Hb and no patients were transfused. There were no significant differences in terms of enucleated tissue weight, catheterization time, IPSS, $Q_{max}$, and PVR improvements during 18 months of follow-up.

The largest published ThuVEP (120 W) case series comprises 207 consecutive, prospectively evaluated patients with a mean prostate volume of 57.8 mL (175). Mean operation time and catheterization time were 64.9 minutes and 2.2 days, respectively. A total of 6.3% of patients required an early postoperative "second-look operation," including one for failed morcellation, four for clot retention, and eight for residual prostate apical tissue. The transfusion rate was 2%; 71% of patients were available for review at 12-month follow-up when percentage improvements in mean IPSS, QOL score, $Q_{max}$, and PVR were 77%, 73%, 150%, and 83%, respectively.

Thulium laser vapo-enucleation of the prostate and ThuLEP have been studied in specific subsets of patients including those with large prostates, urinary retention, and those at increased risk for hemorrhage.

Bach *et al.* report on ThuVEP for 90 consecutive men with LUTS and a prostate volume greater than 80 mL (mean, 108.6 mL) (176). The mean enucleated volume was 70.5 g, and the mean TRUS volume reduction was 86%, suggesting a relatively high proportion of tissue vaporization. Mean operating time was 100 minutes (range, 40–220 min) and operating efficiency was 0.77 g/min. Blood transfusion was necessary in 2 of 90 patients. There was one ureteric orifice injury managed by stent

placement. Mean catheterization time was 2.24 days (range, 1–6 days). Follow-up at 12 months was available for 62% of patients. Mean PSA and TRUS volume reductions at 12 months were 88% and 86%, respectively; 3.6% of patients had persistent grade I stress incontinence at 12 months. ThuVEP was durable, with no re-operations for persistent/recurrent BPH by 12-month follow-up. Percentage improvements in mean IPSS, QOL score, $Q_{max}$, and PVR at 12 months were 80%, 76%, 226%, and 91%, respectively.

Bach *et al.* have also reported on ThuLEP for men with refractory urinary retention (177). Consecutive patients (*n*=208) were divided into two groups: Group A with urinary retention (*n*=65) and Group B with LUTS (*n*=143). Mean prostate volumes and operation times for Groups A and B were 45.6 mL versus 43.1 mL, and 72.4 minutes versus 65.6 minutes, respectively. There were no differences between the groups in terms of improvements in $Q_{max}$ and PVR, although follow-up duration is not specified. Complications were more frequent in Group A. For example, transfusion was noted in 1.5% versus 0.7%; 7.7% versus 4.2% were discharged with a catheter; and significant hematuria was noted in 3.1% versus 1.4% and UTI in 15.4% versus 4.2%.

In a paper suggesting that ThuVEP is safe in patients with therapeutic anti-coagulation, bleeding disorders, and platelet aggregation inhibitors, 15 of 39 patients were taking aspirin alone (178). Anti-coagulation was not paused for surgery. Mean prostate volume was 50.3 mL and operation time was 92 minutes. One patient was transfused, and 13% of patients had delayed hematuria which did not require surgical intervention.

The use of the latest 200-W thulium laser for ThuVEP was studied in a small cohort of 28 consecutive patients who were compared with a matched cohort of 28 patients who had undergone 120-W ThuVEP (179). Despite similar prostate volumes (65.39 mL vs. 68.62 mL) the percentage of resected tissue was smaller in the 120-W group (58.48% vs. 72.93%) due to the higher proportion of vaporized tissue. It is not possible to interpret the complication rates given the small number of patients. Outcomes at 12-month follow-up were equivalent.

## 5.6.5    Discussion

The quality of evidence for the use of the thulium laser to treat obstructive BPH is modest and mostly consists of cohort and *ex vivo* studies. Although thulium can be used for vaporization, resection, and enucleation, resection is the most studied thulium technique. Due to its laser-tissue interaction, thulium is perhaps best suited to resection, rather than vaporization or enucleation; however, with the advent of B-TURP, it faces strong competition as a resecting energy source, and good-quality randomized trials comparing these two modalities would be helpful. The single ThuLEP RCT suggests that it results in similar outcomes to HoLEP, but that HoLEP is superior as an energy source for endoscopic enucleation given the clearer operative view that it affords and its ability to act bluntly and therefore more closely mimic the finger in open simple prostatectomy.

### 5.6.6 Recommendation

Thulium can be recommended for use as a resecting tool. Its use for vaporization and enucleation should be limited to the context of randomized clinical trials for the time being until more, good-quality evidence is available.

# 5.7 Diode Laser

Diode lasers use electrical current to stimulate a semiconductor bar, which in turn generates laser light in continuous mode (180). The structure of the semiconductor bar can be varied by using different elements and layer structures in varying combinations. These variations translate to variations in wavelength for the diode lasers. Diode-laser wavelengths used for BPH surgery include 940, 980, 1318, and 1470 nm. Each of these wavelengths can have very different interactions with tissues, and the diode lasers are grouped together solely on the basis of their shared method of generation.

## 5.7.1 Diode vaporization

Vaporization of the prostate with diode lasers can be achieved using either traditional SF or new contact "twister" laser fibres.

In the single randomized trial to date for diode vaporization, 200-W vaporization using a 980-nm diode laser ($n$=55) is compared with GreenLight HPS vaporization ($n$=84) (181). There were no significant differences in baseline characteristics and peri-operative data except for mean applied energy, which was higher for diode (318 kJ) than for GreenLight (206.7 kJ). Mean prostate volume, laser time, catheterization time, and hospital time for diode versus GreenLight were 66.3 mL versus 60.3 mL, 50.1 minutes versus 50.0 minutes, 34.8 hours versus 39.9 hours, and 2.8 days versus 2.4 days, respectively. Two or more fibres were used in 3.6% of diode and 25% of GreenLight cases. There were no significant differences between the groups in IPSS, QOL score, $Q_{max}$, and PVR at all follow-up time points to 12 months. Mean reduction in prostate volume at 6 months was 52% for diode and 38% for GreenLight. In terms of complications, 12% of GreenLight cases needed electrocautery to control bleeding compared with none in the diode group. The difference in hemostatic ability is due to laser physics. The GreenLight laser is highly absorbed by Hb and when it encounters a large vessel it induces vapour bubbles within it, which can tear the vessel wall. Transient re-catheterization was required in 12% in the GreenLight group compared with 11% in the diode group. Re-do TURP to resect residual adenoma or obstructive necrotic tissue was required in 9.1% of diode and 3.6% of GreenLight cases. There were significant differences favouring GreenLight in terms of transient incontinence (14.5% vs. 2.4%), transient urgency (34.5% vs. 16.7%), epididymitis (9.1% vs. 1.2%), and dysuria with tissue sloughing (18.2% vs. 0%). The deeper coagulation zone induced by the diode laser might account for these differences.

There is also a prospective, non-randomized trial comparing 980-nm, 200-W diode vaporization ($n$=55) with GreenLight HPS ($n$=62) (182). This study has findings consistent with the randomized trial. A significantly higher amount of energy was used with diode laser (313 kJ vs. 187 kJ),

despite similar prostate volumes (64.7 mL vs. 67.4 mL) and lasing times (39.2 min vs. 33.2 min). The diode laser was superior to GreenLight in terms of hemostasis. Severe intra-operative bleeding that impaired vision was noted in 13% of GreenLight cases and none of the diode cases. Only 4% of diode cases needed post-operative irrigation compared with 40% of GreenLight cases. Capsular perforation occurred in 5% of GreenLight cases and caused severe bleeding in one patient who required a blood transfusion. Some complications were more common in the diode group including transient urge incontinence (7% vs. 0%), bladder neck contracture (15% vs. 2%), and stress incontinence (9% vs. 0%). Obstructive necrotic tissue necessitating secondary TURP occurred in 18% of diode patients. Re-operation for inadequate dis-obstruction was necessary in one patient who underwent GreenLight HPS during 6 months of follow-up.

Several, mostly small, case series for diode vaporization have been published. Most confirm the excellent hemostatic and vaporizing properties of the diode laser, but some raise concerns over deep-tissue damage that results in a number of complications including tissue sloughing and dysuria (183–187).

Modification of the fibre used for diode vaporization has led to some reduction in complications and side effects (188). In a randomized trial of high-power 980-nm diode vaporization with a traditional SF fibre ($n$=57) compared with a novel quartz head (QH) contact (Twister) fibre ($n$=56), there were no differences in intra-operative bleeding complications and vaporization rate. There were, however, differences in complications related to deep-tissue damage in favour of the QH group. Secondary hemorrhage occurred in 5% in the SF group compared with none in the QH group. Passage of significant tissue remnants and prolonged dysuria for more than 1 month were both more common in the SF group (52% vs. 16% and 42% vs. 17%, respectively). There was no difference in IPSS and QOL score improvements between the groups; however, there was significantly greater $Q_{max}$ improvement in the QH group, probably due to greater immediate vaporization of tissue with the QH fibre.

Modification of the wavelength and/or pulse mode may also be necessary to reduce the depth of tissue damage.

A large Twister fibre (LTW) is now available for diode vaporization and, in an RCT provided the highest rate of vaporization (1.54 g/min) and highest resistance to degradation, compared with the standard Twister fibre and standard SF fibre (189).

### 5.7.2  Diode resection

The single published paper relating to 980-nm diode laser resection of the prostate examined the quality of the histology from the resected fragments (190). Samples ranged in size from 4 mm to 30 mm and had brownish margins with a coagulation rim of 0.5 mm (range, 0.2–1 mm).

There are no papers reporting on any clinical aspects of diode resection.

### 5.7.3 Diode enucleation

Endoscopic enucleation of the prostate using the diode laser is known as both Eraser laser enucleation of the prostate (ELEP) and diode laser enucleation of the prostate (DiLEP). Both attempt to employ the same surgical technique as that used for HoLEP. In a randomized trial comparing 1318-nm, 120-W ELEP (*n*=30) with B-TURP (*n*=30), ELEP was superior in terms of blood loss (116.8 mL vs. 409.8 mL), catheterization time (32.8 hours vs. 65.7 hours), and hospital time (45.1 hours vs. 91.2 hours) (191). There were no significant differences between the groups with respect to complications, IPSS, QOL score, $Q_{max}$, and PVR to 6 months.

Diode laser enucleation of the prostate (*n*=74) was compared with TURP (*n*=52) in a non-random-ized cohort study (192). Diode laser enucleation of the prostate was superior in terms of change in Hb (0.9 g/dl vs. 1.6 g/dl); catheterization time (41.2 hours vs. 67.7 hours); and hospital stay (2.9 days vs. 4.1 days). Improvements in voiding parameters were comparable to 1 year.

### 5.7.4 Discussion

The diode lasers have mostly been used for vaporization rather than resection or enucleation. There appear to be distinct advantages of diode vaporization over GreenLight HPS, although fine-tuning is required, as there remain concerns regarding the depth of tissue damage caused by high-powered diode lasers. The evidence for diode resection and enucleation is too limited currently to make any firm recommendation other than that more good-quality clinical trials are required.

### 5.7.5 Recommendation

All forms of diode laser surgery for BPH should be investigated further in RCTs until better-quality evidence is available.

# 5.8 Minimally Invasive Surgical Treatments

Patient and physician concern over the morbidity associated with treatment for BPO with TURP or open simple prostatectomy was a primary driving force behind the development of minimally invasive surgical treatment (MIST) approaches. As these alternative treatments have developed, the comparative data for conventional surgery have also improved, therefore further increasing the demands upon MISTs to justify their place in the treatment of male LUTS.

Minimally invasive surgical treatments usually cover procedures that do not lead to the physical removal of prostatic tissue. Laser prostate treatments are not included in this section, as they are generally used to remove tissue by ablation, resection, or enucleation. Currently, MISTs include technologies that destroy or denature prostate tissue using a variety of energy sources, injected agents, or physical methods to draw open the prostatic urethra.

Recent studies suggest that MISTs such as microwave and TUNA are on a significant decline and that current laser treatments have essentially replaced ILC (1).

The Medline, Cochrane, and Embase databases were searched with terms including "benign prostatic hyperplasia or BPH or prostate" AND "transurethral microwave or TUMT"; "radiofrequency ablation or RFA or transurethral needle ablation or TUNA"; "ethanol or alcohol"; "botulinum or Botox or Dysport"; "Urolift or prostatic urethral lift". Relevant full-text papers were obtained and additional references found in papers' and books' reference lists. The United States ClinicalTrials.gov website was also searched to identify currently enrolling clinical trials relevant to each of the technologies in question. This report is based on manuscripts available in the English language.

## 5.8.1  Radiofrequency ablation of the prostate

Radiofrequency ablation (RFA) relies upon the effects of passing electric current through tissue. The alternating current is at "radio" frequency, and the effects on tissue are the creation of lesions leading to coagulative necrosis. Initially, RFA was delivered as a monopolar technology in the form of TUNA of the prostate but bipolar technology was subsequently developed.

A systematic review and meta-analysis was published in 2006 (193) subsequent to the compiling of the last ICUD report. This identified 35 studies with nine comparative and 26 non-comparative studies on TUNA of the prostate. While this meta-analysis considers no new data since the last ICUD report, the clear messages are that further surgical intervention is more likely to occur with TUNA compared with TURP, although the overall risk for morbidity clearly favours TUNA.

Of particular note is the fact that the current version of TUNA known as the Prostiva has had minimal further studies, although there have been some reports in the non-English–language literature.

There have been a couple of reports of experience using bipolar RFA using a generator and transurethrally introduced ablation needle that was manufactured briefly by Celon AG, which was subsequent acquired by Olympus AG (**Figure 2**). A long needle with two electrodes at its tip is used to puncture the prostate endoscopically under direct vision (**Figure 3**). Typically, one puncture and treatment is made for each 5-g increment in prostate size. It appears that this technology is no longer being actively marketed. A small study (194) demonstrated poor long-term outcomes with 9 of the 12 subjects requiring a further surgical procedure to relieve LUTS over the course of follow-up. While initial outcomes by 12 months were meaningful, only one patient had continued symptom benefit at 5 years.

**FIGURE 2**

Geometry of CelonPro BPH®.
The shaft diametre is 2 mm.

Electrode 1    Electrode 2    Markings    Shaft



4    7    3    7    5    8    2    550

21

36
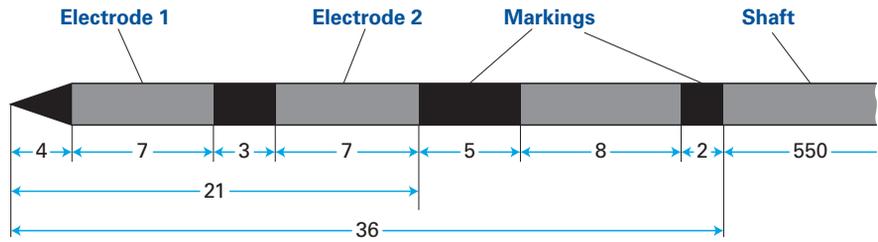
**FIGURE 3**

Endoscopic view of puncture
of the prostate.
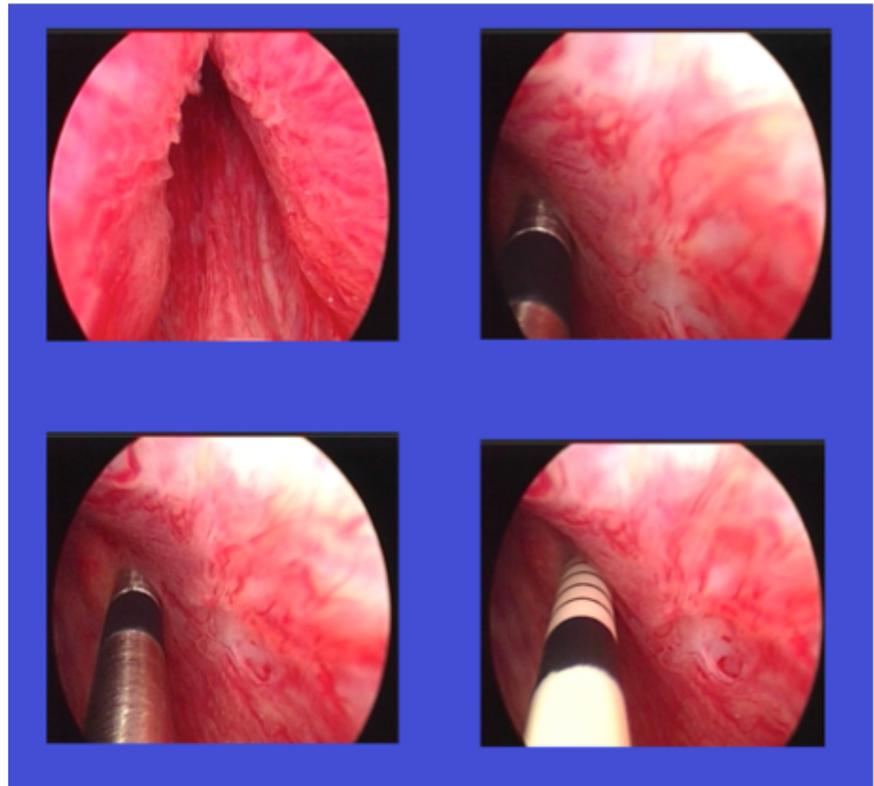


A larger Polish study evaluated 131 men who were treated with radiofrequency interstitial thermo-therapy (RFITT) using the Celon technology and followed out to a maximum of 4 years (195). The average operation time was 24.6 minutes and the average duration of hospitalization was 1.9 days. The mean duration of follow-up was 24.6 months. While the time points for each subject's analy-sis is unclear, the study reports improvements in IPSS, peak urinary flow, and the PVR as being 12.4, 3.9 mL/s and 57.6 mL, respectively. Further surgery in the form of TURP or "adenectomy" was performed in 16 of the 125 men who were able to be followed up at any time following RFITT. Few adverse events were reported, with the only one of significance being a death within 24 hours of the procedure due to cardiovascular disease. With the majority of men in this study having short follow-up, it is likely that the true treatment failure rate in terms of re-operation or continued catheteriza-tion is higher than reported.

There is insufficient data to suggest that bipolar RFA of the prostate in the form of RFITT has any advantages over monopolar RFA of the prostate. Early data suggests that re-treatment rates are higher than observed for TUNA, though they are high for both.

Monopolar RFA of the prostate in the form of TUNA of the prostate is effective in treating male LUTS and with acceptable morbidity, but likely with reduced efficacy and durability compared with TURP.

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(LOE 1, Grade of recommendation A)

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Bipolar RFA of the prostate in the form of radiofrequency interstitial thermotherapy remains experimental.

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(LOE 3, Grade of recommendation D)

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## 5.8.2   Microwave thermotherapy

There have been relatively few publications with new data since the last International Consultation on Urological Diseases (ICUD) review in 2006. There have, however, been publications on imaging and others dealing with adverse events, particularly urinary retention.

A Cochrane review with meta-analysis of microwave thermotherapy in RCTs has recently been published (196). As this is an update from a similar review by the same authors and in the same journal in 2007 (197), only the findings from the 2012 study will be considered. A total of 15 RCTs using microwave thermotherapy for the treatment of BPH met the inclusion criteria for analysis, and there were no additional studies to those used in the first meta-analysis. The most recent of these studies that was considered to have provided evaluable effectiveness data had been published in 2002. Each of the individual studies analyzed has been covered in the previous ICUD report.

A total of 15 comparisons were analyzed for TUMT versus TURP RCTs, while a total of 11 comparisons were analyzed for TUMT versus Sham treatment RCTs. The final summary conclusion (196) was that TUMT was an effective alternative to medications and alpha-blockers in the treatment of symptomatic BPH for prostates between 30 mL and 100 mL in size. It also commented on the greater improvement in symptoms and urinary flow rates with TURP compared with TUMT. Re-treatment rates also appeared to be superior for TURP compared with TUMT.

The number of studies published on TUMT has significantly dropped off since the last ICUD report. Five studies have since reported longer-term results and are summarized in **Table 1**1. One of these studies (198) was focused on demonstrating that smaller prostates had as good outcomes as larger-sized prostates in terms of symptom scores and flow rates. Only 156 men had evaluable symptoms score data and 46 had flow data at 5 years of follow-up. While this study did report some data extending out to 5 years of follow-up, there was primarily subgroup analysis to determine if prostate

size made a difference to outcomes such as symptoms scores, quality of life, and flow rate. The final conclusion was that prostate size did not seem to alter outcomes and that TUMT could be offered to men, without prostate size detracting from responsiveness to treatment.

In a large study, 841 men (199) were treated using Prostatron technology and followed for a mean of 8.8 years and 2.5 years for Program 2.0 and 3.5, respectively, and data was collected through mailed questionnaires and instruments. In the study, 67% of men treated with low-energy TUMT (Program 2.0) reported satisfaction, although 37% reported deterioration in their symptoms. Further treatment, including medical therapy, was required in 32%. In comparison, 82% of men treated with high-energy TUMT (Program 3.5) were satisfied with their treatment, and 17% reported deterioration of their symptoms but further treatment was only necessary in 7%. Need for additional treatment was seen in 31.5%.

The study by Gravas and colleagues (200) was primarily interested in assessing the differences in outcomes for men with and without urinary retention at baseline. The figures shown in the table reflect those for men who were not in retention given that baseline IPSS, QOL score, and $Q_{max}$ are not practically measurable in men who are in urinary retention. Nevertheless, while actual re-treatment rates were high for both groups and while re-intervention rates were 28.6% and 37.8% for men without and with urinary retention, respectively, Kaplan Meier cumulative re-treatment risk at 5 years was 42.3% and 58.8%, respectively. A cautionary comment is that the number of men who were evaluable at 5 years had measurable data points in no more than 20% of the men where data was measurable at baseline.

The study by Matthiason and colleagues (201) was part of a small RCT comparing TUMT with TURP. The randomization was 2:1, and men were followed to 5 years, with 66% completing the 5-year follow-up. While functional improvements appear to have been equivalent, re-treatment rates were higher for TUMT compared with TURP–10% vs. 4.3%. Caution should be applied to the interpretation of these outcomes given the small number of men treated initially and therefore evaluable at long-term follow-up.

The fifth of the longer-term studies by Lucarelli and colleagues (202) has found high re-treatment rates similar to those in the Gravas study (200).

**TABLE 11** Recent Long-term Microwave Outcome Studies

| Study | No. | Machine | F/U | IPSS | QOL | $Q_{max}$ | PVR | Additional treatment/ comments |
|-------|-----|---------|-----|------|-----|-----------|-----|--------------------------------|
| Vessely 2005 (199) | 841 | Prostatron 2.0 | 8.8 | 24.5% | 27.6% | NS | NS | 7% |
| Larson 2006 (198) | 713 | Urologix | 5 | NS | NS | NS | NS | NS |
| Gravas 2007 (200) | 213 | Prostasoft 3.5 | 5 | 40.0% | 42.5% | 16.5% | NS | 28.6% (37.8% for retention) |
| Matthiason 2007 (201) | 62 | Coretherm | 5 | 63.7% | 74.4% | 48.1% | 34.0% | 10% |
| Lucarelli 2011 (202) | 135 | Prostasoft 3.5 | 5 | 68.5% | 46.3% | 67.0% | 75% | 34.8% |

F/U = Follow-up; NS = Not stated; percentages represent improvements from baseline and No. refers to numbers of men treated at baseline.
TUMT is an alternative treatment to alpha-blockers and TURP for the treatment of LUTS. The re-treatment rates for TUMT appear to be significantly greater than those for TURP, however.

(LOE 1, Grade of recommendation A)

## 5.8.3  Ethanol ablation of the prostate

Since the last ICUD report, there have been few further studies on transurethral ethanol ablation of the prostate (TEAP). The commercial delivery device referred to as the Prostaject is no longer marketed.

A small study reported on 16 Japanese men with persistent urinary retention due to BPH who were unfit for conventional surgery and underwent TEAP (203). Of these, 14 (87.5%) were able to re-establish voiding after a mean of 12.4 days. No major complications were reported.

The largest study published was a United States, multicentre study in more than 15 sites (204). The primary endpoint was safety and tolerability and the secondary endpoint was dosing. Three dosing regimens were used and proved to make no significant differences to outcomes. Adverse events were meticulously recorded–95% were mild to moderate, with the majority requiring no intervention. The early post-procedure urinary retention rate was high, with 17 of 79 (21.5%) patients.

The longest-term study for TEAP had follow-up out to 54 months (205). Only 14 of the originally treated 56 men were evaluable at that time. Of the remainder, 11 had undergone TURP, two had undergone repeat TEAP, and some had not reached the maximum follow-up of 54 months. It is unclear as to how many had not reached this maximum follow-up point and how many were lost to follow-up. A further small study (206) published recently found similar results to previous studies and was associated with a post-procedure urinary retention rate of 7% (**Table 1**2).

**TABLE 12** A Summary of TEAP Studies

| | Number | Follow-up | AUA/IPSS | QOL | $Q_{max}$ | PVR |
|---|---|---|---|---|---|---|
| Plante 2007 (204) | 79 | 6 months | 52% | 50% | 72% | 14% |
| Sakr 2009 (207) | 35 | 4 years | 55% | NS | 187% | 48% |
| El-Husseiny 2011 (205) | 56 | 54 months | 32% | 57% | 43% | 62% |
| Faruque 2012 (206) | 30 | 3 months | 63% | NS | 122% | 69% |

There continues to be an absence of high-level evidence to support efficacy and safety of TEAP. Adequate long-term data is required. There are currently no further studies registered with clinical-trials.gov.

Transurethral ethanol ablation of the prostate remains an experimental modality for the treatment of LUTS.

<p align="center">(LOE 3, Grade of recommendation C)</p>

## 5.8.4    Botulinum toxin injection into the prostate

No data was presented on this in the previous ICUD report. Many reports of clinical trials in men have since been reported.

Botulinum Toxin A (BTX) has been injected directly into the prostate using the transurethral, trans-rectal, or transperineal approach, although the transperineal technique under transrectal ultrasound guidance has been by far the most favoured approach. In animal models, the mechanism of action has been suggested to be as a result of apoptosis, reduction in proliferative cells, and down-regulation of alpha-1 receptors with the extent appearing to be dose dependent (208). Muscarinic receptors may also play a role in the action of BTX (209).

The clinical results are made up of several studies of generally small numbers of men treated and with only short-term follow-up. There are no adequately powered RCTs published.

The first report of BTX injection into the human prostate was reported in 2003 (210) in a small randomized trial comparing BTX with saline injection into the prostate. These initial results at 2 months following treatment appeared promising, with a 65% reduction in symptom scores, a 51% decrease in PSA levels, and a 33% reduction in prostate volume. No side effects to BTX injection were reported, and therefore this study gave encouragement to pursue this modality further. The vast majority of studies published since have small numbers of subjects and short follow-up. To date, there have been no phase 3 RCTs comparing BTX with placebo. Randomized trials have been either comparing administration options for BTX or small phase 2 studies.

A small study of 10 men in chronic urinary retention described significant improvement in voiding parameters in eight and "improved" voiding in two. This study carries little clinical applicability due to the small number of patients and study design (211).

The pressure flow urodynamic effects and histological changes associated with transrectally delivered BTX injection has been studied in 15 men (212). Pressure flow urodynamic measures were essentially unchanged at repeated intervals out to 12 months. There was no decrease in cell proliferation on post-treatment biopsies, which were compared with pre-treatment biopsies.

A small study looking specifically at sexual function in 16 sexually active men was unable to establish any impact of BTX treatment on erectile, orgasmic, or ejaculatory function (213). Interestingly, the men in this study had a mean age of 73 years and the mean International Index of Erectile Function (IIEF-5) Questionnaire score at baseline was 16.5.

One RCT utilizing botulinum toxin injections into the prostate and with the primary objective of evaluating its impact on LUTS to BPH has been recorded on clinicaltrials.gov. NCT00284518 is a phase 2 RCT that has set out to treat 380 men with either botulinum toxin (doses of 100, 200, and 300 units) or saline injection into the prostate. Recruitment is recorded to have commenced in December 2005 and completed in May 2010. Publication is still awaited.

Botulinum injection treatment into the prostate for LUTS remains experimental.

(LOE 3, Grade of recommendation D)

## 5.8.5   Other injectable agents into the prostate

New injectable agents, namely NX-1207 and PRX302, have recently emerged, although the precise nature of the former compound has not been made publically available.

NX-1207 is administered as an office-based procedure using the transrectal route under ultrasound guidance (214). Current studies include NCT01438775, which evaluates the role of repeated NX-1207 injections in men who have previously participated in trials with this agent. A further phase 2 study has completed enrolment of 85 men who have been randomly allocated to receive NX-1207 at either the 0.125 mg or 2.5 mg dose or oral drug treatment with finasteride. A multicentre RCT (NCT00918983, NCT0094590) enrolling 500 men comparing NX-1207 with placebo is currently recruiting.

The nature of PRX302 has been described. Proaerolysin, which is the precursor of a bacterial cytolytic pore-forming protein, is described as having been genetically modified to produce PRX302 (215). This agent is biologically inactive until it undergoes proteolytic activation by PSA, which then enables aerolysin to interact with the cell wall to create pores, with the effect of lytic cell death. Phase 1 and 2 study results have recently been published (216). In the phase 1 study, 15 men received transperineal-injected PRX302 at various concentrations in a fixed injected volume and in the phase 2 study, 18 men received transperineal-injected PRX302 at various injected volumes of a fixed concentration.

In the combined results for the phase 1 trial group, 64% of patients had a greater than 30% improvement in IPSS out to 360 days and for the combined results for the phase 2 group, 64% of patients had a greater than 30% improvement in IPSS out to 360 days. Men who received ≥1 mL had better results, but there were inadequate numbers to allow for meaningful analysis of dose-concentration effects. For both groups, statistically significant improvements were observed in quality of life and reduction of prostate volume, but not with peak urinary flow. No serious adverse events were reported. The primary limitation of this study is the low numbers of patients treated, and further larger-scale, multicentre studies are needed before any recommendations for its adoption can be made.

The use of PRX302 and NX-1207 remains experimental.

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(LOE 3, Grade of recommendation D)

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## 5.8.6 Prostatic urethral lift

This is a new mechanical-based treatment that draws open the prostatic urethra (217–219). Prostheses are implanted transurethrally under endoscopic control using a specially designed delivery system (220). The prosthesis is made of a two metallic tabs connected by non-absorbable suture material. One tab is positioned on the capsular side of the prostate and the other on the urethra surface and the suture is placed under tension, thereby creating a compressing effect between the two tabs (Figures 4 and 5). Animal work has demonstrated that the internal tab has the potential to become incorporated into the tissue. Typically, between 2 to 4 of these prostheses are placed, and the procedure can be performed under local anaesthesia with or without sed-analgesia and in an ambulatory setting.

**FIGURE 4**

The UroLift™ device
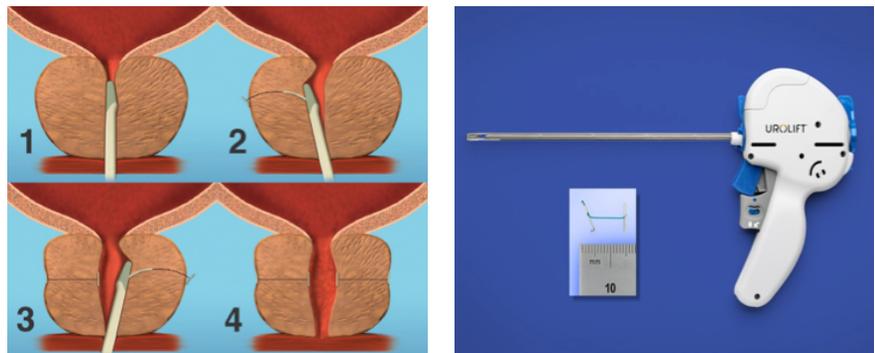


Limited data has been published on the prostatic urethral lift (PUL), but to date the outcomes demonstrate clinically relevant improvements in urinary symptoms that appear to be sustained in the short-to-medium term. The first published study report of 19 men with LUTS (219) demonstrated safety and feasibility with a prototype delivery system. An Australian multicentre experience (218) in 64 men subsequently demonstrated IPSS reduction by 42%, 49%, and 42% at 2 weeks, 6 months, and 2 years, respectively, in evaluable patients. Peak flow improvement was modest at 30% (2.4 mL/s) or more at all intervals compared with baseline. Key observations were the relatively rapid

onset of symptom improvement and the absence of sexual dysfunction following this treatment. Further analysis of the latter supported the absence of erectile or ejaculatory dysfunction following these procedures (217).

**FIGURE 5**

Endoscopic view of a tensioned internal tab invaginating the prostatic urethra.
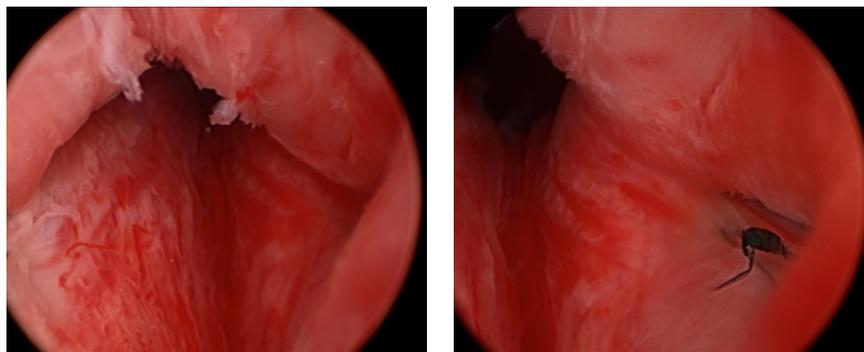


There are two prospective randomized controlled studies which are currently in progress.

A prospective, multi-institutional RCT comparing PUL with a sham procedure, namely cystoscopy, has recently completed an enrolment of more than 200 subjects after commencing in February 2011. Randomization was assigned 2:1 in favour of PUL in a single-blinded, controlled clinical trial comparing the IPSS of the treatment group with that of the control group at the 3-month follow-up, with follow-up out to 12 months (clinicaltrials.gov identifier NCT01294150).

Another multicentre RCT referred to as the "BPH-6: Comparison of the UroLift System to Transurethral Resection of the Prostate (TURP) for Benign Prostatic Hyperplasia" study is currently recruiting. This study provides a novel evaluation of outcomes using six endpoint thresholds as follows:

1. LUTS: ≥30% reduction in IPSS compared with baseline.
2. Recovery experience: Return to pre-operative activity levels by 1 month.
3. Erectile function: Less than 6-point reduction in Sexual Health Inventory for Men (SHIM) compared with baseline.
4. Ejaculatory function: Response on Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD) that indicates emission of semen.
5. Continence: Incontinence Severity Index (ISI) score of 4 points or less at all follow-up time points.
6. Safety: No procedure-related adverse event greater than Grade I on the Clavien-Dindo classification system modified for TURP at any time during the procedure or follow-up (clinical trials identifier NCT01533038).

The role of the PUL as a treatment of male LUTS remains under evaluation.

(LOE 3, Grade of recommendation D)

### 5.8.7　Discussion

For the established MISTs, there has been little additional data published since the last ICUD review. As such, the strength of data supporting their role in the management of male LUTS is unchanged. There have, however, been several publications on newer forms of MIST and in particular with the injectable agents. Unfortunately, most of the experience is low-level evidence but a search on clinicaltrials.gov indicates that a greater commitment to higher-level studies is present. MISTs will continue to be pursued, and this has clearly been evident in the research that has arisen since the last ICUD report.

# 5.9　Incontinence After Prostatectomy for Benign Disease

### 5.9.1　Incidence and risk factors

The incidence of urinary incontinence after prostatectomy for benign disease has been reviewed and described in the AHCPR "Benign Prostatic Hyperplasia" Clinical Practice Guidelines (54). The following percentages for stress incontinence and total incontinence, respectively, were reported:

Open surgery (retropubic or transvesical prostatectomy): 1.9% and 0.5%.
TUIP (transurethral incision of the prostate): 1.8% and 0.1%.
TURP (transurethral resection of the prostate): 2.2% and 1.0%.

These figures were based on studies reported before 1990. Several other series were published after 1990. These series were reviewed for the 1st, 2nd, and 3rd International Consultations on Incontinence (221–223). A clear description of the method of follow-up and assessment of the continence status was indicated in only about one third of these studies. The incidence of incontinence after open surgery, TURP, TUIP, and HoLEP is low: the reported percentages ranged between 0% and 8.4%. As the method of assessment of the continence status and the definition of incontinence is rarely stated, it is actually not possible to make a distinction between simple stress incontinence and total incontinence. There is generally no clear indication that the incidence is affected by patient age or (resected) prostatic volume (221). However, a recent study out of Brazil did demonstrate that the rate of urinary incontinence following "BPH" surgery is higher in older patients. However, most of the increased incidence in incontinence was due to bladder dysfunction rather than to sphincter insufficiency. In a retrospective chart review from Wendt-Nordahl and colleagues (224), the incidence of incontinence following TURP was reported to have decreased over 17 years, from 3.3% in 399 patients operated on between 1987 and 1997, compared to 1.3% in 550 patients operated on from 1997 to 2004. It is not clear whether this statistically significant ($p < 0.05$) difference was due to improvement in surgical technique or patient characteristics. However, both the earlier and later incontinence rates are consistent with those in the AHCPR and AUA guidelines reports.

In 2003, the AUA published guidelines for the management of "benign prostatic hyperplasia" (225). The estimated frequency of incontinence following TURP was 3% (from 19 trials that included >5,000 patients). However, the Veterans Affairs Cooperative Study reported an incontinence rate of only 1% in patients who underwent TURP, which was not different from the watchful waiting arm (226). The AUA conducted a meta-analysis of RCTs comparing TURP with TUIP or transurethral electrovaporization, which did not reveal any statistically significant differences in incontinence rates (225,227–231). The 2010 AUA updated guideline provided no additional information (232).

Over the past decade, transurethral HoLEP has become a standard treatment for BPO. Review of RCTs by the AUA as well as a meta-analysis of RCTs comparing TURP with HoLEP did not reveal any significant differences in incontinence rates (141,144,145,147,225,231,233–235). While incontinence did not increase with age in men undergoing HoLEP with morcellation, it was noted that the overall complication rate, including bladder mucosal injury, urethral stricture disease, and bladder neck stenosis, was higher in patients with prostate volumes >50 g (236). Moreover, it does not appear that either bipolar resection of the prostate or photovaporization of the prostate is associated with a substantially different rate of urinary incontinence than are other surgeries for BPO (42). While incontinence following PVP is comparable to that of other surgeries for BPO, and more often than not improves over 12–36 months post-operatively with conservative management, the rate of post-operative dysuria is higher than that of TURP, recently reported at a rate of 10.1% (237).

In summary, the incidence of urinary incontinence after open surgery, TURP, TUIP, and HoLEP is low, and does not differ appreciably among the various techniques.

## 5.9.2 Timing of surgical intervention

There are no clear data on timing of a surgical intervention for the treatment of incontinence, therefore, at present, guidelines as to the timing of surgery cannot be formulated. A certain period of watchful waiting supplemented with conservative measures, particularly pelvic floor physiotherapy, seems to be a reasonable option. Thus, conservative management may be tried for periods of up to 6–12 months depending on whether there is any progress noted by the patient. (LOE 4, Grade of recommendation C)

## 5.9.3 Surgical treatment options

### I. Artificial sphincter
The literature on this subject was reviewed for the 1st, 2nd, and 3rd International Consultations on Incontinence (221–223). Candidates for treatment with the artificial urinary sphincter (AUS) are patients with incontinence due to intrinsic sphincter deficiency that have normal bladder compliance (238). Detrusor overactivity is not a contraindication (Lai and Boone). The AUS has been placed around the bulbar urethra via a perineal route or transverse scrotal routes (239) or around the bladder neck (221–223). The aforementioned review of the results obtained with the AUS indicated that more than 70% of the men treated with the AUS for this indication are dry or almost dry after a follow-up of more than 2–3 years. However, most series on the AUS include both post-prostatectomy incontinence for benign and malignant disease (221).

In summary, the AUS is a successful surgical treatment option for post-prostatectomy incontinence. It is the most commonly performed surgery for post-prostatectomy incontinence, with the longest follow-up and therefore longest record of success. (LOE 2, Grade of recommendation B)

## II. Injectable agents

Most series with these agents include post-prostatectomy incontinence after treatment for benign and malignant disease, with the majority after prostate cancer surgery. For collagen, "success rates" range from 36–69%, with 4–20% of patients reporting being dry (240–247). Study results are inconsistent, with both TURP (248) and radical prostatectomy (249) showing better outcomes.

Other bulking agents, such as polydimethylsiloxane (PDMS; Macroplastique®), have shown some initial success, but results also deteriorate over time. Bugel and co-workers treated 15 patients. They noted rapid deterioration of the initial improvements, with success rates of 40%, 71%, 33%, and 26% at 1, 3, 6, and 12 months, respectively (250). Kylmala *et al.* prospectively studied 50 patients with mild-to-moderate stress urinary incontinence (average, 48 mL on 1-hour pad test), with 12% achieving continence following one injection, and an additional 20%, 18%, and 10% achieving continence with two, three, and four injections, respectively (251). Follow-up, however, was only 3 months. In a randomized trial of the AUS versus Macroplastique injection in patients with minimal stress urinary incontinence (the vast majority had stress urinary incontinence following BPO surgery, with less than one third of the cohort suffering from it following resection of the prostate), Imamoglu and colleagues demonstrated no difference in success with the AUS versus Macroplastique. However, in patients with more severe incontinence, the AUS was superior, with minimal improvement following transurethral Macroplastique (252). There has also been some initial work with sphincteric injections of muscle stem cells (253,254).

Bulking therapy fails in up to 75% of men. Of those who are improved, only a minority actually become dry with short-term follow-up. Although bulking therapy may be slightly more efficacious in treating stress urinary incontinence following TURP compared with stress urinary incontinence following prostate cancer surgery, bulking is of limited value in those men with all but minimal stress urinary incontinence. (LOE 3, Grade of recommendation C)

## III. Male sling procedures

Since Frangenheim described his first successful urethral sling suspension for post-traumatic stress urinary incontinence in 1914, various sling materials and surgical methods have been reported (255). Rectus fascia, as described by Frangenheim, has distinct advantages over alloplastic materials with respect to erosion and infection risks. Allograft off-the-shelf materials such as lyophilized fascia lata have a higher infection risk than does autologous fascia, whereas the use of synthetic materials such as polypropylene mesh or polytetrafluoroethylene slings is associated with a higher incidence of urethral erosion (256). According to various published techniques, the sling can be placed either underneath the bladder neck, the urethral bulb, or the membranous portion of the urethra. The principle of continence support is similar for all sling procedures and comprises passive compression of the urethra, which is dependent on the applied sling tension (257). This mode of action favours sling procedures as a treatment option for intrinsic sphincter deficiency. However, the sling tension needed for restoration of continence has not been standardized, with tensioning techniques ranging from perfusion sphincterometry, to a cough test, to visual approximation (258,259), and therefore

the success of the procedure probably depends heavily on the surgeon's experience and the degree of sphincteric incompetence. Over-correction with consequent urinary retention (especially in the setting of detrusor underactivity) and under-correction with persistent or recurrent incontinence are certainly possible, which may adversely affect continence, bladder emptying, and patient satisfaction. Most series of sling surgeries deal with a preponderance of men following surgery for prostate cancer. Therefore, it is difficult to draw conclusions about any differences in sling efficacy between those with stress urinary incontinence following surgery for BPO versus those with stress urinary incontinence following resection of the prostate due to small numbers of patients with BPO in most of the cohort series.

## 5.10 Recommendations

New and established BPH therapies can be categorized in 2013 as current, emerging, declining, and obsolete. It follows that the evidence levels can be applied according to these groups.

For current therapies, a Grade A recommendation can be made for the following:
- TURP (<80 g prostate volume) and BNI (<30 g)
- Open prostatectomy (>80 g)
- HoLEP (size independent)
- 532-nm vaporization (size independent)

These are appropriate alternatives based on surgeon/patient preference (LOE 1a and 1b). The durability of 532 nm could not be assessed, however. (LOE 3)

For some current and emerging therapies, a Grade C recommendation is possible:
- Thulium laser prostatectomy (vaporization [VP], enucleation [EP] and resection [RP])
- Diode laser prostatectomy (VP and EP)
- Holmium laser prostatectomy (VP and RP)
- Electrosurgical vaporization (VP and EP)

These are alternatives to TURP (LOE 1b, 2, and 3). Durability could not be assessed.

For declining and obsolete therapies, a Grade A recommendation is possible for:
- TUMT
- TUNA
- VLAP/ILC

These are alternatives to TURP (LOE 1a) though durability is less (LOE 1a).

A Grade C recommendation is appropriate for prostatic stents, botulinum toxin, ethanol, and high-intensity focused ultrasound (HIFU). LOE 2 and 3 exist for these treatments.

Only a Grade D recommendation is possible for many emerging investigational treatments (LOE 3):
- Laparoscopic and robotic simple prostatectomy
- UroLift
- Intra-prostatic injection therapies
- Non-thermal energy sources

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# C6

# Detrusor Underactivity

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# CONTENTS

## Detrusor Underactivity

# 6.1  Introduction

Lower urinary tract symptoms (LUTS) are a major cause of reduced quality of life (1) and a significant economic burden to society (2). Prevalence of LUTS increases with age in both men (3) and women (4), which is important considering the aging population (5). The focus of the cause of LUTS has traditionally been on the bladder outlet. However, the influence of the bladder has increasingly been recognized (6). Detrusor underactivity (DU) is an important contributor to LUTS in a significant proportion of both men and women seen in clinical practice and is present in 9% to 48% of individuals being urodynamically evaluated for LUTS (7–9). This prevalence rises up to two thirds in the institutionalized elderly population (10). In stark contrast to the overactive bladder (OAB) syndrome, DU has been largely under-recognized and under-researched. Detrusor underactivity is related to persistent, problematic LUTS after prostatectomy for benign prostatic enlargement (BPE) (11) and may be a contributory factor in up to 30% of men who do not gain benefit from surgery (12,13), highlighting the importance of recognizing the diagnosis.

The presentation of DU is often very similar to other lower urinary tract dysfunctions and is often indistinguishable from bladder outlet obstruction (BOO). Urodynamic studies are the only way to diagnose DU, and current DU definitions are based on urodynamic findings. However, there is much debate on these findings, and no standardized diagnostic criteria exist (14,15). Additionally, urinary retention or post-void residual (PVR) measurement cannot be used as proxy measures, precluding the acquisition of meaningful epidemiological data. Indeed, there is much debate about how best to define urinary retention and what exactly constitutes an abnormal PVR. As such, there is a deficit in the understanding of the pathogenesis of DU, and most therapeutic approaches are in their infancy or considered experimental.

Following recent calls for new initiatives into all aspects of DU research (15,16), the current evidence on prevalence, etiology, pathogenesis, diagnosis, and therapeutic approaches is summarized here, with the aim of enhancing awareness among clinicians and researchers of this important yet understudied problem.

# 6.2  Definitions

A variety of terms have been used to describe the non-obstructive impairment of voiding function, which we have here referred to as DU, in accordance with International Continence Society (ICS) terminology. Other terms in usage include impaired detrusor contractility (17), underactive bladder (UAB) (18), detrusor areflexia (19), hypotonic bladder (20), detrusor or bladder failure (21), and chronic retention, reflecting ambiguity and a lack of consensus. It is generally agreed that DU is a urodynamic diagnosis of the voiding phase of the micturition cycle. Impaired detrusor contractility (IDC) is a term widely used to mean DU; however, the two are not synonymous. Impaired detrusor contractility implies a deficiency in muscular contractile properties of the detrusor, whereas, it has been argued, DU is a "statement about a clinical syndrome" relying upon a urodynamic diagnosis (22). A change of muscle contractility is defined as altered isometric contraction tension, independent of

resting muscle length (23). Experimentally this is measured directly using muscle strips. Urodynamic estimation of contractility is something quite different–it is a measure of the pressure generated to allow flow through a patent bladder outlet.

The 2002 ICS standardization report defined DU as "a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span" (24). This definition is hampered by the fact that what constitutes reduced strength, reduced length of contraction, or prolonged emptying has not been quantified. Nevertheless, the ICS definition does provide a useful conceptual framework for considering DU in that the underlying etiology (or etiologies) may manifest in 1) a contraction that is not strong enough, 2) a contraction that is not long enough, or 3) a combination of the two, with the outcome being incomplete bladder emptying, prolonged voiding, or a combination of both. It has also been suggested that the contribution of a slow shortening velocity should be incorporated into the definition (25). The ICS report separately considers an "acontractile detrusor" as when no detrusor contraction whatsoever is generated. While the distinction between this and DU is useful in clinical terms, it is as yet unknown whether the acontractile detrusor represents an extreme of a spectrum of DU. The addition of symptoms to the current definition would relate urodynamic findings to clinical impact and is an important topic of future discussion.

The ICS report did not sub-classify DU by underlying mechanism, such as neurogenic or idiopathic. As has been the case in detrusor overactivity (DO), it has been suggested recently that sub-classification may better represent the likely causes of DU (16) and provide a framework for future research aimed at understanding the underlying mechanisms and developing novel therapies. However, this may not be feasible given the lack of insights into how particular etiologies affect detrusor function. Therefore, the current terminology, while non-specific, does at least encompass any etiopathogenic factors that are yet to be discovered.

In clinical studies, some investigators have either applied their own specific urodynamic parameters to define DU, such as detrusor pressure at maximum flow ($P_{det}Q_{max}$) <40 and maximum flow rate ($Q_{max}$) <15 (26), or they have based the diagnosis on indices derived from urodynamic data. These diagnostic criteria and the nomograms/calculations on which they are based will be discussed later.

It has been proposed that DU be considered the antithesis of OAB in order to raise the profile of DU and focus research efforts (27). It has also been suggested that the term UAB is more likely to be understood by the general public. While this approach has clear merits, and while symptoms are a driver of treatment-seeking behaviour, the two entities are not strictly antithetical, in that OAB, as currently defined, is a symptom-based syndrome (although associated with DO in a large proportion of patients), whereas DU cannot currently be defined in distinctive, symptom-based terms. In OAB, the initial management approach does not differ if DO is present or absent, whereas best practice is yet to be defined for DU. Given the complexities surrounding DU and the infancy of knowledge, introducing the term UAB may be problematic, and its use is currently not recommended according to the ICS research panel (16).

### 6.2.1  Key issues

1. a contraction that is not strong enough
2. a contraction that is not sustained enough
3. a combination of the two

Leading to:
1. incomplete bladder emptying
2. prolonged voiding
3. a combination of both.

### 6.2.2  Recommendations

Adding symptoms and functional data to the current definitions would relate urodynamic findings to clinical impact and is an important topic of future discussion.

Need to consider quality-of-life impact

Monitor upper tract function (creatinine)

Consider size of residual relative to functional capacity (40%?)

Question neurogenic versus idiopathic etiology

# 6.3  Epidemiology

## 6.3.1  Challenges in acquiring epidemiological data

While LUTS are a major global health issue with an age-related increase in prevalence, the contribution of DU as an underlying mechanism is as yet unknown (**Table 1**). As DU is a urodynamic diagnosis requiring pressure-flow studies (PFS), the acquisition of meaningful large-scale epidemiological data has not been possible, which limits our knowledge of the incidence, prevalence, risk factors, and natural history of the problem. The clinical features of DU are frequently seen with other lower urinary tract dysfunctions; weak stream, intermittency, and straining are common symptoms of BOO and thus cannot be used to distinguish DU. Flow rate measurements are used as a screening test for BOO, but do not distinguish between BOO and DU as the possible cause of either LUTS or raised PVR (28)

Both raised PVR and urinary retention may result from DU, yet neither can be used as proxy measures. A raised PVR is commonly seen in patients with BOO (29), and there is no agreement on thresholds for an abnormal PVR (30). Most guidelines do not give values (e.g. American Urological Association,

European Association of Urology, National Institute for Health and Clinical Excellence), though Italian guidelines define abnormal PVR as 1/3 of bladder capacity (Level 4 evidence) (31). Additionally, PVR measurement has poor test-retest reliability; in a study of 40 men awaiting transurethral resection of the prostate (TURP), variation in volumes ranged between 150–670 mL over a three-month period (32). Post-void residual has been shown to increase with age in men by 2.2% per year from age 40 onwards ($p=0.03$), with an annual decrease in voided volume of 2.1% per year ($p<0.01$) (33).

Although it is generally considered a product of BOO and/or DU, urinary retention is a non-specific term that has a variety of meanings. It may be classified as acute or chronic, partial or complete, painful or painless, and high pressure or low pressure. It is triggered by a myriad of factors and is often multifactorial in etiology. Acute urinary retention is the sudden inability to pass urine and is usually associated with pain, clinically evidenced by a tender, palpable bladder. Chronic retention (CR) has an insidious presentation and may be associated with minimal or no urinary symptoms. The ICS defines CR as "a non-painful bladder, which remains palpable or percussible after the patient has passed urine" (24). Some have questioned the utility of this definition in view of the widespread use of the modern bladder scanner to measure PVR (34). In terms of actual volumes, Abrams quantified the threshold value as PVR >300 mL, based on the volume at which the bladder was palpable supra-pubically (35). Others have similarly applied set values, largely on an arbitrary basis, including >200 mL (36), PVR >400 mL (37), and >1000 mL, as in the recent UK National Institute for Health and Care Excellence guidelines on male LUTS (38,39). Interestingly, Thomas *et al.* showed a mean PVR of 108–126 mL at the end of a 10-year follow-up study of 58 men with urodynamically proven DU (defined as $P_{det}Q_{max}$ <40 and $Q_{max}$ <15). This suggests that DU is often not associated with CR, as it is usually defined, in this group (39). In an earlier study, however, Abrams *et al.* showed that all men presenting with CR (PVR >300 mL) had evidence of BOO, which suggests that this is a key factor in many men with CR (35).

**TABLE 1**  Epidemiological measures of DU

| Potential epidemiological measure of DU | Pros | Cons |
| --- | --- | --- |
| **LUTS** | - Feasible to collect large-scale data using questionnaires or surveys | - Commonly found in other LUT dysfunctions<br>- Impossible to differentiate from BOO |
| **Free flow measurement** | - Non-invasive and easy to perform<br>- Objective data<br>- Positive findings in DU | - Does not distinguish DU from BOO |
| **Post-void residual** | - Non-invasive and easy to perform<br>- Objective data | - Poor test-retest reliability<br>- No accepted threshold for abnormal PVR<br>- May not be a constant feature of DU |
| **Urinary retention** | - Feasible to collect large-scale data | - Variable definitions<br>- -No accepted threshold for PVR in chronic retention<br>- Multifactorial etiology |

The majority of research in the male population has focused on BPE. This has led to regarding BOO as the cause of voiding LUTS, retention, and raised PVR, though it is estimated that 10%–20% of patients with low flow at presentation have an element of DU (40). The relationship between BOO and DU is incompletely understood; it is certainly the case that not all men with BOO develop DU, and not all men with DU have BOO (26). It may be that BOO is a cause of DU in some men, whereby contractile function of the detrusor dissipates due to prolonged BOO. In others, DU may represent an entirely independent disease process.

While it is difficult to determine the contributions of BOO and DU as the mechanisms of LUTS, retention, or raised PVR in the male population, in females BOO is far less common, occurring in only 2.7% of females referred for urodynamic studies from the general population (41). Therefore, retention and raised PVR in women are far more likely to represent DU. The main causes of BOO in women are iatrogenic (most commonly after incontinence surgery), pelvic organ prolapse, or urethral stricture as a consequence of atrophic vaginitis.

## 6.3.2 Prevalence in clinical studies

While no large-scale population-based data is available to estimate the prevalence of DU, we can obtain an approximation of the proportion of patients with DU in patients undergoing urodynamic evaluation (bearing in mind that this is a highly selected patient group, which may not be representative of the general population; **Table 2**). As noted earlier, there is also a wide variation in the definitions used for DU, limiting inter-study comparisons.

### Males

A retrospective study of 541 consecutive men (aged 26–89 years) referred for evaluation of LUTS found IDC, defined as $P_{det}Q_{max} \leq 30$ cm $H_2O$ and $Q_{max} \leq 12$ mL/s, in 10% of patients on videourodynamic assessment (42). Similarly Kuo retrospectively reviewed details of 1,407 men, aged 46–96 years with both voiding and storage symptoms and found low detrusor contractility in 10.6%, diagnosed if sphincter EMG was relaxed with an open membranous urethra during voiding and a low flow rate (43). Nitti *et al.* defined IDC as a bladder outlet obstruction index of <20 and uroflow <12 mL/s and found a prevalence of 9% in a prospective urodynamic evaluation of 85 neurologically normal young men (aged 18–45 years) presenting with LUTS (8). Similarly, in a study with 90 young men (age 18–50) presenting LUTS and low flow rate without neurological disease, Wang *et al.* found impaired detrusor contractility, defined as $P_{det}Q_{max}$ <30 cm $H_2O$, $Q_{max}$ <15 mL/s, and no radiological obstruction in 10% of the participants (44). Kaplan *et al.* performed a videourodynamic evaluation of 137 men (aged <50 years) with chronic voiding problems and found 17% with impaired detrusor contractility ($Q_{max}$<12 mL/s and $P_{det}Q_{max}$ <45 cm $H_2O$) and a further 5% with an acontracile detrusor (no detrusor contraction, no flow) (45). More recently, Karami *et al.* conducted a larger retrospective evaluation of 456 young men (age range 18–40 years) without any neurological dysfunction (46). Using ICS definitions, the study showed acontractile detrusor in 10.5% of participants and an underactive detrusor in 2.4%.

Abarbanel and Marcus conducted a retrospective review of urodynamic data for all patients over the age of 70 who were referred for urodynamic studies at a tertiary referral centre over a two-year period (9). Data from a total of 181 patients was reviewed (82 men) and revealed IDC, defined as $Q_{max}<10$ mL/s and $P_{det}Q_{max}<30$ cm $H_2O$, in 48% of them, two thirds of whom also had detrusor overactivity or low bladder compliance. Jeong *et al.* recently published a series from a tertiary centre that included 1,179 elderly patients (>65 years) evaluated for LUTS, finding 40.2% of a total 632 men with DU, defined as bladder contractility index <100 ($P_{det}Q_{max}+5(Q_{max})$) (7). Of these, 46.5% also had DO or BOO. They also found that DU increased with age, though this was not statistically significant ($p=0.053$).

## Females

Detrusor overactivity associated with IDC, termed "detrusor hyperactivity impaired contractility" (DHIC), was first recognized as an important cause of incontinence in frail elderly women in the late 1980s. A seminal study by Resnick *et al.* evaluated 94 incontinent institutionalized patients, 77 of whom were women, with PFS finding DHIC as the cause of incontinence in 30% of the cases (10). Detrusor underactivity occurring independently or as part of DHIC was present in 59% of study participants. A further study on incontinent elderly female nursing home residents (mean age 87.6 years) by Resnick *et al.* showed that 45% of the patients had IDC or DHIC (47). In the afore-mentioned study by Abarbanel and Marcus, 12% of women (age >70 years) had impaired contractility, half of whom also had non-voiding detrusor contractions or low bladder compliance. Similarly Jeong *et al.* found that 13.3% of women had DU ($Q_{max}\leq12$ mL/s, $P_{det}Q_{max}\leq10$ cm $H_2O$), associated in 72.6% of cases with stress incontinence or DO (7). An age-related increase in DU was also observed ($p=0.002$). Groutz *et al.* assessed 206 consecutive women attending a urogynecology clinic with PFS, defining those with impaired bladder emptying as $Q_{max}<12$ mL/s or PVR >150 mL on ≥2 readings (48). Using the ICS definition, DU was found in 19% of the participants. Recently, Valentini *et al.* studied 442 women (>55 years) referred with LUTS and found DU, defined as impaired detrusor contraction leading to prolonged voiding time and high residual volume, in 13.8% of the women (49).

In these studies, DU consistently represents at least 10–20% of urodynamic diagnoses of men of all ages undergoing evaluation for LUTS, which goes up to 48% in the elderly. In women, a similar prevalence was observed, with DHIC representing an important cause of incontinence in frail older women. However, these retrospective series are reliant upon *post hoc* interpretation of urodynamic data and thus have inherent limitations (50). Furthermore, considering the inconsistently defined primary outcome measures, the results cannot be extrapolated to the general population. However, the results do demonstrate that DU is sufficiently common in the group of patients seen in clinical practice to warrant careful consideration of patients' symptoms before treatment.

**TABLE 2** Prevalence of DU in clinical studies

| Study | Population | Size | Age range (years) | Prevalence of DU (% of acontractile detrusors) |
|---|---|---|---|---|
| Fusco *et al.*, 2001 (42) | Male | 541 | 26–89 | 10% |
| Kuo *et al.*, 2007 (43) | Male | 1,407 | 46–96 | 10.6% |
| Nitti *et al.*, 2002 (8) | Male | 85 | 18–45 | 9% |
| Wang *et al.*, 2003 (44) | Male | 90 | 18–50 | 10% |
| Kaplan *et al.*, 1996 (45) | Male | 137 | 18–50 | 23% (5%) |
| Karami *et al.*, 2011 (46) | Male | 456 | 18–40 | 12.9% (10.5%) |
| Abarbanel and Marcus 2007 (9) | Male<br>Female | 82<br>99 | >70<br>>70 | 48%<br>12% |
| Jeong *et al.*, 2012 (7) | Male<br>Female | 632<br>547 | >65<br>>65 | 40.2%<br>13.3% |
| Resnick *et al.*, 1989 (10) | Male<br>Female | 17<br>77 | 87[†] | 30%* |
| Resnick *et al.*, 1996 (47) | Female | 97 | 87.6[†] | 45%* |
| Groutz *et al.*, 1999 (48) | Female | 206 | 62.6 ± 15.8[†] | 19% |
| Valentini *et al.*, 2011 (49) | Female | 442 | >55 | 13.8% |

*IDC/DHIC, [†]mean ± SD.

# 6.4 **Etiology**

## 6.4.1 **Detrusor contractility and aging**

Whether detrusor function declines as part of normal aging is yet to be resolved, as the evidence base is small, heterogeneous, and often directly conflicting. Current insights are derived either from *in vitro* studies using animal and human tissue or urodynamic data, mostly from symptomatic individuals. Ultrastructural studies using electron microscopy have also yielded interesting insights into normal, age-related changes in detrusor morphology.

### *In vitro* studies

#### Animal

*In vitro* studies investigating the effect of aging on bladder contractility have yielded conflicting results. Studies comparing "young" to "old" rats utilizing electrical (ionic [e.g. $K^+$]) or chemical stimuli (e.g. carbachol) to cause contraction in the longitudinal muscle layer are most common. The advantage of bench work is that contractility is directly measured physiologically, whereas PFS contractility is estimated.

Longhurst *et al.* found that contractions in bladder muscle strips triggered by electrical stimulation were larger in 24-month old versus 6-month old Fischer 344 rats, whereas there was no difference in muscle contraction from the bladder base (51). Conversely, Zhoa *et al.* found an increased response in younger rats (Fischer/brown Norway) (52). Yet another study showed no difference in old versus young Sprague Dawley rats, but observed a significantly lower maximal shortening velocity in the older group (53). Pagala *et al.* found no difference in responses to electrical stimulation of longitudinal muscle from older compared to younger rats, but there were significantly greater contractions in the circular muscle of older rats (54).

Potassium-induced contraction was reported to be greater in older rats from the study by Longhurst *et al.* (51), whereas Gomez-Pinilla *et al.* found aging impaired contractile response (55). Saito *et al.* found no significant age-related difference in contractile response (56).

Carbachol, a cholinergic agonist, has been found to cause greater contractions in bladder body samples from younger rats (53), but another study observed higher responses in older rats (51). Yu *et al.* found that another specific muscarinic agonist, bethanochol, led to a lower magnitude and speed of contraction in older rats (57), whereas Chun *et al.* found no age-related changes in contractility (58). Adenosine triphosphate (ATP)-induced contraction in bladder body strips has been observed to be enhanced by aging (51,55,59), but not in strips from the bladder base (51).

Lin *et al.* electrically stimulated whole bladders from 3-month and 24-month old rats in organ baths (60). Bladders were subjected to repeated electrical stimulation and the generated pressure, rate of pressure generation, and emptying ability were measured. The findings showed that older bladders became fatigued faster than the bladders in younger rats. Tissue analysis revealed phosphocreatine and ATP concentrations to be significantly lower in aged bladders, suggesting reduced capacity for energy production as the underlying mechanism.

The contradictory evidence to a variety of physiological and non-physiological stimuli may be due to inter-strain differences (52) or variations in biopsied regions (54). It may also suggest that an *in vivo* decline in contractility is explained by age-related changes in the afferent/efferent function or central control mechanisms of detrusor function (58).

## Human

*In vitro* studies of human tissue are less common. Recently, Fry *et al.* studied bladder biopsies from patients with normal bladders (controls), BOO, idiopathic DO, and neurogenic DO, for a total of 227 samples (61). Multiple stimuli were used, including nerve-mediated and direct electrical stimulation, as well as agonists such as carbachol, ATP, and potassium. Although there was no evidence of any age-related decrease in contractility in any of the groups studied, there was a decrease in nerve-mediated stimulated contraction in the BOO and DO groups, suggesting a decline in functional innervation with age in these groups. Similarly, Yoshida *et al.* studied the contractile responses to electrical field stimulation, potassium, ATP, and carbachol in biopsies from patients in three age groups (<50, 51–70, and >70 years), finding no significant difference in contractile response between the groups (62). Additionally, Mark *et al.* did not find any decline in contractility with age in asymptomatic men (63).

## Clinical studies

Urodynamic estimation of contractile function is based upon the detrusor pressure required to expel urine through a patent urethra. Such an estimation is likely to underestimate contractility, as the contraction generates both flow and pressure (64). Instead, methods that measure isovolumetric detrusor pressure, such as urethral occlusion, or stop tests may be used (65).

Pfisterer *et al.* studied 85 ambulatory community-dwelling women as part of a cross-sectional study of DO and aging (66). Patients were assessed using video-urodynamics and were divided into three age groups: 20–39, 40–59, and >60 years. Detrusor contraction strength was determined using projected isovolumetric detrusor pressure (PIP), a modification of the Schaefer contractility parameter, the detrusor contraction coefficient (DECO) (67). Both flow rate and contraction strength declined significantly with age ($p=0.006$ and $p<0.001$, respectively), regardless of whether DO was diagnosed. The maximal urethral closure pressure and bladder sensation also showed age-related declines ($p<0.001$ and $p<0.01$, respectively). Smith *et al.* compared urodynamic data from PFS in 176 women (aged >75 years) to 737 women (aged <75 years) and found a significantly lower $Q_{max}$ (11.9 vs 16.3 mL/s, $p<0.01$), $P_{det}Q_{max}$ (34.3 vs 42.7 cm $H_2O$, $p=0.03$), and higher PVR (128.3 vs 83.0 mL, $p=0.03$) in the older group (after excluding those with stress incontinence) (68). Valentini *et al.* performed a similar study in a group of 449 older women with LUTS referred for urodynamic studies (49). Patients were stratified into three age groups: 55–64, 65–74, and 75–93 years. Maximal detrusor pressure and flow rate declined with age in those without DO (no $p$ value given). Conversely, Karram *et al.* found that maximal detrusor pressure did not correlate with age in a study comparing 30 healthy, asymptomatic female volunteers to 70 women with stress incontinence (69). Similarly, Madersbacher *et al.* observed no age-related changes in maximum detrusor pressure or $P_{det}Q_{max}$ in 436 patients (253 men) aged >40 years referred with LUTS (70).

## Tissue composition and ultrastructural changes

Contractile function may be affected by changes in tissue composition and ultrastructure that accompany normal aging. Lepor *et al.* conducted a quantitative morphometric study in 86 bladder specimens from autopsies in young and old patients of both sexes (71). An age-related decline in the ratio of smooth muscle to connective tissue was found in both sexes, with no difference between the sexes. Similar findings were observed in a semi-quantitative study by Holm *et al.* (72), who concluded that aging was associated with detrusor fibrosis, independent of the presence of benign prostatic hyperplasia (BPH). Meanwhile, Gosling *et al.* observed normal smooth muscle cell morphology, but a reduction in innervation in non-obstructed aged bladders (73). Elbadawi *et al.* proposed that a distinct ultrastructural pattern, seen on electron microscopy, represents the normally contractile aging detrusor (74). Termed the "dense band pattern," its features are sarcolemma with depleted caveolae (plasma membrane invaginations that modulate signal transduction and alterations) and long dense bands. A clinic-pathological validation study showed this pattern to be dominant in all elderly individuals (>65 years) with stable, unobstructed, normally contractile bladder on PFS (74). A similar age-related depletion in caveolae has been observed in rats (75) where muscarinic and purinergic receptors are clustered (76) and are thought to play an important role in cholinergic-mediated detrusor contractions (77–79).

## 6.4.2 Other etiological factors

The presence of DU in diverse clinical groups (**Table 3**) suggests a multi-factorial etiopathogenesis (80), rather than occurring solely as a function of normal aging. Current theories are based on bridging knowledge from *in vivo* and *in vitro* investigations in both animal and humans with clinical evidence. It is helpful to consider the possible underlying etiologies to be myogenic, involving efferent or afferent pathways, or the central control mechanisms of lower urinary tract function.

**TABLE 3**  Etiological factors

| Type | Possible Causes |
|------|-----------------|
| Idiopathic | Normal aging*<br>Unknown cause in younger population* |
| Neurogenic | Parkinson's disease<br>Diabetes<br>Guillane-Barré syndrome<br>Multiple sclerosis<br>Spinal-lumbar dischernia/spinal cord injury/congenital |
| Myogenic | Bladder outlet obstruction*<br>Diabetes* |
| Iatrogenic | Pelvic surgery<br>Radical prostatectomy<br>Radical cystectomy<br>Radical hysterectomy<br>Anterior resection, abdomino-perineal resection |

*Likely major contributory factors.

# 6.5 Pathophysiology

## 6.5.1 Myogenic etiology

### Detrusor underactivity

The myogenic basis of DU may be considered to lie in the cellular contractile mechanisms or in the extracellular matrix. Myogenic activity is considered to be the intrinsic propensity of the myocyte, which generates contractile activity in the absence of external stimuli (81). The ultrastructural changes accompanying normal aging were described by Elbadawi *et al.*, who also characterized the patterns occurring in other lower urinary tract dysfunctions, including DU (82–84). Although there has been some disagreement regarding the overall applicability and consistency of this classification system (85,86), the particular changes associated with DU, termed the "degeneration pattern," have since been reproduced by other groups (87,88).

The degeneration pattern consists of widespread detrusor myocyte disruption and axonal degeneration superimposed on the dense band pattern described earlier (82). The degeneration pattern correlated well with impaired contractility, defined as PVR >50 mL (the lowest of three measurements taken by draining the bladder), in the absence of straining, obstruction, and detrusor sphincter dysnergia in a clinical validation study (74). The identifying features, sarcoplasmic vacuolation, sequestration, or blebbing; cell fragmentation and shriveling; and the occurrence of cellular debris in intercellular space were shown by Hindley *et al.* to consistently occur in a qualitative study of 21 patients with urodynamically proven DU (PVR >300 mL and no obstruction by Schaefer nomogram). A follow-up prospective quantitative study from the same group compared biopsies from 14 patients with DU (using the same definition) to 17 age-matched normal controls and found a significantly higher median disruptive cell count in the DU group versus the control group, 96.5 and 20 (per 500 cells), respectively ($p<0.0001$). Conversely, some have failed to demonstrate any specific ultrastructural changes in patients with DU (89).

It is not clear whether ultrastructural changes represent a cause or effect of DU. The disruption to detrusor myocytes could, in theory, account for impairments in cell contractile properties by affecting ion storage/exchange, excitation-contraction coupling mechanisms, calcium storage, or energy generation so that even in the presence of normal extrinsic neuronal activity, a reduced contraction may still occur (87).

## Detrusor underactivity with bladder outlet obstruction

A degenerative pattern has also been observed in a subset of patients with BOO and large PVR (>150 mL) (90). The mechanisms of BOO-related DU have been well studied in animal models (mainly rat and rabbit), where sequential changes have been described. Initially, there is detrusor muscle hypertrophy and hyperplasia leading to thickening of the bladder wall, which then leads to increased tension during contraction and vascular compression, resulting in tissue ischemia and hypoxia. Following this initial period, contractile function increases to overcome the obstruction, with normal or high detrusor pressure, before stabilizing. Functionally, during this stage, rats show increased urinary frequency, increased PVR, and DO. After a variable length of time, detrusor function dissipates and emptying is impaired, heralding the decompensation phase (91).

Tissue ischemia and hypoxia are thought to be the likely pathways leading to decompensation. Studies in rats with severe urethral obstruction demonstrated reduced blood flow, which leads to tissue ischemia and hypoxia (92). In humans, studies in healthy volunteers showed increased blood flow during bladder filling, but significant reductions when capacity is reached, suggesting a similar process is occurring (93). Additionally, in the decompensation phase, cyclic perfusion/reperfusion during the micturition cycle leads to the generation of reactive oxygen species (94), known to damage cellular apparati (sarcoplasmic reticulum and mitochondria). The end sequelae of the process are denervation and cell damage leading to permanent contractile dysfunction (95). Clinically, why some men will develop decompensation leading to DU and low-pressure CR after BOO while others will have preserved contractility, including the important subset of high-pressure CR, is as yet unresolved (96,97).

## 6.5.2   Central control mechanisms

It has been proposed that dysfunction of central neural control of the voiding reflex may lead to DU by impacting key processes in perception, integration, and outflow (80). The micturition reflex is mediated by the spino-bulbo-spinal pathway, passing through the sacral parasympathetic nucleus and the pontine micturition center (PMC), which is modulated by higher centres in the cerebral cortex. Functional imaging has provided many insights; rat and cat studies show that some populations of PMC neurons, termed direct neurons, fire just before and during reflex bladder contractions (98–100), and are inactive outside of these periods. A large proportion of these neurons pass to the lumbosacral spinal cord. Functional neuroimaging human studies suggest that similar areas in the brain stem and cortex are involved in the voiding reflex, namely the insula, hypothalamus, periaqueductal grey and PMC regions (101).

Magnetic resonance imaging in patients with DU of neurogenic origin may be helpful in understanding the central influence on contractile activity. Araki *et al.* found a correlation between site of demyelination and urodynamic diagnosis in a study of 32 patients with multiple sclerosis undergoing evaluation for voiding dysfunction (102). DU or acontractility correlated significantly with a pontine lesion ($p<0.05$), although a similar larger study by Kim *et al.* did not demonstrate any such correlation (103).

## 6.5.3   Efferent function

Disruption to the efferent nerves may result in a lack of or reduced activation, which in turn may manifest in an absent or poor detrusor contraction. In DU that is not of neurogenic origin, the exact contribution of efferent dysfunction is unknown. The work of Groen *et al.* assessed the impact of nerve-mediated electrical stimulation on bladder contractility at 2 different intensities on both *in vivo* and *in vitro* bladder contractility parameters in guinea pigs (104,105). At the higher level of stimulation, a significantly greater isovolumetric pressure was generated, as well as a faster detrusor shortening velocity. The authors postulated that at lower levels of stimulation, the detrusor may not be uniformly stimulated, so that some parts of the muscle do not contribute to the contraction. *In vivo,* such sub-optimal stimulation may result in insufficient release of neurotransmitters to generate uniform contractions. The decline in autonomic nerve innervation seen in normal human bladders with aging (106) as well as BOO (107) may also contribute to insufficient activation for contraction to occur (80).

## 6.5.4   Afferent function

Although most research has focused on the myogenic and efferent contributions to the pathogenesis of DU, the importance of the afferent system is increasingly being recognized. The afferent system is integral to the function of the efferent system in the neural control of micturition, both during the storage and the voiding phases. The afferent system monitors the volumes in the bladder during urine storage and also the magnitude of bladder contractions during voiding. As such, it has a role in the initiation of the voiding reflex and provides the feedback that maintains it. Urethral afferents respond to flow and are important in potentiating the detrusor contraction (108,109). The afferent system is composed of mainly two types of fibres: A-δ fibres, which are myelinated, and C fibres,

which are unmyelinated. These fibres are carried to the lumbosacral cord through pelvic, hypogastric, and pudendal nerves. The nuclei of the pelvic and pudendal nerves lie in the dorsal root ganglion of spinal segments S2-S4, whereas the nuclei of the hypogastric nerve lie in the dorsal root ganglion of segments T11-T12. The A-$\delta$ fibres, which are found mainly in the muscle layer, detect distention of the bladder, whereas C fibres are located in the lamina propria close the urothelium and are thought to mainly mediate nociception.

Bladder and urethral afferent dysfunction may lead to DU by reducing or prematurely ending the micturition reflex, which may manifest in a loss of voiding efficiency (80). The most probable example of this would be diabetic cystopathy, where a decrease in emptying efficiency is observed in a time-dependent fashion with the course of the disease (110,111). Diabetes leads to axonal degeneration and segmental demyelination causing impaired transmission of afferent signals from the bladder (112); this was shown clinically by the decreased response of both A-$\delta$ and C fibres in the measurement of intravesical current thresholds (113). A reduction in nerve growth factor (NGF) may also impair axonal transport leading to afferent dysfunction. Studies in rats have shown reduced levels of NGF in the dorsal root ganglia that were associated with increased PVR and bladder capacity (114,115). An age-related increase in volume thresholds for voiding has been shown in women, and it may be that normal aging is associated with a degree of afferent dysfunction (66,116).

Smith recently proposed a hypothesis for the pathogenesis of DU that integrates findings from ultrastructural studies of the tissue changes that accompany normal aging with the altered afferent function seen in aging and disease (22). This can be summarized as follows: aging results in tissue changes that alter the biomechanical properties of the bladder, namely a reduction in elasticity. This results in changes in the passive compliance curve, with an initial greater compliance at low volumes followed by a precipitous increase in pressure, and hence wall stress, as capacity is reached. Afferent outflow can be considered a function of wall stress; therefore, clinically, this scenario would result in a delayed desire to void (i.e. at higher volumes) followed by sudden desire when capacity is reached. Conversely, when a small volume of urine is passed, there is a dramatic decline in wall stress, resulting in a reduction in afferent activity, which in turns leads to an early termination of detrusor contraction and thus reduced voiding efficiency.

**Figure 1** depicts the various possible pathophysiological mechanisms in DU.

**FIGURE 1**

Possible pathophysiological mechanisms in DU

**BOO**
Tissue ischemia and hypoxia
Cyclical perfusion/reperfusion injury

**Aging**
Ultrastructural changes
⬆ fatigability
Impaired cellular processes

**BOO**
⬇ in autonomic innervations

**Aging**
⬇ in autonomic innervations

Myogenic
**Loss of Intrinsic Contractility**

Efferent
**Impaired activation of detrusor**

**Aging**
Age-associated afferent dysfunction

**DETRUSOR UNDERACTIVITY**

**Decreased stimulation**
Insufficient neurotransmitter

Afferent
**Early termination of voiding reflex**

Central control
**Failure of integration/processing**

**Diabetes**
Axonal degeneration
Segmental demyelination

**⬇ Nerve growth factor**

**Lesion/impairment of higher centres**

# 6.6 **Diagnosis**

There is wide variation in the urodynamic criteria used for diagnosing DU in clinical studies. From these studies, two things are evident: 1) most criteria assess only detrusor contraction strength (as opposed to sustainability or speed), and 2) estimation of strength is based on the $Q_{max}$ and $P_{det}Q_{max}$, with threshold values set around the lower limits of the normal range (for men, this range is derived from historical series of patients undergoing bladder outlet surgery) (29,117). Clearly these ranges may not be applicable to all groups. As such, some authors have studied healthy young men (118,119) and women (66) to obtain a more accurate picture, although these studies are few.

Several algorithms and tests have been proposed to estimate detrusor contraction strength during uninterrupted or interrupted voiding as part of PFS. Some of these are rather confusing, which may be the reason for their limited use in clinical studies. Most have their basis in the bladder outlet relation (BOR) (120), the inverse relation between pressure and flow, which is equivalent to the Hill equation for actively contracting muscle (121). The BOR can be summarized as follows: in any given bladder, if outflow is stopped, the detrusor pressure reaches its highest possible value (isovolumetric pressure); when increasing flow is allowed, pressure decreases, reaching a minimum when flow reaches a maximum. On this basis, measuring detrusor pressure at the time of high flow (i.e. $P_{det}Q_{max}$)

does not provide an accurate estimation of the strength of contraction. Consequently, methods that assess isovolumetric detrusor pressure have been suggested and are either based on *post hoc* mathematical analysis of urodynamic data or real-time interruption of urine flow (**Table 4**).

**TABLE 4** Summary of diagnostic methods

| Type | Method | Advantages | Limitations |
|---|---|---|---|
| **Mathematical Calculations** | Watts factor | 1. Measure of bladder power<br>2. Minimally dependent on volume of urine<br>3. Not affected by presence of BOO | 1. Lengthy and complex calculation<br>2. No validated thresholds<br>3. Does not measure sustainability of contraction |
|  | Detrusor shortening velocity | 1. May identify early-stage DU |  |
| **Indices** | Detrusor contraction coefficient (DECO) | 1. Simple to use<br>2. Measurement easy to obtain<br>3. Estimation of isovolumetric contraction | 1. Does not measure sustainability of contraction<br>2. May not be applicable to other groups<br>3. Does not conceptually consider co-existence of BOO and DU |
|  | Bladder contractility index (BCI) |  |  |
| **Occlusion testing** | Voluntary stop test | 1. Real-time indication of isovolumetric contraction strength<br>2. No calculations | 1. Uncomfortable or painful for patients<br>2. Impractical<br>3. No information on sustainability of contraction (continuous occlusion)<br>4. May underestimate isovolumetric pressure (stop test)<br>5. Unusable in some patient groups |
|  | Mechanical stop test |  |  |
|  | Continuous occlusion |  |  |
| **Ranges of urodynamic measurements** | $P_{det}Q_{max}$ (e.g. <40 cm $H_2O$)<br>$Q_{max}$ (e.g. <15 mL/s) | 1. Simple to use | 1. No widely accepted "normal" ranges<br>2. Underestimates contraction strength<br>3. Does not conceptually consider co-existence of BOO and DU |

## 6.6.1 **Watts factor**

The watts factor estimates the power per unit area of bladder surface that is generated by the detrusor, corrected for the finite power required for either isometric contraction or for shortening against no load. This is represented by the following formula, where $P_{det}$ represents detrusor pressure, $v_{det}$ is detrusor shortening velocity, and "a" and "b" are fixed constants (a=25 cm $H_2O$, b=6 mm/s), obtained from experimental and clinical studies (122).

$$WF=[(P_{det}+a)\ (v_{det}\ b)-ab]/2\pi$$

As $P_{det}$ and $v_{det}$ vary through the voiding cycle, the WF will also vary. Two points have been proposed as being most representative of detrusor contractility: the maximum WF ($WF_{max}$) (123) and WF at maximum flow ($Wq_{max}$). The advantages of the WF are that it is minimally dependent upon bladder volume (122), and it is not affected by the presence of BOO (124). However, it does not provide a

measure of contraction sustainability and involves a complex calculation limiting its use in routine clinical practice. Additionally, there are no validated threshold values of normality, although experts have suggested 7 W/m$^2$ (16).

### 6.6.2 Indices: Projected isovolumetric pressure, detrusor contraction coefficient, and bladder contractility index

Schafer proposed a simple method to assess detrusor contraction strength by drawing the linear passive urethral resistance relation onto Schafer's pressure/flow nomogram, whereby the peak of the passive urethral resistance relation signifies the detrusor contraction strength (125). The maximum isovolumetric pressure can be estimated using the point $P_{det}/Q_{max}$, if the angle and curvature of the BOR are known. To do this, the BOR is simplified to a straight line with a fixed angle (K) taken as 5 cm $H_2O$/mL/s (male BPH population); the isovolumetric pressure is then estimated by projecting back to the Y-axis ($P_{det}$) in a line parallel to the BOR. This is represented by the formula:

Projected isovolumetric pressure (PIP)=$P_{det}Q_{max}$+5$Q_{max}$ (126)

Threshold values for contraction strength were suggested with >150 representing strong contraction, 100–150 representing normal contraction, 50–99 weak contraction, and <50 very weak contraction. By drawing the corresponding BORs on the pressure flow plot, a contractility nomogram was developed. As a PIP greater than 100 cm $H_2O$ represents normal contraction strength, the actual PIP divided by 100 gives the DECO coefficient, whereby a value <1 signifies weak contraction.

Abrams described the bladder contractility index (BCI) based on the PIP formula, which divides contractility into three groups (strong ≥150, normal=100–150, and weak ≤100); this is, in principle, the same as DECO (127). In common with the watts factor, these methods do not measure the sustainability of contractions. Additionally, the fixed angle K needs adjusting to the particular group studied, where a value of 5 cm $H_2O$/mL/s is suitable for men with BPH. This is unlikely to be applicable in other groups; an angle of 1 cm $H_2O$/mL/s was found to be more accurate in older women (65).

### 6.6.3 Occlusion testing

By utilizing voluntary or mechanical interruption of the urine flow, an estimation of isovolumetric detrusor pressure ($P_{det}$,iso) can be obtained (128). In voluntary stop tests, the patient is asked to interrupt the flow mid-stream by contracting the external urethral sphincter. Mechanical interruption, on the other hand, involves blocking the urethra, for example by pulling a catheter balloon against the bladder neck mid-stream. A continuous occlusion test has been described, where the outflow is occluded before the onset of detrusor contraction. The three techniques show good correlation with one another in both males (129) and females (130). However, the voluntary stop test gives a $P_{det}$,iso of around 20% less than the other two (129). This is thought to occur due to a reflex inhibitory effect on the detrusor as a result of external sphincter contraction. Voluntary stop tests are not possible in some patients, especially in those with neurological dysfunction, stress incontinence, or frailty. Continuous occlusion has a better test-retest reliability than mechanical stop tests, possibly due to the discomfort associated with the latter, and has the advantage of allowing an assessment of

isometric contraction sustainability. It has also been found to correlate well with bladder voiding efficiency (36). However, continuous occlusion is problematic, as it does not allow the measurement of flow, it may be painful, and it is impractical.

Non-invasive techniques assessing contraction strength have been explored, but have not replaced standard PFS in clinical practice. McIntosh *et al.* used an infla   penile cuff to interrupt voiding, finding this method to overestimate $P_{det}$,iso by 16.4 cm $H_2O$, attributed to the positioning of the cuff below the bladder (131). Patients generally found cuff assessment more acceptable than invasive PFS; however, the test was limited by frequent failure and variability of agreement. Another technique is to use condom catheters, where a continuous column of fluid from the condom via catheter to the urethra and bladder allows measurement of pressure. With this method, measurements of $P_{det}$,iso correlate well with invasive PFS in non-obstructed patients, but less so in BOO patients (132). Several problems can lead to artifacts, such as leakage around the condom, closure of the external sphincter in response to line occlusion, and increased compliance within the system (133). One problem common to both techniques is the lack of appreciation of abdominal straining.

### 6.6.4   Detrusor shortening speed

From the WF equation, it can be seen that WF is the product of $P_{det}$ and $v_{det}$. Therefore, conceptually, a low WF could result from a reduced $v_{det}$ and a normal $P_{det}$. As such, patients with DU could have bladders that are slow and weak, but others may only have slow bladders. In a series of longitudinal studies in both men (25,134) and women (135) with idiopathic DU, a reduction in $v_{det}$ preceded the reduction in $P_{det}$, suggesting a two-stage process in the development of DU. Shortening velocity was calculated using the following equation, where Q represents the flow rate (mL/s), V represents bladder volume (mL), and Vt represents the volume of non-contracting bladder wall tissue.

$$v_{det}=Q/2[3/(V+Vt)/4\pi]0.66$$

The authors hypothesized that the initial total number of cross-bridges between actin myosin filaments is unchanged, but the time taken to form cross-bridges is increased (due to an unknown cause) accounting for the slow contraction. Eventually there is a reduction in the number of cross-bridges, which accounts for the reduced strength (136). On the basis of these studies, Cucchi *et al.* recently proposed a new definition of DU incorporating contraction speed: "slower and/or weaker bladder with or without poorly sustained micturition contractions" (136).

### 6.6.5   Ambulatory urodynamics

Ambulatory urodynamics may have a role in the diagnosis of DU when detrusor acontracility is demonstrated in conventional PFS. A study by van Koeveringe *et al.* found that in 71% of patients in whom no detrusor contraction was demonstrable on conventional PFS, there was obvious contractility in ambulatory studies (137). The probable reason may be that during PFS, patient anxiety leads to pelvic floor/sphincter contraction, which triggers the guarding reflex thus impairing detrusor contraction (138). The authors concluded that ambulatory studies should be conducted in all patients with reduced contractility on conventional PFS.

# 6.7 **Management**

## 6.7.1 **General considerations**

A lack of both a widely accepted definition and diagnostic criteria has limited the development of any evidence-based management approaches for DU. Ideally, management would be tailored to the underlying cause; however, given the lack of insight into the etiopathogenesis of DU, this has not been possible in most instances. Invariably, patients are managed in a generalized fashion, with either a "watchful waiting" approach or bladder drainage. The development of DU-specific pharmacotherapy remains in its infancy and aims to either increase the contractile function or reduce the outlet resistance. Most other approaches are currently experimental and include modalities such as intravesical or injection-based treatments, neurostimulation/modulation, and innovative reconstructive surgical procedures involving transposition of the abdominal muscle groups.

## 6.7.2 **Conservative management**

The aim of conservative management is to facilitate bladder emptying and reduce PVR as well as managing the risk of associated complications, such as recurrent urinary tract infections (UTIs) or bladder stones. Initially, a careful assessment of potential factors that may cause or contribute to DU, such as pharmacotherapy, is undertaken. Similarly, factors that may cause or worsen BOO should be excluded. Following this, patients may be managed expectantly, by monitoring symptom severity and observing PVR.

A 10-year urodynamic follow-up study by Thomas *et al.* of men diagnosed with DU ($Q_{max}$ <15mL/s, $P_{det}Q_{max}$ <40 cm $H_2O$) and initially managed with watchful waiting (no catheterization) provides interesting insights into the natural history of DU (26). Sixty-nine men who initially opted for watchful waiting were followed up with PFS (mean follow-up of 13.6 years). The main finding was that there was no significant deterioration in symptomatic or urodynamic parameters over time. Only 11 patients failed the initial watchful waiting approach and underwent TURP – 8 (11.6%) due to worsening LUTS and 3 (4.35%) due to acute retention. Those with worsening LUTS had repeat flow studies pre-operatively, which showed no significant change compared to baseline values. The main conclusions from this study were that DU is not progressive in the majority of non-neurogenic male patients and an initial conservative approach is justified.

Pelvic floor physiotherapy has been used to treat pediatric patients with dysfunctional voiding (139) and is of potential use in individuals with poorly relaxed pelvic floors and who may have DU as a result of the guarding reflex. In the study by van Koeveringe *et al.*, 24% of the patients with acontractile bladders on conventional PFS but not on ambulatory studies were successfully treated with physiotherapy (137), suggesting a potential role for physiotherapy in this group.

Interestingly, in the series reported by Thomas *et al.*, the initial mean PVR (after free flow) was 108 mL (±166.6) at baseline and did not change significantly with time, suggesting that in the majority of individuals, PVRs are less than 300 mL and not progressive. Those identified as having chronic retention are often managed with some form of catheterization to reduce the risk of UTI and bladder

stones. Clean intermittent self-catheterization (CISC) is the preferable method; provided that cognition and dexterity are adequate, CISC is a safe and effective method of bladder drainage with lower infection rates than indwelling catheters. Problems include urethral bleeding (one third of patients) (140) and false passages. Additionally, the technique can be time-consuming and socially restricting, and some patients may be unable to overcome the psychological barriers of fear of self-harm or infection (141).

## 6.7.3 **Pharmacotherapy**

### Parasympathomimetic drugs

A heterogeneous group of small clinical trials has investigated the use of agents that potentiate muscarinic receptors. Direct muscarinic agonists (e.g. bethanechol) and anticholinestrases (e.g. distigmine) have both been investigated. Conceptually, this approach is more likely to work if the pathophysiological cause of DU is a lack of contractile stimulus rather than impaired tissue response (i.e. muscle cell degeneration). A common problem to all these agents is the systemic side effects of cholinergic agonism, including nausea, bronchospasm, abdominal cramping, flushing, and visual disturbance, which limit their dosing. A rare but serious complication is severe cardiac depression resulting in cardiac arrest. Most studies have assessed the efficacy of agents in either the prevention or treatment of acute urinary retention in the post-operative setting, including prostatectomy (142), anorectal surgery (143), vaginal surgery (144), and radical hysterectomy (145), as well as in post-partum patients (146). A minority of studies assessed the efficacy in patients with suspected DU, including females, males, and mixed groups (147–150). The results of these have recently been summarized in a review by Barendrecht *et al.* (151) (**Table 5**). Only in three out of 10 trials reviewed was there a statistically significant benefit of the agent versus the control, in six studies there was no significant benefit, and in one a detrimental effect was observed. Bethanechol was used in all three studies showing a statistically significant benefit and the effect was marginal; a further four studies showed no benefit with the same agent. The authors concluded that parasympathomimetic agents show little, if any, benefit in preventing or treating DU.

**TABLE 5** An overview of RCTs of parasympathomimetic agents in the treatment of UUB

| Intervention | Indication and endpoint | n | Outcome | Evidence level |
|---|---|---|---|---|
| Bethanechol 50 mg x 3 oral from 3 days after surgery, vs no treatment | I: prophylaxis of detrusor hypotonia after W-G op.<br>E: hospital stay, catheter treatment, rate of cystitis and residual urine | 40 | Hospital stay 18.6 vs 15.5 days, catheter treatment 13.3 vs 9.6 days; rate of cystitis 25.0 vs 18.8%; residual urine <50 mL after 13 vs 8 days for no treatment vs bethanechol; all differences $P$<0.01 | 2b |
| Bethanechol 10 mg x 1 s.c. vs midazolam vs combination vs placebo | I: treatment of AUR after anorectal surgery;<br>E: incidence of catheterization | 132 | 0 vs 69% responders for placebo and bethanechol ($P$=0.05) irrespective of other treatment | 2b |

*UUB-Underactive urinary bladder, WG-Wertheim-Meig.
Modified from Barendrecht *et al.* (151)

**TABLE 5** An overview of RCTs of parasympathomimetic agents in the treatment of UUB, *Cont'd*

| Intervention | Indication and endpoint | n | Outcome | Evidence level |
|---|---|---|---|---|
| Carbachol/diazepam 2 mg each vs alfuzosin 2.5 mg vs placebo, all x 1 oral | I: treatment of AUR after general surgery;<br>E: voiding within 2 h after medication | 249 | No significant difference between groups | 2b |
| Distigmine 0.5 mg i.m. x 1 for 4 days vs placebo | I: treatment of AUR after prostatectomy;<br>E: flow rates and re-catheterization rate | 93 | No significant difference between groups | 2b |
| Bethanechol 25, 50 or 100 mg x 1 oral vs placebo 60 min before urodynamic investigation | I: women with persistent high residual urine but no sign of neurological disease or BOO;<br>E: urodynamic changes | 48 | No significant difference between groups for voided volume, residual volume, % residual volume, mean flow rate and intravesical pressure | 2b |
| Bethanechol 4 x 50 mg daily oral + intravesical $PGE_2$ x 1/week vs placebo for 6 weeks | I: treatment of UUB;<br>E: residual urine | 19 | Relative to baseline statistically significant reduction with active treatment but not with placebo, but effect size judged as 'limited therapeutic effect' by investigator | 1b |
| Distigmine 5 mg x 1 oral vs phenoxybenzamine 10 mg x 2 oral vs intravesical $PGF_2\alpha$ 7.5 mg vs placebo from 1 day after surgery | I: prevention of AUR after vaginal surgery for genital prolapse;<br>E: residual volume after surgery | 100 | Statistically significant increase of residual urine for distigmine vs placebo | 2b |
| Bethanechol 15 mg every 4 h (6 doses) vs no treatment | I: prevention of AUR post-partum;<br>E: catheterization and residual volume | 1,796 | No significant difference between both groups | 2b |
| Bethanechol 20 mg x 3 or distigmine 5 mg x 3 oral vs urapidil 30 mg x 2 vs combined for 4 weeks | I: treatment of UUB;<br>E: mean and max flow rate, post-void residual volume IPSS | 119 | No significant effect of cholinergic agonists vs baseline | 2b |
| Bethanechol 25 mg x 1 oral vs placebo for 2 weeks in cross-over design | I: treatment of UUB;<br>E: residual urine, max detrusor pressure and urinary flow | 16 | Significant reduction of residual urine and increase in max urinary flow vs placebo ($P<0.02$ and $<0.03$), detrusor pressure tended to increase | 1b |

*UUB-Underactive urinary bladder, WG-Wertheim-Meig.
Modified from Barendrecht *et al.* (151)

## Alpha-blockers

Alpha-blockers (ABs) improve voiding symptoms and voiding efficiency by reducing bladder outlet resistance and are usually used in men with BOO and in adults and children with neurogenic bladder dysfunction. Combining the use of an AB with a cholinergic agonist has been suggested as a therapeutic option in DU (152). Yamanishi *et al.* studied 119 men and women with DU (defined as

maximum $P_{det}$ <20 cm $H_2O$, $Q_{max}$<10 mL/s, PVR>50 mL) and randomized them into three groups: those receiving ABs ($n$=38), parasympathomimetics ($n$=40), or a combination of the two ($n$=41) (149). Patients were treated for 4 weeks before having repeat uroflowmetry and PVR measurements. The results showed that $Q_{max}$ increased significantly in the combination group (2.66 mL/s in women [$p$<0.01], and 4.33 mL/s in men [$p$<0.05]), but not in the monotherapy groups. PVR, however, was reduced significantly in women in the combination group (54.1 mL/s [$p$<0.01]), but not men. In the AB groups, a significant reduction in women (47.6 mL/s [$p$<0.05]), but not men was observed. No significant reduction in PVR occurred in either sex taking the cholinergic agonist. Additionally, the International Prostate Symptom Score (IPSS) improved significantly with AB monotherapy and combination treatment, but not with cholinergic agonist treatment.

### 6.7.4 Intra-vesical therapy

#### Intra-vesical prostaglandings
Prostaglandins (PG) are synthesized in the bladder wall and released into the bladder lumen and general circulation (153,154). Prostaglandin $E_2$ is thought to increase detrusor pressure and relax the urethra (155,156). It also enhances the effect of other contraction mediators, such as ATP and acetylcholine. Prostaglandin $E_2$ also increases afferent activity through urothelial and myogenic pathways and may be associated with OAB (157). Prostaglandin $E_2$ acts through four receptors (EP1-EP4); EP1 and EP3 are thought to mediate contraction, whereas $EP_2$ mediates bladder and urethral relaxation (158). Early reports of the efficacy of intra-vesical instillation of PG in improving bladder emptying were conflicting (159,160). Subsequently, several groups investigated the use of intra-vesical PG to prevent urinary retention/accelerate return of spontaneous voiding after vaginal surgery. A beneficial effect was found by some (161–163), but not others (164,165). Both the E and F series of PG are important in stimulating uterine contractions (166), and this may be an important side effect of treatment.

#### Intra-urethral Botulinum Neurotoxin type A
Intra-urethral Botulinum Neurotoxin type A (BoNT-A) has been used with good effect to reduce outlet resistance and improve bladder emptying in neuropathic patients with detrusor-sphincter dyssynergia (167,168). As urethral sphincter contraction has an inhibitory effect on detrusor contraction (guarding reflex) (169), and inadequate relaxation may result in low-pressure low-flow voiding (170), there is a strong rationale for approaches aimed at preventing urethral contraction. Kuo studied the effect of intra-urethral BoNT-A in 20 patients with DU, 15 of whom had acontracile detrusors (171). There were 5 patients with cauda equina lesions, 5 with dysfunctional voiding due to urethral sphincter spasticity, 6 with presumed denervation after radical hysterectomy, and 4 with idiopathic DU. Post-injection, the 7 patients who previously were reliant upon indwelling catheters could void with PVRs of ≤150 mL. In the 7 performing CISC at baseline, CISC was stopped or reduced in frequency after injection. A further study by Kuo evaluated the effects of urethral BoNT-A injection in 27 patients (5 men and 22 women) with idiopathic DU (low or no $P_{det}$ and $Q_{max}$ of <10 mL/s and PVR >150 mL in the absence of neurological disease and BOO) (172). Video-urodynamic studies were performed at baseline and 1-month follow-up after injection. Recovery of contractility (increase in $P_{det}$ with an increase $Q_{max}$ and reduction in PVR) occurred in 13 patients (48%), all of whom could

void without abdominal straining. Analysis of baseline characteristics identified the responders as having normal bladder sensation during filling; in contrast, non-responders had poor bladder sensation (mean volume at first sensation: 233 vs 368 mL, $p$=0.01). In 87% of the responders, recovery of detrusor contractility was associated with poor relaxation of the urethral sphincter.

## 6.7.5 Neurostimulation and neuromodulation

Neurostimulation and neuromodulation have both been investigated as treatments for DU. Anterior sacral root stimulators have long been used in patients with spinal cord injury to achieve continence and bladder emptying. The stimulator consists of an implantable receiver, stimulation wires, and an external transmitter. To trigger voiding, a radio transmitter is placed over the skin where the receiver lies (usually on the abdomen), which is connected by cables to the spinal electrodes that pass on the electrical impulses to the nerves. Brindley first implanted these stimulators in 1982 (173) and the first 50 cases were subsequently reported (174). All patients were shown to have evidence of at least some innervation to the detrusor pre-operatively, indicated by the presence of reflex contractions during filling or electroejaculation where no contraction occurred. The results showed that bladder emptying could be achieved in most patients and have been reproduced by other groups (175). Sauerwein subsequently modified the technique by combining it with total sacral root rhizotomy, thereby abolishing all reflex activity (176).

Transurethral electrotherapy was first described by Katona in 1958 (177) and was revisited by several groups in the 1970s to 1990s. Stimulation occurs via an electrode placed on the tip of a catheter connected to a stimulator by an intraluminal wire. The bladder is then filled with saline. A neutral electrode is connected to an area of normal sensation elsewhere on the body. The current is applied and can be varied in terms of intensity, pulse duration, etc. Activation of mechanoreceptor afferents is thought to lead to restoration of bladder sensation and thereby to sufficient activation of bladder efferents (178) rather than direct activation of myocytes. Electrotherapy was studied in different groups, including children, with neurogenic bladder (179), incomplete spinal cord injury (180), as well as patients with DU after gynecological surgery. Many reports have demonstrated enhanced bladder sensation and improved detrusor contractions; however, this has not always translated into an improvement in volitional voiding. Electrotherapy is usually conducted along intensive bladder training, which can be partially responsible for successful outcomes (181). A major drawback is the time-consuming requirements (daily sessions of 1 hour or more) and 10–15 sessions considered a trial period. There are no standardized treatment schemes and the technique remains experimental, receiving little attention in recent years.

Xu *et al.* recently studied the effect of transcutaneous low-frequency electrotherapy (LFE) in a non-randomized study of 102 women with recent onset (<8 weeks) DU due to a variety of causes (e.g. hysterectomy, rectal surgery, intravertebral disc prolapse) (182). Pressure flow studies were performed pre-treatment and patients were stratified into four groups: LFE with normal compliance, LFE with low compliance, and 2 control groups with normal and low compliance. Electrodes were placed over the 2nd sacral foramina and below the umbilicus. Each patient received two treatment sessions per day for 2 weeks. The primary outcome measures were recovery of detrusor contractility (based on parabolic detrusor contraction waveform) and method of voiding (normal, straining, or catheter). At 4 weeks post-treatment, 82% of the LFE-normal compliance group recovered contractility (parabolic

waveform + normal voiding). The overall proportion of patients needing an indwelling catheter decreased by 43%, whereas only 8% of the controls with normal compliance regained contractility. In comparison, no patients from the LFE-low compliance and control-low compliance groups had a recovery of contractility. The persistence of any effect is unknown.

Sacral neuromodulation has been used to good effect in patients with reduced contractility and poorly relaxing sphincters (183,184). Neuromodulation may work by blocking urethral inhibition of afferent signals from the bladder, resulting in restoration of transmission of afferent signals to the brain and a resumption of bladder sensation and voiding (185). Alternatively, a direct effect on bladder efferents is also possible (186). A similar picture may be seen in spasticity of the pelvic floor associated with pain, where neuromodulation may inhibit pain and enhance detrusor contraction.

## 6.7.6  Surgical

### Transurethral resection of the prostate

The outcome of TURP in men with DU was assessed by Thomas *et al.* in a study of 22 men, with a mean follow-up of 11.3 years (39). Detrusor underactivity was defined as $Q_{max}$ <15 mL/s and $P_{det}Q_{max}$ <40 cm $H_2O$, roughly corresponding to the weak contractility zone on the BCI. Patients had either undergone TURP at diagnosis, after failed conservative management, or after acute urinary retention. Eighteen patients had urodynamic data from the baseline assessment available and 16 had data at follow-up. $Q_{max}$, bladder voiding efficiency (BVE), and BCI did not change significantly, although there was a reduction in $P_{det}Q_{max}$ from 31 to 25 cm $H_2O$ (*p*=0.027), which resulted in a small decrease in the bladder outlet obstruction index. There was no significant difference in the proportion of patients reporting storage or voiding symptoms. When compared to an age-matched cohort of men with DU managed conservatively, those undergoing TURP had significantly higher PVR and significantly lower BVE, although symptomatically there was no difference. It was concluded that there was no long-term benefit of performing TURP in men with DU and that PFS are important in identifying this group of patients pre-operatively.

### Reconstructive surgery

Detrusor myoplasty was first reported in man in 1998 by Stenzl *et al.* using latissmus dorsi harvest and transfer (187). Microsurgical anastomosis of the muscle pedicle to the inferior epigastric vessels with nerve coaptation to the intercostal branch is undertaken before wrapping the muscle in a spiral arrangement around the bladder, covering approximately 75% of its surface. The muscle is then fixed to the ligamentous and fascial structures of the pelvic floor based on intra-operative considerations. The long-term outcomes of this technique have recently been reported (188). A total of 24 catheter-dependent patients with acontractile detrusors underwent the procedure with a median follow-up of 46 months. Etiologies included tethered cord syndrome, spinal cord injury, idiopathic, and acontractility post-hysterectomy. Seventeen of the 24 patients recovered the ability to spontaneously void (mean PVR=25 mL). The mean BCI increased significantly from 20.1±7.6 to 176.2±25.4 (*p*<0.001). Compliance was >50 mL/mbar in all patients and vesico-ureteric reflux was identified post-operatively. The overall complication rate was 33% and included thromboembolism, pelvic abscess, and wound infection, although this rate would seem acceptable given the complex experimental nature of the procedure. There was no long-term donor site morbidity (muscular deficit or chronic pain) reported, although this has to be interpreted with caution given the small numbers.

# 6.8 **Conclusions**

Detrusor underactivity is a frustrating diagnosis for both the patient and caregiver, with no simple or effective treatments. There is a pressing need for research across the whole spectrum of the problem, which has been largely overlooked in comparison to BPH and OAB. A major obstacle has been the wide variation in terminology and definitions used despite the ICS definition being published 10 years ago, reflecting the inadequacies of that particular definition.

It is currently not possible to distinguish DU from BOO except by PFS, which is the main reason why acquiring epidemiological data is a major challenge. Retrospective case series have provided useful information on the prevalence of DU in patients seen in clinical practice, but is hampered by the differences in definitions and diagnostic criteria. Nevertheless this data appears to show a similar distribution between the sexes, with peak prevalence in the very elderly and frail populations, where the condition frequently co-exists with DHIC.

It is clear that even basic insights into the etiopathogenesis are lacking, although it is almost certainly multifactorial and not simply due to aging or BOO. Ultrastructural changes accompanying aging and disease appear to tell part of the story. The possible roles of the afferent and efferent systems, as well as central control mechanisms, are important avenues for future study.

There is no consensus on urodynamic diagnostic criteria, which are mostly based on the BOR, and most are unvalidated.

With conservative management, men with DU appear to show no deterioration in symptoms or urodynamic parameters, whereas those operated on by way of TURP appear to gain minimal benefit from surgery. There is currently no pharmacotherapy that is effective. Preliminary studies suggest that pelvic floor physiotherapy, neuromodulation, and intra-urethral BoNT-A may be useful approaches in patients who also have non-relaxing urethral sphincters, possibly by counteracting the guarding reflex. Electrotherapy remains experimental, and a transcutaneous method would be more acceptable than trans-urethral. Detrusor myoplasty is potentially an option for younger patients that accept the risk of surgical morbidity, but expertise with this procedure is currently limited to a small number of groups worldwide.

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# C7

# Male Chronic Pelvic Pain Syndrome (CPPS)

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# Committee 7

# CONTENTS

## Male Chronic Pelvic Pain Syndrome (CPPS)

# 7.1 Introduction and Definition

Chronic pelvic pain syndrome (CPPS) in men is characterized by lower urinary tract symptoms consisting of pelvic pain and variable urinary symptoms and sexual dysfunction. Chronic pelvic pain syndrome affects approximately 7% of men and causes significant morbidity, disability, and cost. Chronic pelvic pain syndrome is differentiated from other so-called prostatitis syndromes by not being associated with positive traditional uropathogenic bacteria by employing standard microbiological techniques. The National Institutes of Health (NIH) 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/CPPS,** characterized by chronic pelvic pain symptoms and possibly voiding symptoms in the absence of UTI.

4. **Category IV: asymptomatic inflammatory prostatitis,** in which prostate inflammation exists in the absence of genitourinary tract symptoms.

This chapter will address the more common condition of category III CPPS (referred to in this International Consultation on Urological Diseases [ICUD] document as male CPPS). **The ICUD definition of male CPPS is the presence of chronic lower urinary tract symptoms (LUTS) characterized by pelvic and/or genitourinary pain as well as variable voiding, storage, and sexual symptoms in the absence of infection or other identifiable cause.** The etiology of the syndrome is being studied, but at this time, no firm conclusions on the etiology or pathogenesis can be made. The diagnosis is suspected in a man with chronic urological pelvic pain and evaluation is primarily that of exclusion based on history, physical examination, and sterile microbial cultures. Significant clinical trial activity in the past decade is leading to a more evidence-based, rather than empiric, treatment strategy that may be best described as an individualized, clinical phenotype–directed therapeutic approach.

Following ICUD recommendations and protocols, only papers published or accepted for publication in the peer-reviewed issues of journals were included in this systematic review. Papers published in non-peer–reviewed supplements were not included. For the Fukuoka 2012 Consultation, a list was obtained through the major databases covering the previous 15 years (e.g. Medline, Embase, Cochrane Library, Biosis, Science Citation Index). Search terms employed were consistent with the specific section addressed. Level of evidence and grade of recommendation were according to ICUD recommendations (2).

# 7.2  Etiology and Pathogenesis

The etiology and pathogenesis of male CPPS remains unknown. Our current working hypothesis is that there is likely a trigger event, such as infection, trauma, or even stress, that in susceptible individuals results in chronic pelvic pain. Pelvic floor dysfunction also appears to play a role in some patients. There is also a growing body of evidence that CPPS may be part of a larger systemic disease process in some men. Once established, the pain is either modulated or perpetuated by factors including psychological, inflammatory/immune, neurologic, and endocrine factors. The clinical manifestation may also be affected by the patient's social and psychological situation (**Figure 1**).

**FIGURE 1**

Proposed etiology and pathophysiology of CPPS.

ACTH: adrenocorticotropic hormone; CFS: chronic fatigue syndrome; Hx: history; IBS: irritable bowel syndrome; MCP-1: monocyte chemoattractant protein-1; MIP-1α: macrophage inflammatory protein 1-alpha; NGF: nerve growth factor; STD: sexually transmitted disease.
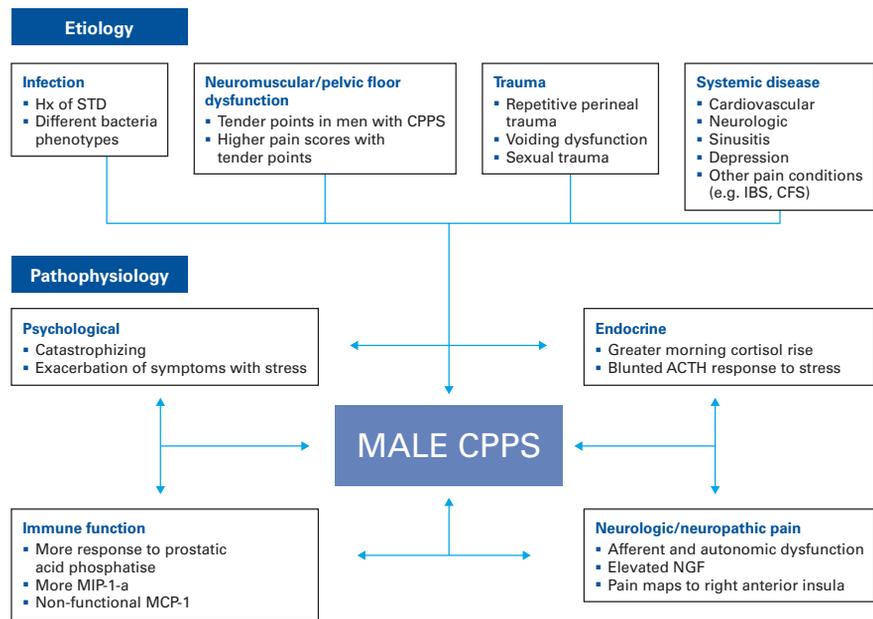


## 7.2.1  Factors which may be related to etiology

### Infection

Many studies have looked for specific infectious agent responsible for male CPPS, similar to *H. pylori* in stomach ulcers. A recent report indicates that blood samples examined for *H. pylori* antibodies were positive in 76% of men with CPPS compared with 62% in controls ($p<0.05$). Although this is significantly greater, a large number of the patients without symptoms were seropositive (3). Infection may be a trigger, as a history of STD is almost twice as common in men with CPPS compared with men without the condition, indicating a possible role for urethritis as a causative factor (4). Localizing cultures in men with CPPS and asymptomatic controls show almost identical numbers of bacteria isolated from urine, prostatic fluid, and post-prostate massage urine (5). A newer concept is that it may not be the specific type of bacteria, but that the virulence of bacteria in men with CPPS may be greater, resulting in symptoms (6–9).

### Neuromuscular/Pelvic floor dysfunction

Pain associated with CPPS in men may originate from the pelvic floor. In the Chronic Prostatitis Collaborative Research Network (CPCRN) study, 51% of men with CPPS had abdominal/pelvic tenderness compared with 7% of controls. Patients with tenderness had significantly higher NIH Chronic Prostatitis Symptom Index (NIH-CPSI) pain scores at baseline and at 1 year compared with those without tenderness (10). Physical exam can reproduce patient self-report of pelvic tenderness up to 50% of the time (11).

### Association with systemic diseases

The epidemiology of male CPPS suggests that at least in some men, it may be associated with other systemic diseases. In the NIH-sponsored Chronic Prostatitis Cohort (CPC) study, men with CPPS were six times more likely to report a history of cardiovascular disease than age-matched asymptomatic controls (4). Further investigation has revealed that men with CPPS are more likely to have evidence of increased arterial stiffness and vascular endothelial dysfunction as compared with controls (12). Men with CPPS were also five times more likely to report a history of neurologic disease, and twice as likely for sinusitis and anxiety/depression (10). A recent review of the overlap between male CPPS, interstitial cystitis/painful bladder syndrome (IC/PBS), and systemic pain conditions such as irritable bowel syndrome (IBS), fibromyalgia, and chronic fatigue syndrome (CFS) found that 21% of men with CPPS report a history of musculoskeletal, rheumatologic, or connective tissue disorder. Men with CPPS report CFS twice as often as asymptomatic controls, and 19–79% of men with CPPS report IBS or IBS symptoms (13). The conclusion from these findings is that in some men, CPPS may be part of a systemic pain syndrome, and there may be abnormalities unrelated to the pelvis that contribute to pelvic pain.

## 7.2.2    Factors which may be related to pathogenesis

### Neuropathic pain

Given that the cardinal symptom in CPPS is pain, it also makes sense that the nervous system plays a role. Nerve growth factor is a neuropeptide that plays a role in nociception and regulates the sensitivity of adult neurons to capsaicin, which excites C-fibers, in addition to mediating long-term depolarization via N-methyl-D-aspartate (NMDA) receptors. Nerve growth factor levels are higher in expressed prostatic secretions (EPS) of men with CPPS compared with controls and correlate with symptoms [15,16]. Men with CPPS have also been found to have alterations in both afferent and efferent autonomic nervous system function (17,18). There may be an anatomic basis for the pain. Using functional magnetic resonance imaging (fMRI), spontaneous pain as rated by men with CPPS maps to the right anterior insula, and correlates with clinical pain intensity (18).

### Immune function

The role of inflammation remains unclear in CPPS. The fact that men with category IIIB have pain with no inflammation makes this link questionable. In addition, in men with CPPS who have inflammation, the amount of inflammation does not correlate with symptoms (19). There is evidence, however, that autoimmunity may be a factor in some men. CD4+ T cells purified from men with CPPS are significantly more likely to recognize and become activated by part of the prostatic acid phosphatase molecule than cells from asymptomatic controls (20). Although the utility of cytokines as biomarkers has been mixed so far in CPPS, two new candidate molecules have emerged as likely

being important in this syndrome. MIP-1αα and MCP-1 have both been found in significantly greater amounts in the expressed prostatic secretions of men with CPPS compared with asymptomatic controls and men with benign prostatic hypertrophy (BPH) (21). MIP-1αα levels correlated with pain levels in these men. In addition to levels of cytokines, the function of the cytokines in men with CPPS may be a factor. MCP-1 found in men with CPPS appears to be nonfunctional and unable to mediate human monocyte chemotaxis. Also, EPS from men with CPPS inhibits cytokine activation of nuclear factor kappa-light-chain-enhancer of activated B cells through heat-sensitive proteases (22).

### Endocrine abnormalities

Abnormalities of the hypothalamic-pituitary-adrenal axis have been found in other chronic pain syndromes, and in men with CPPS. There is a significantly greater cortisol rise on awakening in men with CPPS compared with controls (23). In addition, men with CPPS have a lower baseline ACTH level and blunted ACTH rise in response to stress than men without symptoms (24).

### Psychological factors

The same biological insult in given individuals can result in different pain experiences. Greater perceived stress predicts higher pain scores (25), and men who catastrophize also have greater pain (27). There is also a psychosocial context to the presentation of pain. This includes how the individual interacts with those around him including spousal support. Solicitous responses (sympathetic) by spouses to pain increased the negative impact of pain on disability, whereas distracting responses to pain decrease the negative impact of pain on disability in men with CPPS (29).

## 7.2.3   **Summary**

There may be common underlying mechanisms that we can identify to target treating CPPS as a whole. However, we must also consider that on some level, given the apparent complexity and variation in factors described above, the pathogenesis and thus treatment of each patient with CPPS may be unique to that patient (29) (Level of Evidence [LOE] 3).

# 7.3   **Epidemiology**

## 7.3.1   **Preamble**

### Identification of studies for systemic analysis

Search terms employed (see Introduction) included: prostatitis, pelvic pain, and epidemiology. These approaches identified 179 references. After reviewing the titles and abstracts, 28 articles were identified for detailed review (**Table 1**).

**TABLE 1** Epidemiological studies of prostatitis.

| Author, year, country, reference | Population | N, age range (y) | Prevalence of prostatitis-like symptoms | Type of study conducted |
|---|---|---|---|---|
| Moon, 1997, USA (47) | National Guard | 184, 20–49 | 4.3% | Patient self-report |
| Roberts, 1998, USA (35) | Minnesota | 2,115, 40–79 | 9% | Physician diagnoses |
| Collins, 1998, USA (36) | National Ambulatory Medical Care Survey | 58,955, >18 | 5% overall Urology: 8% Primary care: 1% | Physician diagnosis database study |
| Mehik, 2000, Finland (53) | Randomly selected | 1,832, 20–59 | 14.2% | Population-based survey |
| Nickel, 2001, Canada (9) | Patients of family practitioners | 868, 20–74 | 9.70% | Population-based survey |
| Ku, 2001, South Korea (51) | Military conscripts | 16,321, 20 | 6% | Population-based survey |
| Tan, 2002, Singapore (48) | Cross-sectional study | 1,087, 20–70 | 2.70% | Population-based survey |
| Collins, 2002, USA (38) | Health care professionals without prostate cancer | 31,681, 46–81 | 16% | Patient self-report |
| Roberts, 2002, USA (39) | Random community-dwelling men, Minnesota | 1,541, 40–79 | 2.20% | Population-based survey |
| Cheah, 2003, Malaysia (33) | Random sample | 3,147, 20–50 | 8.70% | Physician diagnoses |
| Clemens, 2006, USA (40) | Managed care population | 1,550, 25–80 | 5.9% | Population based |
| Kunishima, 2006, Japan (49) | Population of men in Hokkaido, Japan | 512, 20–79 | 4.90% | Population-based survey |
| Daniels, 2007, USA (41) | Community health survey, Massachusetts | 2,301, 30–79 | 6.30% | Population-based survey |
| Marszalek, 2007, Austria (54) | Voluntary health examination, Vienna | 1,765, 20–79 | 2.70% | Physician diagnoses |
| Walz, 2007, Canada (45) | Prostate screening | 1,273, 40–89 | 10.5% | Population-based survey |
| Clemens, 2007, USA (43) | Managed care database | 120,553, 25–80 | 4.4% | Physician diagnosis database study |
| Tripp, 2008, Canada (42) | University and high school population, Canada | 246, 16–19 | 6% | Patient self-report |
| Ejike, 2008, Nigeria (55) | Cross section of Nigerian city | 1,507, 16–64 | 12.2% | Population-based survey |
| Wallner, 2009, USA (44) | Community sample | 703, 40–79 | 6.7% | Patient self-report |
| Ferris, 2009, Australia (57) | National survey | 1,373, 16–64 | 7.6% | Population based |
| Liang, 2009, China (50) | Population of Chinese men | 12,743, 15–60 | 8.40% | Population-based survey |
| Cheng, 2010, USA (46) | Managed care population | 68,675, 58 (mean age) | 6.2% | Patient self-report |
| Lan, 2011, China (52) | Community population | 5,916, 20–49 | 11.5% | Population based |
| Tripp, 2012, Kenya (56) | School population | 166, 16–19 | 13.3% | Population based |

## Criteria for including epidemiological studies

Included studies possessed at least four of the five criteria that have been outlined by Krieger *et al.* (29) for epidemiological studies of prostatitis:

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 (2). To facilitate evaluation of varied populations, the NIH-CPSI has been translated and validated for use in English (30), Spanish (31), Japanese (32), Chinese (33), Malay (33), and German (34). 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 centres.

## 7.3.2 Prevalence

We identified 24 studies that met the criteria for inclusion (**Table 2**). Of these studies, 13 were from North America (35–47), six were from Asia (33,48–52), two were from Europe (53,54), two from Africa (55,56), and one from Australia (29).

There were three types of methods to establish the diagnosis of prostatitis: 1) physician diagnosis, including large database studies looking at coding for the diagnosis; 2) patient recollection surveys; and 3) population-based surveys which employed a symptom score.

**TABLE 2** Prevalence of prostatitis by continent.

| Continent | Number of patients studied | Number with prostatitis | Prevalence % |
|---|---|---|---|
| Africa | 1,673 | 206 | 12.2 |
| Asia | 39,726 | 2,989 | 7.5 |
| Australia | 1,373 | 105 | 7.6 |
| Europe | 3,597 | 308 | 8.6 |
| North America | 290,643 | 20,144 | 6.9 |

### Prevalence from all studies
Compiling the results of all studies includes a total of 336,846 patients, with a prevalence of 7.1%. The range was from 2.2 % (11) to 16% (10). The median was 6.7%.

### Population-based studies
This represented the majority of epidemiology studies examined. Thirteen studies examined 48,824 subjects. The prevalence overall was 7.7% with a range of 2.2% (39) to 14.2% (53). The median prevalence rate was 8.4%.

### Physician diagnosis
Five studies depended on physician diagnoses of prostatitis-like symptoms, including those using large databases to extract codes made by physicians for diagnosis. The reported prevalence ranged from 2.7% (54) to 8.8% (35). The overall prevalence for these studies was 10,592 patients diagnosed out of 186,533 examined for 5.7%. The median prevalence in these studies was 8%.

### Self-report
Five studies used patient recollection of a diagnosis of prostatitis. Of 101,489 subjects, 9,388 self-reported a diagnosis of prostatitis for a prevalence of 9.3%, ranging from 4.3% (47) to 16% (38).

### By continent
The mean prevalence in studies according to continent of origin is listed in **Table 2**, ranging from 7.5% in Asia to 12.2% in Africa.

## 7.3.3   **Incidence**

One study evaluated the incidence of male CPPS in a managed care population (58). The incidence was 3.30 cases per 1,000 men per year, representing an incidence of 267,000 cases per year if these data can be extrapolated to the overall US population.

## 7.3.4   **Commentary**

These studies support the conclusion that prostatitis is an important worldwide problem that merits additional investigation. The prevalence of prostatitis-like symptoms ranged from 2.2% to 16%, with a median prevalence rate approximating 7.1%. Given that this condition is found in a relatively consistent rate across continents, it may be that this develops independent of environmental or social factors specific to a given society.

Prostatitis results in a substantial number of physician visits. The Urologic Disease in America study reported an annualized visit rate of 1,798/100,000 population for prostatitis (59). 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 have a much higher cumulative probability of subsequent episodes of prostatitis (35,60).

There are limitations to estimating the prevalence of prostatitis. A diagnosis is much more likely from a visit to a urologist than a primary care doctor, by 13-fold in one study (36). Symptom surveys do not always correlate with self-reported or physician-diagnosed prostatitis (61). This has been taken to indicate a limitation of the symptom score. However, the current clinical definition of prostatitis, or category III, is that the distinguishing feature is pain, which separates a diagnosis of CPPS from a diagnosis of LUTS or BPH. The symptom score that bases the diagnosis on the presence of pain may reflect the current diagnosis more accurately than a physician diagnosis that does not have specific criteria.

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 (33). 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 centres. We need to define the natural history and consequences of prostatitis, as well as define risk factors that may give insight into the etiology of this syndrome.

### 7.3.5 Summary

The prevalence of prostatitis-like symptoms ranges from 2.2% to 16%, with a median prevalence rate approximating 7.1% for chronic prostatitis/chronic pelvic pain syndrome (LOE 3).

# 7.4 Evaluation

Assessment of men suffering from CPPS involves a cascade of diagnostic steps, including evaluation of symptoms and associated medical conditions, physical examination including a focused pelvic and prostate assessment, and culture of specific urine samples and possibly EPS. Cystoscopy, urodynamics, and imaging studies might also be helpful to detect abnormalities in selected patients. Histological examination of prostatic biopsied tissue may have research benefit. It is hoped that specific biomarkers for male CPPS will be forthcoming and eventually be useful in the clinical assessment. The evidence and recommendations, for the most part, are based on expert review of the literature and international best practice patterns (LOE 3: Grade of Recommendation [GOR] C).

### 7.4.1 History

#### General history

Although no studies, randomized controlled trials (RCTs), or specific studies have addressed the general medical history taking in men with CPPS, it is apparent that a comprehensive history must be a primary focus of the initial encounter with a patient with chronic pelvic pain. Important information would include past medical and surgical history; allergies; other extra-pelvic chronic pain conditions (e.g. irritable bowel syndrome); smoking; drug history (past and present prescribed,

over-the-counter and illicit drugs); alcohol ingestion history; and psychological/social history. More research (described below) is available with regard to specific pain, voiding, and sexual and psychological symptoms.

## Recommendation

A comprehensive history is mandatory for the evaluation of a man with CPPS.

### The NIH-CPSI

The NIH-CPSI (**Figure 2**) has become the established international standard for symptom evaluation of men presenting with chronic pelvic pain (30). The validated NIH-CPSI has been recommended for evaluation of the characteristics of the pain (location, frequency, and severity); urination symptoms (voiding and storage); and impact of symptoms on quality of life and interference with activities (62,63) as an outcome measure for a variety of therapeutic agents for male CPPS (see Treatment section of this chapter for details of CPSI use in clinical trials) and with various definitions as a potential epidemiological tool (see Epidemiology section of this chapter). The sensitivity of the CPSI in clinical trials has been established (64). It has been translated and validated into many languages (see Epidemiology section for details). As an evaluative tool, the CPSI provides insight into the severity and frequency of symptoms relevant to male CPPS. However, while its role as a diagnostic tool has been debated (65), specific CPSI definitions of male CPPS have being employed successfully in many epidemiological studies (see Epidemiology section).

## Recommendation

The NIH-CPSI is recommended for the evaluation of symptoms in men presenting with CPPS.

**FIGURE 2**

The NIH-CPSI (30).

| | Yes | No |
|---|---|---|
| **1.** In the last week, have you experienced any pain or discomfort in the following areas? | | |
| **a.** Area between rectum and testicles (perineum) | □ **1** | □ **0** |
| **b.** Testicles | □ **1** | □ **0** |
| **c.** Tip of the penis | □ **1** | □ **0** |
| **d.** Below your waist, in your pubic or bladder area | □ **1** | □ **0** |

| | Yes | No |
|---|---|---|
| **2.** In the last week, have you experienced: | | |
| **a.** Pain or burning during urination | □ **1** | □ **0** |
| **b.** Pain or discomfort during or after sexual climax (ejaculation)? | □ **1** | □ **0** |

**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** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
| No pain | | | | | | | | Pain as bad as you can imagine | | |

**Urination**

**5.** How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?
  □ **0** Not at all                                □ **3** About half the time
  □ **1** Less than 1 time in 5                     □ **4** More than half the time
  □ **2** Less than half the time                   □ **5** Almost always

**6.** How often have you had to urinate again less than 2 hours after you finished urinating, over the last week?
  □ **0** Not at all                                □ **3** About half the time
  □ **1** Less than 1 time in 5                     □ **4** More than half the time
  □ **2** Less than half the time                   □ **5** Almost always

**7.** How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?
  □ **0** None                                      □ **2** Some
  □ **1** Only a little                             □ **3** A lot

**8.** How much did you think about your symptoms, over the last week?
  □ **0** None                                      □ **2** Some
  □ **1** Only a little                             □ **3** A lot

**Quality of life**

**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                                   □ **4** Mostly dissatisfied
  □ **2** Mostly satisfied                          □ **5** Unhappy
  □ **3** Mixed (about equally satisfied and and dissatisfied)   □ **6** Terrible

**Scoring the NIH-CPSI 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        = _____

## Sexual and ejaculatory dysfunction in male CPPS

Sexual dysfunction, premature ejaculation, decrease of libido, erectile dysfunction, and ejaculatory pain are prevalent in CPPS patients (65–67).

Patients with CPPS and persistent ejaculatory pain have more severe symptoms and are less likely to improve with time (65). However, the association of sexual dysfunction and correlation with the various CPPS phenotypes remains controversial (68–70). Yet, there is no controversy about its negative impact on quality of life and the fact that treatment of coexisting sexual dysfunction in CPPS patients is an important management issue.

## Recommendation

It is recommended that the evaluation of male patients with CPPS should include assessment of erectile dysfunction, libido, and ejaculation pain.

## Psychological and social status evaluation

Psychosocial factors are often neglected in evaluation of male CPPS in urologic practice. Depression, maladaptive coping behaviours, and anxiety/stress are prevalent in male patients with CPPS and impact on the patients' severity of symptoms and general health (71–75). Moderate and/or severe depression can be particularly debilitating for CPPS patients (76) and is believed to limit treatment success. A number of studies evaluated the presence and importance of pain catastrophizing (maladaptive coping) among men diagnosed with CPPS (26,77,78). Two further maladaptive coping behaviours identified in men with CPPS include pain contingent resting (resting instead of exercising as a coping mechanism) (26) and looking for solicitous responses from significant others (27,79).

## Summary

Evaluation of men presenting with CPPS should include addressing the involvement of relevant psychological and social factors.

## 7.4.2    Physical examination

### Digital rectal examination (DRE) and abdominal examination

No systemic review, RCTs, or clinical trials were found to contribute to the evaluation of these procedures. In a data review of 384 men with CPPS and 121 asymptomatic controls (10), overall 51% of patients with CPPS but only 7% of controls had any significant prostate tenderness on DRE. The most common site of pain was the prostate (41%), followed by the external and internal pelvic floor (13% and 14%), and the suprapubic area (9%). Extraprostatic tenderness may identify a cohort of male patients with a neuromuscular source of pain. Male CPPS patients may perceive pressure pain rather than tenderness on DRE of the prostate (80). Digital rectal exam combined with expression of expressed prostatic secretion and or a post-prostatic massage urine specimen is helpful in differential diagnosis of chronic bacterial prostatitis (see later in this section for details of prostate localization tests) and other prostate-related conditions (e.g. cancer, BPH).

## Recommendation

Examination of abdomen, external genitalia, perineum, and prostate is mandatory.

## Myofascial trigger points and musculoskeletal evaluation

Myofascial pain is prevalent in men with CPPS, either as a secondary symptom or as the primary cause of the chronic pain. Pathological tenderness of the striated muscle can be observed in many men with CPPS (11,81–84). Clinical phenotyping demonstrates pelvic tenderness to be an important component of urological CPPS (87).

## Recommendation

The assessment for myofascial trigger points and musculoskeletal pain/dysfunction is a mandatory part of the physical examination.

## 7.4.3 Microbiological and microscopic evaluation

### Culture of midstream urine

The absence of a positive urine culture for traditional uropathogens supports the diagnosis of male CPPS.

## Recommendation

Culture of midstream urine specimen is mandatory in the initial evaluation of a man presenting with a possible diagnosis of CPPS.

### Traditional microbiological evaluation of chronic prostatitis

The traditional Meares-Stamey 4-glass test (86) has been used for decades to differentiate categories II and III with an accuracy exceeding 95%, simply on the basis of uropathogenic bacterial counts in $VB_1$ (initial voided urine specimen); $VB_2$ (second voided or midstream urine specimen); EPS (during prostate massage); and $VB_3$ (third voided specimen after prostate massage of urinary white blood cell count and culture results) (**Table 3**). But clinical urologists rarely or never use the 4-glass technique (87). The 2-glass technique (pre- and post-massage test, or PPMT; **Table 3**), which is easier to perform and more cost-effective, has 91% sensitivity and specificity compared with the 4-glass test (88–90).

A case-controlled study with 463 men enrolled in the NIH-CPC study compared with that of 121 age-matched men without urinary symptoms showed a similar prevalence of positive bacterial cultures in both groups, which raised questions about the clinical usefulness of culture localization testing as a diagnostic tool for male CPPS (5,20). However, this CPPS cohort specifically excluded men with UTI or history of category II chronic bacterial prostatitis; therefore, the results cannot be extrapolated to initial clinical practice evaluation.

## Recommendation

It is recommended that patients initially presenting with CPPS symptoms undergo a 2-glass culture. While the traditional 4-glass bacterial localization culture test is not recommended for the initial evaluation of the typical patient, it can be an option in patients with a history of UTI, predominant UTI-like symptoms, UTI suggested on urinalysis, or past history of bacterial prostatitis and/or favourable response to antibiotics.

## Microbiological evaluation for non-traditional organisms

Several studies imply that the existence of potential and yet unknown infectious pathogens in the etiology of male CPPS and suggest that it may be important to identify these organisms for the diagnosis and treatment of type III prostatitis. Studies have implicated nanobacteria (91,92), coryne-form bacteria (6,9), chlamydia (93), and mycoplasma (93) species in the etiology of both prostate inflammation and prostatitis-related symptoms; however, the evidence is contradictory and far from conclusive.

## Recommendation

Culture for non-traditional pathogens is not recommended for the initial evaluation of the typical patient presenting with symptoms suggestive of CPPS.

## Semen and urethral cultures

There have been no high-level reports regarding any added value of culturing semen since the large case-control cohort study from 2003 describing no difference between cultures of semen and/or EPS/VB$_3$ (5). Semen cultures may be helpful in CPPS patients being evaluated for infertility. Cultures from the urethra appear to only add value in patients presenting with urethritis. Assessment for sexually transmitted infection (STI) may be considered for men with significant urethral symptoms and a history suggestive of an STD.

## Recommendation

Semen and urethral cultures and evaluation for STIs are not recommended for the initial evaluation of the typical man presenting with CPPS symptoms. These may be considered optional in a select number of patients.

## Urine and EPS microscopy

Microscopy of the segmented urine and EPS specimens can be used to sub-classify CPPS into inflammatory (IIIA) and non-inflammatory (IIIB) types. The number of white blood cells in VB$_3$ and EPS is compared with the number in VB$_1$ and VB$_2$ (**Table 3**). A number of controlled studies (88–90) have indicated that the 2-glass PPMT provides very high sensitivity (90%) and specificity compared with the traditional 4-glass test. There is no standardization of the number of white blood cells in the various specimens, no standardized volume/centrifugation protocol, and no standard microscopic examination technique (94). There are no studies confirming the clinical value in terms of treatment selection or response based on the microscopic evaluation of urine and prostate specimens.

# Recommendation

Until such time as the clinical usefulness of microscopic evaluation of urine and prostate-specific specimens is determined, this evaluation technique is recommended for research studies only.

**TABLE 3A** Interpretation of the Meares-Stamey 4-glass lower urinary tract localization test for chronic prostatitis and CPPS.

| Classification | Specimen | $VB_1$ | $VB_2$ | EPS | $VB_3$ |
|---|---|---|---|---|---|
| CAT II | WBC | – | +/– * | + | + |
| | Culture | – | +/– * | + | + |
| CAT IIIA | WBC | – | – | + | + |
| | Culture | – | – | – | – |
| CAT IIIB | WBC | – | – | – | – |
| | Culture | – | – | – | – |

*If uropathogenic bacteria are cultured in $VB_2$ (+), then a one log increase in the number of colony-forming units must be cultured from $VB_3$ and/or EPS in order for the diagnosis to be confirmed.

**TABLE 3B** Interpretation of the Pre- and Post-massage 2-glass lower urinary tract localization test for CPPS.

| Classification | Specimen | Pre-M | Post-M |
|---|---|---|---|
| CAT II | WBC | +/– * | + |
| | Culture | +/– * | + |
| CAT IIIA | WBC | – | + |
| | Culture | – | – |
| CAT IIIB | WBC | – | – |
| | Culture | – | – |

* If uropathogenic bacteria (+) are cultured in Pre-M, then a one log increase in the number of colony-forming units must be cultured from Post-M in order for the diagnosis to be confirmed.
CAT: Category; M: Massage; WBC: White blood cell.

### Urine cytology

Patients with CPPS presenting with storage urination symptoms (e. g. urinary frequency, urgency), bladder-related pain and/or dysuria, and/or hematuria should have a urine cytology test. Reports are available that show that these particular patients may actually have carcinoma *in situ* or bladder cancer (95).

## Recommendation

Urine cytology is recommended for all CPPS patients presenting with urinary storage symptoms, bladder-related pain and/or dysuria, and/or hematuria.

### 7.4.4  **Cystoscopy**

Bladder outflow or urethral obstruction can be found in men with CPPS. The urodynamic findings of increased detrusor pressure, decreased maximum flow rate, and increased post-void residual urine implied that the cystoscopic findings are compatible with a bladder neck dysfunction (96–98). This finding has not been replicated in other studies (101). Cystoscopy cannot been recommended as a routine procedure for initial evaluation of CPPS patients, except in selected patients with obstructed voiding symptoms non-responsive to medical therapy, unusual symptoms or clinical findings, hematuria, or other suspected lower urinary tract pathology (e.g. Hunner's lesion associated with interstitial cystitis/bladder pain syndrome (100,101).

## Recommendation

Cystoscopy is not recommended for the routine evaluation of men with male CPPS. However, cystoscopy may be indicated in selected patients with definite indications.

### 7.4.5  **Imaging**

### Ultrasound

The diagnostic role of transrectal ultrasonography in male CPPS evaluation remains debatable and ultrasound features alone cannot be used for definitive diagnoses. Colour Doppler ultrasound is believed by some to add diagnostic information, while others believe that diagnosis of prostatic calculi provides useful information (102–105). Pelvic floor muscle ultrasound has been used to show that men with CPPS had a more acute anorectal angle which correlated with greater pain report and sexual dysfunction (100,106). Trans-abdominal or pelvic ultrasound may be useful to determine post-void residual urine volumes and in patients in whom obstructive uropathy and/or other extra-prostatic causes of pelvic pain are suspected.

## Recommendation

Ultrasound is not recommended in the routine assessment of the typical man presenting with CPPS, but may be considered optional in selected cases.

## Magnetic resonance imaging (MRI)

Magnetic resonance imaging differentiation of prostatitis from cancer and other prostate disorders is difficult (107,108) and likely not helpful as a clinical tool. Magnetic resonance imaging studies provide no additional clinically useful information in the diagnosis of male CPPS.

## Recommendation

Magnetic resonance imaging studies are not recommended for the initial evaluation of men with CPPS.

### 7.4.6 Urodynamics and neurophysiological testing

A number of urodynamic studies have shown dysfunctional voiding and/or obstructive urodynamic findings in male patients with CPPS (96–98). These studies imply a potential overlap between CPPS and male lower urinary tract symptoms due to bladder neck or urethral obstruction and/or dysfunction in some, but not all, CPPS patients.

Neurophysiological testing for central sensitization in men with CPPS noted that they had significantly higher pain intensity at lower temperatures, higher peak computer-generated analogue visual analogue pain scores than controls, as well as more pronounced heat/burning sensation intensity on capsaicin thermal skin testing (17,109,110).

**Recommendation:** Urodynamic evaluation is not recommended in routine evaluation, but may be indicated in selected patients with obstructive voiding symptoms. Neurophysiological testing may have future potential in evaluation of male CPPS, but it is not recommended for the routine evaluation of the CPPS patient at this time.

# 7.5 Testing

### 7.5.1 Biopsy (histology/culture)

Prostatic inflammation is a common histopathological observation, albeit its association with men with CPPS has not yet been completely defined (111–113). Biopsies have been used to culture and identify potential uropathogens that have proven difficult to culture using standard urine and EPS cultures (166); however, this remains a research tool only.

## Recommendation

Prostate biopsies are not indicated in the evaluation of patients with CPPS.

## 7.5.2   **Biomarkers**

### Prostate-specific antigen (PSA)

One cohort, age-matched control study (114) suggested that although minor elevations in PSA and percent-free PSA were present in men with CPPS, these differences neither appeared to be clinically relevant, nor could they be used as effective biomarkers for this condition.

### Recommendation

Prostate-specific antigen is not recommended for the diagnosis of men with CPPS (and should not be done during assessment except for prostate cancer screening or if there is a clinical suspicion of prostate cancer).

### Cytokines

The following cytokines have been evaluated in serum, urine, EPS, and semen: anti-proliferative factor, heparin-binding epidermal growth factor (EGF), NGF, tumor necrosis factor alpha (TNFα), interleukin (IL)-1, IL-2, IL-6, IL-8, IL-1, IL-6, HSP70, MCP, MIP-1, interferon gamma (IFNγ), and transforming growth factor beta 1 (TGF-β1) (15,21,115–120).

Based on these studies, some of which were reasonably well controlled, it seems that a number of these cytokines (or a combination of cytokines) may prove valuable for diagnosis or evaluation of male CPPS. However, the data is not conclusive, and it would be premature to use these cytokines clinically in the standard evaluation of patients with CPPS.

### Recommendation

Cytokines are currently the subject of extensive research to determine the occurrence and levels associated with categories of CPPS, but are not presently recommended for diagnosis or evaluation.

## 7.5.3   **Clinical phenotyping (UPOINT)**

A clinical phenotype system (based on clinical categories of urinary, psychosocial, organ-specific, infection, neurologic/systemic, and tenderness [UPOINT]) has been proposed to classify patients with urologic pelvic pain to help understand the etiology and guide therapy (85,121). This system has been evaluated and validated in a number of studies (68–70). The number of positive domains correlates with symptom severity and a longer duration of symptoms with increased number of positive domains (10,145). This phenotypic approach to evaluating patients appears to have clinically important therapeutic value (121,122).

### Recommendation

It is recommended that a clinical phenotype system (e. g. UPOINT or some variation) to classify patients with CPPS be considered to guide multimodal therapy strategies.

## 7.5.4    Summary

**Table 4** outlines the ICUD recommendation for the assessment tests that are mandatory, recommended, and not recommended (optional in selected cases) for the initial evaluation of a man presenting with symptoms suggestive of a diagnosis of CPPS. **Figure 3** shows the consensus-based evaluation algorithm (LOE 3: GOR C).

**TABLE 4**    Mandatory, recommended, and not recommended evaluation tests for the typical man presenting with CPPS (LOE 3: GOR C).

| **Mandatory** |
| --- |
| History |
| Physical examination, including DRE |
| Urinalysis and culture |
| **Recommended** |
| 2–glass lower urinary tract evaluation |
| Symptom inventory or index (NIH-CPSI) |
| Sexual functioning assessment (questionnaire) |
| Flow rate |
| Residual urine determination |
| Urine cytology |
| **Not recommended (for routine initial evaluation)*** |
| 4–glass lower urinary tract evaluation |
| Semen analysis and culture |
| STI evaluation or urethral culture |
| Pressure-flow studies |
| Video urodynamics (including flow-EMG) |
| Transrectal ultrasound of the prostate (TRUS) |
| Pelvic imaging (US, CT scan, MRI) |
| Prostate-specific antigen (PSA) |

*optional in selected patients.  CT: computed tomography; EMG: electromyography; US: ultrasound.

**FIGURE 3**

Proposed evaluation of a man with CPPS.

**EVALUATION OF A MAN WITH CPPS**

**MANDATORY**

*History*
*Physical examination (DRE and pelvic floor)*
*Urinalysis, midstream culture*

Recurrent UTIs → **Cat II chronic bacterial prostatitis**
Positive culture

**RECOMMENDED**

*NIH-CPSI/sexual history*
*2-glass test*
*Cytology*
*Flow rate/residual urine*

**OPTIONAL**
(NOT RECOMMENDED for routine evaluation of typical patient diagnosed with CPPS)

| Hematuria Suspicoius cytology Obstruction | Obstruction (symptoms, flow rate, residual urine) | Urethral symptoms (discharge dysuria, penile pain) | Abnormalities suggested by other tests | Semen abnormalities (discoloured "foul semen") | Abnormal DRE > 45 years Family history or risk factors | Major psychopathology (depression, suicidal) | Bacteria localized in 2-glass test |
|---|---|---|---|---|---|---|---|
| *Cystoscopy* | *Urodynamics* | *STI assessment* | *TRUS, CAT, MRI* | *Semen culture* | *Serum PSA* | *Psychological evaluation* | *4-glass test?* |

*CAT: Computer axial tomography.*

# 7.6 **Treatment**

## 7.6.1 **Preamble**

Studies of therapy for CPPS have traditionally been hampered by lack of controls, lack of validated outcome measures, small numbers, and difficulty in defining the study population. For the 2005 Paris Consultation of the ICUD (2), only 11 studies fulfilled the criteria for evidence-based trials:

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

The intervening 7 years has seen an additional 12 studies that met these criteria (and a number that came close to meeting these very rigid criteria), although we are no closer to being able to recommend a "one-size-fits-all" treatment plan (**Table 5**). The following sections describe these evidence-based trials according to treatment category, including both high-quality, prospective, randomized, sham-controlled trials and mention of other potential treatments within the class with support that is not as strong but promising. The level of evidence and grade of recommendation for each of these interventions are listed in **Table 6**.

## TABLE 5  Summary of treatment trials that met the ICUD criteria.

| Active agent | Reference | Duration of treatment, wk | Patients, n | | Outcome assessment tool | Age mean (SD) | Total NIH-CPSI mean (SD) | Change in NIH-CPSI | | Treatment effect |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Active | Placebo | | | | Active | Placebo | |
| **Alpha-blocker** | | | | | | | | | | |
| Silodosin 8 mg vs placebo | Nickel *et al.* 2011 (135) | 12 | 45 | 54 | NIH-CPSI | 48.2 | 26.0–27.9 | −10.2 | −8.5 | 1.7 |
| Silodosin 4 mg vs placebo | | | 52 | | NIH-CPSI | | | −12.1 | | 3.6* |
| Alfuzosin vs placebo | Nickel *et al.* 2008 (136) | 12 | 138 | 134 | NIH-CPSI | 40.1 (1.4) | 24.4 (0.7) | −7.1 | −6.5 | 0.6 |
| Doxazosin vs placebo | Tugcu *et al.* 2007 (164) | 24 | 30 | 30 | NIH-CPSI | 29.1 (5.2) | 23.0 (0.4) | −12.4 | −1.0 | 11.4 |
| Tamsulosin vs placebo | Alexander *et al.* 2004 (124) | 6 | 49 | 49 | NIH-CPSI | 44.6 (3.2) | 24.8 (1.7) | −4.4 | −3.4 | 1 |
| Tamsulosin vs placebo | Nickel *et al.* 2004 (133) | 6 | 27 | 30 | NIH-CPSI | 40.8 (21–56) | 26.3 | −9.1* | −5.5 | 3.6 |
| Terazosin vs placebo | Cheah *et al.* 2003 (131) | 14 | 43 | 43 | NIH-CPSI | 35.5 (20–50) | 26.2 (1.6) | −14.3* | −10.2 | 4.1 |
| Alfuzosin vs placebo | Mehik *et al.* 2003 (134) | 24 | 17 | 20 | NIH-CPSI | 49.5 | 24.4 | −9.9* | −3.8 | 6.1 |
| **Antibiotics** | | | | | | | | | | |
| Ciprofloxacin vs placebo | Alexander *et al.* 2004 (124) | 6 | 49 | 49 | NIH-CPSI | 44.6 (3.2) | 24.8 (1.7) | −6.2 | −3.4 | 2.8 |
| Levofloxacin vs placebo | Nickel *et al.* 2003 (123) | 6 | 35 | 45 | NIH-CPSI | 56.1 (36–78) | 23.0 (1.7) | −5.4 | −2.9 | 2.5 |
| Tetracycline vs placebo | Zhou *et al.* 2008 (93) | 12 | 24 | 24 | NIH-CPSI | n.r. | 34.3 (1.2) | −18.5 | −1 | 17.5* |
| **Hormonal agents** | | | | | | | | | | |
| Finasteride vs placebo | Nickel *et al.* 2004 (149) | 24 | 33 | 31 | NIH-CPSI | 44.4 (0.5) | n.r. | −3.0 | −0.8 | 2.2 |
| Mepartricin vs placebo | de Rose *et al.* 2004 (151) | 8 | 13 | 13 | NIH-CPSI | 32–34 | 25.0 (18–45) | −15.0 | −5.0 | 10.0 |

n.r.: no response.
* Significant difference in reduction of NIH-CPSI verum versus placebo.

**TABLE 5**  Summary of treatment trials that met the ICUD criteria, *Cont'd*

| Active agent | Reference | Duration of treatment, wk | Patients, n | | Outcome assessment tool | Age mean (SD) | Total NIH-CPSI mean (SD) | Change in NIH-CPSI | | Treatment effect |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Active | Placebo | | | | Active | Placebo | |
| **Anti-inflammatories** | | | | | | | | | | |
| Rofecoxib 25 mg vs placebo | Nickel *et al.* 2003 (138) | 6 | 53 | 59 | NIH-CPSI | 46.8 (2.5) | 21.8 (1.1) | −4.9 | −4.2 | 0.7 |
| Rofecoxib 50 mg vs placebo | | | 49 | | | | | −6.2 | | 2.0 |
| Prednisolone vs placebo | Bates *et al.* 2007 (142) | 4 | 6 | 12 | NIH-CPSI | 40.8 (4.6) | 24.3 (3.0) | n.r. | n.r. | No sig. difference |
| Celecoxib vs placebo | Zhao *et al.* 2009 (139) | 6 | 32 | 32 | NIH-CPSI | n.r. | 24.4 (1.4) | −8.0 | −4.0 | 4.0* |
| **Phytotherapy** | | | | | | | | | | |
| Pollen extract (Cernilton) vs placebo | Wagenlehner *et al.* 2009 (145) | 12 | 70 | 69 | NIH-CPSI | 39.5 (8.1) | 19.8 (5.2) | −7.46 | −5.37 | 2.09* |
| Quercetin vs placebo | Shoskes *et al.* 1999 (143) | 4 | 15 | 13 | NIH-CPSI | 44.9 (5.4) | 20.6 (2.1) | −7.9 | −1.4 | 6.5* |
| **Glucosaminoglycan** | | | | | | | | | | |
| Pentosan polysulfate vs placebo | Nickel *et al.* 2005 (140) | 16 | 51 | 49 | NIH-CPSI | 39.2 (21–59) | 26.5 (1.6) | −5.9 | −3.2 | 2.7 |
| **Neuroleptics** | | | | | | | | | | |
| Pregabalin vs placebo | Pontari *et al.* 2010 (146) | 6 | 217 | 104 | NIH-CPSI | n.r. | 26.1 (5.7) | −6.5 | −4.3 | 2.2* |
| **Antibodies** | | | | | | | | | | |
| Tanezumab 20 mg vs placebo | Nickel *et al.* 2012 (165) | Single IV dose | 30 | 32 | NIH-CPSI | n.r. | n.r. | −4.26 | −2.83 | 1.43 |

n.r.: no response.
* Significant difference in reduction of NIH-CPSI verum versus placebo.

**TABLE 5**  Summary of treatment trials that met the ICUD criteria, *Cont'd*

| Active agent | Reference | Duration of treatment, wk | Patients, n | | Outcome assessment tool | Age mean (SD) | Total NIH-CPSI mean (SD) | Change in NIH-CPSI | | Treatment effect |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Active | Placebo | | | | Active | Placebo | |
| **Multimodal therapy** | | | | | | | | | | |
| Alpha-blocker vs Alpha-blocker + anti-inflammatory + muscle relaxant vs placebo | Tugcu *et al.* 2007 (164) | 24 | 30 | 30 | NIH-CPSI | 29.1 (5.2) | 23.0 (0.4) | −12.7 | −1.0 | 11.7 |
| Tamsulosin + ciprofloxacin vs placebo | Alexander *et al.* 2004 (124) | 6 | 49 | 49 | NIH-CPSI | 44.6 (3.2) | 24.8 (1.7) | −4.1 | −3.4 | 0.7 |
| Zafirlukast + doxycycline vs placebo + doxycycline | Goldmeier *et al.* 2005 (141) | 4 | 10 | 7 | NIH-CPSI | 35.9 (5.7) | n.r. | | | No sig. difference |
| **Physical therapy** | | | | | | | | | | |
| Posterior tibial nerve stimulation vs placebo | Kabay *et al.* 2009 (155) | 12 | 45 | 44 | NIH-CPSI | 37.7 (7.4) | n.r. | −13.4 | −1.4 | 12.0* |
| Acupuncture vs placebo | Lee *et al.* 2008 (157) | 10 | 44 | 45 | NIH-CPSI | 40.9–42.8 | 24.8–25.2 | −10 | −6 | 4* |
| Electroacupuncture vs placebo | Lee *et al.* 2009 (158) | 6 | 12 | 12 | NIH-CPSI | 36.4–39.8 | 25.5–26.9 | −9.5 | −3.5 | 6* |
| Extracorporal shock wave therapy vs placebo | Zimmermann *et al.* 2009 (154) | 4 | 30 | 30 | NIH-CPSI | 42–43 | 23.20–25.07 | −3.67 | −0.1 | 3.57* |

n.r.: no response.
* Significant difference in reduction of NIH-CPSI verum versus placebo.

**TABLE 6**  Therapies for CP/CPPS: NIH Category III (LOE: GOR)

| **Recommended** |
| --- |
| Alpha-blocker therapy for newly diagnosed, alpha-blocker–naïve patients who have voiding symptoms (1: C) |
| Antimicrobial therapy trial for newly diagnosed, antimicrobial-naïve patients (1: C) |
| Selected phytotherapies: Cernilton (1: B) and quercetin (2: C) |
| Multimodal therapy directed by clinical phenotype (3: B) |
| **Not recommended** |
| Alpha-blocker monotherapy, particularly in patients previously treated with alpha-blockers (1: C) |
| Anti-inflammatory monotherapy (1: B); does not refer to recommended phytotherapies |
| Antimicrobial therapy as primary therapy, particularly in patients who have previously failed treatment with antibiotics (1: C) |
| Five alpha-reductase inhibitor monotherapy (1: B); can be considered in older patients with benign prostatic hyperplasia (BPH) (2: C) |
| Minimally invasive therapies such as transurethral needle ablation (TUNA), laser therapies, etc. (3: C) |
| Invasive surgical therapies such as transurethral resection of the prostate (TURP) and radical prostatectomy (4: D) |
| **Requiring further evaluation** |
| Mepartricin |
| Low-intensity extracorporeal shock wave treatment |
| Biofeedback |
| Acupuncture |
| Electromagnetic stimulation |
| Immunomodulating agents |
| Muscle relaxants |
| Neuromodulating agents |
| Invasive neuromodulation (e.g. pudendal nerve modulation) |

## 7.6.2  Antibiotics

There are two placebo-controlled studies of quinolone antibiotics in CPPS: a trial of levofloxacin for 6 weeks (123) and a trial of ciprofloxacin (alone or in combination with tamsulosin) for 6 weeks (124). Both studies showed either a greater symptom score improvement or response rate; however, no statistical improvement in symptoms compared with placebo. The first study was underpowered and the latter study was not powered for the subset analysis of antibiotic alone.

Despite the lack of proven efficacy of empiric antibiotics in CPPS, in the absence of positive cultures, they remain commonly prescribed (125). Temporary or longer-lasting symptomatic benefit seen in prospective clinical trials (126) may be experienced by patients due to uncultured or unculturable bacterial organisms (see Evaluation section), or alternatively, due to the anti-inflammatory cytokine-blocking effects of antibiotics such as quinolones, independent of their antimicrobial properties (127,128).

Meta-analysis of antimicrobial trials (129,130) shows a small statistically significant overall benefit that may or may not be clinically significant for individual patients.

### 7.6.3    Alpha-blockers

Alpha-blockers have been used in CPPS both to treat bothersome urinary symptoms through relaxation of smooth muscle around the prostate and bladder neck and for potential analgesic modulation of alpha-receptors in the spinal cord. Several prospective, randomized, placebo-controlled studies have shown benefit in CPPS, including studies of terazosin (131), tamsulosin (132,133), alfuzosin (134), and silodosin (135). Two large NIH-sponsored studies failed to show the benefit of alpha-blockers. Alexander *et al.* (124) found no benefit with tamsulosin; however, patients enrolled may have failed prior alpha-blocker therapy and again the study was not powered for subset analysis of tamsulosin monotherapy versus placebo. Nickel *et al.* (136) studied alfuzosin in patients with shorter duration of symptoms and without prior exposure to this class of drugs, but again at 12 weeks, there was no difference between drug and placebo. A number of meta-analyses examining alpha-blockers (129,130,137) clearly indicate that there is likely an overall treatment effect measured by overall reduction of symptoms scores. However, the clinical implications in terms of actual clinically significant treatment response in individual patients remain to be clarified.

### 7.6.4    Anti-inflammatories

There have been several trials of medications whose mode of action is primarily anti-inflammatory. A study of rofecoxib showed modest benefit in symptoms at the high (50 mg) dose (138). A study of celecoxib 200 mg a day showed significant improvement in symptoms versus placebo, but this effect did not persist once the drug was stopped (139). A study of pentosan polysulfate, which is a mast cell inhibitor, showed some improvement in symptoms but not significantly better than placebo (140). A study of zafirlukast, a leukotriene antagonist, showed no benefit versus placebo (141). Finally, short-course therapy with corticosteroids did not significantly improve symptoms (142). Meta-analyses (129,130) show a possible overall small treatment effect, but questionable individual clinically significant treatment response for anti-inflammatories used as monotherapy.

### 7.6.5    Phytotherapy

Two phytochemical agents have shown efficacy in randomized, placebo-controlled trials. Quercetin, which has antioxidant and anti-inflammatory properties, improved symptoms in a small single-centre study after 4 weeks of therapy (143). Pollen extract given for 6 months improved

symptoms compared with placebo, although a non-validated outcome measure was used (144). Cernilton, a standardized pollen extract, significantly improved pain and quality of life after 12 weeks of therapy in a well-powered, multicentre, randomized, placebo-controlled trial (145).

### 7.6.6 Neuromodulatory therapy

A component of pain in CPPS may be neuropathic or central. A study of pregabalin showed no statistically significant improvement in the primary outcome of 6-point decrease in total NIH-CPSI scores between groups (146). However, there was almost a statistically significant difference in the proportion of patients with a clinically significant 6-point decrease and a significant improvement in total CPSI scores in the treatment group compared with the placebo group.

Although there appeared to be a possible treatment effect with amitriptyline in a subgroup of female patients with bladder pain syndrome, this medication has not been rigorously assessed in male CPPS.

### 7.6.7 Hormonal agents

Two underpowered, randomized, placebo-controlled trials of finasteride for 24 or 52 weeks showed more improvement with the 5-alpha reductase inhibitor therapy, but failed to show a statistically significant improvement over the placebo group (148,149). A preplanned analysis of the impact of long-term dutasteride in patients with CPPS symptoms in a prostate cancer reduction trial suggested that in an older patient group, there was some statistical and possibly clinical benefit with this intervention over the long term (150). A different hormonal agent, mepartricin, which reduces serum estrogen levels and prostatic estrogen receptors in rats, has been shown to have beneficial effects in total NIH-CPSI scores in men with CPPS in a small study (151).

### 7.6.8 Physical therapies

Many men with CPPS have associated pelvic floor spasm, and there is some evidence that pelvic floor physical therapy can alleviate symptoms associated with this spasm (152). As sham physical therapies can be challenging to blind, a multicentre, randomized study compared traditional Western massage with targeted myofascial release physical therapy in men and women with chronic pelvic pain (153). Of note, the study was not powered to detect meaningful differences, but it was a feasibility study of carrying out a multicentre, sham-controlled effort in this area. While myofascial release physical therapy resulted in significantly improved symptoms versus sham in women, there was no difference in the male patients.

Low-intensity extracorporeal shock wave treatment (ESWT) has been used in several chronic and myofascial pain conditions. A randomized, sham-controlled trial in men with CPPS showed benefit of perineal ESWT versus sham, which persisted for weeks after the final treatment (154).

A small single-centre trial of percutaneous tibial nerve stimulation versus sham showed benefit in both voiding and pain symptoms (155). Similar results were seen in a small study with electromagnetic therapy (156). In sham-controlled trials, standard acupuncture (157) or electroacupuncture (158) produced durable improvement in symptoms.

### 7.6.9 Psychological intervention

Psychosocial problems can be associated with worse pain and quality of life in CPPS patients (discussed in Etiology and Evaluation sections). Development (159) and preliminary validation (161) of a cognitive behavioural therapy program strongly suggest that psychologically based therapies may be important with patients identified with psychopathology.

### 7.6.10 Surgery

Procedures designed to treat an enlarged prostate by minimally invasive or surgical approaches have been tried in CPPS with good results in small non-randomized studies, but have failed in sham-controlled studies (160). Surgical procedures can have a role in men with symptomatic prostatic enlargement, bladder neck obstruction, urethral stricture disease, or other definitive surgical indication in addition to their CPPS, but cannot be recommended specifically for the pain of CPPS alone.

### 7.6.11 Monotherapy vs multimodal therapy vs phenotype-directed therapy

Chronic pelvic pain syndrome is a syndrome without a clear unifying pathophysiology, and patients may exhibit widely different degrees and location of pain, voiding difficulties, muscle spasm, and systemic and psychological symptoms. Failure of monotherapy, either clinically or in scientific trials, may be due to the heterogeneity of the treated population (161). Indeed, multimodal therapy may be required for patients with a combination of symptoms (162). The recently described UPOINT classification system phenotypes patients with CPPS (see Evaluation section) according to six clinically assessed and relevant domains (85,121). UPOINT (or variations of UPOINT) have proven effective in categorizing and assessing patients from several countries (68–70,163). Using multimodal therapy driven by specific presenting phenotypes may be one way to maximize clinical outcome (121,122). **Figure 4** describes a best-evidence strategy using this phenotype multimodal approach. However, the ultimate proof of this apparent clinically successful management strategy will ultimately require complex multilevel placebo and sham-controlled cohorts before high-level, evidence-based recommendation can be made.

FIGURE 4

Proposed management of a
man with a CPPS diagnosis.

**CPPS Diagnosis**

**Evaluation Algorithm**

**Urinary** — Voiding Storage → Alpha-blockers, Antimuscarinics, Diet modification

**Psychological** — Depression Catastrophizing Depression → Cognitive behavioural therapy, Anti-depression medication, Appropriate referral

**Organ-specific** — Prostate Tenderness Inflammation → Cernilton Quercetin Anti-inflammatories — Bladder Improvement with voiding → Pentosan polysulfate Quercetin Intravesical therapy (see BPS guidelines)

**Infection** — Positive cultures Antibiotic response → Antibiotics

**Neuropathic/extra-pelvic** → Gabapentinoids Amitriptyline Neuromodulation Acupuncture Pain clinic

**Tenderness** — Pelvic floor muscle pain or spasm → Pelvic floor physical therapy Biofeedback ESWT

**Sexual** — Dysfunction or pain → Sexual dysfunction Therapy (e.g. PDE-5 inhibitors)

BPS: bladder pain syndrome; PDE-5 inhibitors: phosphodiesterase type 5 inhibitors.

## 7.6.12   Summary

A review of the literature and personal experience by the members of the consensus panel lead us to a conclusion that there is no optimal therapeutic plan that can be recommended for all patients presenting with CPPS. **Table 6** describes the level of evidence and grade of recommendations decided upon by the consensus panel for the treatment of male CPPS. Our task was to make recommendations for management of the typical patient diagnosed with CPPS, but our conclusion is that there is not a typical patient with CPPS, but rather a spectrum of clinical phenotypes, perhaps based in part by a variable spectrum of etiologies and pathogenic pathways. **Figure 4** is a consensus-based attempt to provide a best-evidence, phenotype-directed, multimodal treatment algorithm.

# 7.7 Summary of Recommendations

## 7.7.1 Etiology and pathogenesis

While the etiology and pathogenesis of male CPPS remain unknown, evidence and consensus opinion suggest that a trigger event such as infection, trauma, or even stress in susceptible individuals results in chronic pelvic and pelvic floor pain modulated or perpetuated by psychological, inflammatory/immune, neurologic, and endocrine factors (LOE C: GOR D).

## 7.7.2 Epidemiology

The prevalence of prostatitis-like symptoms ranges from 2.2% to 16%, with a median prevalence rate approximating 7.1% (LOE 3: GOR C).

## 7.7.3 Evaluation

- Mandatory
  - History
  - Physical examination, including DRE
  - Urinalysis and culture

- Recommended
  - 2-glass lower urinary tract evaluation
  - Symptom inventory or index (NIH-CPSI)
  - Sexual functioning assessment (questionnaire)
  - Flow rate
  - Residual urine determination
  - Urine cytology

- Not recommended (for routine initial evaluation)*
  - 4-glass lower urinary tract evaluation
  - Semen analysis and culture
  - STI evaluation or urethral culture
  - Pressure-flow studies
  - Video urodynamics (including flow-EMG)
  - Transrectal ultrasound of the prostate (TRUS)
  - Pelvic imaging (US, CT scan, MRI)
  - Prostate-specific antigen (PSA)

  *optional in selected patients.

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(LOE 3: GOR C)

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## 7.7.4    **Treatment**

- Recommended
  - Alpha-blocker therapy for newly diagnosed, alpha-blocker–naïve patients who have voiding symptoms (LOE 1: GOR C)
  - Antimicrobial therapy trial for newly diagnosed, antimicrobial-naïve patients (LOE 1: GOR C)

  - Selected phytotherapies: Cernilton (LOE 1: GOR B) and quercetin (LOE 2: GOR C)
  - Multimodal therapy directed by clinical phenotype (LOE 3: GOR B)

- Not recommended
  - Alpha-blocker monotherapy, particularly in patients previously treated with alpha-blockers (LOE 1: GOR C)
  - Anti-inflammatory monotherapy (LOE 1: GOR B); does not refer to recommended phytotherapies
  - Antimicrobial therapy as primary therapy, particularly in patients who have previously failed treatment with antibiotics (LOE 1: GOR C)

  - Five alpha-reductase inhibitor monotherapy (LOE 1: GOR B); can be considered in older patients with BPH (LOE 2: GOR C)
  - Minimally invasive therapies such as TUNA, laser therapies, etc. (LOE 3: GOR C)
  - Invasive surgical therapies such as TURP and radical prostatectomy (LOE 4: GOR D)

- Requiring further evaluation
  - Mepartricin
  - Low-intensity extracorporeal shock wave treatment
  - Biofeedback
  - Acupuncture
  - Electromagnetic stimulation

  - Immunomodulating agents
  - Muscle relaxants
  - Neuromodulating agents
  - Invasive neuromodulation (e.g. pudendal nerve modulation)

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# C8

# Male Lower Urinary Tract Symptoms: Medical Management and New Therapeutic Targets

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# Committee 8

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### Male Lower Urinary Tract Symptoms: Medical Management and New Therapeutic Targets

# Committee 8

# 8.1 **Introduction**

## 8.1.1 **Population statistics**

The world's population is currently growing at a rate of around 1.1% per year; about 75 million people per year. The annual growth rate reached its peak in the late 1960s, when it was at 2%.

The annual growth rate is now declining, and is projected to continue to decline over the coming years, but the pace of future change is uncertain. This means that the world's population will continue to grow throughout the 21st century, but at a slower rate than in the recent past.

In 2011, the world's population crossed the 7 billion mark, and the latest United Nations projections indicate that the world's population will stabilize at just over 10 billion people after 2100. There are regions with significantly higher growth rates and others with much lower growth rates, but the population is aging at a high rate overall.

Compared to Europe, North America, and Latin America, Asia and Africa are experiencing–and will continue to experience–the highest population growth rate over the next 90 years. Over this period, the median age of the world's population will increase from 25 (2000) to 42 (2100), and the proportion of the population over the age of 65 will increase from 5%–10% to 20%–25% by 2100 (**Figures 1** and **2**) (1).

**FIGURE 1**

Increase in total world population by major area from 1950 to 2100 (1).
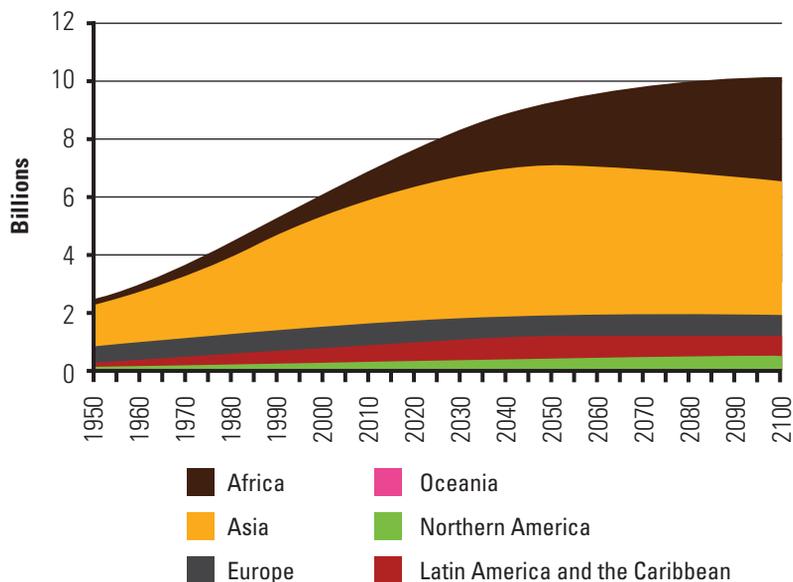
**FIGURE 2**

Percentage of the population older than 65, by major area, from 1950 to 2100 (1).



Legend:
- World
- Asia
- Europe
- Oceania
- Northern America
- Africa
- Latin America and the Caribbean
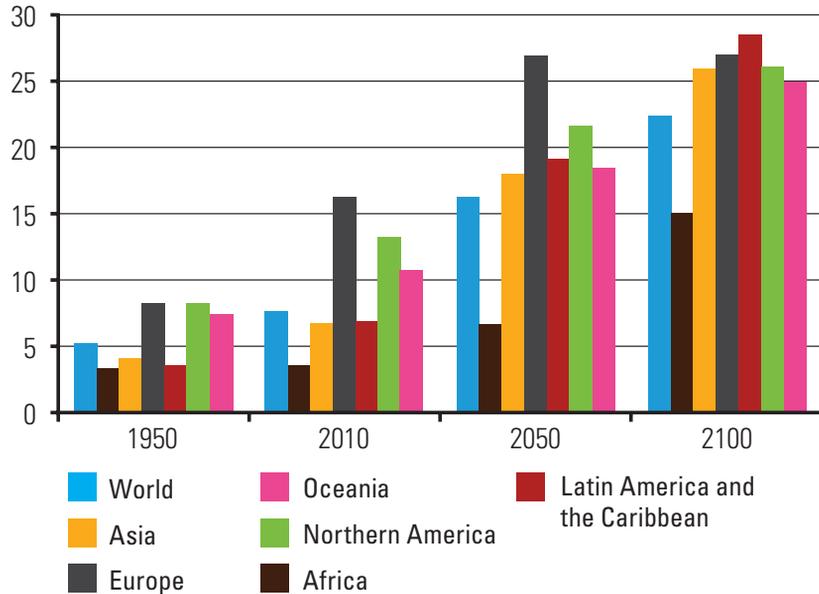
From 2010 to 2020, the population aged 65 and older will increase from 523 million to 714 million, an increase of 36%, and two-thirds of this population will live in developing countries (**Figure 3**) (2).

About half of this aging population will be men, representing an unprecedented increase in patients presenting with lower urinary tract symptoms (LUTS) and benign prostatic obstruction (BPO), as well as other diseases predominantly affecting the elderly.

**FIGURE 3**

Population aged 65 and over in developed and developing countries, by age: 2000 to 2050 (in millions) (2).



Legend:
- 80 and over
- 65 to 79
- Total 65 and over

Developed Countries

| Year | Total | 80 and over | 65 to 79 |
|------|-------|-------------|----------|
| 2000 | 171.1 | 37.4 | 133.7 |
| 2010 | 195.1 | 52.9 | 142.2 |
| 2020 | 238.2 | 64.8 | 173.4 |
| 2030 | 284.6 | 81.9 | 202.7 |
| 2040 | 312.7 | 105.3 | 207.4 |
| 2050 | 326.5 | 121.0 | 205.5 |

Developing Countries

| Year | Total | 80 and over | 65 to 79 |
|------|-------|-------------|----------|
| 2000 | 249.0 | 34.4 | 214.6 |
| 2010 | 327.8 | 53.2 | 274.6 |
| 2020 | 476.0 | 80.1 | 395.9 |
| 2030 | 689.5 | 121.0 | 568.5 |
| 2040 | 950.7 | 198.5 | 752.2 |
| 2050 | 1,175.7 | 305.3 | 870.4 |

## 8.1.2 Definitions

Historically, voiding symptoms have been defined as being related to bladder outlet obstruction (BOO), putting undue focus on the prostate as the sole source of these symptoms and leading to the outdated term "prostatism" (3). It is well recognized that voiding symptoms poorly correlate with underlying pathophysiology (4). Similar symptoms can be caused by different causes of obstruction, such as urethral stricture, or conversely, by poor function of the lower urinary tract (LUT) in circumstances in which there is impaired detrusor contractility.

Lower urinary tract symptoms are commonly related to BOO as a result of BPO, which is often associated with benign prostatic enlargement (BPE) resulting from the histological condition of benign prostatic hyperplasia (BPH), although this is not invariably the case. For example, women also commonly present with voiding symptoms (5). Failure to empty can be related either to an outlet obstruction or to detrusor underactivity of the bladder, or a combination of both.

Post-micturition symptoms, such as post-void dribbling, occur in both sexes, but more often in men, in whom these symptoms are very common and troublesome, and cause significant interference with quality of life (QOL) (6).

Storage symptoms are currently largely encompassed by the term overactive bladder (OAB) syndrome, which is defined as urgency, frequency, nocturia, and urgency incontinence (7), and which is believed to correlate with underlying detrusor overactivity. These symptoms tend to be more bothersome than do voiding symptoms, especially if they are associated with incontinence (8). In men, particularly older men with prostatic enlargement, clinicians have traditionally assumed that these symptoms are due in some way to prostatic pathology, ignoring the bladder as a possible etiology, whereas in women, these symptoms have been thought to originate exclusively from the bladder.

## 8.1.3 Prevalence of lower urinary tracts symptoms, overactive bladder, and benign prostatic hyperplasia

Lower urinary tract symptoms are measured quantitatively with standardized, validated symptom-assessment tools, of which there are many in widespread use. The most widely used tool is the International Prostate Symptom Score (IPSS), also known as the American Urological Association Symptom Index (AUA-SI), which was developed in 1992 (9–11). This index has been translated into and linguistically validated in 56 different languages, and is commonly used for LUTS/BPO research.

An ISI Web of Knowledge (Thomson Reuters, New York, NY) search performed on March 24, 2011, identified 1,192 citations of the original 1992 AUA-SI validation report in the subsequently published scientific literature, by investigators in 49 countries. The index spans from 0 to 35 points in order of increasing severity, and the original description suggested that a score of ≤ 7 represents mild symptom severity, a score of 8–18 moderate severity, and a score of >18 severe symptoms. Based on this categorization, a third or more of all men over the age of 60, in samples from four different continents, have at least moderate symptoms (**Figure 4**) (12).

**FIGURE 4**

Proportion of men by decade of life with at least moderate symptom severity, based on the validated IPSS score (12).
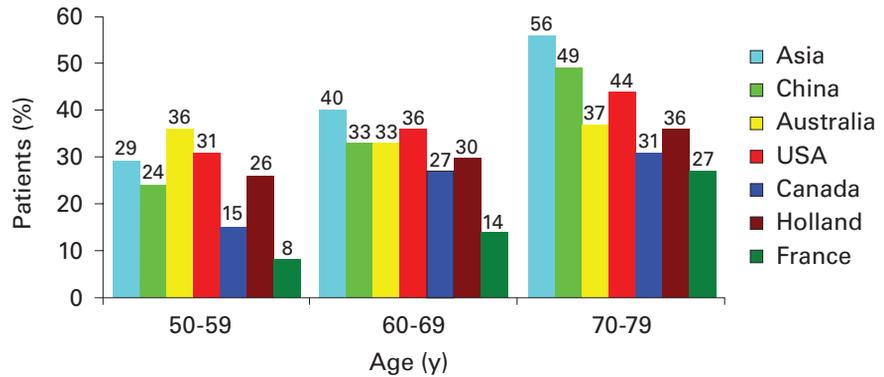


Two surveys, from 1997 and 2005 (**Figure 5**), convincingly demonstrate that OAB and storage symptoms are equally common among men and women, increasing in prevalence among both sexes at around 40–45 years of age, and reaching 20%–30% in both sexes in the late 60s and 70s, with a lifetime prevalence of 12%–17% (13,14).

**FIGURE 5**

Overactive bladder symptoms in men and women in two independent surveys (the 1997 Swedish Institute for Opinion–SIFO–Study and the 2005 Enlarged Prostate International Comparator Study–EPICS), by age category (5,13).
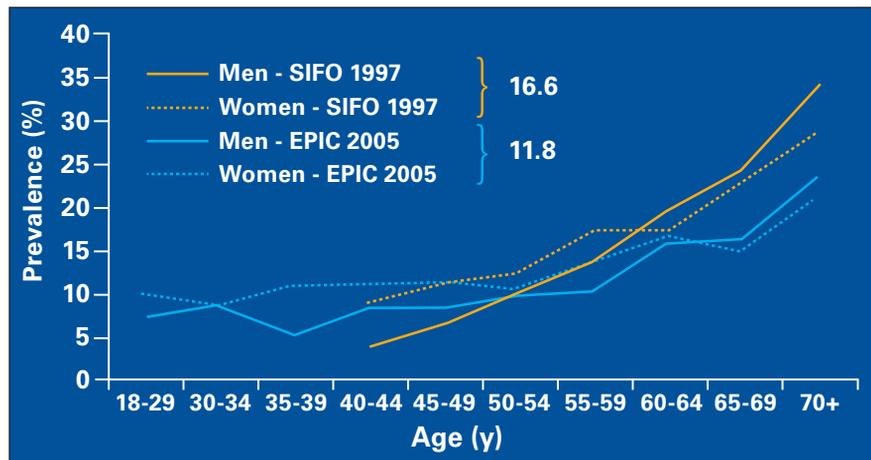


There is strong evidence regarding the histological prevalence of BPH, from autopsy studies conducted on different continents and in different ethnic groups. These data suggest a uniform linear increase in prevalence reaching nearly 90% among men in their 90s, and suggesting that about 50% of men over the age of 40 may have histological BPH; about twice the number of men with moderate to severe LUTS (by IPSS), and more than twice the number with OAB (**Figure 6**) (15).

**FIGURE 6**

Prevalence of histological BPH from various autopsy studies conducted on different continents and in different ethnic groups (15).
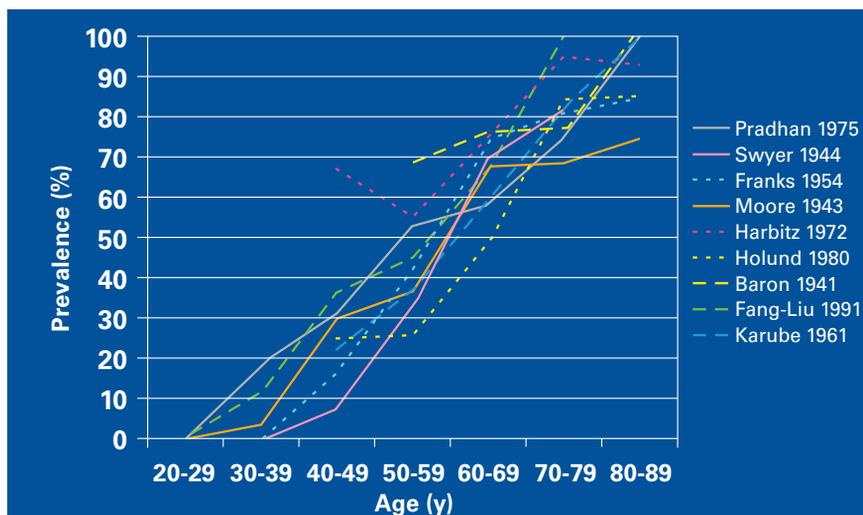


### 8.1.4  Treatment options

Medical therapy for male LUTS did not enter mainstream medical practice until the early 1990s, when alpha-adrenergic-receptor antagonists (alpha-blockers), and later, 5-alpha-reductase inhibitors (5 ARIs), were approved by the FDA and introduced into practice. Prior to this, the choices available to patients were to "do nothing," a strategy we would today call watchful waiting, or to undergo surgery, most often trans-urethral resection of the prostate (TURP), which at one time was one of the most often-performed surgical procedures in the US and other parts of the word.

The availability of effective medical therapy, direct-to-consumer outreach by pharmaceutical industries, the relative frequency of side effects with surgery, and an increasing focus on QOL have all led to a steady proportional decrease in the number of surgical procedures performed and an increase in the use of medical therapy in the US, Europe, and other parts of the world.

According to the Urologic Diseases in America project, in the year 2000, approximately 4.5 million visits were made to physician offices for a primary diagnosis of BPH, and almost 8 million visits were made with a primary or secondary diagnosis of BPH. In the same year, approximately 87,400 inpatient prostatectomies for BPO were performed in non-federal hospitals in the US. While the number of outpatient visits for BPH increased consistently during the 1990s, there was a dramatic decrease in the use of trans-urethral prostatectomy (from 136,377 in 1994), inpatient hospitalization, and length of hospital stay for this condition.

These trends reflect the changing face of the medical management of BPO–i.e. the increasing use of pharmacological agents and minimally invasive therapies. In 2000, the direct cost of BPO treatment was estimated to be $1.1 billion, excluding outpatient pharmaceuticals (**Table 1**) (16).

**TABLE 1**  Inpatient surgical procedures to treat BPH symptoms (Healthcare Cost and Utilization Project Nationwide Inpatient Sample) (16).

| Surgical Procedure | No. 1994 | No. 1996 | No. 1998 | No. 2000 |
|---|---|---|---|---|
| Open prostatectomy | 5,648 | 4,617 | 4,341 | 4,354 |
| TURP | 136,377 | 103,644 | 88,907 | 87,407 |
| Balloon dilation | 279 | 161 | 148 | 161 |
| Laser prostatectomy | 0 | 10,616 | 3,019 | 2,045 |
| TUNA | 0 | 0 | 0 | 35 |
| TUMT | 0 | 0 | 0 | 14 |

TUMT: trans-urethral microwave thermotherapy; TUNA: trans-urethral needle ablation of the prostate.

A very recent survey of about 600 urologists in the US suggested that three quarters of those who operate on BPO still perform open prostatectomy and monopolar TURP, although laser vapourization and enucleation are gaining in popularity among younger surgeons (44).

Considering the cost involved in the outpatient assessment, diagnostic work-up, and subsequent treatment of men with LUTS due to BPO or other causes, and considering the increase in the male population in a prime age group for LUTS and BPO–much of this increase occurring in developing countries with less readily and abundantly available resources–it is clear that the report of this International Consultation on Urological Diseases (ICUD) Consultation overall, as well as the report on medical management in particular, should take the cost of both evaluation and treatment into strong consideration when making recommendations.

## 8.1.5  **Outcome assessment**

Any comparison of treatments must be based on standardized, reproducible, and relatively objective measures. Outcomes of interventions for male LUTS can be categorized as either beneficial (benefits) or harmful (harms). Furthermore, they can affect the patient directly (e.g. getting up less often at night) or indirectly (e.g. having a stronger urinary flow rate), and they may be dichotomous (e.g. having an infection or not), categorical (e.g. having incontinence to a varying degree), or continuous (e.g. improving the symptom score by a certain number of points) (**Table 2**).

**TABLE 2** Beneficial and harmful changes in parameters and outcomes.

| Beneficial Changes | | | Harmful Changes |
|---|---|---|---|
| Probability of symptom improvement | D | D | Probability of symptom worsening |
| Magnitude of symptom improvement | D | Co | Magnitude of symptom worsening |
| Magnitude of bother improvement | D | Co | Magnitude of bother worsening |
| Magnitude of QOL improvement | D | Co | Magnitude of QOL worsening |
| Flow rate improvement | I | Co | Flow rate worsening |
| Residual urine volume reduction | I | Co | Residual urine volume increase |
| Prostate volume reduction | I | Co | Prostate volume increase |
| Pressure-flow parameter improvement | I | Co Ca | Pressure-flow parameter worsening |
| | D | D or Ca | Urinary incontinence |
| | D | D or Ca | Erectile dysfunction |
| | D | D | Acute urinary retention |
| | D | D | Need for treatment/surgery |
| | D | D or Ca | Hematuria |
| | D | D | Urinary tract infection |
| | D | D | Bladder stones |
| | D | D | Bladder diverticula |
| | D | D or Ca | Detrusor failure |
| | D | D or Ca | Upper tract obstruction/deterioration |
| | D | Co | Azotemia/renal failure |
| | D | D | Death |

Left-centre column – D: direct/biological outcome; I: indirect/proxy outcome.
Right-centre column – D: dichotomous outcome; Ca: categorical outcome; Co: continuous outcome.

Most medical therapy studies have been performed in the era of standardized symptom severity questionnaires (e.g. the IPSS), and thus, comparisons can be based on the magnitude of improvement in this direct treatment benefit. However, most studies also report urinary flow rate changes, and residual urine values. In longer-term studies, incidence rates of total urinary retention and need for prostate surgery play an important role.

It is therefore important to review some of the issues affecting the reporting of IPSS scores (and other continuous scales) in the literature:

- These scales are not usually open ended, (i.e. there is a worst or most severe score). Scores that start off very low at baseline can therefore not get much worse, or can only do so to a limited degree. This affects the ability to study the worsening of symptoms over time.

- Improvement (and worsening) can be expressed as an absolute value or a percentage. The absolute value of a point change on a given scale may impact a patient differently depending on the starting and ending scores. Some experts therefore advocate the use of percentage change values, thinking this will better reflect the impact of change on a scale. But reporting symptom improvement and worsening using percentages may over-emphasize worsening vs. improvement. For example, an increase in score from 6 to 18 represents a 50% worsening, but a decrease from 18 to 6 is only a 33% improvement.

- There is a very strong placebo effect in almost all LUTS outcome measures, including urinary flow rate measurement. This is in part a true placebo (doctor, white coat, office visit) effect, and in part a learning effect (urinary flow rate recording can improve with repetition). The placebo effect is part of every LUTS trial, with the magnitude being different from study to study, and likely also influenced by pre-treatment severity and by cultural and belief systems, and thus by the country in which the study is done.

- When studies use a placebo lead-in design, it is important to establish how the placebo effect was handled:
  - Was the mean value before or after the placebo lead-in used as baseline?
  - Did all patients have to re-qualify based on entry criteria? And were patients with exaggerated placebo response eliminated or not? The latter approach leads to a wider range of baseline observations, with a larger standard deviation (SD) and less statistical power.

- When comparing studies that by the nature of the intervention usually do not have a placebo lead-in (i.e. surgical or minimally invasive treatments) with those that use a placebo lead-in, the former treatment will take full credit for the placebo effect as well as the true intervention effect, but the latter only for the true intervention effect, although for the patient, the outcomes may feel the same, i.e. the same symptom severity level may be reached.

- As a general rule, nearly all studies performed by the pharmaceutical industry as part of a drug approval program have adequate and correct sample size and power calculation. Therefore, the conclusions of the trial are generally valid in the context of the predetermined statistical alpha and beta error. However, this is not true for many published investigator-initiated trials, where sample size and power calculations are often missing, and thus the strength of the conclusions is not the same.

- Treatment effect size is also of great importance. A large study with thousands of participants may show that a difference of 1 point ± an SD of 5 points is significant, but this difference is unlikely to be of clinical relevance. This topic has been the subject of some research and, at least in regards to the IPSS and the BPH impact index (BII), some guidance is available as to what constitutes a clinically meaningful change. It is often stated that an overall −3-point improvement is noticeable to patients, but the range of the required change is from −1.9 to −6.1 for

moderately to severely symptomatic patients (**Table 3**) (18). Other authors have found similar relationships: the higher the symptom score at baseline, the greater a drop is required to reach a subjective improvement threshold (19).

- Side effects are unwanted but natural and anticipated consequences of taking a particular medication. They can be, to a relative degree, inconsequential; or they may be serious, and therefore require prompt attention. An adverse drug event (ADE) is an injury resulting from the use of a drug. By this definition, the term ADE includes harm caused by the drug (i.e. adverse drug reactions–ADR– and overdoses) and harm from the use of the drug (including dose reductions and discontinuations of drug therapy). Adverse drug events may results from medication errors, but most do not. Side effects, ADEs, and ADRs are usually reported as dichotomous harmful outcomes (i.e. they either occurred or did not occur). Occasionally, they are reported as categorical outcomes (i.e. severity of the ADE or ADR). There are several problems associated with the reporting of these events in the literature:
  - The apparent incidence of these events depends on whether or not reports were elicited by letting patients report observed ADEs/ADRs spontaneously or by prompting them with a list of possible side effects, with the latter strategy resulting in higher reported incidences.
  - In most trials, these events are reported in a summary table as either the number/percent of side effects/ADEs/ADRs or as the number of patients experiencing such events. It is nearly impossible to determine from such reporting whether the side effect/ADE/ADR resolved or continued, or whether it was an early or late event with the use of the drug.
  - Because trials are usually set up to show efficacy, they are not powered to allow for statistical comparisons of the incidence rates of side effects/ADEs/ADRs for different treatment arms (and given the rarity of some of these events, a much larger sample size might be needed to show a statistical difference).

- Inclusion and exclusion criteria control enrollment into trials, and thus the mean baseline parameters (e.g. if only men with prostate volumes (PV) over 30 mL are enrolled, the average PV at the beginning of the trial will be larger compared to a trial in which all PVs are enrolled). Since some of these parameters control outcomes, it is difficult to compare outcomes such as total urinary retention between study arms of patients with different baseline PV, for example.

- The duration of trials is also important, as it provides an additional dimension to the results. The longer a trial lasts, the more side effects/ADEs/ADRs may occur. Some interventions may lose benefit over longer time periods, while others may improve over time, and some rate outcomes (such as total urinary retention) may simply not occur in shorter trials, leading to an incorrect assumption that the treatment prevents them.

There are many important factors to consider when comparing reported treatment outcomes from different trials, or even when comparing the arms of a single randomized controlled trial (RCT), but these are some of the considerations of practical importance.

**TABLE 3** Change in IPSS correlating with global subjective assessment of changes in symptoms overall and with baseline severity in 1,218 men participating in the Veteran Affairs Cooperative Study (VA COOP) trial (18).

| Subjective Changes | Overall | Moderate (8–19) | Severe (20–35) |
|---|---|---|---|
| Marked | −8.8 | −7.4 | −15.3 |
| Moderate | −5.1 | −4.0 | −8.7 |
| Slight | −3.0 | −1.9 | −6.1 |
| None | −0.7 | −0.2 | −2.0 |
| Worse | +2.7 | +3.3 | +1.2 |

## 8.1.6 Levels of evidence

It is important to be transparent as to the strength of the recommendations made in a report of this nature, and there are several systems for determining and categorizing the levels of evidence in widespread use. One such categorization is illustrated in **Figure 7**.

**FIGURE 7**

Levels of evidence pyramid (http://ebp.lib.uic.edu/nursing/node/12).



The ICUD has published a document outlining the main steps for developing and grading guideline recommendations (20).

The ICUD follows the Oxford criteria for grading the level of evidence (**Table 4**) (21).

**TABLE 4A** The ICUD/Oxford criteria for grading levels of evidence, March 2009 (21).

| Level | Therapy/ Prevention Etiology/Harm | Prognosis | Diagnosis | Differential Diagnosis/ Symptom Prevalence Study | Economic and Decision Analyses |
|---|---|---|---|---|---|
| 1a | SR (with homogeneity) of RCTs | SR (with homogeneity) of inception cohort studies; CDR validated in different populations | SR (with homogeneity) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centres | SR (with homogeneity) of prospective cohort studies | SR (with homogeneity) of Level 1 economic studies |
| 1b | Individual RCT (with narrow CI) | Individual inception cohort study with >80% follow-up; CDR validated in a single population | Validating cohort study with good reference standards; or CDR tested within one clinical centre | Prospective cohort study with good follow-up | Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses |
| 1c | All or none | All or none case-series | Absolute SpPins and SnNouts | All or none case-series | Absolute better-value or worse-value analyses |
| 2a | SR (with homogeneity) of cohort studies | SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs | SR (with homogeneity) of Level >2 diagnostic studies | SR (with homogeneity) of Level 2b and better studies | SR (with homogeneity) of Level >2 economic studies |
| 2b | Individual cohort study (including low-quality RCT; e.g. <80% follow-up) | Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR or validated on split-sample only | Exploratory cohort study with good reference standards; CDR after derivation, or validated only on split-sample or databases | Retrospective cohort study, or poor follow-up | Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses |
| 2c | Outcomes research; ecological studies | Outcomes research | | Ecological studies | Audit or outcomes research |

CDR: clinical decision rule; SnNout: a diagnostic finding whose sensitivity is so high that a negative result rules-out the diagnosis; SpPin: a diagnostic finding whose specificity is so high that a positive result rules-in the diagnosis; SR: systematic review.

**TABLE 4A**  The ICUD/Oxford criteria for grading levels of evidence, March 2009 (21), *Cont'd*

| Level | Therapy/ Prevention Etiology/Harm | Prognosis | Diagnosis | Differential Diagnosis/ Symptom Prevalence Study | Economic and Decision Analyses |
|-------|-----------------------------------|-----------|-----------|--------------------------------------------------|--------------------------------|
| 3a | SR (with homogeneity) of case-control studies | | SR (with homogeneity) of Level 3b and better studies | SR (with homogeneity) of Level 3b and better studies | SR (with homogeneity) of Level 3b and better studies |
| 3b | Individual case-control study | | Non-consecutive study; or without consistently applied reference standards | Non-consecutive cohort study, or very limited population | Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations |
| 4 | Case-series (and poor-quality cohort and case-control studies) | Case-series (and poor-quality prognostic cohort studies) | Case-control study, poor or non-independent reference standard | Case-series or superseded reference standards | Analysis with no sensitivity analysis |
| 5 | Expert opinion without explicit critical appraisal; or based on physiology, bench research, or first principles | Expert opinion without explicit critical appraisal; or based on physiology, bench research, or first principles | Expert opinion without explicit critical appraisal; or based on physiology, bench research, or first principles | Expert opinion without explicit critical appraisal; or based on physiology, bench research, or first principles | Expert opinion without explicit critical appraisal; or based on economic theory or first principles |

CDR: clinical decision rule; SnNout: a diagnostic finding whose sensitivity is so high that a negative result rules-out the diagnosis; SpPin: a diagnostic finding whose specificity is so high that a positive result rules-in the diagnosis; SR: systematic review.

**TABLE 4B**  The ICUD/Oxford criteria for grades of recommendation, March 2009 (21).

| | |
|---|---|
| A | Consistent Level 1 studies |
| B | Consistent Level 2 or 3 studies or extrapolations from Level 1 studies |
| C | Level 4 studies or extrapolations from Level 2 or 3 studies |
| D | Level 5 evidence or troublingly inconsistent or inconclusive studies of any level |

# 8.2 International Consultation on Urological Diseases: Levels of Evidence and Grades of Recommendation

Any level of evidence may be positive (the therapy works) or negative (the therapy does not work). A level of evidence is given to each individual study.

## 8.2.1 Levels of evidence

Level 1 Evidence (incorporates Oxford 1a, 1b) usually involves meta-analysis of trials (RCTs), a good-quality RCT, or all-or-none studies in which no treatment is not an option, for example, in vesico-vaginal fistula.

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

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

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

## 8.2.2 Grades of recommendation

The ICUD uses the four grades from the Oxford system. As with levels of evidence, the grades of recommendation may apply either positively (do the procedure) or negatively (do not do the procedure). Where there is disparity in the evidence (for example, if three well-conducted RCTs indicated that Drug A was superior to placebo, but the results of another RCT showed no difference), then there has to be an individual judgment as to the grade of recommendation given, and an explanation of the rationale.

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

A Grade B recommendation usually depends on consistent Level 2 and/or 3 studies, or on majority evidence from RCTs.

A Grade C recommendation usually depends on Level 4 studies or majority evidence from Level 2/3 studies or Delphi-processed expert opinion.

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

# 8.3 Phytotherapeutics, Herbal Remedies, and Natural Remedies

Phytotherapy is defined as the use of plants or plant extracts for medicinal purposes (especially plants that are not part of the normal diet). Plant extracts are complex mixtures of various components, and they are all unique, since 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.

Some of the ingredients in many plant extracts used for prostate health are common to several of the plants used, further complicating the assessment of efficacy and the determination of which ingredient is responsible for the efficacy. In addition, many products available in health food stores contain not just one, but several such extracts, plus an array of vitamins and/or trace elements, complicating the assignment of efficacy to individual components even further (**Table 5**).

**TABLE 5** The reported extracted components and suggested mechanisms of action (MOAs) of common phytotherapeutic agents.

| Origin/Name | Components | Suggested MOA |
|---|---|---|
| Serenoa *repens* = *Sabal serrulata* American dwarf palm tree, saw palmetto berry | • Free fatty acids • Phytosterols (β-sitosterol and others) • Aliphatic alcohols | • Anti-androgenic • ↓ 5-AR • ↓ Growth factor • ↓ Anti-inflammatory |
| Pygeum *africanum* African plum | • Phytosterols • Long-chain fatty acids | • ↓ bFGF- and EGF-induced fibroblast proliferation • ↓ Inflammation/edema |
| Cucurbita *pepo* pumpkin seeds | • Sterols • Carotinoids • Minerals (selenium, magnesium) | • Anti-androgenic • Anti-inflammatory |
| Secale *cereale* rye pollen | • Alpha amino acids • Phytosterols • Carbohydrates | • ↓ Urethral resistance • ± Alpha receptor • ↓ 5-AR |
| Urtica *dioica* stinging nettle | • Lectins • Phenol • Sterols • Lignans | • ↓ Growth factors • ↓ ATPase • ↓ Cell growth • Modulates SHBG |
| Hypoxis *rooperi* South African star grass | • Phytosterols (β-sitosterol and others) | • ↑ TGF-β, which enhances apoptosis • Anti-inflammatory |

bFGF: basic fibroblast growth factor; EGF: epidermal growth factor; SHBG: sex hormone–binding globulin; TGF-β: transforming growth factor beta.

Phytotherapeutic agents are not regulated by the FDA, and thus are not held to the same standards as chemically constituted drugs. While separate evaluations of each extract or mixture of extracts might be desirable, since the results of basic research and clinical trials cannot automatically be transferred from one product to another, this cannot be mandated, and is therefore not carried out in any rigorous manner. Rather than being subject to FDA guidelines, quality control of production is regulated by rules governing the food industry.

A web search (www.gopubmed.org, accessed on September 7, 2012) for the Medical Subject Headings (MeSH) term "phytotherapy" shows that there was a tremendous spike in the number of publications on this topic in the first decade of this century (**Figure 8A**) peaking at around 2,000 publications in 2007. A similar search, for "phytotherapy" and "prostate" yields about 475 publications, with a peak of 35 articles, also in 2007 (**Figure 8B**), demonstrating a strong interest on the part of physicians, researchers, and industry in conducting studies and trials and submitting them to peer review for publication in scientific journals.

FIGURE 8

The number of publications by year for a search on www.gopubmed.org on September 7, 2012 for (A) "phytotherapy" and (B) "phytotherapy" and "prostate."

**A**



Topic: Phytotherapy [mesh]

**B**



Topic: Phytotherapy [mesh] and prostate
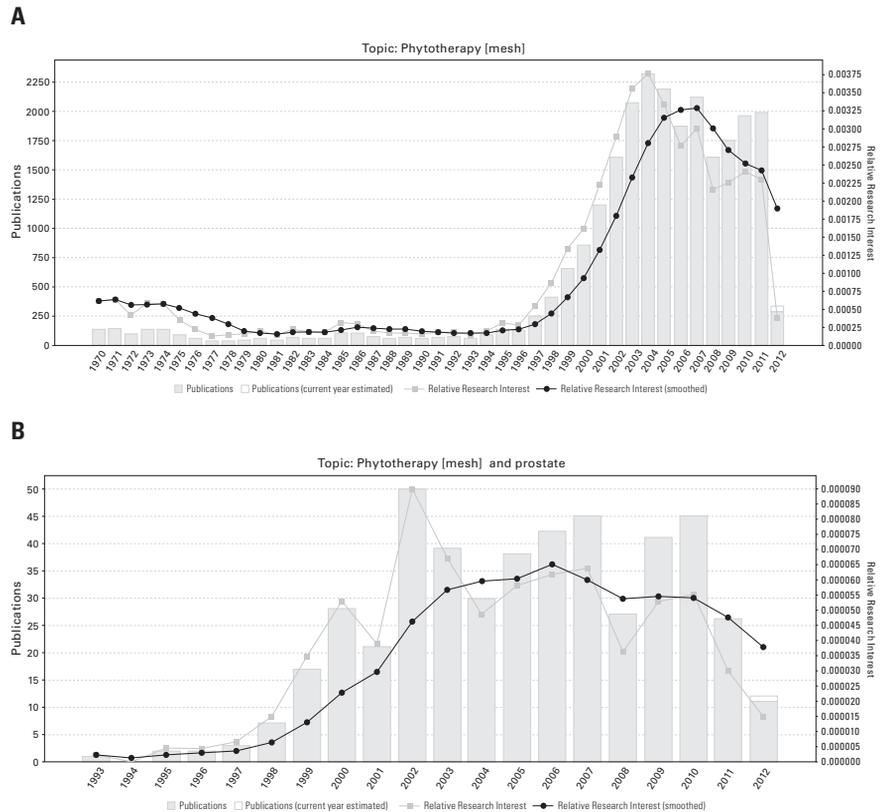
However impressive this number of publications may be, many of them–particularly the older ones–suffer from significant shortcomings, such as:

- Short duration
- No proper sample size or power calculation
- No placebo control group
- No placebo lead-in or defined washout periods
- Poorly defined or non-standardized outcome parameters
- Undue focus on just one of the many LUTS symptoms (e.g. nocturia)
- Inexplicably high effect size in certain outcome parameters, often higher than those reported with standard treatments; occasionally reporting greater-than-before-reported effect sizes for such standard treatments used as direct comparator
- Lack of pharmacology data such as absorption rates, bioavailability, serum and tissue concentration, elimination mechanisms, and serum half-life
- Use of supraphysiological doses in basic and animal experiments that cannot be duplicated in human trials

One might argue that methodological flaws in the design of individual trials either prevent successful meta-analyses and systematic review, or that the flaws of individual studies get even more exaggerated when the studies are combined in such efforts. Nonetheless, there are also high-quality individual RCTs available, as well as systematic reviews conducted by members of the Cochrane Collaboration for many of these compounds.

### 8.3.1  *Serenoa repens* (saw palmetto)

#### 8.3.1.1  **Plant of origin and composition of extracts**

The most widely used plant extract is that from the berries of the American dwarf palm tree (*Serenoa repens*), also known by the botanical name *Sabal serrulata* and colloquially as saw palmetto. The various extracts are mainly composed of free and esterified fatty acids, phytosterols, long-chain alcohols, cycloartenol, lupeol, lupenone, and methylcycloartenol. However, since the extraction procedures differ and the origin of the plant differs, individual extracts differ in their final composition.

Feifer *et al.* tested the analytical accuracy and reliability of commonly used nutritional supplements in prostate disease, and found that of six products containing saw palmetto extracts, three contained less than 20% of the stated ingredient, and one contained more than twice the stated amount (22). Habib examined the ingredients of 14 saw palmetto extracts by chromatography, and found substantial variability in their composition (**Table 6**) (23).

**TABLE 6**   Differing content of 14 brands of saw palmetto extract (23).

| Product | FFA, Mean % | Methyl and Ethyl Esters, Mean % | Long-Chain Esters, Mean % | Glycerides, Mean % | Unsaponified Matter, Mean % |
|---|---|---|---|---|---|
| Permixon | 80.7 | 2.5 | 1.36 | 6.8 | 2.27 |
| Prosteren | 74.0 | 3.7 | 1.3 | 10.8 | 2.37 |
| Saba | 70.25 | 2.85 | 1.2 | 14.4 | 2.15 |
| Rilaprost | 68.8 | 2.4 | 1.0 | 21.43 | 1.87 |
| Prostess | 68.4 | 9.5 | 1.2 | 10.6 | 2.6 |
| Sita | 62.9 | 9.35 | 1.3 | 13.45 | 2.2 |
| Quanterra prostate | 63.1 | 6.3 | 1.03 | 19.55 | 1.9 |
| Ratiopharm uno | 62.3 | 4.25 | 0.9 | 24.25 | 1.6 |
| Talso uno | 61.4 | 4.4 | 0.8 | 25.3 | 1.8 |
| Prostamol uno | 59.3 | 12.6 | 0.97 | 15.37 | 2.4 |
| Prostagutt uno | 59.2 | 9.25 | 0.85 | 19.7 | 2.0 |
| Strogen uno | 54.8 | 6.6 | 1.2 | 27.1 | 2.4 |
| Prosta-urgenine | 54.05 | 16.7 | 0.7 | 16.55 | 2.2 |
| Solaray | 40.7 | 1.5 | 0.9 | 52.15 | 1.6 |

### 8.3.1.2 Suggested mechanism(s) of action

Many MOAs of saw palmetto extracts have been suggested over time, each one with references in the literature of lesser or greater scientific veracity. These include suggestions for the following effects:

- Anti-androgenic effect (24,25)
- Inhibition of 5-alpha reductase (5-AR) types 1 and 2 (26,27)
- Inhibition of prolactin- and growth factor–induced proliferation (28,29)
- Anti-estrogenic effect
- Anti-edematous effect (30)
- Anti-inflammatory effect (29)

### 8.3.1.3 Clinical studies

#### Single-arm and placebo-controlled studies

There are more studies conducted with various extracts from the berries of *Serenoa repens* than with any other phytotherapeutic agent for male LUTS and BPO. Despite the fact that many of the older studies are of poor scientific quality, early efforts have been made to combine them in meta-analyses and systematic reviews.

Of note are the meta-analyses by Boyle *et al.* of Permixon, probably the most widely used standardized extract in Europe (31,32), as well as the original and updated systematic Cochrane reviews conducted by Wilt *et al.* (33–37). Some of the best RCTs in the field of medical therapy for male LUTS and BPH were also conducted using standardized *Serenoa repens* extracts, such that strong conclusions can be drawn regarding defined and pure extracts.

Many of the individual uncontrolled studies and RCTs found superior efficacy of the *Serenoa repens* extract, even if only in selected outcome parameters (38–46). Some of the pivotal trials testing *Serenoa repens* extracts, alone or against placebo or comparators, are discussed below.

Gerber *et al.* (42) treated 50 men with a commercially available extract. They found that while symptoms improved from $19.5 \pm 5.5$ to $12.5 \pm 7.0$ ($p<0.001$) among the 46 men who completed the study, there were no improvements in objective parameters such as serum prostate-specific antigen (PSA), maximum flow rate ($Q_{max}$), or invasive urodynamic parameters.

Willets *et al.* conducted a double-blind, placebo-controlled, randomized trial in 100 men who were randomly allocated to 320 mg *Serenoa repens* extract or placebo (paraffin oil). The main outcome measures were the IPSS, $Q_{max}$, and the Rosen International Index of Erectile Function (IIEF) questionnaire. They found no significant difference between the treatments over the 12 weeks of the study in IPSS, $Q_{max}$, or the IIEF questionnaire (46).

Bent *et al.* randomly assigned 225 men over the age of 49 years who had moderate-to-severe symptoms of BPH to 1 year of treatment with *Serenoa repens* extract (160 mg twice a day) or placebo. The primary outcome measures were change in AUA-SI scores and $Q_{max}$. They found no significant difference between the saw palmetto and placebo groups in change in AUA-SI scores (mean difference: 0.04 points; 95% confidence interval–CI: 0.93 to 1.01); $Q_{max}$ (mean difference: 0.43 mL/min; 95% CI: −0.52 to 1.38); PV, post-void residual (PVR), QOL, or serum PSA levels during the 1-year study. The incidence of adverse events was similar in the two groups (47).

The most recent trial, a dose escalation study akin to the phase 2 dose-ranging or dose-finding studies commonly conducted by the pharmaceutical industry prior to a phase 3 program, confirmed the absence of any effect of a standardized *Serenoa repens* extract. The study was a double-blind, multicentre, placebo-controlled, randomized trial at 11 North American clinical sites, conducted in 369 men aged 45 years or older, with a $Q_{max}$ of at least 4 mL/s, an AUA-SI score of between 8 and 24 at two screening visits, and no exclusions. The dosage was increased from 320 mg/day to 640 mg/day and 960 mg/day at 6 and 12 months, respectively. From baseline to 72 weeks, mean AUA-SI scores decreased from 14.42 to 12.22 points (−2.20 points; 95% CI: −3.04 to −0.36) with saw palmetto extract, and from 14.69 to 11.70 points (−2.99 points; 95% CI: −3.81 to −2.17) with placebo (**Table 7**). The group mean difference in AUA-SI score change from baseline to 72 weeks between the saw palmetto extract and placebo groups was 0.79 points favouring placebo (Upper bound of the one-sided 95% CI most favourable to saw palmetto extract: 1.77 points, one-sided $p$=0.91). Saw palmetto extract was no more effective than placebo for any secondary outcome. No clearly attributable adverse events were identified (48).

**TABLE 7** Change in primary and secondary outcome measures from baseline to week 72 (48).

| Outcome Measure | Saw Palmetto Extract (*n*=176) | | | Placebo (*n*=181) | | | 1-Sided *P* Value |
|---|---|---|---|---|---|---|---|
| | Baseline Mean | Week 72 Mean | Mean Difference (95% CI) | Baseline Mean | Week 72 Mean | Mean Difference (95% CI) | |
| **Primary** | | | | | | | |
| AUA-SI score | 14.42 | 12.22 | −2.20 (−3.04 to −0.36) | 14.69 | 11.70 | −2.99 (−3.81 to −2.17) | 0.91 |
| **Secondary** | | | | | | | |
| BII | 3.43 | 2.62 | −0.81 (−1.16. to −0.46) | 3.70 | 2.47 | −1.23 (−1.60 to −0.87) | 0.95 |
| AUA-SI QOL | 3.20 | 2.86 | −0.34 (−0.52 to −0.16) | 3.23 | 2.74 | −0.49 (−0.67 to −0.31) | 0.87 |
| AUA-SI Nocturia | 2.09 | 1.84 | −0.36 (−0.72 to 0) | 2.26 | 1.78 | −0.15 (−0.44 to 0.13) | 0.19 |
| $Q_{max}$, mL/s | 15.03 | 14.84 | −0.18 (−1.07 to 0.70) | 14.78 | 13.99 | −0.79 (−1.58 to 0) | 0.84 |
| PVR, mL* | 37.5 | 44.5 | 4.78 (−30.00 to 52.00) | 43.00 | 42.00 | 1.17 (−33.00 to 34.00) | 0.31* |
| PSA level, ng/mL | 2.20 | 2.41 | 0.32 (−0.08 to 0.73) | 1.93 | 2.07 | −0.19 (−0.53 to 0.14) | 0.97 |

ICS: International Continence Society; MSHQ-EjD: Male Sexual Health Questionnaire-Ejaculatory Dysfunction; NIH-CPSI: National Institutes of Health Chronic Prostatitis Symptom Index.
*Median (interquartile range) are shown; *p* value based on Wilcoxon rank sum test.

**TABLE 7** Change in primary and secondary outcome measures from baseline to week 72 (48), *Cont'd*

| Outcome Measure | Saw Palmetto Extract (*n*=176) | | | Placebo (*n*=181) | | | 1-Sided *P* Value |
|---|---|---|---|---|---|---|---|
| | Baseline Mean | Week 72 Mean | Mean Difference (95% CI) | Baseline Mean | Week 72 Mean | Mean Difference (95% CI) | |
| IIEF scale | 18.81 | 18.29 | −0.52 (−1.63 to 0.59) | 19.92 | 18.86 | −1.06 (−2.11 to −0.02) | 0.76 |
| MSHQ-EjD scale | 10.56 | 10.18 | −0.38 (−1.04 to 0.28) | 11.18 | 11.09 | −0.09 (0.63 to 0.45) | 0.25 |
| ICS male incontinence scale score | 3.44 | 2.96 | −0.48 (−0.80 to −0.16) | 4.17 | 3.32 | −0.84 (−1.17 to −0.51) | 0.94 |
| Jenkins Sleep Dysfunction Scale score | 6.96 | 6.15 | −0.80 (−1.34 to −0.27) | 7.75 | 6.12 | −1.63 (−2.25 to −1.01) | 0.98 |
| **NIH-CPSI** | | | | | | | |
| Pain scale* | 0 | 0 | 0 (−0.08 to 0) | 0 | 0 | 0 (−1.00 to 0) | 0.20* |
| Urinary symptom scale | 4.02 | 3.67 | −0.35 (−0.67 to −0.03) | 4.27 | 3.41 | −0.86 (−1.22 to −0.49) | 0.98 |
| QOL scale | 4.45 | 3.61 | −0.85 (−1.16 to −0.53) | 4.57 | 3.49 | −1.08 (−1.39 to −0.77) | 0.85 |

ICS: International Continence Society; MSHQ-EjD: Male Sexual Health Questionnaire-Ejaculatory Dysfunction; NIH-CPSI: National Institutes of Health Chronic Prostatitis Symptom Index.
*Median (interquartile range) are shown; *p* value based on Wilcoxon rank sum test.

## Direct comparator studies

A 6-month double-blind randomized equivalence study comparing the effects of a saw palmetto extract (320 mg Permixon) with those of a 5-ARI (5 mg finasteride) enrolled 1,098 men with moderate BPH. Both Permixon and finasteride decreased IPSS (−37% and −39%, respectively), improved QOL (by 38% and 41%, respectively), and increased $Q_{max}$ (+25% and +30%, respectively, *p*=0.035), with no statistical difference in the percent of responders with a 3 mL/s improvement. Finasteride markedly decreased PV (−18%) and serum PSA levels (−41%). Permixon improved symptoms with little effect on PV (−6%) and no change in PSA levels. Permixon fared better than finasteride in a sexual function questionnaire and gave rise to fewer complaints of decreased libido and impotence (49).

A 12-month, double-blind randomized trial recruited 811 with symptomatic BPH (IPSS ≥10) in 11 European countries. After a 4-week run-in period, 704 patients were randomly assigned to either tamsulosin 0.4 mg/day (*n*=354) or Permixon 320 mg/day (*n*=350). International Prostate Symptom Score, QOL and $Q_{max}$ were evaluated at baseline and periodically for 1 year. Prostate volume and serum PSA were measured at selection and at endpoint. The endpoint analysis was performed on the per-protocol population of 542 patients (tamsulosin: *n*=273; Permixon: *n*=269). At 12 months, IPSS had decreased by 4.4 points in each group and no differences were observed in either irritative or obstructive symptom improvements. The increase in $Q_{max}$ was similar in both treatment groups (Permixon: 1.8 mL/s; tamsulosin: 1.9 mL/s). In the Permixon-treated patients, PSA remained stable, while PV decreased slightly. The two compounds were well tolerated; however, ejaculation disorders occurred more frequently in the tamsulosin group (50).

## Meta-analyses and systematic reviews

A meta-analysis was performed on all studies using the standardized and widely used extract Permixon (31,32). The updated meta-analysis included 14 randomized clinical trials and three open-label trials, for a total of 4,280 patients, the baseline characteristics of whom are shown in **Table 8**. The trials were of different sizes (22–1,100 patients) and durations (21–720 days). Nocturia and $Q_{max}$ were the two common endpoints. The statistical analysis was based on a random-effects meta-analysis. Permixon was associated with a mean (standard error–SE) reduction in the IPSS of 4.78 (0.41). The mean placebo effect on $Q_{max}$ was an increase of 1.20 (0.49) mL/s. The estimated effect of Permixon was a further increase of 1.02 (0.50) mL/s (*p*=0.042). Placebo was associated with a reduction in the mean number of nocturnal voids of 0.63 (0.14), and there was a further reduction attributable to Permixon of 0.38 (0.07) (*p*<0.001). There was some heterogeneity among the studies for nocturia; one 2-year study that involved 396 patients and showed no difference between placebo and Permixon had a large effect on the results. The changes in IPSS and $Q_{max}$ in the moderate- to long-term trials included in the meta-analysis are summarized in **Table 9**.

Wilt *et al.* performed a systematic Cochrane review that has been updated several times in the past 15 years (33–37). The early reviews found that *Serenoa repens* provided mild to moderate improvement in urinary symptoms and flow measures; provided similar improvement in urinary symptoms and flow compared to finasteride; and was associated with fewer adverse events. However, the most recent review, from 2012, came to a very different conclusion after including more recent trials by Willet (46), Bent (47), and Barry (48); stating that "*Serenoa repens* therapy does not improve LUTS or $Q_{max}$ compared with placebo in men with BPH, even at double or triple the usual dose."

**TABLE 8** Baseline characteristics in trials using *Serenoa repens* extract (51).

| Reference/Country | N | With-drawals, n (%) | Intervention Daily Dose, mg | Duration, Months | Mean Age, Years* | AUA-SI/ IPSS, Points* | $Q_{max}$, mL/s* |
|---|---|---|---|---|---|---|---|
| **Long-Term Trials (≥12 months)** | | | | | | | |
| Barry *et al.* 2006/US | 369 | 36 (10) | Serenoa *repens* extract 320–960 (×1, 2, and then 3 doses) | 18 | 61 | 14.6 | 14.9 |
| Bent *et al.* 2006/US | | | | | | | |
| Moderate-term trials (≥6 to <12 months) | 225 | 19 (8) | Serenoa *repens* extract 320 | 12 | 63 | 15.4 | 11.5 |
| Gerber *et al.* 2001/US | 95 | 6 (7) | Serenoa *repens* extract 320 | 6 | 65 | 16.2 | 11.9 |
| Bauer *et al.* 1999/ Germany, Italy | 101 | 3 (3) | Sabal extract (LG 166/S) 320 | 6 | 66 | 9.2 | 12.3 |
| **Short-Term Trials (<6 months)** | | | | | | | |
| Willetts *et al.* 2003/ Australia | 100 | 7 (7) | Serenoa *repens* extract 320 | 3 | 63 | 14–17** | 11.2 |
| Mohanty *et al.* 1999/ India | 75 | 2 (3) | Serenoa *repens* extract | 2 | – | – | 11.8 |
| Descotes *et al.* 1995/ France | 215 | 39 (18) | Permixon 320 | 2 | – | – | 12.1 |
| Braeckman *et al.* 1994/Belgium | 239 | 33 (14) | Serendar 320 | 3 | 65 | – | 10.7 |
| Löbelenz 1992/ Germany | 60 | 0 | Sabal extract 100 | 1.5 | – | – | 12.7 |
| Mattei *et al.* 1990/ Italy | 40 | 2 (5) | Talso 320 | 3 | – | – | – |
| Reece-Smith *et al.* 1986/UK | 80 | 10 (13) | Permixon 320 | 2 | 67 | – | 6.2† |
| Cukier *et al.* 1985/ France | 168 | 22 (13) | Permixon 320 | 2 | 69 | – | – |
| Tasca *et al.* 1985/Italy | 30 | 3 (10) | Permixon 320 | 2 | 62 | – | 12.1 |
| Champault *et al.* 1984/France | 110 | 16 (15) | Permixon 320 | 1 | – | – | 5.2 |
| Boccafoschi *et al.* 1983/Italy | 22 | 0 | Permixon 320 | 2 | 68 | – | 9.9 |
| Emili *et al.* 1983/Italy | 30 | 0 | Permixon 320 | 2 | – | – | 9.8 |
| Mandressi *et al.* 1983/Italy | 60‡ | 0 | Permixon 320 | 1 | – | – | – |

*Overall (*Serenoa repens* and placebo); **From graph, there was a statistically significant difference between treatment groups; †From graph; ‡three-arm trial with *Pygeum africanum*.

**TABLE 9** Changes in IPSS and $Q_{max}$ in moderate- to long-term trials using *Serenoa repens* extract (51).

| Reference | Treatments, n | Study Duration, Months | Baseline, Mean (SD)* | Endpoint, Mean (SD)* | Mean Change (SD) | Difference Between Groups (95% CI); I2** |
|---|---|---|---|---|---|---|
| **AUA-SI** | | | | | | |
| Barry *et al.* 2011 | Serenoa *repens*, 176<br>Placebo, 181 | 18 | 14.4<br>14.7 | 122<br>11.7 | –2.20 (9.1)<br>–2.99 (5.6) | 0.79<br>(–0.78 to 2.36) |
| Bent *et al.* 2006 | Serenoa *repens*, 112<br>Placebo, 113 | 12 | 15.7 (5.7)<br>15.0 (5.3) | –<br>– | –0.68 (3.7)<br>–0.12 (3.7) | 0.04<br>(–0.93 to 1.01) |
| Gerber *et al.* 2001 | Serenoa *repens*, 41<br>Placebo, 44 | 6 | 16.7 (4.9)<br>15.8 (4.8) | 12.3 (5.5)<br>13.6 (6.6) | –4.4 (5.9)<br>–22 (5.4) | –2.20<br>(–4.61 to 0.21) |
| Weighted mean difference: –0.16 (–1.45, 1.14); 52% | | | | | | |
| **$Q_{max}$ (mL/s)** | | | | | | |
| Barry *et al.* 2011 | Serenoa *repens*, 176<br>Placebo, 181 | 18 | 15.0<br>14.8 | 14.8<br>14.0 | –0.18 (6.0)<br>–0.79 (5.4) | 0.61<br>(–0.58 to 1.80) |
| Bent *et al.* 2006 | Serenoa *repens*, 112<br>Placebo, 113 | 12 | 11.4 (3.5)<br>11.6 (4.3) | –<br>– | 0.42 (3.6)<br>–0.01 (3.6) | 0.43<br>(–0.51 to 1.37) |
| Gerber *et al.* 2001 | | | | | | |
| Weighted mean difference: 0.40 (–0.30 to 1.09); 0% | | | | | | |

*If reported; **I2 test for heterogeneity: 50% or greater indicates substantial heterogeneity.

## Adverse events and adverse reactions

There is consistent evidence from various individual trials, direct comparator trials, meta-analyses, and systematic reviews that side effects, ADEs, and ADRs are no more common in the *Serenoa repens* arms compared to the placebo arms.

The Complementary and Alternative Medicine for Urological Symptoms (CAMUS) trial (48) suggests that even with dosages three times those commonly recommended, there is no increased reporting of any adverse events with *Serenoa repens* compared with placebo (**Table 10**).

**TABLE 10** Number of adverse events by treatment group in the modified intention-to-treat population (48).

| Type of Adverse Event | No. of Adverse Events | | P Value* | No. of Participants | | P Value* |
|---|---|---|---|---|---|---|
| | Saw Palmetto Extract | Placebo | | Saw Palmetto Extract | Placebo | |
| All adverse events | 530 | 476 | 0.17 | 136 | 137 | 0.80 |
| Musculoskeletal | 81 | 72 | 0.46 | 53 | 46 | 0.35 |
| Genitourinary | 58 | 59 | 0.96 | 41 | 42 | >0.99 |
| Upper respiratory tract | 54 | 60 | 0.72 | 39 | 34 | 0.43 |
| Gastrointestinal | 52 | 58 | 0.71 | 38 | 39 | >0.99 |
| Physical injury or trauma | 28 | 11 | 0.11 | 24 | 10 | 0.01 |
| Oral or dental | 26 | 14 | 0.19 | 21 | 12 | 0.10 |
| Flu-like symptoms | 19 | 15 | 0.77 | 16 | 12 | 0.43 |
| Dermatological | 17 | 26 | 0.33 | 12 | 20 | 0.20 |
| Increased PSA | 15 | 15 | 0.95 | 14 | 13 | 0.84 |
| Increased blood pressure | 14 | 6 | 0.21 | 13 | 6 | 0.10 |
| Ophthalmic | 11 | 11 | 0.95 | 8 | 9 | >0.99 |
| Abnormal serum chemistry | 11 | 10 | 0.80 | 11 | 7 | 0.34 |
| Arrhythmia | 8 | 10 | 0.72 | 8 | 10 | 0.81 |

*Based on comparison of Poisson rates; **Based on Fisher exact test.

### 8.3.1.4 Recommendations: *Serenoa repens*

1. Certain extracts of the saw palmetto berry, such as Permixon and those studied in other clinical trials, are no more effective than placebo, and their use is not recommended in men with LUTS (Level 1a).

2. Other saw palmetto extracts have been studied (alone or in combination with other ingredients) in RCTs of lower quality and in cohort studies. In some of these studies, the extracts have been found to be superior to placebo regarding specific outcomes, but this effect is not consistent. The use of these extracts is not recommended for the treatment of men with LUTS (Level 2c).

3. Extracts of the saw palmetto berry, alone or in combination with other ingredients, are generally safe (Level 2b).

### 8.3.2 *Pygeum africanum* (African plum tree)

#### 8.3.2.1 Plant of origin and composition of extracts

*Pygeum africanum* extract comes from the bark of the African plum tree (also called *Prunus africana*), a member of the Rosaceae family. The tree is an evergreen up to 150 feet tall, with red berries and hard wood used for building and red/brown bark used for medicinal purposes.

The major bark components are tannins and fat-soluble compounds, which include triterpenes (14%) such as ursolic and oleanolic acid. The lipid fraction contains 12–24 carbon fatty acids, ferulic acid esters bound to n-docosanol, and phytosterols (-sitosterol and β-sitosterone).

*Pygeum africanum* extracts have traditionally been used as an aphrodisiac, as well as for the treatment of inflammation, kidney diseases, malaria, stomachache, fever, madness, infertility, and functional symptoms of the LUT, including LUTS and BPO.

*Pygeum africanum* bark extracts are most widely used in France under the brand name Tadenan, for which there is the richest database in terms of basic and clinical studies.

#### 8.3.2.2 Suggested mechanism(s) of action

*In vitro* data indicate several effects, mostly focusing on growth-factor inhibition and some effects on detrusor function (52):

- No effect on 5-AR activity (53)
- Inhibition of basic fibroblast growth factor (bFGF)– and epidermal growth factor (EGF)-induced fibroblast proliferation (antiproliferative effect) (54,55)
- Inhibition of production of chemotactic leukotrienes and other 5-lipoxygenase metabolites (anti-inflammatory effect) (56)
- Phyto-estrogenic effects (57)
- Reduction in luteinizing hormone (LH), testosterone, and prolactin (n-docanosol) (58)
- Improvement of detrusor contractility and altered bladder function (55,59–61)

#### 8.3.2.3 Clinical studies

##### Single-arm and placebo-controlled studies

There have been several single-arm, two-arm (at two different dosages), and placebo-controlled studies performed using the *Pygeum africanum* bark extract Tadenan, using subjective and objective outcome parameters (60–63). However, most of these studies were either of limited duration, had a limited number of participants, or did not adhere to the strict guidelines recommended by the International Consultation Conferences.

##### Direct comparator studies

Abbou *et al.* reported in 1996 on a direct comparator trial with alfuzosin (64), in which 331 patients completed an 8-week study. Alfuzosin was more effective than *Pygeum africanum* with regard to $Q_{max}$, decrease of PVR, and improvement of storage symptom score.

## Meta-analysis and systematic review

In 2002, Wilt *et al.* performed a Cochrane systematic review of 18 RCTs involving 1,562 patients. Only one of the studies reported a method of treatment allocation concealment, though 17 were double blinded. The mean study duration was 64 days (range: 30 to 122 days). Many of the studies did not report results in a manner that permitted meta-analysis.

Compared to placebo, *Pygeum africanum* provided a moderately large improvement in the combined outcome of urological symptoms and flow measures, as assessed by an effect size (**Table 11**), defined as the difference of the mean change for each outcome divided by the pooled SD for each outcome (−0.8 SD; 95% CI: −1.4 to −0.3, *n*=6 studies). Men receiving *Pygeum africanum* were more than twice as likely as those receiving placebo to report an improvement in overall symptoms (relative risk–RR: 2.1; 95% CI: 1.4 to 3.1). Nocturia was reduced by 19%, PVR by 24%, and $Q_{max}$ was increased by 23% (65).

**TABLE 11** Systematic review of *Pygeum africanum* vs. placebo (65).

| Outcome or Subgroup Title | No. of Studies | No. of Participants | Statistical Method | Effect Size |
|---|---|---|---|---|
| Symptoms improvement: Overall improvement/ global assessment/physician rating | 5 | 430 | RR (Mantel-Haenszel, random, 95% CI) | 2.07 (1.40 to 3.06) |
| Nocturia (times per evening) | 3 | 325 | Mean Difference (Instrumental variable, random, 95% CI) | −0.91 (−1.95 to 0.14) |
| $Q_{max}$ (mL/s) | 4 | 363 | Mean difference (Instrumental variable, random, 95% CI) | 2.50 (0.29 to 4.71) |
| PVR (mL) | 2 | 264 | Mean difference (Instrumental variable, random, 95% CI) | −13.17 (−23.34 to −2.99) |

## Adverse events and adverse reactions

In all studies, and in the systematic review, the adverse events due to *Pygeum africanum* were mild and comparable to those associated with placebo. The overall dropout rate was 12%, and was similar between the *Pygeum africanum* (13%), placebo (11%), and other control (8%) groups (65).

### 8.3.2.4 Recommendation: *Pygeum africanum*

1. *Pygeum africanum* extracts have been found superior to placebo and inferior to active comparators in low-quality RCTs and cohort trials. Efficacy is restricted to certain select outcomes and not consistent. The use of these extracts is not recommended for the treatment of men with LUTS (Level 2c).

### 8.3.3 *Cucurbita pepo* (pumpkin seeds)

#### 8.3.3.1 Plant of origin and composition of extracts

Pumpkin seeds contain a sweet, oily substance mainly composed of linolic acid, delta-5- and delta-7-sterols, tocopherol, selenium, magnesium, and carotenoids. The extract is suggested to have an anti-androgenic and antiphlogistic MOA (66).

#### 8.3.3.2 Clinical studies

Single-arm and placebo-controlled studies

There is only a single RCT published, which enrolled 476 men who were treated for 12 months with pumpkin seed extract or placebo. The improvements in IPSS were −6.8 vs. −5.6 for active vs. placebo (drug attributable effect: −1.2), and the improvements in $Q_{max}$ were +3.9 vs. +3.3 mL/s (drug attributable effect: +0.6 mL/s) (66).

Direct comparator studies

Meta-analysis and systematic review

None

Adverse events and adverse reactions

None reported

#### 8.3.3.3 Recommendation: *Cucurbita pepo*

1. Pumpkin seeds have been studied in only one moderate-quality RCT, and have been found to be marginally superior to placebo. Their use is not recommended in men with LUTS (Level 2c).

### 8.3.4 *Secale cereale* (rye pollen)

#### 8.3.4.1 Plant of origin and composition of extracts

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, and Greece), Japan, Korea, and Argentina (67–70).

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 MOA have suggested several possible effects.

#### 8.3.4.2 Clinical studies

Single-arm and placebo-controlled studies

Becker administered 120 mg of *Secale cereale* extract daily over 12 weeks in 103 patients in a placebo-controlled study. *Secale cereale* was superior to placebo only in terms of nocturia, while it was not superior to placebo in terms of overall symptom score and $Q_{max}$ (70). Buck *et al.* administered 120 mg of *Secale cereale* extract daily over 24 weeks in 53 patients in a placebo-controlled study. Again, *Secale cereale* was only superior to placebo in terms of nocturia, and not in terms of $Q_{max}$ (67).

Dutkiewicz reported on 89 patients randomized to Cernilton or Pygeum africanum (Tadenan), and found Cernilton to be superior regarding symptoms and $Q_{max}$ (71).

Wilt *et al.* published a Cochrane systematic review of Cernilton in 2000 (72,73) and reached the following conclusions: 444 men were enrolled in two placebo-controlled and two comparative trials lasting from 12 to 24 weeks. Three of the studies used a double-blind method, although treatment allocation concealment was unclear in all. Cernilton improved self-rated urinary symptoms (percent reporting satisfactory or improving symptoms) versus placebo and Tadenan.

The weighted RR for self-rated improvement with Cernilton versus placebo was 2.40 (95% CI: 1.21 to 4. 75), and the weighted RR versus Tadenan was 1.42 (95% CI: 1.21 to 4. 75). Cernilton reduced nocturia compared with placebo and Paraprost. Versus placebo, the weighted RR was 2.05 (95% CI: 1.41 to 3.00), and versus Paraprost, the weighted mean difference was −0.40 times per evening (95% CI: −0. 73 to −0.07). Cernilton did not improve urinary flow rates, PVR, or PV compared to placebo or the comparative study agents. Adverse events were rare and mild. The withdrawal rate for Cernilton was 4.8%, compared with 2.7% for placebo and 5.2% for Paraprost.

The Cernilton trials analyzed were limited by short duration, limited number of enrollees, gaps in reported outcomes, and unknown quality of the preparations used. The comparative trials lacked a proven active control. The available evidence suggests that Cernilton is well tolerated and modestly improves overall urological symptoms, including nocturia. Additional randomized placebo- and active-controlled trials are needed to evaluate the long-term clinical effectiveness and safety of Cernilton.

However, this systematic review was withdrawn in 2011 (74).

The adverse events reported were mild and rare.

### 8.3.4.3   Recommendation: *Secale cereale*

1. Rye pollen has been studied in RCTs and cohort studies of low to moderate quality. A meta-analysis was withdrawn from the literature in 2011. Efficacy superior to placebo was reported for selected outcomes only. The use of rye pollen in men with LUTS is not recommended (Level 2c).

## 8.3.5   *Hypoxis rooperi* (South African star grass)

### 8.3.5.1   Plant of origin and composition of extracts

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 sp.* (pine), or *Picea sp.* (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 beta (TGF-β) as an apoptosis inducer is also reported. However, whether these effects play a relevant role in BPO remains uncertain (75–77).

### 8.3.5.2 **Clinical studies**
#### Single-arm and placebo-controlled studies
Several mostly positive open-label trials and RCTs were conducted using several preparations of β-sitosterol (Harzol and Azuprostat) in the 1980s (78–82).

Berges *et al.* conducted an RCT in 200 patients randomized to 20 mg Harzol (β-sitosterol) three times daily vs. placebo over 6 months. The IPSS improvement was −7.3 vs. 2.7 points, and the $Q_{max}$ improvement was +5.2 vs. 1.1 mL/s in the β-sitosterol vs. placebo groups, respectively (83). The authors also reported on an 18-month open-label follow-up study (84).

Klippel *et al.* conducted a very similar 6-month RCT in 177 patients randomized to 65 mg Azuprostat twice daily vs. placebo, and reported an IPSS improvement of −8.2 vs. −2.8 points, and a $Q_{max}$ improvement of +8.8 vs. 4.4 mL/s in the β-sitosterol vs. placebo groups, respectively (85).

#### Direct comparator studies
A randomized study comparing the stinging nettle extract Prostagutt with β-sitosterol was published in 1986 by Rugendorff *et al.*, reporting equal efficacy (81).

#### Meta-analysis and systematic review
Five hundred and nineteen men from four randomized, placebo-controlled, double-blind trials (lasting 4 to 26 weeks) were assessed. Three trials used non-glucosidic β-sitosterols and one used a preparation that contained 100% β-sitosteryl-B-D-glucoside (**Table 12**).

Beta-sitosterols improved urinary symptom scores and flow measures. The weighted mean difference in the IPSS was −4.9 points (95% CI: −6.3 to −3.5, *n*=2 studies); the weighted mean difference in $Q_{max}$ was 3.91 mL/s (95% CI: 0.91 to 6.90, *n*=4 studies); and the weighted mean difference in PVR was −28.62 mL (95% CI: −41.42 to −15.83, *n*=4 studies).

The trial using 100% β-sitosteryl-B-D-glucoside (WA184) showed improvement in urinary flow measures. Beta-sitosterols did not significantly reduce PV compared to placebo. Withdrawal rates for men assigned to β-sitosterol and placebo were 7.8% and 8.0%, respectively. The evidence suggests that non-glucosidic β-sitosterols improve urinary symptoms and flow measures. Their long-term effectiveness, safety, and ability to prevent BPO complications are unknown (86,87).

**TABLE 12** Systematic review of β-sitosterol vs. placebo (86).

| Outcome or Subgroup Title | No. of Studies | No. of Participants | Statistical Method | Effect Size |
|---|---|---|---|---|
| Symptom score/IPSS (points) | 2 | 342 | Mean Difference (Instrumental variable, Random, 95% CI) | −4.91 (−6.29 to −3.53) |
| Symptom score/ Boyarsky QOL scale (points) | 1 | 200 | Mean Difference (Instrumental variable, Random, 95% CI) | −4.50 (−6.05 to −2.95) |
| Patient overall evaluation of efficacy (rated very good or good) | 1 | 80 | RR (Mantel-Haenszel, Random, 95% CI) | 8.25 (3.22 to 21.13) |
| Physician overall evaluation of efficacy (rated very good or good) | 1 | 80 | RR (Mantel-Haenszel, Random, 95% CI) | 11.00 (3.67 to 32.97) |
| Nocturia (times per evening) | 1 | 80 | Mean Difference (Instrumental variable, Random, 95% CI) | −1.00 (−1.75 to −0.25) |
| $Q_{max}$ (mL/s) | 4 | 474 | Mean Difference (Instrumental variable, Random, 95% CI) | 3.91 (0.91 to 6.90) |
| $Q_{max}$ (mL/s): Sensitivity analysis | 3 | 421 | Mean Difference (Instrumental variable, Random, 95% CI) | 5.13 (2.37 to 7.89) |
| PVR (mL) | 4 | 475 | Mean Difference (Instrumental variable, Random, 95% CI) | −28.62 (−41.42 to −15.83) |
| PVR (mL): Sensitivity analysis | 3 | 422 | Mean Difference (Instrumental variable, Random, 95% CI) | −29.97 (−38.27 to −21.66) |
| PV (mL) | 2 | 216 | Mean Difference (Instrumental variable, Random, 95% CI) | −6.19 (−15.29 to 2.91) |

### Adverse events and adverse reactions

The adverse events reported were mild and rare.

### 8.3.5.3  Recommendation: *hypoxis rooperi*

1. 1.Beta-sitosterol extracts from South African star grass have been studied in RCTs and direct comparator trials, and a systematic review has been published. The studies are of moderate quality and suggest improvements in LUTS. The extracts appear to be safe. No recommendations regarding their use in men with LUTS are made, pending more high-quality RCTs (Grade D).

### 8.3.6  *Urtica dioica* (stinging nettle)

#### 8.3.6.1  Plant of origin and composition of extracts

Extracts from the roots of the stinging nettle (*Urtica dioica*) have been widely used in Germany, and there are many 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 (88–96). For example, Hirano *et al.* suggested suppression of prostatic cell metabolism and growth by inhibition of membrane Na+,K(+)-ATPase, and Hryb postulated that the binding of sex hormone–binding globulin to its receptor on prostatic membranes might be modulated (96,97).

#### 8.3.6.2  Clinical studies
##### Single-arm and placebo-controlled studies
Bodarenko reported favourable results in an open, long-term study with a combination of *Sabal* and *Urtica dioica* (98). Pavone conducted a single-arm prospective study in 320 men and found subjective improvement and benefit in 85% of them (99).

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 durations (100,101),

Metzker *et al.* reported the results of a 6-month RCT with a 6-month open-label extension, comparing Prostagutt and placebo (102). In that trial, IPSS scores changed from 18.6 to 11.1 (−7.5 points) in the active treatment group vs. 19.0 to 17.6 (−1.4 points) in the placebo group ($p=0.002$). Improvement in $Q_{max}$ was +3.2 vs. +0.4 mL/s.

Melo *et al.* performed a very small RCT of only 27 and 22 *Urtica dioica* and placebo patients, respectively. The major variables analyzed during the study were IPSS variation, $Q_{max}$, and side effects. Reduction of ≥30% and ≥50% in IPSS were the parameters used to define a clinically significant response They also analyzed ≥30% and ≥50% $Q_{max}$ increases.

After 6 months of treatment, there were no significant differences in clinical improvement potential between the phytotherapeutic combination and placebo groups. The IPSS drop of 21.6% in the phytotherapeutic group was similar to the 19.7% drop obtained in the placebo group ($p=0.928$). There was also no difference ($p=0.530$) in QOL improvement between the phytotherapeutic (9.26%) and placebo (5.98%) groups. The alterations of $Q_{max}$ followed the trend line observed in clinical data, with no significant difference ($p=0.463$) in percent increased $Q_{max}$ between the phytotherapeutic (17.2%) and placebo (13.3%) groups. The clinically significant response evaluation of clinical and urodynamic data was also similar between the groups. The combination of 25 mg Pygeum africanum and 300 mg stinging nettle extracts produced clinical and urodynamic effects similar to placebo in a group of BPH patients (90).

Lopatkin compared Prostagutt with placebo in an RCT followed by an open-label extension study (103,104). A total of 257 patients were randomized into two groups. Group 1 ($n$=129) received Prostagutt, and group 2 ($n$=128) received placebo. In a 2-week induction-blind phase of placebo, the patients received one capsule of the drug or placebo twice a day for 24 weeks, in a double-blind fashion. The double-blind phase was followed by an open control period for 24 weeks, when all patients received Prostagutt. Treatment efficacy evaluation was based on IPSS, QOL index, and urodynamic and ultrasonography evidence.

Prostagutt was superior to placebo in attenuating LUTS assessed by IPSS, and in improving obstructive and irritative symptoms. It was effective in patients with moderate and severe symptoms. Tolerance of the plant extract was good.

Two hundred and nineteen subjects participated in the follow-up. From baseline to the end of observation (Week 96), the IPSS total score was reduced by 53% ($p$<0.001), $Q_{max}$ and average flow rate (Qave) increased by 19% ($p$<0.001), and PVR decreased by 44% ($p$=0.03). The incidence of adverse events during follow-up was one in 1,181 treatment days; and in only one event a causal relationship with Prostagutt intake could not be excluded. Treatment with Prostagutt thus provides a clinically relevant benefit over a period of 96 weeks.

Safarinejad conducted a 6-month, double-blind, placebo-controlled, randomized, partial crossover, comparative trial of *Urtica dioica* with placebo in 620 patients (105). Patients were evaluated using IPSS, $Q_{max}$, PVR, serum PSA, testosterone levels, and PV. At the end of the 6-month trial, unblinding revealed that patients who initially received the placebo were switched to *Urtica dioica*. Both groups continued the medication up to 18 months.

A total of 558 patients (90%) completed the study (91% of the *Urtica dioica* group, and 86% of the placebo group). By intention-to-treat analysis, at the end of the 6-month trial, 232 of 287 patients (81%) in the *Urtica dioica* group reported improved LUTS, compared with 43 of 271 patients (16%) in the placebo group ($p$<0.001). Both IPSS and $Q_{max}$ showed greater improvement with the drug than with placebo. The IPSS went from 19.8 down to 11.8 with *Urtica dioica* and from 19.2 to 17.7 with placebo ($p$=0.002). Maximum flow rate improved by 3.4 mL/s for placebo recipients and by 8.2 mL/s for treated patients ($p$<0.05). In the *Urtica dioica* group, PVR decreased from an initial value of 73 mL to 36 mL ($p$<0.05). No appreciable change was seen in the placebo group. Serum PSA and testosterone levels were unchanged in both groups. A modest decrease in PV as measured by transrectal ultrasound (TRUS) was seen in the *Urtica dioica* group (from 40.1 mL initially to 36.3 mL; $p$<0.001). There was no change in the PV at the end of study with placebo. At the 18-month follow-up, only patients who continued therapy had a favourable treatment variables value. No side effects were identified in either group.

### Direct comparator studies

Sökeland and Albrecht conducted a 12-month RCT comparing finasteride with *Urtica dioica* (Prostagutt) in 489 patients, and found both compounds equally effective in terms of IPSS and $Q_{max}$ improvement (−5.7 vs. −4.8 points) (106).

In 2006, Engelmann *et al.* conducted an RCT to investigate the efficacy and safety of PRO 160/120 (Prostagutt forte), a fixed-combination preparation of 160 mg *Sabal* fruit extract WS 1473 and 120 mg urtica root extract WS 1031 per capsule, in comparison to the alpha1-blocker tamsulosin (CAS 106463–17–6) in LUTS caused by BPH. A total of 140 elderly out-patients suffering from LUTS caused by BPH, with an initial score ≥13 points in the IPSS, received two PRO 160/120 capsules/day or tamsulosin 0.4 mg/day, and were treated for 60 weeks, with interim visits at weeks 8, 16, 24, 36, and 48.

The primary outcome measure for efficacy was the change in IPSS total score, and the percentage of patients with an IPSS score ≤ 7 points at endpoint (responders) was analyzed as well. During 60 weeks of randomized treatment, the IPSS total score was reduced by a median of 9 points in both groups. In total, 32.4% of the patients in the PRO 160/120 group and 27.9% in the tamsulosin group were responders (test for non-inferiority of PRO 160/120: $p=0.034$; non-inferiority margin: 10%). Both drugs were well tolerated, with one adverse event in 1,514 treatment days with PRO 160/120 and one event in 1,164 days with tamsulosin. The study supports the non-inferiority of PRO 160/120 in comparison to tamsulosin in the treatment of LUTS caused by BPH (107).

## Meta-analysis and systematic review
None

## Adverse events and adverse reactions
The adverse events reported were mild and rare.

### 8.3.6.3   Recommendation: *Urtica dioica*
1. Extracts from the stinging nettle have been studied in cohort studies, moderate-quality RCTs, and direct comparator studies. These studies have shown its superiority over placebo and its equivalence with a direct comparator (finasteride). The extracts were found to be safe. No recommendations regarding use in men with LUTS are made, pending more high-quality RCTs (Grade D).

# 8.4   Alpha-Blockers

## 8.4.1   Pharmacology, mechanism of action, and effects in the lower urinary tract

Improved understanding of alpha1-adrenergic receptor ($\alpha$1AR) stress hormone receptors led to the use of $\alpha$1AR-selective blocking drugs in treating LUTS. Alpha1-adrenergic receptors bind the catecholamines adrenaline and noradrenaline; cellular responses include modulation of blood pressure and flow, neuronal activity, digestion, micturition, reproduction, pupil diameter, endocrine and metabolic processes, and behaviour.

Several key clinical studies have demonstrated the effectiveness of $\alpha$1AR blockade over other treatments, in first-line therapy, combination therapy, and extended treatment regimes.

Adrenergic receptors were originally divided into αAR and βAR categories, but the application of molecular biological methods has confirmed a total of nine adrenergic receptor subtypes: α1a (formerly named α1c), α1b, α1d, α2a, α2b, α2c, β1, β2, and β3 (**Figure 9**) (108). These subtypes are distinguished by their pharmacology, structure, and interaction(s) with second messenger systems.
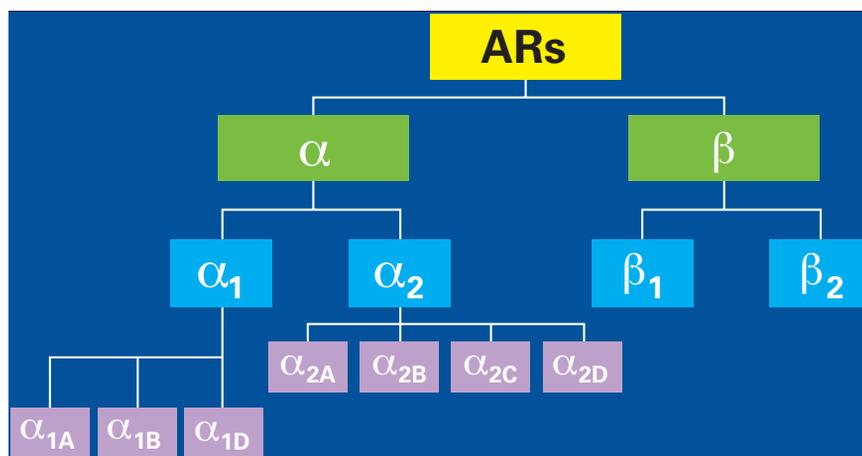
Alpha1-adrenergic receptor generally mediate their actions through members of the Gq/11 family of G proteins, which stimulate inositol phosphate (membrane phospholipid) hydrolysis, with each subtype demonstrating different efficacy of coupling to phosphoinositide hydrolysis: α1a >α1b >α1d (110).

In addition, α1AR subtypes can be pharmacologically distinguished on the basis of differential binding to alpha1-blockers, as well as differential inactivation by the alkylating agent chloroethylclonidine (111,112). A concise review of α1AR subtype signalling has been published by Hawrylyshyn *et al.* (110).

Although α1ARs are consistently found in specific organs and tissues, there is great variability across species (species heterogeneity) regarding which α1AR subtype is present in a given tissue. All three α1AR subtypes exist in a wide range of human tissues. The α1aAR subtype shows the highest levels of expression in the human liver, followed by slightly lower levels in the heart, cerebellum, and cerebral cortex; the α1bAR subtype has the highest expression in the spleen, kidney, and fetal brain; whereas the α1dAR has the highest levels in the cerebral cortex and aorta (**Figure 10**) (113).
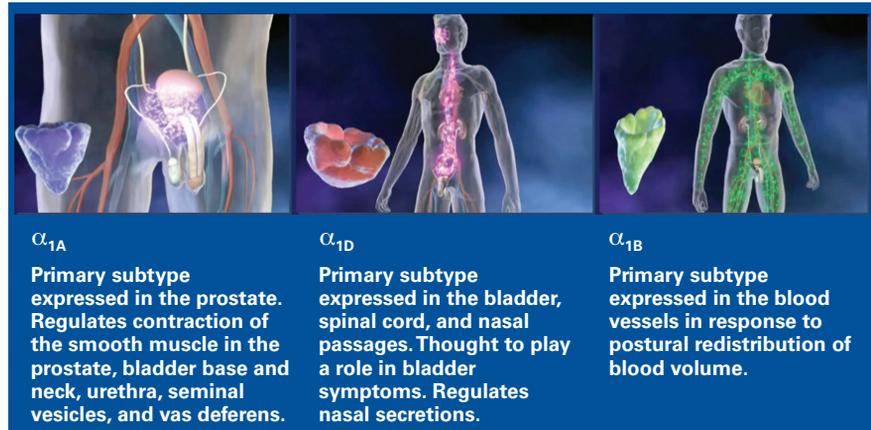
In terms of LUTS, $\alpha$1AR expression in the prostate, urethra, spinal cord, and bladder is important. Molecular and contraction studies in human prostate tissue demonstrate that the $\alpha$1aAR subtype functionly predominates in prostate stroma, despite demonstration of both $\alpha$1aAR and $\alpha$1dAR messenger ribonucleic acid (mRNA) (114).

Because baseline tone is present in prostate smooth muscle (due to its rich sympathetic innervation), blockade of prostate $\alpha$1aARs results in the relaxation of prostate smooth muscle. Hence, $\alpha$1AR blockade is capable of modifying the dynamic (prostate smooth muscle contraction) component in BPO.

Another tissue important in LUTS is the urethra. To date, most studies show that all regions of the human urethra (including the bladder neck and intraprostatic urethra) contain only $\alpha$1aARs. Because of reflex arcs, spinal cord $\alpha$1AR expression may be important in LUTS. Expression of $\alpha$1ARs in the human spinal cord has been detected by in situ ribonucleic acid (RNA) hybridization and RNA hybridization techniques in tissue slices (to maintain anatomic structure), with $\alpha$1dAR mRNA expression predominating over $\alpha$1aAR and $\alpha$1bAR at all spinal cord levels (115).

The important role of the bladder in symptoms associated with LUTS is now recognized. Normal detrusor (bladder smooth muscle tissue), obtained from surgical patients, expresses predominantly $\alpha$1dARs, although other subtypes are present to a lesser extent (116). Indeed, commercially available $\alpha$1AR antagonists that contain $\alpha$1dAR antagonist activity (non-subtype–selective $\alpha$1AR blockers as well as subtype-selective drugs such as tamsulosin and naftopidil, and to a lesser extent, silodosin) improve bladder-based symptoms in humans. Of note, nocturia appears to respond to the blockade of $\alpha$1dARs (117,118).

Such findings confirm the important role of the $\alpha$1dARs in LUTS. Studies demonstrating increased $\alpha$1dAR expression and function in models of bladder hypertrophy provide a mechanistic explanation for increased symptoms associated with LUTS (119). In terms of the precise mechanism of bladder storage, symptoms remain unknown. However, unstable bladder smooth muscle contractions

and a role for bladder urothelium α1dARs in initiating premature contractions, with filling (H$_2$O) or mild irritation (ascorbic acid) are both being explored. Spinal afferents originating in the bladder have also been suggested to be modified by α1AR blockade.

Alpha1-blockers mediate vasodilation in vasculature; therefore, one of the side effects of treating LUTS with alpha1-blockers is hypotension. Alpha-1A-adrenergic receptors predominate in human splanchnic (mesenteric, splenic, hepatic, and distal omental) resistance arteries (120). Interestingly, α1AR expression increases two-fold in representative (mammary) arteries with aging, with the ratio of α1b/ α1a increasing, whereas no alteration occurs in veins.

These findings are consistent with the fact that the α1aAR/1dAR–selective antagonist tamsulosin (which lacks α1bAR activity at clinical doses) has less effect on blood pressure in elderly men than does a non–subtype-selective α1AR antagonist (which would block α1bARs) (121).

Studies of pharmacy databases in Europe suggest that the administration of α1AR blockers increases the incidence of hip fractures (chosen as a surrogate for clinically important orthostatic hypotension) (121); further analysis regarding the precise α1AR antagonists prescribed suggests that the avoidance of α1bAR blockade may result in fewer overall blood pressure changes and hip fractures (122,123).

In summary, for the treatment of LUTS, distribution studies suggest that α1aAR-selective antagonists relieve obstructive outflow symptoms and improve urine flow via relaxation of prostate smooth muscle, whereas α1dAR-specific antagonists relieve bladder symptoms through direct action on either the bladder or spinal cord reflexes (**Table 13**).

**TABLE 13** Alpha1-adrenergic receptor subtypes and function (124).

- Three α1AR subtypes: α1A, α1B, and α1D
- α1AR subtype tissue expression varies with species
- α1AARs predominate in human prostate; blockade relaxes prostate smooth muscle and increases urine flow
- α1DARs predominate in human detrusor (bladder smooth muscle), spinal cord, and afferent nerves; blockade decreases LUTS symptoms
- Animal models of BOO show detrusor α1DARs increase with bladder hypertrophy
- α1D >α1A, α1B mRNA in the human spinal cord
- α1AR subtypes vary in human vascular beds: α1AARs predominate in splanchnic resistance vessels, α1BARs present to lesser extent in some small arteries, α1DARs in conduit arteries (aorta)
- Aging increases vascular α1AR density two-fold (mammary artery) and α1B increasingly predominates over α1A; with no change in α1D subtype

The use of α1bAR antagonist drugs has little benefit with respect to LUTS, and may promote blood pressure–related side effects, particularly in elderly patients, in whom vascular α1bARs become predominant over α1aARs. Furthermore, these data hint that in the absence of BOO (as in most female LUTS), bladder symptoms might be treated by targeting α1dARs selectively.

**Table 14** summarized the clinical pharmacology of the various alpha1-blockers used to treat LUTS (109,124).

**TABLE 14** Clinical pharmacology of alpha1-blockers used to treat LUTS (109,124).

| | Terazosin | Doxazosin | Alfuzosin | Tamsulosin | Naftopidil | Silodosin |
|---|---|---|---|---|---|---|
| α1AR subtype selectivity | Non-subtype selective | Non-subtype selective | Non-subtype selective | Subtype selective | Subtype selective | Subtype selective |
| Pharmacological selectivity | N | N | N | Y | Y | Y |
| Clinical selectivity | N (α1a=α1b= α1d) | N (α1a=α1b= α1d) | N (α1a=α1b= α1d) | Y (α1a=α1d >α1b) | Y (α1d≥α1a >α1b) | Y (α1a>α1d >α1b) |
| Registered for use in hypertension? | Y | Y | (N)± | N | N | N |
| Reduces elevated blood pressure? | Y | Y | Y | N | N | N |
| Usual daily dose, mg | 1–10 | 1–8 | 7.5–10 | 0.4 | 25–75 | 4–8 |
| Regimen, doses/day | 1 | 1 | 1–3 | 1 | 1–2 | 1 |
| Modified-release formulation | N | Y | N–Y | Y | N | N |
| Tmax (hours) | 1–2 | 2–3/8–12 | 1.5/9 | 6/4–6 | | 2.5 |
| T1/2 (hours) | 8–14 | 20/20 | 4–6/11 | 10–13/ | | |
| 14–15 | | 11–18 | | | | |
| Side effects | Asthenia, dizziness, somnolence, hypotension, nasal congestion/ rhinitis, impotence | Dizziness, fatigue, edema, dyspnea, hypotension | Dizziness, headache, nausea, dry mouth, diarrhea, hypotension | Abnormal ejaculation, dizziness, headache, flu-like symptoms | Abnormal ejaculation, nasal congestion, dizziness | Abnormal ejaculation, nasal congestion, dizziness |

## 8.4.2 Clinical studies

Alpha1-blockers have been in clinical use for over 20 years, and are the most widely used medication for male LUTS worldwide. There have been countless randomized and controlled clinical trials of alpha1-blockers, mostly comparing their efficacy and safety against placebo, but also against each other, although to a lesser degree.

Due to the multitude of the clinical trials available, the reader is referred to previous editions of the ICUD Consultations and other guidelines and authoritative reviews of these trials.

### 8.4.3 Meta-analyses, systematic reviews, direct comparator trials, and adverse events

Over time, there have also been a multitude of systematic reviews and meta-analyses following more or less stringent methodological criteria. A very recent article provides an overview of 15 systematic reviews and meta-analyses (125).

Out of over 700 retrieved articles, the authors selected 15 for consideration: 3 Cochrane systematic reviews and 12 other meta-analyses (**Table 15**) (126–134).

**TABLE 15** Baseline characteristics and methodology of included systematic reviews and meta-analyses (125).

| Study/ Country | Intervention (No. of studies) | Sample Size of Population | AMSTAR* |
|---|---|---|---|
| MacDonald 2005 | Alfuzosin vs. placebo (8); alfuzosin vs. finasteride (1); alfuzosin vs. tamsulosin (1); alfuzosin vs. doxazosin (1) | Alfuzosin ($n$=1,928), placebo ($n$=1,039), active control ($n$=581), alfuzosin-finasteride combination therapy ($n$=349) | C/C/Y/N/N/Y/Y/Y/N/Y** |
| Wilt 2006 /US | Doxazosin vs. placebo (8); doxazosin + finasteride vs. placebo + finasteride (2); doxazosin vs. alfuzosin (1); doxazosin vs. terazosin (1); doxazosin vs. tamsulosin (1); doxazosin vs. doxazosin + propiverine (1) | Doxazosin ($n$=2,413), placebo ($n$=1,460), active control ($n$=1,208), doxazosin-finasteride combination therapy ($n$=1,054), doxazosin-propiverine combination therapy ($n$=152) | Y/Y/Y/Y/N/Y/Y/Y/Y/N/Y |
| Liu 2009/China | Doxazosin vs. tamsulosin (6) | Doxazosin ($n$=268), tamsulosin ($n$=274) | C/Y/Y/N/N/Y/Y/Y/Y/C/N |
| Garimella 2008/US | Naftopidil vs. tamsulosin (5); naftopidil vs. phytotherapy (1); naftopidil monotherapy vs. co-therapy with anticholinergic (1); low-dose vs. high-dose naftopidil (1) | Naftopidil ($n$=349), tamsulosin ($n$=198), eviprostat ($n$=13) | Y/Y/Y/N/Y/Y/Y/Y/N/N/Y |

*AMSTAR items: (1) Was an *a priori* design provided? (2) Was there duplicate study selection and data extraction? (3) Was a comprehensive literature search performed? (4) Was the status of publication used as an inclusion criterion? (5) Was a list of studies (included and excluded) provided? (6) Were the characteristics of the included studies provided? (7) Was the scientific quality of the included studies assessed and documented? (8) Was the scientific quality of the included studies used appropriately in formulating conclusions? (9) Were the methods used to combine the findings of studies appropriate? (10) Was the likelihood of publication bias assessed? (11) Was the conflict of interest stated?. **Y: yes; N: no; C: cannot answer; NA: not applicable.

The drugs considered in this review are alfuzosin, tamsulosin, doxazosin, naftopidil, and terazosin, and there are direct comparisons available for many of the drugs (**Figure 11**). Silodosin is not considered in this review article.

**TABLE 15** Baseline characteristics and methodology of included systematic reviews and meta-analyses (125), *Cont'd*

| Study/ Country | Intervention (No. of studies) | Sample Size of Population | AMSTAR* |
|---|---|---|---|
| Wilt 2003/US | Tamsulosin vs. placebo (6); tamsulosin vs. terazosin (4); tamsulosin vs. alfuzosin (1); tamsulosin vs. prazosin (1); tamsulosin vs. permixon (1); tamsulosin vs. allylestrenol (1) | Tamsulosin (*n*=2,486), placebo (*n*=781), active controls (*n*=851) | Y/Y/Y/N/Y/Y/Y/N/N/Y |
| Ren 2008/China | Tamsulosin vs. placebo (7) | Tamsulosin (*n*=1,390), placebo (*n*=1,101) | C/Y/Y/N/N/Y/Y/Y/Y/N |
| Ren 2006/China | Tamsulosin vs. terazosin (8) | Tamsulosin (*n*=457), terazosin (*n*=478) | C/Y/Y/Y/N/Y/Y/Y/N/C/N |
| Xiong 2005/China | Tamsulosin vs. terazosin (7); tamsulosin vs. finasteride (3); finasteride vs. terazosin (2); terazosin/finasteride vs. finasteride (1); terazosin/finasteride vs. terazosin (1) | Tamsulosin (*n*=467), terazosin (*n*=931), active controls (*n*=1,255) | C/Y/Y/N/N/Y/Y/Y/N/N |
| Dong 2009/China | Tamsulosin vs. terazosin (12) | Total (*n*=2,816) | C/Y/Y/N/N/Y/Y/Y/N/N |
| Gu 2009/China | Tamsulosin vs. terazosin (12) | Tamsulosin (*n*=457), terazosin (*n*=478) | C/Y/Y/N/N/Y/Y/Y/N/N |
| Boyle 2001/Italy | Terazosin vs. placebo (9) | Total (*n*=3,648) | C/C/N/N/N/Y/N/N/Y/N/Y |
| Wilt 2000/US | Terazosin vs. placebo (10); terazosin vs. finasteride and vs. terazosin/finasteride combination (1); terazosin vs. tamsulosin (4); terazosin vs. doxazosin, prazosin or alfuzosin (3); terazosin vs. trans-urethral microwave therapy (1) | Terazosin (*n*=2,438), placebo (*n*=1,821), active controls (*n*=990) | Y/Y/Y/N/Y/Y/Y/Y/N/N/Y |
| Mudiyala 2003/UK | Terazosin vs. placebo (9) | Total (*n*=3,948) | C/C/N/N/N/N/N/N/C/N/N |
| Ye 2005/China | Terazosin vs. tamsulosin (6); finasteride vs. terazosin (3); finasteride vs. tamsulosin (1) | Terazosin (*n*=901), tamsulosin (*n*=331), placebo (*n*=310), active control (*n*=1,102) | C/Y/Y/N/N/N/Y/Y/Y/N/N |
| Nickel 2008/US | Alfuzosin (4); tamsulosin (8); terazosin (7); doxazosin GITS (2); doxazosin (8) | Total (*n*=7,827) | Y/Y/Y/N/N/Y/Y/N/N/Y/Y |

*AMSTAR items: (1) Was an *a priori* design provided? (2) Was there duplicate study selection and data extraction? (3) Was a comprehensive literature search performed? (4) Was the status of publication used as an inclusion criterion? (5) Was a list of studies (included and excluded) provided? (6) Were the characteristics of the included studies provided? (7) Was the scientific quality of the included studies assessed and documented? (8) Was the scientific quality of the included studies used appropriately in formulating conclusions? (9) Were the methods used to combine the findings of studies appropriate? (10) Was the likelihood of publication bias assessed? (11) Was the conflict of interest stated?. **Y: yes; N: no; C: cannot answer; NA: not applicable.

The drugs considered in this review are alfuzosin, tamsulosin, doxazosin, naftopidil, and terazosin, and there are direct comparisons available for many of the drugs (**Figure 11**). Silodosin is not considered in this review article.

**FIGURE 11**

Comparison network of alpha1-blockers for male LUTS (125).



Terazosin    Tamsulosin

Doxazosin              Naftopidil

Alfuzosin    Placebo

———— Direct evidence     - - - - - - Indirect evidence
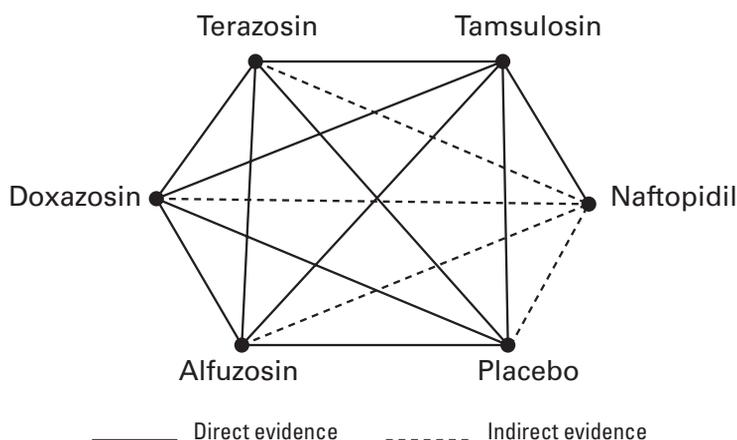
### 8.4.3.1 Alfuzosin
#### Alfuzosin vs. placebo
Two systematic reviews compared alfuzosin with placebo. Meta-analysis indicated that the mean change in IPSS (mean difference: −1.80; 95% CI: −2.49 to −1.11) and the Boyarsky symptom scores at endpoint (mean difference: −0.90; 95% CI: −0.94 to −0.87) favoured alfuzosin. Treatment with alfuzosin was also associated with a larger mean change in $Q_{max}$ (mean difference: 1.20; 95% CI: 0.76 to 1.64) and lower $Q_{max}$ at endpoint (mean difference: 0.45; 95% CI: 0.29 to 0.60).

In terms of safety, the included studies indicated that alfuzosin was similar to placebo on most outcomes, except dizziness.

#### Alfuzosin vs. doxazosin
Two systematic reviews compared alfuzosin (8.8 mg) with doxazosin (6.1 mg). These studies suggested that the mean change in the IPSS score from baseline favoured doxazosin (mean difference: 1.7; 95% CI: 0.76 to 1.64).

#### Alfuzosin vs. terazosin/tamsulosin
Alfuzosin was compared with terazosin and tamsulosin in one systematic review. There was no significant difference in either efficacy or safety profiles.

### 8.4.3.2 Doxazosin
#### Doxazosin vs. Placebo
Two systematic reviews compared doxazosin with placebo. Both reviews demonstrated that doxazosin (4–8 mg) reduced urinary tract symptoms and improved $Q_{max}$ more efficiently than did placebo.

In terms of safety (see **Table 17** in the Summary Tables section later on), Wilt *et al.* suggested that doxazosin could lead to higher rates of total adverse events, dizziness, asthenia, and postural hypotension (RR: 2.72; 95% CI: 1.21 to 6.15). The other systematic review compared the rate of vascular-related adverse events (dizziness, hypotension, and syncope), and found that men treated with doxazosin were more likely to suffer vascular related adverse events (odds ratio–OR: 3.32; 95% CI: 2.10 to 5.23).

## Doxazosin vs. Tamsulosin

Two systematic reviews compared doxazosin with tamsulosin, but conflicting results were obtained. One systematic review (125) indicated that doxazosin was associated with greater improvement in IPSS (mean difference: −1.60; 95% CI: −1.80 to −1.40), but it was not significantly more effective in improving $Q_{max}$ at endpoint.

In contrast, the other systematic review (135), which combined six RCTs, suggested that there was no significant difference between doxazosin and tamsulosin regarding mean change in either urinary symptoms (mean difference: −0.23; 95% CI: −1.70 to 1.23) or $Q_{max}$ (mean difference: −0.08; 95% CI: −0.88 to 0.73).

The original studies included in the later systematic review were closely checked, and some mistakes in data extraction and duplicated studies were found. The conclusion from the previous study is therefore considered to be more reliable.

No significant difference between doxazosin and tamsulosin was found in safety-related outcomes, except nausea (RR: 0.15; 95% CI: 0.03 to 0.86), favouring doxazosin.

## Doxazosin vs. Terazosin

Two systematic reviews based on one RCT demonstrated that doxazosin 4 mg and terazosin 5 mg were similar in efficacy and safety.

### 8.4.3.3   Terazosin

## Terazosin vs. Placebo

A total of four systematic reviews compared terazosin with placebo. All the studies indicated that terazosin, in doses ranging from 2 to 10 mg, improved urinary tract symptoms (mean difference: −3.40; 95% CI: −4.29 to −2.51) and $Q_{max}$ (mean difference: 1.27; 95% CI: 0.91 to 1.63) more than placebo did.

In terms of safety (see **Table 17** in the Summary Tables section later on), one systematic review demonstrated that terazosin was associated with more adverse event–related withdrawals (RR: 1.50; 95% CI: 1.23 to 1.83), dizziness, asthenia, and postural hypotension (RR: 5.27; 95% CI: 2.59 to 10.72). The other study indicated that terazosin could cause more vascular-related adverse events (OR: 3.71; 95% CI: 2.48 to 5.53).

## Terazosin vs. Tamsulosin

Seven systematic reviews compared terazosin with tamsulosin. Although there are some inconsistencies among the conclusions, conflicts do not exist, because the primary outcomes of these studies differed. Specifically, the primary outcomes in two of the studies were mean change in IPSS score and $Q_{max}$, and both of these studies suggested that there was no significant difference in efficacy between the two drugs. In the other four studies, the primary outcomes were IPSS and $Q_{max}$ at endpoint, and these studies demonstrated that tamsulosin was associated with significant lower IPSS scores.

The safety of terazosin and tamsulosin was compared in six systematic reviews (see **Table 17** in the Summary Tables section later on), which suggested that patients treated with terazosin tended to have higher incidences of adverse events, total withdraws, adverse event–related withdraws (RR: 6.88; 95% CI: 1.83 to 25.91), and dizziness.

### 8.4.3.4 **Tamsulosin**
#### Tamsulosin vs. Placebo
Three systematic reviews compared tamsulosin with placebo. All studies suggested that tamsulosin (0.4 and 0.8 mg) was superior to placebo in reducing urinary symptom scale scores (mean difference: −3.15; 95% CI: −5.01 to −1.28) and improving $Q_{max}$ (mean difference: 1.07; 95% CI: 0.65 to 1.48).

Compared with placebo, tamsulosin was associated with higher incidences of dizziness, abnormal ejaculation (RR: 17.03; 95% CI: 2.54 to 114.05), and rhinitis (RR: 1.84; 95% CI: 1.24 to 2.71) (see **Table 17** in the Summary Tables section following this section).

### 8.4.3.5 **Summary tables**
**TABLE 16** Direct evidence of the efficacy profiles of the different alpha1-blockers for BPH (125).

| Experimental Group vs. Control Group | Change in Urinary Symptom Scores | | Change in $Q_{max}$ | |
|---|---|---|---|---|
| | Weighted Mean Difference (95% CI) | Quality of Evidence | Weighted Mean Difference (95% CI) | Quality of Evidence |
| Alfuzosin vs. placebo | −5.4 vs. −3.6, −1.8 (−2.49 to −1.11)↑ | Moderate[a] | 2.6 vs. 1.1 mL/s, significant↑ | Moderate[b] |
| Alfuzosin vs. doxazosin | −7.4 vs. −9.2, 1.7 (0.76 to 1.64)↓ | Moderate[c] | 2.9 vs. 3.0 mL/s, −0.10 (−0.22 to 0.02)‡ | Moderate[c] |
| Alfuzosin vs. terazosin | −48% vs. 51%, not significant‡ | Low[d] | − | − |
| Alfuzosin vs. tamsulosin | −3.8 vs. −4.1, 0.30 (0.21 to 0.39)↓ | Moderate[c] | 1.6 vs. 1.6 mL/s, 0.00 (−0.07 to 0.07)‡ | Moderate[c] |
| Doxazosin vs. placebo | −, −2.49 (−3.20 to −1.78)↑ | High | 1.5~3.6 vs. −0.3~1.8 mL/s, 1.73 (1.26 to 2.21)↑ | Moderate[e] |
| Doxazosin vs. terazosin | −5.0 vs. −5.4, not significant‡ | Low[f] | 3.1 vs. 3.1 mL/s, not significant‡ | Low[f] |

Outcomes favouring the experimental group; ↓Outcomes favouring the control group; ‡Comparable outcomes
[a]Concealment was inadequate in all three studies; [b]Blinding method in one study was unclear, two studies did not use intention-to-treat analysis, adequate allocation concealment was reported only in one study; [c]Total population size is less than 400; [d]Randomization and concealment is unclear, total population size is 74; [e]Four of the five pooled studies were only assessed as three points by Jadad scale; [f]Blinding and concealment were not described, total population size is 43; [g]Randomization and concealment is unclear, total population size is 52; [h]Randomization and concealment are not described, loss of follow-up in three studies, total population size is less than 400; [i]Randomization was not clearly reported in three studies and inadequate in one study, blinding was not adequate in three studies, intention-to-treat was not applied in any study; [j]Randomization was not clearly reported in three studies and inadequate in one study, blinding was not adequate in two studies, intention-to-treat was not applied in any study.

**TABLE 16** Direct evidence of the efficacy profiles of the different alpha1-blockers for BPH (125), *Cont'd*

| Experimental Group vs. Control Group | Change in Urinary Symptom Scores | | Change in $Q_{max}$ | |
|---|---|---|---|---|
| | Weighted Mean Difference (95% CI) | Quality of Evidence | Weighted Mean Difference (95% CI) | Quality of Evidence |
| Doxazosin vs. tamsulosin | −8.0 vs. −6.4, −1.60 (−1.80 to −1.40)↑ | Low[g] | 2.6 vs.1.7 mL/s, significant↑ | Low[g] |
| Terazosin vs. placebo | −37% vs. −15%, −3.40 (−4.29 to −2.51)↑ | High | 2.2 vs. 1.1 mL/s, 1.27 (0.91 to 1.63)↑ | High |
| Terazosin vs. tamsulosin | −40% vs. −41%, 0.72 (−1.51 to 2.94)‡ | Low[h] | 25% vs. 29%, 0.26(−0.6 to 1.12)‡ | Low[h] |
| Tamsulosin vs. placebo | −20 to −48% vs. −18 to −28%, −3.15 (−5.01 to −1.28)↑ | High | 1.2~4.0 vs. −0.1~1.4 mL/s, 1.07 (0.65 to 1.48)↑ | High |
| Tamsulosin vs. naftopidil | −8.9 vs. −8.4, not significant‡ | Low[i] | 2.8 vs. 2.1 mL/s, unclear | Low[j] |

↑Outcomes favouring the experimental group; ↓Outcomes favouring the control group; ‡Comparable outcomes
[a]Concealment was inadequate in all three studies; [b]Blinding method in one study was unclear, two studies did not use intention-to-treat analysis, adequate allocation concealment was reported only in one study; [c]Total population size is less than 400; [d]Randomization and concealment is unclear, total population size is 74; [e]Four of the five pooled studies were only assessed as three points by Jadad scale; [f]Blinding and concealment were not described, total population size is 43; [g]Randomization and concealment is unclear, total population size is 52; [h]Randomization and concealment are not described, loss of follow-up in three studies, total population size is less than 400; [i]Randomization was not clearly reported in three studies and inadequate in one study, blinding was not adequate in three studies, intention-to-treat was not applied in any study; [j]Randomization was not clearly reported in three studies and inadequate in one study, blinding was not adequate in two studies, intention-to-treat was not applied in any study.

**TABLE 17** Direct evidence of the safety profile of alpha1-blockers for BPH (125).

| Experimental Group vs. Control Group | Total Withdrawals RR (95% CI) | Total Adverse Event RR (95% CI) | Dizziness RR (95% CI) | Headache RR (95% CI) | Asthenia RR (95% CI) | Impotence RR (95% CI) |
|---|---|---|---|---|---|---|
| Alfuzosin vs. placebo | 210/1,424 vs. 182/1,118, 0.98 (0.82 to 1.17)‡ | 271/666 vs. 81/504, 1.07 (0.92 to −1.24)‡ | 68/1,298 vs. 25/1,000, 2.04 (1.29 to 3.22)↓ | 37/1,266 vs. 21/969, 1.42 (0.83 to 2.43)‡ | 18/1,090 vs. 18/792, 0.69 (0.35 to 1.34)‡ | 9/896 vs. 9/596, 0.67 (0.26 to 1.76)‡ |
| Alfuzosin vs. doxazosin | 18/105 vs. 12/105, 1.50 (0.76 to 2.96)‡ | − | 11/93 vs.14/99, 0.84 (0.40 to 1.75)‡ | 6/93 vs. 5/99, 1.28 (0.40 to 4.04)‡ | 5/93 vs. 5/99, 1.06 (0.32 to 3.56)‡ | 1/93 vs. 0/99, 0.31 (0.01 to 7.6)‡ |
| Alfuzosin vs. terazosin | 1/35 vs. 3/39, 2.69 (0.29 to 24.71)‡ | − | 2/35 vs. 2/39, 0.90 (0.13 to −6.04)‡ | 0/35 vs. 2/39, 4.50 (0.22 to −90.64)‡ | − | − |

↑Outcomes favouring the experimental group; ↓Outcomes favouring the control group; ‡Comparable outcomes

**TABLE 17** Direct evidence of the safety profile of alpha1-blockers for BPH (125), *Cont'd*

| Experimental Group vs. Control Group | Total Withdrawals RR (95% CI) | Total Adverse Event RR (95% CI) | Dizziness RR (95% CI) | Headache RR (95% CI) | Asthenia RR (95% CI) | Impotence RR (95% CI) |
|---|---|---|---|---|---|---|
| Alfuzosin vs. tamsulosin | 9/124 vs. 14/131, 0.68 (0.30 to 1.51)‡ | 59/124 vs. 69/131, 0.90 (0.71 to 1.16)‡ | 9/124 vs. 9/131, 1.06 (0.43 to 2.57)‡ | 4/124 vs. 10/131, 0.42 (0.14 to 1.31)‡ | 2/12 vs. 4/131, 0.53 (0.10 to 2.83)‡ | 3/124 vs. 4/131, 0.79 (0.18 to 3.47)‡ |
| Doxazosin vs. placebo | 198/1,282 vs. 125/640, 0.93 (0.64 to 1.35) I22 | 265/536 vs. 98/268, 1.35 (1.12 to 1.62)↓ | 163/1,450 vs. 49/693, 1.92 (1.40 to 2.61)↓ | 99/147 vs. 70/714, 0.81 (0.39 to 1.72)‡ | 93/1,450 vs. 17/693, 3.33 (1.97 to 5.61)↓ | 16/275 vs. 9/269, 1.71 (0.77 to 3.79)‡ |
| Doxazosin vs. terazosin | 3/22 13.6 5/21 23.8 1 0.57 (0.16–2.10)‡ | – | 1/22 vs. 3/21, 0.32 (0.04 to 2.82)‡ | 1/22 vs. 1/21, 0.95 (0.06 to 14.30)‡ | – | – |
| Doxazosin vs. tamsulosin | – | 38/48 vs. 39/50, 1.01 (0.83 to 1.25)‡ | 8/48 vs. 8/50, 1.04 (0.43 to 2.55)‡ | 6/48 vs. 8/50, 0.78 (0.29 to 2.08)‡ | 6/48 vs. 12/50, 0.52 (0.21 to 1.28)‡ | – |
| Terazosin vs. placebo | 521/1,904 vs. 555/1,621, 0.94 (0.76 to 1.17)‡ | – | 252/1,802 vs. 98/1,586, 2.43 (1.82 to 3.25)↓ | 40/749 vs. 25/555, 1.20 (0.71 to 2.00)‡ | 153/1,736 vs. 62/1,566, 2.24 (1.68 to 3.00)↓ | 24/386 vs. 15/384, 1.97 (0.51 to 7.65)‡ |
| Terazosin vs. tamsulosin | 39/229 vs. 20/230, 1.82 (1.00 to 3.32)↓ | 18/49 vs. 1/49, 18.00 (2.5 to 129.6)↓ | 42/229 vs. 10/230, 3.53 (1.92 to 6.51)↓ | 7/165 vs. 1/154, 4.83 (0.85 to 27.52)‡ | – | – |
| Tamsulosin vs. placebo | 168/1,376 vs. 82/686, 1.02 (0.80 to 1.30)‡ | 897/1,676 vs. 401/781, 1.07 (1.00 to 1.15)↓ | 179/1,473 vs. 56/714, 1.50 (1.13 to 1.99)↓ | 221/1,473 vs. 104/714, 1.00 (0.81 to 1.23)‡ | 89/1,473 vs. 31/714, 1.33 (0.89 to 1.97)‡ | – |
| Tamsulosin vs. naftopidil | – | – | – | – | – | – |

↑Outcomes favouring the experimental group; ↓Outcomes favouring the control group; ‡Comparable outcomes

### 8.4.3.1 Silodosin

Silodosin had not been included in this review, but in the last two years alone, four meta-analyses have been produced regarding the silodosin clinical database (135–138). The most recent and comprehensive meta-analysis, by Wu, identified five RCTs, encompassing a total of 2,595 patients.

Meta-analysis indicated that silodosin achieved significant improvement versus placebo in total IPSS, IPSS subscores, and $Q_{max}$. Silodosin was associated with a greater improvement in voiding symptoms than was tamsulosin, and a higher incidence of retrograde ejaculation than both placebo and tamsulosin. No significant differences were observed in total IPSS, IPSS storage symptoms, $Q_{max}$, or QOL versus tamsulosin. Silodosin was associated with the same low incidence of dizziness and headache as was placebo and tamsulosin (**Tables 18** and **19**) (135).

**TABLE 18** Efficacy outcomes for silodosin, tamsulosin, and placebo; change from baseline at 12 weeks (135).

| | Change from Baseline | | |
|---|---|---|---|
| | **Silodosin** | **Tamsulosin** | **Placebo** |
| **IPSS** | | | |
| Kawabe *et al.* | | | −5.3 (6.7) |
|    Total | −8.3 (6.4) | −6.8 (5.7) | −1.5 (2.6) |
|    Storage | −2.5 (2.9) | −2.1 (2.6) | −3.8 (4.8) |
|    Voiding | −5.8 (4.6) | −4.8 (4.1) | |
| Yu *et al.* | | | |
|    Total | −10.6 (5.1) | −10.0 (5.1) | / |
|    Storage | −3.5 (2.2) | −3.3 (2.2) | / |
|    Voiding | −7.1 (3.8) | −6.7 (3.9) | / |
| Marks *et al.* | | | |
|    Total | −6.4 (6.63) | / | −3.5 (5.84) |
|    Storage | −2.3 (2.93) | / | −1.4 (2.66) |
|    Voiding | −4.0 (4.31) | / | −2.1 (3.76) |
| Yokoyama *et al.* | | | |
|    Total | −4.9 (1.2) | −7.3 (1.4) | / |
|    Storage | nr | nr | / |
|    Voiding | nr | nr | / |
| Chapple *et al.* | | | |
|    Total | −7.0 | −6.7 | −4.7 |
|    Storage | −2.5 | −2.4 | −1.8 |
|    Voiding | −4.5 | −4.2 | −2.9 |
| **$Q_{max}$** | | | |
| Kawabe *et al.* | 1.70 (3.31) | 2.60 (3.98) | 0.26 (2.21) |
| Yu *et al.* | 0.9 (4.2) | 1.6 (4.2) | / |
| Marks *et al.* | 2.6 (4.43) | / | 1.5 (4.36) |
| Yokoyama *et al.* | 0.2 (0.9) | 3.5 (1.5) | / |
| Chapple *et al.** | 3.77 | 3.53 | 2.93 |
| **QOL** | | | |
| Kawabe *et al.* | −1.7 (1.4) | −1.4 (1.3) | −1.1 (1.2) |
| Yu *et al.* | −1.4 (1.1) | −1.2 (1.1) | / |
| Marks *et al.* | nr | nr | nr |
| Yokoyama *et al.* | −1.1 (0.2) | −1.8 (0.3) | / |
| Chapple *et al.** | −1.1 | −1.1 | −0.8 |

nr: not reported
Values are mean (SD); *Adjusted means

**TABLE 19** The main treatment-emergent adverse events for silodosin, tamsulosin, and placebo at 12 weeks (135).

| | Adverse Events No. (%) | | |
|---|---|---|---|
| | **Silodosin** | **Tamsulosin** | **Placebo** |
| **Retrograde ejaculation** | | | |
| Kawabe *et al.* | 8 (9.7) | 1 (1.0) | / |
| Yu *et al.* | 131 (28.1) | / | 4 (0.9) |
| Marks *et al.* | 8 (17.8) | 1 (2.2) | / |
| Yokoyama *et al.* | 54 (14.2) | 8 (2.1) | 2 (1.1) |
| Chapple *et al.** | 8 (9.7) | 1 (1.0) | / |
| **Dizziness and headache** | | | |
| Kawabe *et al.* | 9 (5.1) | 14 (7.3) | 4 (4.5) |
| Yu *et al.* | 8 (7.8) | 3 (2.9) | / |
| Marks *et al.* | 26 (5.6) | / | 9 (2.0) |
| Yokoyama *et al.* | 1 (2.2) | 0 | / |
| Chapple *et al.** | 11 (2.9) | 21 (5.5) | 9 (4.7) |

*Adjusted means

Silodosin has a 162-fold selectivity for the $\alpha$1AAR subtype, and this is likely the reason for the high rate of anejaculation, which is the more correct term compared to "retrograde ejaculation," as demonstrated in the elegant experiment by Hellstrom (139,140).

The recorded rates for ejaculatory abnormalities with silodosin have been as high as 28%, but it has been shown that the patients experiencing anejaculation also have a greater improvement in both symptoms and $Q_{max}$ (141,142). This fact can be viewed as supporting evidence for the supposed MOA of alpha1-blockers of relaxing the muscles in the LUT to the point of preventing the ejaculation contraction, and allowing a more forceful flow of urine, with symptomatic relief.

## 8.4.4 Urodynamic studies

Bosch published an extensive review of the urodynamic effects of various treatments for male LUTS and BPO in 1997, including the best available evidence at that time (143).

**Figures 12** and **13** show that while in controlled trials, placebo had a minimal, if any, effect on the detrusor pressure ($P_{det}$) at $Q_{max}$ ($P_{det}.Q_{max}$) on the Abrams-Griffiths nomogram, most studies done with alpha-blockers reduced the pressure and/or improved $Q_{max}$, even if not bringing the mean $P_{det}$.$Q_{max}$ below the line that at that time reflected the boundary between unobstructed and equivocal. It is noteworthy, however, that the mean pre-treatment $P_{det}.Q_{max}$ was in the obstructed range in each of the studies analyzed.

**FIGURE 12**

Effects of alpha-blocker therapy on $P_{det}.Q_{max}$ during invasive urodynamic testing. Mean pre-treatment data points (closed circles) are connected with mean post-treatment data points (open circles) for studies of prazosin (lines 1, 2, 3, 5, and 6), indoramine (line 4), doxazosin (line 7 and 11), alfuzosin (line 8), and terazosin (lines 9 and 10) (143).
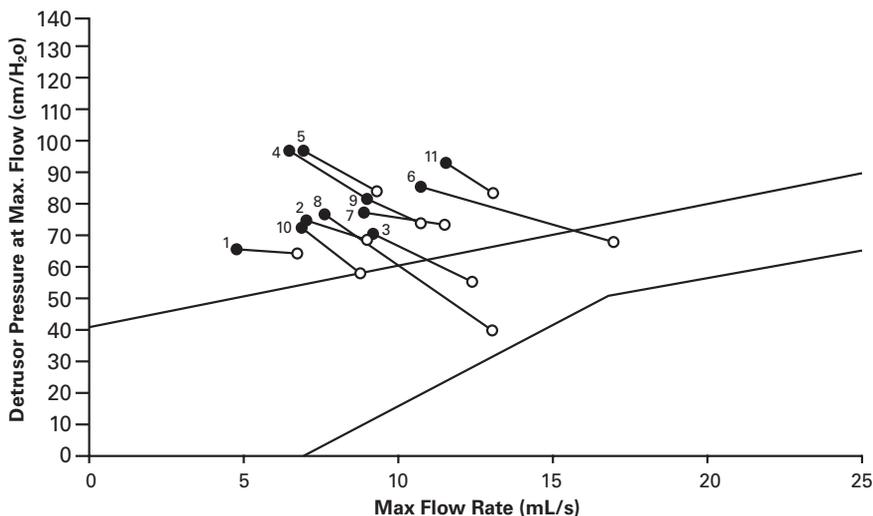
**FIGURE 13**

Effects of placebo treatment on $P_{det}.Q_{max}$ during invasive urodynamic testing. Mean pre-treatment data points (closed circles) are connected with mean post-treatment data points (open circles) (143).
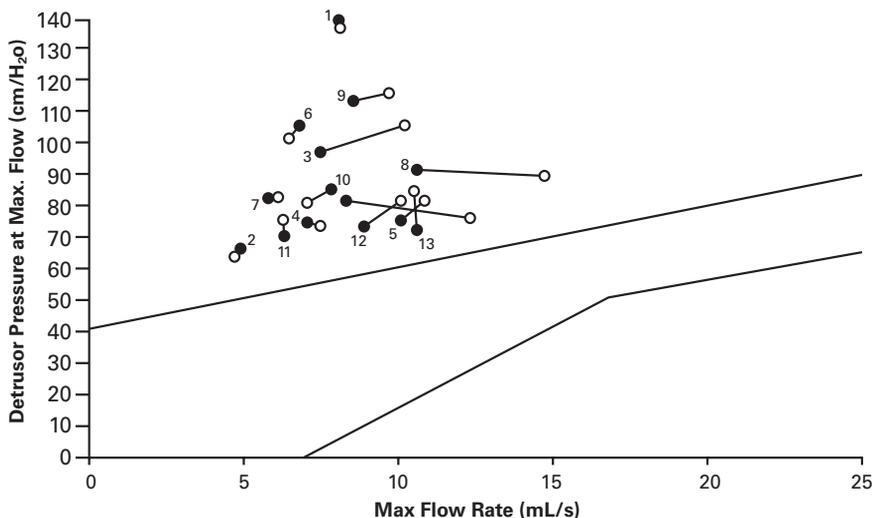
The numerical changes induced by various medical therapies are listed in **Table 20** in terms of duration of treatment, dosage and type of drug, pre and post-treatment $P_{det}.Q_{max}$, $Q_{max}$, mean urethral resistance factor, and mean minimal urethral opening pressure.

**TABLE 20** Effects on urethral resistance of medical treatment for BPH (143).

| Reference | Product | Treatment (Dose/Day) | No. of Men | Follow-Up | Mean $P_{det}.Q_{max}$ Before/After Therapy (cm Water) | Mean $Q_{max}$ Before/After Therapy (mL/s) | Mean Urethral Resistance Factor Before/After Therapy (cm Water) | Mean Minimal Urethral Opening Pressure Before/After Therapy (cm Water) |
|---|---|---|---|---|---|---|---|---|
| **Androgen Deprivation:** | | | | | | | | |
| Bosch *et al.* | Buserelin | 1.2 mg + cyproterone acetate (200 mg) | 8 | 12 weeks | 78/81 | 6.2/7.9 | 47/49 | |
| Rollema *et al.* | Finasteride | 5 mg | 7 | 2 years | | | 45/32 | |
| Tammela & Kontturi* | Finasteride | 5 mg | 19 | 24 weeks | 126/87 | 7.7/10.3 | | 125/86 |
| Eri & Tveter* | Casodex | 50 mg | 14 | 24 weeks | 84/80 | 9.0/8.5 | | 77/72 |
| Eri & Tveter* | Leuprolide | 3.75 mg/28 | 26 | 24 weeks | 79/66 | 5.9/7.4 | | 78/66 |
| Risi *et al.*| Finasteride | 5 mg | 50 | 36 weeks | 89/82 | 10.3/10.4 | | 84/79 |
| **Alpha-Blockers:** | | | | | | | | |
| Hedlund *et al.*| Prazosin | 4 mg | 20 | 4 weeks | 67/65[†] | 4.9/69 | | 47/40 |
| Hedlund & Andersson* | Prazosin | 4 mg | 8 | 4 weeks | 75/69[†] | 7.2/9.2 | | 55/42 |
| Chapple *et al.*| Prazosin | 4 mg | 15 | 12 weeks | 71/56 | 9.4/12.6 | | |
| Stott & Abrams* | Indoramin | 40 mg | 18 | 4 weeks | 98/82 | 6.7/9.4 | | |
| Rollema *et al.*| Doxazosin | 4 mg | 16 | 4 weeks | | | 47/41 | |
| Chapple *et al.*[*‡] | Prazosin | 4 mg | 12 | 12 weeks | 98/84 | 7.2/9.5 | | |
| Chapple *et al.*[*‡] | Prazosin | 4 mg | 20 | 12 weeks | 86/69 | 10.9/17 | | |
| Chapple *et al.*[*‡] | Doxazosin | 4 mg | 53 | 12 weeks | 78/74 | 9.1/11.7 | | |
| Rosier *et al.* | Terazosin | 10 mg | 24 | 26 weeks | | | 44/35 | 40/30 |
| Martorana *et al.*| Alfuzosin | 7.5 mg | 15 | 12 weeks | 90/39 | 6.7/12.3 | | 97/29 |
| Martorana *et al.*| Alfuzosin | 7.5 mg | 25 | 12 weeks | 78/40 | 7.8/13.1 | | |

*Results were derived from randomized (and in most cases placebo) controlled studies; [†]These authors have reported maximum voiding (detrusor) pressure instead of $P_{det}.Q_{max}$; [‡]These results are from 2 different study locations reported in 1 paper.

**TABLE 20** Effects on urethral resistance of medical treatment for BPH (143).

| Reference | Product | Treatment (Dose/Day) | No. of Men | Follow-Up | Mean $P_{det}.Q_{max}$ Before/After Therapy (cm Water) | Mean $Q_{max}$ Before/After Therapy (mL/s) | Mean Urethral Resistance Factor Before/After Therapy (cm Water) | Mean Minimal Urethral Opening Pressure Before/After Therapy (cm Water) |
|---|---|---|---|---|---|---|---|---|
| Risi *et al.** | Terazosin | 5 mg | 50 | 36 weeks | 82/75 | 9.2/10.9 | | 79/72 |
| Witjes *et al.* | Terazosin | 10 mg | 33 | 26 weeks | 73/59 | 7.1/8.9 | | |
| Gerber *et al.* | Doxazosin | 4 mg | 44 | 3 months | 94/83 | 11.7/13.2 | | 39/30 |

*Results were derived from randomized (and in most cases placebo) controlled studies; †These authors have reported maximum voiding (detrusor) pressure instead of $P_{det}.Q_{max}$; ‡These results are from 2 different study locations reported in 1 paper.

Several urodynamic studies have been reported with the more recently approved drug silodosin. Sixty men with LUTS and BPH were given 8 mg silodosin over 4 weeks. In the voiding phase of the urodynamic study, they experienced a mean $P_{det}.Q_{max}$ decrease from 72.5 to 51.4 cm $H_2O$, and the mean BOO index decreased significantly, from 60.6 to 33.8. Obstruction grade assessed by the Schäfer nomogram improved in all except one patient (144).

In another study, patients were treated for 12 months, and in pressure-flow studies (*n*=27), the obstruction grade was improved in 15 patients (56%). Detrusor opening pressure, $P_{det}.Q_{max}$, BOO index, and Schäfer's obstruction class decreased significantly after therapy (all *p*<0.01) (145).

### 8.4.5 Alpha-blockers for chronic pelvic pain syndrome

Alpha-blockers are extensively used for the treatment of men with chronic prostatitis (CP) or chronic pelvic pain syndrome (CPPS). A recent review by Nickel concluded that the data suggest that alpha-blocker treatment confers a modest benefit in some patients with CP/CPPS. Despite negative results of two phase 3 studies, one with alfuzosin and one with tamsulosin, other data suggest that alpha1-blockers may provide overall improvement of CP/CPPS-associated symptoms as assessed by National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) total scores, especially in alpha1-blocker–naïve patients with acute symptoms (**Table 21**).

Data from studies with longer follow-up periods after the cessation of therapy further suggest that lasting symptom improvement may require persistent therapy. Longer treatment periods may be required for treatment effects that develop slowly over time, or simply to compensate for the possibility of inadequate washout periods, which can skew the data in favour of inactive treatment. Consequently, large-scale, placebo-controlled studies of longer duration in specifically selected patients (i.e. patients with a voiding dysfunction phenotype) are needed to validate the use of these treatments in patients with CP/CPPS (146).

**TABLE 21** Randomized placebo-controlled clinical studies that evaluated the use of alpha-blockers for treatment of CP/CPPS using NIH-CPSI score as the primary efficacy outcome (146)

| Study | Randomized | Blinding | Treatment Duration | Treatments | Baseline Scores Mean ± SD | Change from Baseline Mean ± SD | P Value |
|---|---|---|---|---|---|---|---|
| Chen *et al.* | *N*=100 | Double-blind | 6 months | Tamsulosin 0.2 mg/day | 23.3 ± 6.2 | –7.5 ± 1.9 | <0.01 |
| | | | | Placebo | 22.5 ± 5.6 | –4.0 ± 2.3 | |
| Nickel *et al.* | *N*=148 | Double-blind | 12 weeks | Silodosin 4 mg/day | 26.0 ± 6.3 | –12.1 ± 9.3 | 0.02 |
| | | | | Silodosin 8 mg/day | 26.8 ± 5.9 | –10.2 ± 8.8 | 0.59 |
| | | | | Placebo | 27.9 ± 6.2 | –8.5 ± 7.2 | |
| Nickel *et al.* | *N*=272 | Double-blind | 12 weeks | Alfuzosin 10 mg/day | 23.8 ± 6.3 | –7.1 ± 9.0 | 0.70 |
| | | | | Placebo | 25.1 ± 5.9 | –6.5 ± 8.5 | |
| Tuğcu *et al.* | *N*=60* | nr | 6 months | Doxazosin 4 mg/day | 23.1 ± 1.8 | –12.4 | <0.05 |
| | | | | Placebo | 22.9 ± 1.2 | –1.0[†] | |
| Alexander *et al.* | *N*=98[‡] | Double-blind | 6 weeks | Tamsulosin 0.4 mg/day | 24.6 ± 6.2 | –4.4 ± 6.3 | >0.2 |
| | | | | Placebo | 25.0 ± 5.1 | –3.4 ± 5.0 | |
| Nickel *et al.* | *N*=57 | Double-blind | 6 weeks | Tamsulosin 0.4 mg/day | 26.4 ± 4.9 | nr | 0.04 |
| | | | | Placebo | 26.2 ± 6.5 | nr | |
| Mehik *et al.* | *N*=40[§] | Double-blind | 6 months | Alfuzosin 10 mg/day | 26.0 | –9.9 | 0.01 |
| | | | | Placebo | 23.0 | –3.8 | |
| Cheahm *et al.* | *N*=86 | Single-blind | 14 weeks | Terazosin 1–5 mg/day | 25.1 ± 7.1 | –14.3[†] | 0.01 |
| | | | | Placebo | 27.2 ± 7.7 | –10.2[†] | |

NR: not reported
*Data not shown for the group treated with a combination of doxazosin, ibuprofen, and thiocolchicoside (*n*=30); [†]Difference in mean score at baseline and end of treatment; [‡]Not all treatment groups are listed; a total of 196 patients were studied using a 2 × 2 factorial analysis plan that also included two groups randomized to ciprofloxacin alone (*n*=49) or a combination ciprofloxacin/tamsulosin (*n*=49); [§]Only randomized treatment arms are shown.

### 8.4.6  Recommendations: alpha-blockers

1. The efficacy of alpha-blockers on symptoms has been demonstrated in placebo-controlled studies out to 5 years (Level 1, Grade B).
2. The benefit of alpha-blockers is not related to PV in short- to medium-term trials, but in longer-term trials, the efficacy deteriorates in prostates of larger PV (Level 1, Grade B).
3. The efficacy of all alpha-blockers is similar (Level 1, Grade A).
4. The adverse event profiles of alpha-blockers differ substantially. Tamsulosin, alfuzosin, and silodosin have no impact on blood pressure and fewer vascular-related adverse events. Silodosin has higher rates than tamsulosin of ejaculatory abnormalities (Level 1, Grade A).
5. Alpha-blockers are superior to 5-ARIs in terms of symptoms, bother, and QOL improvement in unselected men with LUTS in high-quality RCTs of up to 5 years' duration (Level 1, Grade A).
6. In men with larger prostates, alpha-blockers were inferior to dutasteride after 1–2 years of treatment in one high-quality RCT (Level 1, Grade B).
7. Alpha-blockers improved the rate of spontaneous voiding after a trial without catheter in men with acute urinary retention (AUR) due to BPO (Level 1, Grade A).

# 8.5  Antimuscarinics

### 8.5.1  Introduction

Treatment of male LUTS has historically focused on the management of BOO, most commonly caused by an enlarged prostate or a high bladder neck. It is likely that this tradition developed not only out of necessity, but also because it was the most treatable diagnosis. It has become understood that there is a bladder component to LUTS, due to primary or secondary bladder dysfunction. Much work in this area has been performed among women, and only recently has this been extended to men. Randomized clinical trials certainly support the efficacy of this class of medication among women. The reasons for this may include fear of urinary retention, low efficacy of antimuscarinic agents, and lack of clinical trial evidence. However, there is a growing body of work supporting the role of antimuscarinic agents as a therapeutic option for men with LUTS.

While it makes intuitive sense that men would have symptoms of OAB, most of the published literature is based on women. It may be the case that men typically have more symptoms due to obstruction; however, this does not preclude the need to diagnose and treat bladder dysfunction. In fact, bladder hyperactivity may contribute to LUTS in approximately 15% of adult men (13). Part of the difficulty in establishing an accurate prevalence rate is the lack of a standardized definition. Clinical trials tend, as is often the case, to select for men with the worst symptoms, including urgency and frequency. It is also recognized that there is a prevalence of urinary incontinence among men.

Normal micturition requires that the bladder detrusor muscle relax between voids, and that it contract to overcome bladder outlet (i.e. prostate and bladder neck) resistance during voiding. Recent work published by Andersson has more clearly delineated the role of muscarinic receptors in the entire

male LUT (147). Muscarinic receptors are widely distributed not only in the bladder detrusor but also throughout the urothelium, urethra, and prostate. These receptors from the G-protein family are classified into five distinct subtypes (M1–M5), each with its own encoding gene. Activation of these receptors can either be inhibitory (M2 and M4) or excitatory (M1, M3, and M5). Inhibitory receptors further couple to adenylyl cyclase in a negative manner, while excitatory receptors increase the level of intracellular calcium ($Ca2+$).

In the human bladder, each of the subtypes of receptors has been reported; however, there is a heavy predominance of M2 and M3 receptors, typically in a 3:1 ratio. A much lesser amount of the M1 receptor subtype has also been noted. Most evidence supports the idea that M3 receptors mediate detrusor contraction, but the role of M2 receptors in humans is less clear, despite the fact that the M2 receptor subtype is far more prevalent than M3. In one study, by Igawa, it was suggested that these receptors have a small effect on increasing the voiding intervals and voiding volumes in mice (148).

Detrusor overactivity typically manifests with symptoms of OAB. The mechanism for such overactivity is mediated primarily by M3-type muscarinic receptors in the bladder detrusor smooth muscle (149). In non-bladder tissues, muscarinic receptors are also found in the salivary glands, cardiovascular system, brain, and intestinal tract, which largely explains the adverse events commonly associated with antimuscarinic therapy (150). This OAB component of LUTS helps to explain why prostate-directed therapies are not universally effective in reducing LUTS, and opens up additional options for management (151).

There is increasing evidence that chronic obstruction may actually alter the density and function of muscarinic receptors. One proposed pathway includes the truce of denervation secondary to chronic obstruction, which may in turn result in a super-sensitivity, possibly leading to clinical detrusor overactivity. Likewise, increased sensitivity to muscarinic stimulation is known to occur in patients with idiopathic and neurogenic cases of detrusor overactivity.

Liu *et al.* recently described detectable levels of nerve growth factor among men with refractory OAB (152). Taken together, this body of work not only suggests a role for antimuscarinic therapy, but also suggests the possibility of a plastic response of the bladder to obstruction, and potentially to relief of obstruction.

While the muscarinic receptor subtype is unknown in the male urethra, further work may be of value in treating a common problem: post-void dribbling. In the prostate, stromal tissues express some M2 receptors; the epithelium is the predominant location of the muscarinic receptors. The role of these receptors in the prostate has yet to be established, although it is postulated that they may be involved in secretion.

### 8.5.2 Mechanism of action

Antimuscarinic agents inhibit muscarinic receptors in the detrusor muscle, thereby decreasing the OAB component of LUTS. A number of antimuscarinic agents have been approved for voiding dysfunction (darifenacin, solifenacin, trospium chloride, oxybutynin, tolterodine, and fesoterodine).

Antimuscarinic agents are classified as uroselective (darifenacin, solifenacin) if they primarily affect the M3-type muscarinic receptors in the bladder detrusor smooth muscle. These are typically tertiary amines, which are capable of crossing the blood–brain barrier. As a result, cognitive impairment has been reported, and these drugs should therefore be used with caution in men who are at risk of or who have cognitive disorders. The non-selective antimuscarinic agents (trospium, oxybutynin, tolterodine, and fesoterodine) inhibit M2 as well as M3 receptors.

### 8.5.3 Treatment of overactive bladder symptoms in men: evidence from randomized controlled trials

Few RCTs have examined the role of antimuscarinic agents in men with BPO. Most of the evidence comes from trials in women, with limited generalizability. In the only RCT with a monotherapy arm consisting of an antimuscarinic agent, Kaplan *et al.* (153) were unable to demonstrate a statistically significant difference between tolterodine and placebo in their primary endpoint. While this may seem surprising given the abundance of efficacy data among women, it may be the case that the component of BOO creates a confounder that influences the apparent efficacy of monotherapy. Secondary endpoints, including voiding diary and IPPS score, were also examined. In the tolterodine monotherapy group, there was a significant reduction in urgency incontinence episodes per 24 hours by week 12. There was no significant difference between placebo and tolterodine monotherapy when it came to total IPS S score.

In 2010, Herschorn *et al.* conducted an RCT with both men and women, examining fesoterodine and tolterodine monotherapies (154). Their primary endpoint was change in incontinence episodes from baseline to 12 weeks. They observed a significant difference in urgency incontinence at 12 weeks with fesoterodine vs. to placebo. Fesoterodine improved the median voided volume per void, as well as the number of voids and urgency episodes vs. placebo. Similarly, tolterodine monotherapy also improved the number of voids and the urgency and frequency of episodes, but not the median voided volume. (Other trials have included men, but they were not adequately designed to look at these model therapies among men.)

Subsequently, Herschorn *et al.* (155) also conducted a meta-analysis by pooling data from two RCTs looking at fesoterodine monotherapy and men-only subgroups (156,157). In their analyses, they found that an 8 mg dose was significantly more efficacious than a 4 mg dose. With 12 weeks of follow-up, they found that both doses of fesoterodine reduced urinary frequency and urgency episodes relative to placebo, but only the 8 mg dose improved the mean voided volume. International Prostate Symptom Score was not evaluated as an endpoint. Common side effects included dry mouth and constipation, while urinary retention did not appear to be increased with monotherapy relative to placebo.

### 8.5.4 Treatment of overactive bladder symptoms in men: evidence from observational studies

Both the American and European guidelines concluded that antimuscarinic therapy could benefit the subset of men with predominantly storage symptoms. This conclusion is supported primarily by observational studies (at least several of which are open-label studies), safety trials, and post-hoc analyses of clinical trials.

In 2006, Elinoff *et al.* examined men and women over age 18 with significant urinary frequency and urgency (158). Based on a voiding diary, they found that tolterodine significantly improved daytime frequency, nocturia, and urgency and urge incontinence (even among the men) relative to baseline severity.

In 2009, Ronchi *et al.* conducted a pre–post study of men aged 40 or older with significant urinary frequency and urgency (159). Solifenacin was given to 49 men, and the primary endpoints were urodynamic parameters including $Q_{max}$, bladder pressures, voided volume, and PVR. Secondary endpoints included patient perception of bladder condition and selected items from the IPSS. These scores were significantly improved after 16 weeks. According to the voiding diaries, the episode of urinary urgency, the number of voids, the median voided volume, and incontinence all improved.

In 2010, Höfner *et al.* conducted an observational study in men with BPO from office-based practices (160). Some of the men were taking alpha-blockers as well as 5-ARIs. The investigators examined the treatment of these men with tolterodine 4 mg and found an improvement in the IPSS total score (−7.3 points), the IPSS QOL score (−2.1 points), and the OAB Questionnaires (OAB-q) score.

### 8.5.5 Antimuscarinic + alpha-blocker combination therapy

In 2003, Athanasopoulos *et al.* enrolled 50 consecutive cases with urodynamically demonstrated BOO according to Schäfer's nomogram (161). All were initially treated with 0.4 mg tamsulosin for a week. They were then randomized to receive either placebo or tolterodine while continuing to take tamsulosin. The investigators examined the European QOL questionnaire score and urodynamic parameters after 12 weeks. There was a statistically significant improvement in the QOL score, as well as a greater improvement in uroflow, $Q_{max}$, and voided volume at first unstable contraction.

In 2005, Lee *et al.* conducted an 8-week randomized clinical trial comparing doxazosin monotherapy with doxazosin plus propiverine (162). The primary endpoint was the mean number of voided episodes within 24 hours. There were significantly fewer episodes in the combination group.

In 2006, Kaplan *et al.* randomized 879 men into three groups: tamsulosin monotherapy, tolterodine monotherapy, and combination therapy with tamsulosin and tolterodine. The primary endpoint was the perception of treatment benefit. In this placebo-controlled trial, a significant difference was seen with the combination vs. the placebo-controlled groups (163).

In 2008, MacDiarmid *et al.* enrolled 420 men with LUTS, aged 45 and older, who had urgency and frequency with or without any urinary incontinence (164). They were randomized to receive either doxazosin or doxazosin plus tolterodine. The primary endpoint was total IPSS score. After 12 weeks of treatment, the combination therapy demonstrated superior efficacy in the total symptom score as well as in the storage subscale, the QOL item, and the symptom problem index score.

In 2009, Chapple *et al.* conducted a randomized clinical trial of 652 men who were on alpha-blockers (165). They were randomized to a 12-week course of tolterodine while maintained on the alpha-blocker therapy. The trial's primary endpoint was the patient-perceived bladder complaints score. While this was not statistically significant, other endpoints were significantly better in the combination group.

In 2011, another randomized trial, led by Lee, enrolled 176 men treated with doxazosin ± tolterodine for 12 weeks (166). In this placebo-controlled trial, the primary endpoint was the IPSS storage subscale. Following 12 weeks of treatment, the subscale score was significantly lower in the treatment arm. This arm also had fewer urgency episodes recorded in the voiding diary and a better IPSS and QOL score.

In 2011, Chung *et al.* enrolled 153 men in a long-term trial investigating standard BPO therapy (alpha-blocker ± 5-ARI). The men were randomized to receive placebo or tolterodine in addition to the primary BPO therapy (167). The primary endpoints were the IPSS storage and voiding subscales. Significantly lower scores on the storage subscales were noted after 12 months of therapy. There was no difference in the voiding subscale.

These trials demonstrate a fairly consistent evidentiary base for an effect of combination therapy with an alpha-blocker and an antimuscarinic agent. The magnitude of the improvement appears to be small, although statistically significant, in many of these trials, based on the primary endpoint. However, secondary endpoints in several of the trials do suggest a meaningful difference with combination therapy.

It is important to note that these trials often selected for men with a preponderance of urinary urgency and frequency symptoms, i.e. OAB symptoms. Generalization of results among these men to all men with BPO should only be done with great caution.

### 8.5.6 Adverse events

These agents, although approved, have generally been studied in women rather than men with BOO. Safety profiles with regards to uroselectivity have recently been reviewed for men (168). Antimuscarinic therapy does not appear to increase the risk of AUR in the trials noted above, which included men with PVR <250 mL. Given the lack of evidence among men with greater PVR, it is recommended that baseline PVR be checked prior to instituting antimuscarinic therapy. Effects on symptoms typically occur within 2 weeks; side effects include dry mouth, dry eyes, and constipation.

## 8.5.7 Conclusion

In randomized trials of men with significant storage symptoms (e.g. ≥8 voids/day), the addition of antimuscarinic therapy (versus placebo) to alpha-blocker therapy resulted in significant reductions in storage symptoms (with total IPSS storage subscale scores decreasing from 2 to 4 points), whereas antimuscarinic monotherapy has not been found to result in significant benefit in well-designed RCTs (**Table 22**) (163) among men where the primary endpoint is IPSS or a comparable validated measure. However, there are uncontrolled observational studies that suggest a positive effect.

The therapies (albeit not antimuscarinic agents) that affect the bladder detrusor muscle include Botox injections directly into the detrusor and neuromodulation. At least one RCT examining the role of Botox has been reported (152).

**TABLE 22** Randomized clinical trials of antimuscarinic therapy for BPO/OAB

| Trial | # | Duration | Group | | | Primary Endpoint | Findings |
|---|---|---|---|---|---|---|---|
| | | | Alpha-Blocker | Antimuscarinic | Combination | | |
| Athanasopoulos et al. (161) | 50 | 12 weeks | Tamsulosin | – | Tamsulosin + tolterodine | UDS and Urolife QOL | Both improved; Better in the combo group |
| Lee et al. (162) | 228 | 8 weeks | Doxazosin | – | Propiverine + doxazosin | Mean # voided episodes | Significantly fewer episodes in the combo group |
| Kaplan et al. (163) | 879 | 12 weeks | Tamsulosin | Tolterodine | Tamsulosin + tolterodine | Perceived treatment benefit | Significant difference; Superiority of combo relative to placebo and both monotherapies |
| Chapple et al. (165) | 652 | 12 weeks | Alpha-blockers | – | Alpha-blocker + tolterodine | PPBC | PPBC not significant; Other endpoints significantly improved |
| MacDiarmid et al. (164) | 420 | 12 weeks | Tamsulosin | – | Tamsulosin + oxybutynin | Total IPSS | Significant decrease in IPSS storage score, IPSS QOL, and SPI |
| Lee et al. (166) | 176 | 12 weeks | Doxazosin 4 mg | – | Doxazosin + tolterodine | IPSS storage subscale | Significant decrease in IPSS storage score, urgency on voiding diary, and IPSS QOL |
| Chung et al. (169) | 153 | 12 months | Alpha-blocker ± 5-ARI | – | Alpha-blocker ± 5-ARI + tolterodine | IPSS subscales | Significant decrease in storage subscale only |

# 8.6 **Hormonal Therapy**

## 8.6.1 **Introduction**

Although androgens do not cause BPH, the development of BPH requires the presence of testicular androgens during prostate development, puberty, and aging (170). Patients castrated before puberty, or who are affected by one of a variety of genetic diseases that impair androgen action or production, do not develop BPH (e.g. eunuchs in the Forbidden City, castrato singers in Renaissance Italy). It is also known that prostatic levels of dihydrotestosterone (DHT), as well as androgen receptor, remain high with aging, despite the fact that peripheral levels of testosterone decrease.

In the brain, skeletal muscle, and seminiferous epithelium, testosterone directly stimulates androgen-dependent processes. In the prostate, however, the nuclear membrane–bound enzyme steroid 5-AR converts the hormone testosterone into DHT, the principal androgen in this tissue (**Figure 14**).

**FIGURE 14**



Androgenic hormones and their actions in the prostate cells. Testosterone is derived from testicular and adrenal precursors. In the prostate, the enzyme 5 AR converts testosterone to DHT. Dihydrotestosterone binds to androgen receptor (AR) and this complex becomes active when it dissociates from heat shock protein (hsp 90). When activated, the DHT–androgen receptor complex enters the nucleus; it binds as a dimer to androgen response elements on deoxyribonucleic acid (DNA) and influences androgen-responsive genes. Dihydrotestosterone in the prostate stimulates production of messenger RNA for growth factors such as EGF and platelet-derived growth factor (PDGF), which in turn stimulate prostate cell division and growth (171).
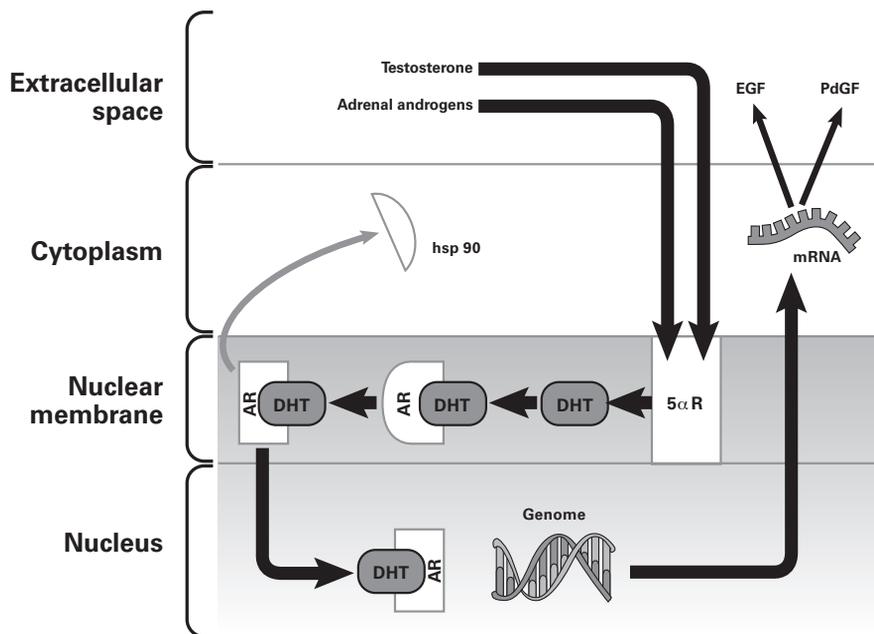
Ninety percent of total prostatic androgen is in the form of DHT, principally derived from testicular androgens. Adrenal androgens constitute the other 10% of total prostatic androgen, although the importance of this stored hormone source in the etiology of BPH is negligible.

Inside the cell, both testosterone and DHT bind to the same high-affinity androgen receptor protein (172). Dihydrotestosterone is a more potent androgen than testosterone, because of its higher affinity for the androgen receptor. Moreover, the DHT–receptor complex may be more stable than the testosterone–receptor complex. The hormone receptor then binds to specific DNA binding sites in the nucleus, which results in increased transcription of androgen-dependent genes and, ultimately, stimulation of protein synthesis (171). Conversely, androgen withdrawal from androgen-sensitive tissues results in a decrease in protein synthesis and tissue involution.

Despite the importance of androgens in normal prostatic development and secretory physiology, there is no evidence that either testosterone or DHT serves as the direct mitogen for growth of the prostate in older men. However, many growth factors and their receptors are regulated by androgens. Thus, the action of testosterone and DHT in the prostate is indirectly mediated through autocrine and paracrine pathways.

The prostate, unlike other androgen-dependent organs, maintains its ability to respond to androgens throughout life. Androgen receptor levels in the prostate remain high throughout aging (173,174). In fact, there is evidence to suggest that nuclear androgen receptor levels may actually be higher in hyperplastic tissue than in normal controls.

The aging prostate maintains a high level of DHT, as well as a high level of androgen receptor; thus, the mechanism for androgen-dependent cell growth is maintained. There is little doubt that androgens have at least a permissive role in the development of the disease process.

## 8.6.2   Androgen deprivation, luteinizing hormone–releasing hormone agonists, and androgen receptor blockade

As early as 1895 and 1896, it was demonstrated that surgical castration may relieve BOO presumed to be due to BPH, and allow men in urinary retention to void spontaneously (175–177).

The availability of medical castration and other forms of androgen deprivation using either steroidal or non-steroidal androgen receptor blocker, commonly used for the treatment of advanced prostate cancer, led in the 1980s and 1990s to several investigations of these classes of drugs for the treatment of male LUTS and BPO. Most notably, Peters and Walsh examined the influence of androgens on BPH, using nafarelin acetate, a potent luteinizing hormone–releasing hormone (LHRH) agonist, to achieve reversible androgen deprivation in men with BPO (178).

Nine patients with BOO due to BPH were treated with subcutaneous nafarelin acetate (400 μg/day) in an open trial for 6 months. In all patients, serum testosterone decreased to castrate levels, the prostate regressed to a mean (± SE) of 75.8% ± 3% of the initial PV (range: 52–86; $p<0.005$), and the regression reached a plateau after 4 months. Morphological analysis of biopsy specimens showed regression of glandular epithelium. Three of the nine patients had clinical improvement with treatment, and 6 months after the cessation of treatment, plasma testosterone levels had returned to normal and the PV had increased to 99% ± 5.5% of the initial PV.

These findings suggest that androgens have an important supportive role in established BPH, and that testicular suppression will benefit some patients. However, this form of treatment could be applicable only in carefully selected patients who are not surgical candidates, and it would have to be maintained indefinitely.

Oesterling reviewed the literature on LHRH agonists and anti-androgens in 1994, and found that all of them reduce the androgenic stimulation to the prostate gland, decrease PV by 25%, and cause modest improvement in symptom score (3–4 points) and $Q_{max}$ (approximately 2.5 mL/s). All of these therapies significantly decrease serum PSA concentration, and the effect is maintained for as long as the treatment is continued. Side effects are most pronounced with the LHRH agonists, with which impotency and decreased libido are universal phenomena (179).

## 8.6.3  Luteinizing hormone–releasing hormone antagonists

There are three drugs in the class of LHRH antagonists, which have the ability to reduce serum testosterone without the initial surge associated with the use of LHRH agonists. These drugs are cetrorelix, ozarelix, and degarelix. *In vivo* and animal studies suggest that there are LHRH receptors in the prostate, and that LHRH antagonists may affect a reduction in PV, and therefore an improvement in male LUTS and BPO (180–183).

Promising dose ranging phase 2 studies using cetrorelix have been published in the literature (184,185), suggesting a dose-dependent improvement in the IPPS and $Q_{max}$ with a temporary reduction of serum testosterone into the hypogonadal (but not castrate) range, and without effect on sexual performance characteristics.

Unfortunately, larger and more rigorous phase 3 trials with both cetrorelix (AEterna Zentaris, NCT00663858) and ozarelix (Spectrum Pharmaceuticals, NCT00427219) failed to show efficacy above placebo (data unpublished, available at http://clinicaltrials.gov/ct2/results?term=bph), and at the time of writing, it is unclear whether Ferring Pharmaceuticals is continuing its research and development of degarelix for a male LUTS and BPH indication.

### 8.6.3.1  Recommendation: luteinizing hormone–releasing hormone antagonists for male lower urinary tract symptoms

1. Moderate- to high-quality RCTs with LHRH antagonists have failed to show superiority against placebo. Luteinizing hormone–releasing hormone antagonists are not recommended for the treatment of men with LUTS (Level 2b).

## 8.6.4  5-alpha-reductase inhibitors

Two types of steroid 5-ARs have been discovered, each encoded by a separate gene (**Table 23**) (186). Type 2 5-AR is found predominantly in the prostate and other genital tissues, whereas type 1 is found throughout the body where 5-AR is expressed, including the skin, liver, and prostate. Studies in mice suggest that the type 1 enzyme is particularly important in the catabolism of androgens and other steroids, whereas the type 2 enzyme is important in androgen synthesis, although both isoenzymes participate in anabolic and catabolic processes.

The genes that encode the isoenzymes are located on different chromosomes, but the homologous coding sequences reflect a common evolutionary precursor. Dihydrotestosterone and testosterone bind to the androgen receptor and activate the protein in the same manner, with similar association rates. However, DHT dissociates from androgen receptor more slowly than does testosterone. Thus, under steady-state conditions, most androgen receptors in the prostate are occupied by DHT rather than testosterone. Therefore, a major role of 5-AR is to enhance the androgen effect by converting testosterone to an androgen that is not only intrinsically more potent, but that also binds more tightly to the androgen receptor (187).

**TABLE 23** Alpha reductase isoenzymes (186).

| Type 1 | Type 2 |
| --- | --- |
| Chromosome 5 | Chromosome: 2 |
| Km: 10 µM | Km: 0.4 µM |
| Optimum pH: 6.5–9.0 | Optimum pH: 5.5 |
| ▪ Skin, sebaceous glands, liver<br>▪ Lower level in benign prostate tissue<br>▪ Higher level in prostate cancer | ▪ Prostate and genital organs<br>▪ Lower levels in other organs |
| Mutations: Not known | Mutation: Male pseudohermaphroditism |

The idea that inhibitors of the 5-AR isoenzymes could be useful in the treatment of androgen-related disease emerged in the early 1970s, as the genetic phenotype of type 2 5-AR deficiency was described and the role of DHT as the primary mediator of androgen action in many tissues was discovered.

The clinical phenotype of 5-AR deficiency, a form of pseudohermaphroditism, was first described in the 1960s, when it was termed "pseudovaginal perineoscrotal hypospadias." Affected patients 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 virilization at puberty. Two patient cohorts with this inherited form of male pseudohermaphroditism caused by deficient DHT production were described by Walsh *et al.* and Imperato-McGinley *et al.* (188,189).

At the time of the first description of this syndrome, it was not known that there are in fact more than one 5-AR isoenzymes. The virilization at puberty was attributed to the sudden increase in testosterone production in the testes. In fact, since Russell *et al.* cloned the two 5-AR isoenzymes, it has become clear that in the deficiency syndrome, only type 2 is affected, while type 1 continues to convert testosterone to DHT in the other organs. It also follows from the clinical phenotype that type 2 is more important for prostate development, since none of the affected individuals ever developed either BPH or prostate cancer, and the prostate remains a small organ with fibrous tissue only and no glandular development (190–192).

The pharmaceutical industry became interested in the deficiency in the 1980s, and the idea emerged to mimic the deficiency syndrome, since affected individuals had no other signs of any illness. The first 5-ARI to be developed was MK-906–finasteride–and it was only by chance that it was a selective inhibitor of the type 2 isoenzyme, thus mimicking the deficiency syndrome, despite that fact that the existence of the second isoenzyme was not yet known. Since then, a number of compounds have been identified as 5-ARIs, including steroidal inhibitors, finasteride, SKF 105687, epristeride, and dutasteride (a dual 5-ARI) (193–199). Only finasteride and dutasteride (**Figure 15**) have reached clinical practice.

**FIGURE 15**

Chemical structure of the two 5-ARI azasteroids: finasteride and dutasteride.



Dutasteride (I)          Finasteride (II)
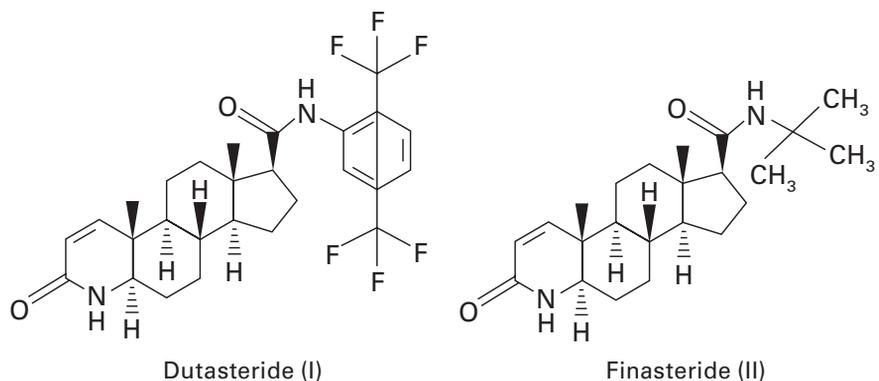
### 8.6.4.1  Pharmacology, mechanism of action, and effects in the prostate

Finasteride selectively blocks type 2, and dutasteride non-selectively blocks both isoenzymes. Finasteride reduces serum DHT by approximately 70%, and dutasteride reduces is by >90%. In the prostate, however, finasteride reduces DHT by 85%–90% (200), while dutasteride reduces it by 94% (201). With both drugs, there is a noticeable initial increase in serum testosterone of about 10%–20% in several clinical studies (202,203). There is also an increase in testosterone in the prostate, but due to the fact that DHT is the more potent androgenic steroid hormone, the overall androgenic load of the prostate is significantly lower (201). **Table 24** summarize some of the most important differences between finasteride and dutasteride.

**TABLE 24** Comparison of finasteride and dutasteride.

| | Finasteride | Dutasteride |
|---|---|---|
| 5-AR inhibition | Type 2 | Type 1 and 2 |
| DHT reduction in serum | ~70% | >90% |
| DHT reduction in the prostate | 85%–90% | 94% |
| Serum testosterone | Increased by 10%–20% | |
| Serum PSA | Total PSA ↓~50%; Free PSA ↓~50% | |
| PV | Reduced by 15%–25% | |
| Dosage | 5 mg/day | 0.5 mg/day |
| Serum $T_{1/2}$ | 6–8 hours | 5 weeks |

The reduction in androgenic load in the prostate leads to certain tissue changes, best characterized by Marks *et al.* (204). In men treated with finasteride over 12 months, the prostate epithelium progressively contracts from baseline (tissue composition: 19.2%; PV: 6.0 mL; and stroma/epithelial ratio: 3.2) to intermediate treatment (12.5%; 3.3 mL; and 5.6, respectively) to long-term treatment (6.4%, 2.0 mL, and 17.4, respectively, $p<0.01$ for all).

The percent epithelial contraction was similar in the peripheral and transitional zones ($p=$ not significant). The transitional zone remained a relatively constant proportion (53%–58%) of PV from baseline to long-term observation. Overall, multiple studies have observed a decrease in PV of 15%–25% with finasteride and/or dutasteride, a change that takes up to 6 months to occur (205–208).

It is interesting to note that in long-term open-label extension studies, the PV reduction is maintained, and there is essentially no further decrease or increase over time (209,210). In contrast, a recent study from Korea that followed men during treatment for 12 months, and then for 12 months after discontinuation of both 5-ARIs, observed that both serum PSA and PV had almost returned back to baseline, suggesting that the effect is reversible (211). Lastly, regarding PV changes, the shrinkage involves the transitional zone and the peripheral zone to the same degree, and the transitional zone index (TZI) remains unchanged (212,213).

With the use of 5-ARIs, the epithelial tissue contracts and the stroma-to-epithelial ratio increases, while the serum level of PSA decreases by a mean of approximately 50%. Since both total and free PSA decrease by the same margin, the ratio of free to total PSA remains stable, and is useful in the diagnosis of prostate cancer (214,215).

The serum half-life of finasteride is 6–8 hours (216), while that of dutasteride is 5 weeks (217,218), which leads to a slower return to normal of serum DHT (and presumably serum PSA) after discontinuation of treatment, which may be important in the interpretation of serum PSA values (**Figure 16**).

**FIGURE 16**

Serum DHT during treatment and after discontinuation of finasteride and dutasteride (217).
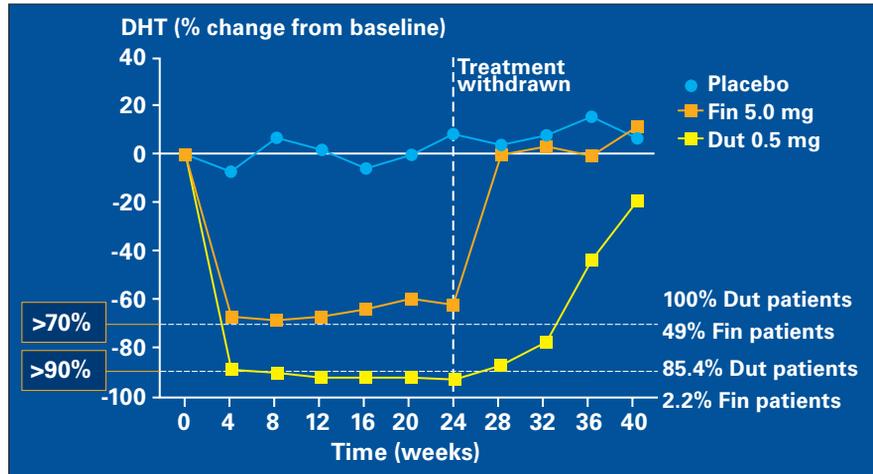


### 8.6.4.2 **Clinical studies**
#### Finasteride
The efficacy and safety of finasteride in men with LUTS/BPO has been demonstrated in many large-scale, randomized, placebo-controlled trials lasting between 1 and 5 years (**Tables 25** and **26**) (215,219–233).

**TABLE 25** Randomized phase 3 clinical trials with more than 100 patients in each study arm conducted with finasteride vs. placebo for the treatment of symptomatic LUTS/BPO. Studies comparing finasteride to other drugs or combinations, with fewer than 100 individuals in each treatment arm, or with a duration less than 1 year are not listed.

| Reference | Name of Study | Study Design | Study Duration | Treatment Arms | N Randomized/ Study Arm | |
|---|---|---|---|---|---|---|
| Gormley *et al.* (220) <br><br> Stoner (234) | North America (1992) | Randomized, double-blind, placebo-controlled, dose-finding | 1 y double-blind <br><br> + 2 y open extension | FIN 1 mg/d FIN 5 mg/d PLA | 305 FIN 1 mg 291 FIN 5 mg 299 PLA <br><br> 192 entered open extension (FIN 5 mg) | |
| Stoner (234) <br><br> Finasteride Study Group (221) | International (1993) | Randomized, double-blind, placebo-controlled, dose-finding | 1 y double-blind <br><br> + 2 y open extension | FIN 1 mg/d FIN 5 mg/d PLA | 249 FIN 1 mg 246 FIN 5 mg 255 PLA <br><br> 105 entered open extension (FIN 5 mg) | |
| Andersen *et al.* (222) | SCARP (Scandinavian BPH Study Group) (1995) | Randomized, double-blind, placebo-controlled, multicentre | 2 y double-blind | FIN 5 mg/d PLA | 347 FIN 346 PLA | |
| Nickel *et al.* (223) | PROSPECT (Proscar Safety Plus Efficacy Canadian Two-Year Study) (1996) | Randomized, double-blind, placebo-controlled, multicentre | 2 y double-blind | FIN 5 mg/d PLA | 307 FIN 306 PLA | |
| Marberger *et al.* (224) | PROWESS (Proscar Worldwide Efficacy and Safety Study) (1998) | Randomized, double-blind, placebo-controlled, multicentre | 2 y double-blind | FIN 5 mg/d PLA | 1,450 FIN 1,452 PLA | |
| McConnell *et al.* (205) <br><br> Roehrborn *et al.* (232) | PLESS (Proscar Long-Term Efficacy and Safety Study) (1998) | Randomized, double-blind, placebo-controlled, multicentre | 4 y double-blind <br><br> + 2 y open extension | FIN 5 mg/d PLA | 1,524 FIN 1,516 PLA <br><br> 803 former FIN & 686 former PLA completed open extension | |

*$p<0.001$; **$p<0.05$; ***$p<0.01$; ****$p<0.002$; †Cohort originally randomized to placebo and switched to finasteride in open extension; §Cohort originally randomized to finasteride and continued with finasteride in open extension.

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| | Primary Outcome At | | Secondary Outcome At | LE |
|---|---|---|---|---|
| **Year 1:**<br>Mod. Boyarscy score<br><br>**Year 3:**<br>Mod. Boyarscy score<br>PV<br>$Q_{max}$ | Change from baseline<br>PLA: –1 pt (–2%)<br>1 mg: –1.8 pt (–9%) (ns)<br>5 mg: –2.7 pt (–21%)\*\*<br><br>5 mg: –2.6 pt (–21%)\*<br><br>5 mg: –26.6%\*<br>5 mg: +2.4 mL/s\* | **Year 1:**<br><br>PV<br><br><br><br>$Q_{max}$ | Change from baseline<br>PLA: –1.3 mL (–3%)<br>1 mg: –11.8 mL (–18%)\*<br>5 mg: –11.1 mL (–19%)\*<br>PLA: +0.2 mL/s (+8%)\*<br>1 mg: +1.4 mL/s (23%)\*<br>5 mg: +1.6 mL/s (22%)\* | 1b |
| **Year 1:**<br>% with change from<br>baseline flow ≥3 mL/s<br><br>**Year 3:**<br>Mod. Boyarscy score<br><br>PV<br>$Q_{max}$ | PLA: 21%<br>1 mg: 33%<br>5 mg: 31%<br><br>Change from baseline<br>PLA: –2.6 pt\*<br>1 mg: –3.9 pt\*<br>5 mg: –3.6 pt\*<br>5 mg: –27.1%\*<br>5 mg: +2.3 mL/s\* | **Year 1:**<br>Mod. Boyarscy<br>score<br><br><br>PV<br><br><br>$Q_{max}$ | Change from baseline<br>PLA: –2.6 pt<br>1 mg: –2.9 pt (ns)<br>5 mg: –3.9 pt\*<br>PLA: –5%<br>1 mg: –23.6%\*<br>5 mg: –22.4%\*<br>PLA: 0.4 mL/s<br>1 mg: nr<br>5 mg: +1.3 mL/s\* | 1b |
| **Year 2:**<br>Mod. Boyarscy score | Change from baseline<br>PLA: +0.2 pt<br>FIN: –2.0 pt\*\*\* | **Year 2:**<br>PV<br><br><br>$Q_{max}$ | Change from baseline<br>PLA: +11.5 mL (95% CI: 4.8 to 18.1)<br>FIN: –19.2 mL (95% CI: –22.4 to –15.9)\*\*\*<br>PLA: –0.3 mL/s (95% CI: 0.7 to 0.0)<br>FIN: 1.5 mL/s (95% CI: 1.1 to 1.9)\*\*\* | 1b |
| **Year 2:**<br>Mod. Boyarscy score | Change from baseline<br>PLA: –0.7 pt<br>FIN: –2.1 pt\*\*\* | **Year 2:**<br>PV<br><br>$Q_{max}$ | Change from baseline<br>PLA: +8.4%<br>FIN: –21%\*\*\*<br>PLA: +0.3 mL/s<br>FIN: +1.4 mL/s\*\*\* | 1b |
| **Year 2:**<br>Mod. Boyarscy score | Change from baseline<br>PLA: –1.5 pt<br>FIN: –3.2 pt\* | **Year 2:**<br>PV<br><br>$Q_{max}$ | Change from baseline<br>PLA: +8.9%<br>FIN: –15.3%\*<br>PLA: +0.7 mL/s<br>FIN: +1.5 mL/s\*\*\*\* | 1b |
| **Year 4:**<br>Quasi–AUA-SI<br>improvement<br><br>**Year 6:**<br>Incidence of AUR<br>Incidence of surgery | –1.6 over PLA<br>(95% CI: –2.5 to –0.7)\*<br><br>0.49%/y (PLA/FIN)†<br>0.55%/y (FIN/FIN)§<br>0.81%/y (PLA/FIN)†<br>1.02%/y (FIN/FIN)§ | **Year 4:**<br>Incidence of<br>AUR or<br>surgery<br><br>Incidence of AUR | PLA: 13%; FIN: 7%<br>RR reduction: 51% (95% CI: 38 to 61)<br>PLA: 7%; FIN: 3%<br>RR reduction: 57% (95% CI: 40 to 69)<br>N/A | 1b |

d: day; FIN: finasteride; LE: level of evidence; m: months; N/A: not applicable; nr: not reported; ns: not statistically significant; PLA: placebo; pt: score points; w: weeks; y: years

**TABLE 26** Study withdrawals and adverse events in randomized phase 3 clinical trials with more than 100 patients in each study arm conducted with finasteride vs. placebo for the treatment of symptomatic LUTS/BPO. Studies comparing finasteride to other drugs or combinations, with fewer than 100 individuals in each treatment arm, or with a duration of less than 1 year are not listed.

| Reference | Name of Study | Study Design | Study Duration | Treatment Arms | N Randomized/ Study Arm | |
|---|---|---|---|---|---|---|
| Gormley *et al.* (220)  Stoner (234) | North America (1992) | Randomized, double-blind, placebo-controlled, dose-finding | 1 y double-blind  + 2 y open extension | FIN 1 mg/d FIN 5 mg/d PLA | 305 FIN 1 mg 291 FIN 5 mg 299 PLA | |
| Stoner (234)  Finasteride Study Group (221) | International (1993) | Randomized, double-blind, placebo-controlled, dose-finding | 1 y double-blind | FIN 1 mg/d FIN 5 mg/d PLA | 249 FIN 1 mg 246 FIN 5 mg 105 PLA | |
| Andersen *et al.* (222) | SCARP (Scandinavian BPH Study Group) (1995) | Randomized, double-blind, placebo-controlled, multicentre | 2 y double-blind | FIN 5 mg/d PLA | 347 FIN 346 PLA | |
| Nickel *et al.* (223) | PROSPECT (Proscar Safety Plus Efficacy Canadian Two-Year Study) (1996) | Randomized, double-blind, placebo-controlled, multicentre | 2 y double-blind | FIN 5 mg/d PLA | 307 FIN 306 PLA | |
| Marberger *et al.* (224) | PROWESS (Proscar Worldwide Efficacy and Safety Study) (1998) | Randomized, double-blind, placebo-controlled, multicentre | 2 y double-blind | FIN 5 mg/d PLA | 1,450 FIN 1,452 PLA | |
| McConnell *et al.* (205) | PLESS (Proscar Long-Term Efficacy and Safety Study) (1998) | Randomized, double-blind, placebo-controlled, multicentre | 4 y double-blind | FIN 5 mg/d PLA | 1,524 FIN 1,516 PLA | |

AE: adverse event; FIN: finasteride; PLA: placebo; y: years

| Withdrawals | | Adverse Events | |
|---|---|---|---|
| **PLA** | **FIN** | **PLA** | **FIN** |
| Due to AE: 18 (6%) | 1 mg: 14 (5%) 5 mg: 16 (5%) | **Decreased libido:** 1.3%  **Other:** | 1 mg: 6.0% ($p<0.05$ vs. PLA) 5 mg: 4.7% ($p<0.05$ vs. PLA)  Other AE reported statistically significantly over PLA |
| None | 1 mg: None 5 mg: 1, due to impotence | **Impotence:** 1 (0.4%)  **Other:** | 1 mg: 10 (4%, $p<0.001$ vs. PLA) 5 mg: 12 (4.9%, $p<0.001$ vs. PLA)  No other AE reported statistically significantly over PLA |
| All: 64 (18.1%) | 66 (18.7%) | **Sexual dysfunction:** 34 (10%)  **Other:** | 67 (19%, $p<0.01$ vs. PLA)  No other AE reported statistically significantly over PLA |
| All: 77 (25%) | 64 (20.8%) | **Sexual dysfunction:** Ejaculation: 5 (1.7%) Impotence: 9 (6.3%) Decreased libido: 19 (6.4%)  **Other:** | 24 (7.7%, $p<0.01$) 49 (15.8%, $p<0.01$) 31 (10%, $p<0.01$)  No other AE reported statistically significantly over PLA |
| All: 360 (24.7%) | 331 (22.8%) | **Sexual dysfunction:** Ejaculation: 9 (0.6%) Impotence: 74 (4.7%)  **Other:** AUR: 35 (2.2%) Hematuria: 24 (1.5%) Myocardial infarction: 8 (0.5%) Asthenia/fatigue: 24 (1.5%) | 33 (2.1%, $p<0.05$) 104 (6.6%, $p<0.05$)  17 (1.1%, $p<0.05$) 10 (0.6%, $p<0.05$) 23 (1.5%, $p<0.05$) 11 (0.7%, $p<0.05$) |
| All: 663 (42%) $p<0.001$ vs. FIN | 524 (34%) | **Sexual dysfunction:** Ejaculation: 0.1% Impotence: 3.7% Decreased libido: 3.4%  **Other:** Breast tenderness: 0.1% Rash: 0.2% | 0.8% ($p=0.002$) 8.1% ($p<0.001$) 6.4% ($p=0.002$) Note: Only ejaculation remained significant over PLA after 1 y  0.5% ($p=0.03$) 0.5% ($p=0.04$) |

AE: adverse event; FIN: finasteride; PLA: placebo; y: years

The Medical Therapy of Prostatic Symptoms (MTOPS) study randomized 3,047 men to receive placebo vs. doxazosin vs. finasteride 5 mg daily vs. combination therapy over a period of 4–5 years (208).

Additional safety data are derived from a 7-year randomized, placebo-controlled study of the efficacy and safety of finasteride 5 mg daily in the prevention of prostate cancer (the Prostate Cancer Prevention Trial–PCPT) (235).

In addition, there have been open-label extension studies done in patients participating in the randomized, placebo-controlled phase 3 studies, as well as in other studies, providing additional longer-term efficacy and safety data up to 10 years (209,210,236,237).

The efficacy of the 5-ARIs finasteride and dutasteride can be measured in terms of biological outcomes such as PV changes, and health outcomes such as symptom and bother improvement, as well as longer-term outcomes such as prevention of AUR and BPO-related surgery.

## Symptom and flow rate improvements

The available studies demonstrate that treatment with finasteride induces a significant decrease in symptom score compared to placebo after 1 year of treatment (–21% vs. –2%, respectively), which was confirmed in 2-year double-blind studies (mean: 17%; range: 13%–22%) and long-term placebo-controlled trials over a study period of 4 years (**Table 25**).

The mean reduction in the IPSS with finasteride treatment is ~3 points from baseline, and it takes 3–6 months of active treatment to reach this level of improvement.

The open-label extension studies with finasteride have demonstrated that this level of symptom improvement is maintained for as long as the patient takes the drug (236).

It is important to note that in all controlled studies conducted with finasteride, patients were enrolled with any PV, essentially including men with limited physical evidence of prostate enlargement, and with any serum PSA levels up to 10.0 ng/mL. Two randomized, placebo-controlled trials of 1 year's duration were performed in which men received placebo vs. an alpha-blocker (terazosin or doxazosin) vs. finasteride 5 mg vs. combination therapy (238,239). Finasteride was not found to be superior to placebo in either of these two trials, nor was the combination therapy found to be superior to the respective alpha-blocker treatment.

These findings prompted a meta-analysis of all available RCTs with finasteride vs. placebo in which patients were stratified by PV and serum PSA at baseline (230,240,241). It had been shown that there is a log-linear relationship of clinical utility between PV and serum PSA in men with BPO and no prostate cancer, and both parameters allowed a stratification of efficacy in terms of symptom and flow rate improvement with finasteride treatment versus placebo. The results of the meta-analysis suggest that finasteride is superior to placebo only in men with a PV >30 mL (or g) and/or a serum PSA of >1.5 ng/mL (**Figure 17**).

**FIGURE 17**

Drug-attributable improvement in quasi-IPSS score and $Q_{max}$ for finasteride vs. placebo, stratified by baseline PV. Results of a meta-analysis of RCTs with finasteride vs. placebo (240).
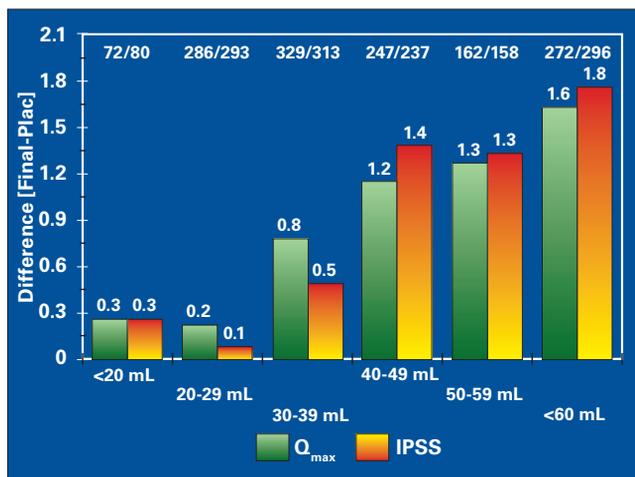


Several placebo-controlled trials demonstrated that finasteride induces an increase in $Q_{max}$ of between 1.8 and 2 mL. A 5-year open extension of an initial double-blind period showed a mean $Q_{max}$ improvement of approximately 13% in patients treated with finasteride 5 mg/day. Similar to its effect on symptom improvement, the effect of finasteride on $Q_{max}$ also depends on PV, with finasteride being most effective in men with large prostates.

## Prostate volume changes

Due to their MOA, finasteride and other 5-ARIs reduce the androgenic load on the prostate glandular epithelial tissue. This induces atrophy akin to that seen with castration (204,242,243). This atrophy eventually leads to PV reduction. Because the BPH/BPE/BPO gland is composed of stromal tissue and glandular epithelial tissue (with the proportion of the two being highly variable), and since only the glandular epithelial component is responsive to the withdrawal of the androgenic stimulus, the PV reduction seen with 5-ARI treatment is limited.

Several RCTs have demonstrated that finasteride reduces PV by ~20% (range: 15%–23%). All placebo-controlled studies that lasted more than 1 year indicate that the PV decreased during the first year, with no further decrease thereafter. In the open-label studies, the largest reductions in PV were also noted during the first year of finasteride therapy, leading to a decrease of around 27% after 3 and 5 years.

Meta-analyses have demonstrated that the percent reduction in PV is constant across all baseline PVs; it remains 15%–25% regardless of baseline PV and baseline serum PSA (**Figure 18**), which implies that the absolute reduction in PV is proportionate to both baseline PV and serum PSA.

**FIGURE 18**

Percent decrease in PV, stratified by baseline serum PSA. Results of a meta-analysis of RCTs with finasteride vs. placebo (240).
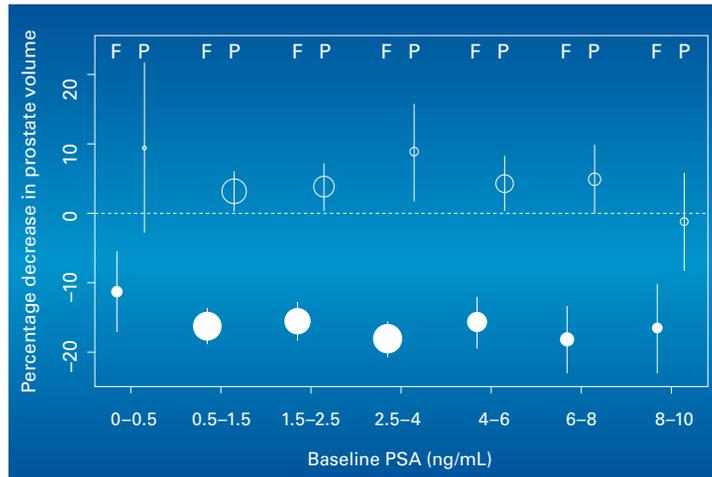
## Urodynamic changes

Several studies have investigated the effect of finasteride on obstructive parameters in pressure-flow studies. In a 12-month placebo-controlled trial, finasteride caused a moderate but significant decrease ($-8.1$ cm $H_2O$) in $P_{det}.Q_{max}$ ($p<0.05$ vs. placebo) (244). Of the finasteride-treated cases, 75% were obstructed and 25% were equivocal at baseline, compared with 67% and 33%, respectively, at month 12. These results have been confirmed by others, who found that the percentage of patients obstructed by the Abrams-Griffiths classification decreased from 76.2% at baseline to 66.7% after 1 year of finasteride treatment, and to 59.6% after 2 years (245). In general, the urodynamic effects of finasteride are small or moderate in amplitude, and are likely a direct consequence of PV reduction.

## Acute urinary retention and bpo-related surgery

Acute urinary retention episodes and the need for BPO-related surgery are long-term outcomes of great significance in the treatment of men with LUTS and BPO.

The results of several long-term placebo-controlled studies with finasteride suggest that the drug induces an approximately 50% relative reduction in risk for AUR and surgery over time, with the absolute reduction depending on the baseline risk of the population studied (i.e. the larger the PV at baseline, the greater the absolute risk).

Long-term placebo-controlled studies with finasteride in large number of patients have demonstrated that finasteride reduced the occurrence of AUR from 2.7% to 1.1% in 4,000 patients within 2 years (246), from 2.5% to 1.0% in 2,900 patients within 2 years (224), and from 6.6% to 2.8% in 3,040 patients within 4 years (231,247).

However, the frequency of AUR with finasteride was comparable to that with placebo (1%) in a 1-year finasteride trial in 750 patients (221). In both a community-based and a primary care study, the incidence of AUR was similar with finasteride (0.6% and 0.2%, respectively) and placebo (0.7% and 0.4%, respectively) (225,248).

Placebo-controlled clinical trials have also shown that finasteride reduced the risk for surgery from 6.5% in 2,109 placebo patients to 4.2% in 2,113 finasteride patients treated for 2 years (246), and from 5.9% to 3.5% in 2,900 patients treated for 2 years (224). In the 4-year placebo-controlled Proscar Long-Term Efficacy and Safety Study (PLESS), the risk for surgery with finasteride was reduced from 10% to 5% (**Table 27**) (205). This benefit was maintained throughout the 6-year open-label extension study (232).

**TABLE 27** Four-year incidence of AUR or surgery for BPH among men in the placebo and finasteride groups of the PLESS trial (205).

| Outcome | Placebo, No. (%) (*n*=1,503) | Finasteride, No. (%) (*n*=1,513) | Risk Reduction, % (95% CI) |
|---|---|---|---|
| Surgery or AUR | 199 (13) | 100 (7) | 51 (38–61) |
| Surgery | 152 (10) | 69 (5) | 55 (41–65) |
| Trans-urethral prostatectomy | 125 (8) | 64 (4) | 49 (33–62) |
| AUR* | 99 (7) | 42 (3) | 57 (40–69) |
| Spontaneous | 56 (4) | 20 (1) | 62 (40–76) |
| Precipitated | 48 (3) | 23 (2) | 52 (23–70) |

*Acute urinary retention was classified as spontaneous when there was no evidence of precipitating factors other than BPH, and as precipitated when there was evidence of precipitating factors in addition to BPH, such as preceding surgery, predisposing medications, or urinary tract infection. A single patient may have had an episode of both spontaneous and precipitated AUR at different times, but each man was only counted once in the total.

The reduction in the risk of AUR and surgery is dependent on the baseline risk of these events, which in turn is dependent on baseline age, PV, and serum PSA levels (**Figure 19**) (249).

**FIGURE 19**

Four-year incidences of either AUR or BPH-related surgery in patients treated with placebo or finasteride, stratified in tertiles by

**A** baseline PV (subset of 10% of patients) or

**B** baseline serum PSA. Arrows denote reduction in risk by the log-rank test (247).

†One placebo patient had a PV of 222 mL
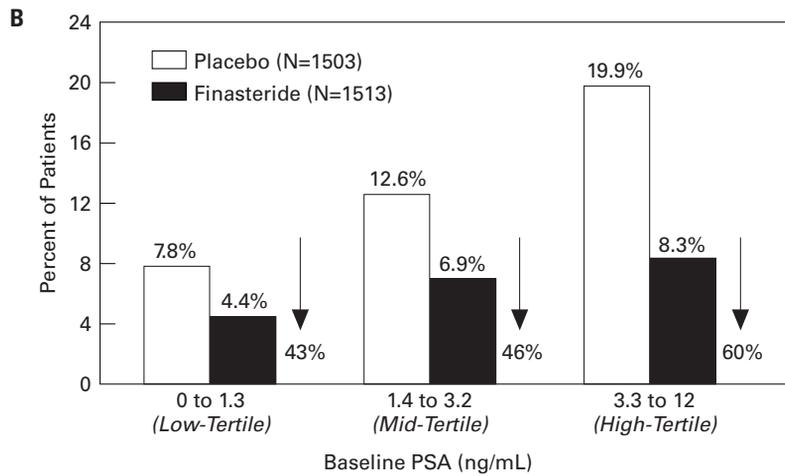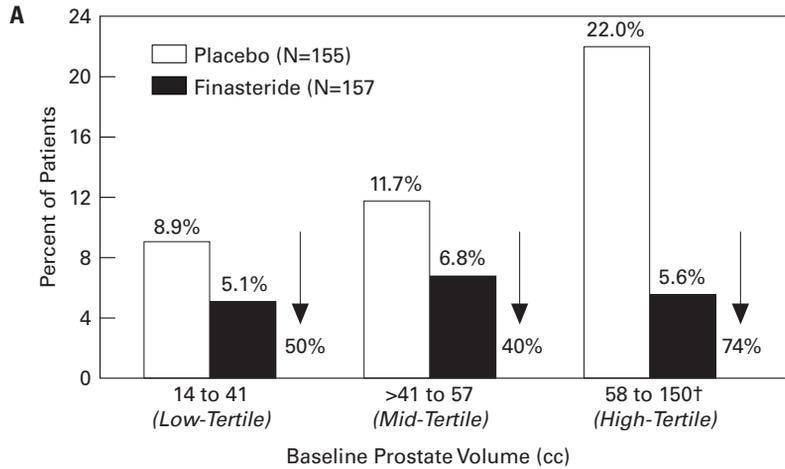
## Dutasteride

Dutasteride was developed to be a dual inhibitor of both isoenzymes of 5-AR, whereas finasteride inhibits only the type 2 isoenzyme, which is more common in BPH tissue. Dutasteride thus reduces serum and intraprostatic DHT levels more profoundly than does finasteride (~95% vs. ~70% in serum, and >95% in the prostate) (201,217,218,250). In addition, dutasteride has a serum half-life of 5 weeks, compared to the much shorter 6- to 8-hour half-life of finasteride. This has important implications, such as the continuation of adverse events after drug discontinuation from dutasteride, and the return of DHT and serum PSA to baseline with a potential loss of benefit in cases of poor drug compliance with finasteride.

The efficacy and safety of dutasteride in men with symptomatic BPO have been demonstrated in three large-scale, randomized, placebo-controlled phase 3 studies, each consisting of a 2-year double-blind phase and a 2-year open extension (ARIA3001, ARIA3002, and ARIB3003; **Tables 28** and **29**) (251–253). The data from these trials have been summarized in several meta-analyses (254).

**TABLE 28** Randomized phase 3 clinical trials conducted with dutasteride for the treatment of symptomatic LUTS/BPO.

| Reference | Name of Study | Study Design | Study Duration | Treatment Arms | N Randomized /Study Arm | |
|---|---|---|---|---|---|---|
| Roehrborn *et al.* (251)<br><br>O'Leary *et al.* (255)<br><br>Roehrborn *et al.* (206) | ARIA3001 | Randomized, double-blind, placebo-controlled, parallel-group | 2 y double-blind<br><br>+ 2 y open label | DUT<br>PLA | 720 DUT<br>720 PLA<br><br>290 former DUT & 255 former PLA completed, open label | |
| Roehrborn *et al.* (251)<br><br>O'Leary *et al.* (255)<br><br>Roehrborn *et al.* (206) | ARIA3002 | Randomized, double-blind, placebo-controlled, parallel-group | 2 y double-blind<br><br>+ 2 y open label | DUT<br>PLA | 677 DUT<br>685 PLA<br><br>287 former DUT & 266 former PLA completed, open label | |

*$p<0.001$
A-G: Abrams-Griffiths; d: day; DUT: dutasteride; FIN: finasteride; LE: level of evidence; m: months; N/A: not applicable; PLA: placebo; TAM: tamsulosin; w: weeks; y: years

| | Primary Outcome (Adjusted Mean Difference) | | Secondary Outcome (Adjusted Mean Difference) | | LE |
|---|---|---|---|---|---|
| **Year 1:** AUA-SI improvement | −1 over PLA (95% CI: −1.7 to −0.5)* | **Year 1:** PV | −21.1% over PLA (95% CI: −23.4 to −18.9) | | |
| | | $Q_{max}$ | +0.7 mL/s over PLA (95% CI: 0.3 to 1.1) | | |
| **Year 2:** Incidence of AUR | RR: 0.43 (95% CI: −0.29 to 0.62)* | **Year 2:** Incidence of surgery | RR: 0.52 (95% CI: 0.37 to 0.74)* | | |
| **Year 4:** Safety & tolerability | s. tab. side effects | **Year 4:** AUA-SI | −6.6 (DUT/DUT) −6.1 (PLA/DUT) | | 1b |
| | | PV | −26.2 (DUT/DUT) −21.4 (PLA/DUT) | | |
| | | $Q_{max}$ | 2.7 mL/s (DUT/DUT) 1.6 mL/s (PLA/DUT) | | |
| **Year 1:** AUA-SI improvement | −1.5 over PLA (95% CI: −2.1 to −0.9)* | **Year 1:** PV | −20.9% over PLA (95% CI: −23.0 to −18.8) | | |
| | | $Q_{max}$ | +0.8 mL/s over PLA (95% CI: 0.3 to 1.2) | | |
| **Year 2:** Incidence of AUR | s.a. | **Year 2:** Incidence of surgery AUA-SI | s.a. −2.2 over PLA (95% CI: −2.8 to −1.5) | | |
| **Year 4:** Safety & tolerability | s. tab. side effects | PV | −24.3% over PLA (95% CI: −26.7 to −21.9) | | 1b |
| | | $Q_{max}$ | +1.1 mL/s over PLA (95% CI: 0.7 to 1.6) | | |
| | | Year 4: AUA-SI | −5.5 (DUT/DUT) −4.5 (PLA/DUT) | | |
| | | PV | −26.1 (DUT/DUT) −20.0 (PLA/DUT) | | |
| | | $Q_{max}$ | +2.8 mL/s (DUT/DUT) +2.0 mL/s (PLA/DUT) | | |

*$p < 0.001$

A-G: Abrams-Griffiths; d: day; DUT: dutasteride; FIN: finasteride; LE: level of evidence; m: months; N/A: not applicable; PLA: placebo; TAM: tamsulosin; w: weeks; y: years

**TABLE 28** Randomized phase 3 clinical trials conducted with dutasteride for the treatment of symptomatic LUTS/BPO, *Cont'd*

| Reference | Name of Study | Study Design | Study Duration | Treatment Arms | N Randomized /Study Arm | |
|---|---|---|---|---|---|---|
| Roehrborn *et al.* (251)<br><br>O'Leary *et al.* (255)<br><br>Roehrborn *et al.* (205)<br><br>Debruyne *et al.* (252) | ARIA3003 | Randomized, double-blind, placebo-controlled, parallel-group | 2 y double-blind<br><br>+ 2 y open label | DUT<br>PLA | 769 DUT<br>753 PLA<br><br>396 former DUT & 374 former PLA completed, open label | |
| Data made public by investigator at gsk.com | ARIA3004 | Randomized, double-blind, placebo-controlled, parallel-group | 6 m double-blind<br><br>+ 6 m open label | DUT<br>PLA | 56 DUT<br>58 PLA<br><br>47 former DUT & 46 former PLA completed, open label | |
| Andriole *et al.* (256)<br><br>Gilling *et al.* (257) | ARIA0001 | Multicentre, randomized, double-blind, double-dummy, parallel-group | 1 y double-blind<br><br>+ 1 y open label | DUT<br>FIN | 813 DUT<br>817 FIN | |
| Barkin *et al.* (258) | ARIA0002 | Multicentre, randomized, double-blind, double-group | 36 w | DUT<br>DUT + TAM | 163 DUT 24 w + TAM 24 w<br>164 DUT 36 w + TAM 36 w | |

*$p<0.001$
A-G: Abrams-Griffiths; d: day; DUT: dutasteride; FIN: finasteride; LE: level of evidence; m: months; N/A: not applicable; PLA: placebo; TAM: tamsulosin; w: weeks; y: years

| | Primary Outcome (Adjusted Mean Difference) | | Secondary Outcome (Adjusted Mean Difference) | | LE |
|---|---|---|---|---|---|
| **Year 1:**<br>AUA-SI improvement | –1.2 over PLA<br>(95% CI: –1.8 to –0.6)* | | **Year 1:**<br>PV | –21.5% over PLA<br>(95% CI: –23.9 to –19.2) | |
| **Year 2:**<br>Incidence of AUR | s.a. | | $Q_{max}$ | +1.1 mL/s over PLA<br>(95% CI: 0.7 to 1.5) | |
| **Year 4:**<br>Safety & tolerability | s. tab. side effects | | **Year 2:**<br>Incidence of surgery<br>AUA-SI | s.a.<br><br>–2.0 over PLA<br>(95% CI: –2.6 to –1.3) | |
| | | | PV | –24.0% over PLA<br>(95% CI: –26.5 to –21.5) | 1b |
| | | | $Q_{max}$ | +1.2 mL/s over PLA<br>(95% CI: 0.7 to 1.6) | |
| | | | **Year 4:**<br>AUA-SI | | |
| | | | PV | –7.1 (DUT/DUT)<br>–6.1 (PLA/DUT) | |
| | | | $Q_{max}$ | –29.9 (DUT/DUT)<br>–24.0 (PLA/DUT)<br>2.5 mL/s (DUT/DUT)<br>1.2 mL/s (PLA/DUT) | |
| **Month 6:**<br>Change in $p_{det}.Q_{max}$ | –2.6 cm $H_2O$ over PLA<br>($p$=0.97) | | **Month 6:**<br>A-G Number<br>No change<br>Decrease<br>Increase | 4.0 DUT, 0.1 PLA<br>89% DUT, 75% PLA<br>4% DUT, 18% PLA<br>7% DUT, 7% PLA | |
| **Month 12:**<br>AUA-SI | –4.9 (DUT/DUT)<br>–4.7 (PLA/DUT) | | **Month 12:**<br>N/A | N/A | 1b |
| $Q_{max}$ | –34.7 (DUT/DUT)<br>–34.5 (PLA/DUT) | | | | |
| PV | 2.0 (DUT/DUT)<br>1.8 (PLA/DUT) | | | | |
| **Year 1:**<br>Change of PV from baseline | 0.4% over FIN<br>(95% CI: –1.6 to 2.3)<br>($p$=0.65) | | **Year 1:**<br>AUA-SI | –0.3 over FIN<br>(95% CI: –0.8 to 0.3) | |
| **Year 2:**<br>Safety & tolerability | s. tab. side effects | | $Q_{max}$ | 0.3 mL/s over FIN<br>(95% CI: –0.1 to 0.7) | 1b |
| | | | **Year 2:**<br>N/A | N/A | |
| **Week 30:**<br>% with improvement or no change in symptoms | –0.11 difference in %<br>(95% CI: –0.18 to –0.04)* | | **Week 36:**<br>% with improvement or no change in symptoms | –0.03 difference in %<br>(95% CI: –0.09 to 0.02) | 1b |

*$p$<0.001
A-G: Abrams-Griffiths; d: day; DUT: dutasteride; FIN: finasteride; LE: level of evidence; m: months; N/A: not applicable; PLA: placebo; TAM: tamsulosin; w: weeks; y: years

**TABLE 29** Study withdrawals and adverse events in the ARIA3001 randomized phase 3 clinical trial conducted with dutasteride for the treatment of symptomatic LUTS/BPO, representative of all ARIAxxxx studies. (As numbers for withdrawals and adverse events do not differ in the other ARIAxxxx trials, they are not listed here.) (206,251,252,255–258, Data made public by investigator at gsk.com).

| Name of Study | Study Design | Study Duration | Treatment Arms | N Randomized /Study Arm | Withdrawals | | Adverse Events | |
|---|---|---|---|---|---|---|---|---|
| | | | | | PLA | FIN | PLA | FIN |
| ARIA3001 | Ran-domized, double-blind, placebo-con-trolled, parallel-group | 2 y double-blind + 2 y open label | DUT PLA | 720 DUT 720 PLA 290 former DUT & 255 former PLA completed open label | **Year 1 (PLA):** All: 133 (18.5%) Due to AE: 33 (5%) **Year 2:** All: 229 (31.8%) Due to AE: 52 (7%) **Year 4:** All: 137 (34.9%) Due to AE: 39 (10%) | (DUT): 117 (16.3%) 36 (5%) 206 (28.6%) 60 (8%) 122 (29.6%) 36 (9%) | **Year 1 (PLA):** Impotence: 22 (3%) Ejaculation: 6 (<1%) Serious AEs: 65 (9%) **Year 2:** Impotence: 32 (4%) Serious AEs: 106 (15%) **Year 4:** Impotence: 19 (5%) Serious AEs: 41 (10%) | (DUT): 47 (7%) 17 (2%) 62 (9%) 61 (8%) 110 (15%) 16 (4%) 49 (12%) |

AE: adverse event; DUT: dutasteride; PLA: placebo; y: years

## Symptom and flow rate improvement

These studies showed a statistically significant decrease in AUA-SI score and $Q_{max}$ during the 2-year double-blind phases.

Of the 4,325 LUTS/BPO patients randomized, a total of 2,340 continued with open-label dutasteride treatment for another 2 years. Among 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 those in the original dutasteride group (206). This finding has been used to suggest that earlier initiation of 5-ARI treatment is of greater benefit than later initiation.

All dutasteride studies have enrolled men with a PV >30 mL (or g) and a serum PSA of >1.5 ng/mL. This is in contrast to the body of evidence for finasteride discussed previously, and may be partially responsible for the different clinical outcomes. The improvements with dutasteride in IPSS of 4.0 points at 24 months and 6.1 points at 48 months, as well as the improvements in $Q_{max}$ of 2.3 mL/s and 2.8 mL/s at the same two time points (**Table 30**), are greater than those observed with finasteride, which may indeed be a reflection of patient selection.

The effect of dutasteride on symptom improvement was greatest in patients with a large TZI (212).

**TABLE 30** Baseline, 24-month, and 48-month data for the participants in the open-label extension trials of dutasteride vs. placebo (206).

| Parameter | Baseline | | 24 Months | | 48 Months | |
|---|---|---|---|---|---|---|
| | P/D | D/D | P/D | D/D | P/D | D/D |
| Age (years) | 66.0 ± 7.0 | 66.1 ± 7.7 | – | – | – | – |
| PV (mL) | 53.8 ± 20.3 | 56.7 ± 24.3 | 55.8 ± 25.6 | 42.6 ± 20.3 | 43.2 ± 20.4 | 42.8 ± 22.8 |
| Mean change in PV (%) | – | – | 3.9 ± 25.60 | −24.4 ± 19.47 | −20.7 ± 22.89 | −26.2 ± 21.98 |
| TZV (mL) | 26.9 ± 16.0 | 28.6 ± 18.0 | 28.6 ± 19.2 | 21.5 ± 14.2 | 22.8 ± 18.8 | 22.4 ± 16.0 |
| Mean change in TZV (%) | – | – | 10.4 ± 42.38 | −21.7 ± 29.78 | −14.2 ± 49.25 | −20.0 ± 39.63 |
| AUA-SI | 16.9 ± 6.0 | 16.7 ± 5.9 | 15.1 ± 7.2 | 12.8 ± 6.7 | 11.6 ± 6.5 | 10.6 ± 6.2 |
| Mean change in AUA-SI | – | – | −1.9 ± 6.68 | −4.0 ± 6.49 | −5.3 ± 6.94 | −6.1 ± 6.24 |
| $Q_{max}$ (mL/s) | 10.9 ± 3.8 | 10.2 ± 3.7 | 11.4 ± 4.8 | 12.5 ± 5.8 | 12.6 ± 5.2 | 12.9 ± 5.7 |
| Mean change in $Q_{max}$ (mL/s) | – | – | 0.5 ± 4.6 | 2.3 ± 5.39 | 1.8 ± 5.21 | 2.8 ± 5.45 |

D/D: dutasteride/dutasteride-treated subjects; P/D: placebo/dutasteride-treated subjects; TZV: transitional zone volume
Data presented as the mean ± SD.

## Prostate volume changes

Despite the greater reduction in intraprostatic DHT, the reduction in PV with dutasteride is very similar to that seen with finasteride; namely, a reduction of about 15%–25%, achieved after about 6 months of treatment and then maintained for the duration of treatment (**Table 28**).

Dutasteride did not have a differential effect on transitional zone volume (TZV) or on peripheral PV. Total PV, TZV, and peripheral PV were reduced by approximately 26% after 2 years of dutasteride treatment (206,213).

## Urodynamic changes

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 ($P_{det}.Q_{max}$) nor any of the secondary outcome parameters were statistically significant compared with placebo. Data from this trial were made public only on the website www.gsk.com (**Table 28**).

## Acute urinary retention and bpo-related surgery

To calculate the primary outcome parameter of incidence of AUR at 24 months, results from three trials were pooled, and an RR reduction of 0.43 over placebo was demonstrated. Men with prostates in the two upper TZI tertiles had statistically significantly fewer incidences of AUR and surgery.

An analysis of the placebo-controlled and the open-label extension studies suggests a roughly 50% reduction in the risk of AUR and surgery among dutasteride- vs. placebo-treated patients (**Table 31**) (252).

**TABLE 31** Crude incidence rates of AUR or BPH-related surgery in the double-blind and open-label phases (double-blind intention-to-treat population) (252).

| Study Phase | | AUR | | BPO-Related Surgery | |
|---|---|---|---|---|---|
| | | P/D (n=2,158) | D/D (n=2,167) | P/D (n=2,158) | D/D (n=2,167) |
| Double-blind phase | Month 0–6 | 1.3% | 0.9% | 0.6% | 0.6% |
| | Month 6–12 | 1.0% | 0.4% | 1.3% | 0.6% |
| | Month 12–18 | 1.1% | 0.2% | 1.0% | 0.7% |
| | Month 18–24 | 0.9% | 0.4% | 1.4% | 0.4% |
| Open-label phase | Month 24–30 | 0.6% | 0.1% | 0.3% | 0.2% |
| | Month 30–36 | 0.6% | 0.4% | 0.5% | 0.2% |
| | Month 36–42 | 0.3% | 0.4% | 0.1% | 0.4% |
| | Month 42–48 | 0.6% | 0.3% | 0.2% | 0.1% |
| Incidence over 48 months | | 5.1% | 2.4% | 4.5% | 2.6% |

D/D: dutasteride double-blind/dutasteride open-label; P/D: placebo double-blind/dutasteride open-label

### 8.6.4.3  Direct comparator trial

In addition to these published trials, one 12-month randomized direct comparison trial of dutasteride versus finasteride, including an additional 12-month open-extension phase, has been conducted (the Enlarged Prostate International Comparator Study–EPICS) (259). The study was conducted to fulfill European registration requirements. Its primary endpoint was the change in baseline PV at 1 year. Safety and tolerability data were also obtained. A total of 1,630 patients 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, 1,454 completed the 12-month double-blind phase (719 dutasteride; 735 finasteride).

The enrollment criteria of the EPICS study are a key component to the correct interpretation of its findings. Only men aged ≥50 years with a clinical diagnosis of BPH according to their medical history and a physical examination (including digital rectal examination–DRE) were eligible for the study. The main inclusion criteria were an AUA-SI score of ≥12 points at screening, PV ≥30 mL assessed by TRUS, two voids with $Q_{max}$ <15 mL/s, and a minimum voided volume of ≥125 mL. Principal exclusion criteria included PVR >250 mL, a history or evidence of prostate cancer, previous prostatic surgery or other invasive procedure to treat BPH, AUR within 3 months of study entry, and total serum PSA <1.5 ng/mL or >10.0 ng/mL. In other words, the criteria matched those of the dutasteride database, but not those of the finasteride database, resulting in a baseline PSA of 4.3 ng/mL and a baseline PV of 52.4–54.2 mL.

Over 12 months, dutasteride and finasteride improved the IPSS by 5.8 and 5.5 points, respectively, and the $Q_{max}$ by 2.0 mL/s and 1.7 mL/s, respectively (**Figure 20**).

**FIGURE 20**

Changes in (**A**) IPSS and (**B**) $Q_{max}$ over 12 months in patients receiving dutasteride vs. finasteride in the EPICS trial (259).
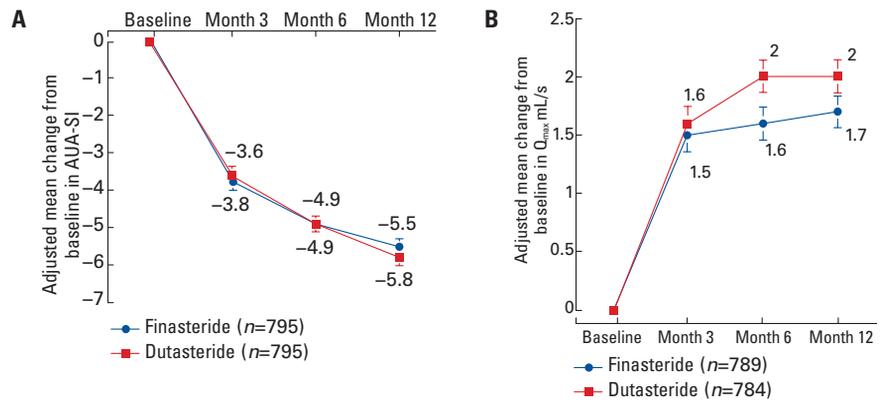


Prostate volume reduction was similar in both groups, and slightly higher in those with PV >40 mL at baseline (**Table 32**).

**TABLE 32** Percent change in PV from baseline in the EPICS trial.

| | PV <40 mL | | | PV ≥40 mL | | |
|---|---|---|---|---|---|---|
| | Finasteride (*n*=239) | Dutasteride (*n*=233) | *P* Value | Finasteride (*n*=573) | Dutasteride (*n*=576) | *P* Value |
| Month 3, n | 229 | 223 | | 552 | 556 | |
| Adjusted mean, % | −16.6 | −13.7 | 0.10 | −19.4 | −20.0 | 0.54 |
| Month 12, n | 230 | 226 | | 558 | 561 | |
| Adjusted mean, % | −24.2 | −22.6 | 0.37 | −27.7 | −27.6 | 0.90 |

The adverse events, and specifically the sexually related adverse events, were nearly identical in both groups (**Table 33**).

**TABLE 33** Adverse events of special interest during the double-blind and open-label phases of the EPICS trial, by year.

| Adverse Event | Double-Blind | | Open-Label* | | |
|---|---|---|---|---|---|
| | FIN Year 1 (*n*=817) | DUT Year 1 (*n*=813) | Total (*n*=448) | FIN/DUT[†] Years 2 & 3 (*n*=226) | DUT/DUT[‡] Years 2 & 3 (*n*=222) |
| Impotence, n (%) | 74 (9) | 63 (8) | 14 (3) | 6 (3) | 8 (4) |
| Decreased libido, n (%) | 50 (6) | 41 (5) | 5 (1) | 5 (2) | 0 (0) |
| Ejaculation disorders, n (%) | 14 (2) | 14 (2) | 4 (<1) | 1 (<1) | 3 (1) |
| Sexual function disorders, n (%) | 2 (<1) | 1 (<1) | 0 (0) | 0 (0) | 0 (0) |
| Gynecomastia, n (%) | 10 (1) | 9 (1) | 3 (<1) | 2 (<1) | 1 (<1) |
| Hypertension, n (%) | 16 (2) | 19 (2) | 29 (6) | 15 (7) | 14 (6) |
| AUR, n (%) | 11 (1) | 16 (2) | – | – | – |
| Prostate surgery[§], n (%) | 1 (<1) | 2 (<1) | – | – | – |
| Prostate cancer, n (%) | 4 (<1) | 3 (<1) | 4 (<1) | 3 (1) | – |

*The incidence of AUR and prostate surgery were not specifically collected in the open-label phase; [†]Subjects received finasteride during the double-blind phase and dutasteride during the open-label phase; [‡]Subjects received dutasteride during both the double-blind and open-label phases of study; [§]All subjects requiring surgery had ≥40 mL baseline PV
DUT: dutasteride; FIN: finasteride

The results of the EPICS trial suggest that in men who are suitable candidates for treatment with 5-ARIs, therapy with dutasteride and finasteride yields similar clinical outcomes over a period of 12 months.

### 8.6.4.4 Discontinuation trials

it is known that the discontinuation of 5-ARIs leads to a reversal of their effects on serum and intraprostatic DHT levels, and a reduction in serum PSA levels; and it had been assumed that the PV would rebound to some extent, which was not well understood.

A formal withdrawal study was conducted, in which a total of 120 patients with BPH were enrolled from December 2004 to May 2008 (260). The patients were randomized into two groups: one group received finasteride 5 mg plus alfuzosin 10 mg or tamsulosin 0.2 mg daily, and the other received dutasteride 0.5 mg plus alfuzosin 10 mg or tamsulosin 0.2 mg daily. All patients received combination therapy for 1 year, followed by 1 year of alpha-blocker monotherapy.

Prostate volume, IPSS, and serum PSA were determined at baseline and at 12 and 24 months after treatment. This very important trial suggests that (a) serum PSA levels decreased at 12 months by about 50% and returned to about 95% or baseline after 12 months off drugs; (b) PV decreased by 24%–26% and returned to about 88%–91% of baseline after 12 months off drugs; and (c) even the IPSS increased, although not quite to baseline (**Tables 34–36**). Temporary discontinuation or intermittent therapy with 5-ARIs is therefore not recommended.

**TABLE 34** Comparison of change in PV according to study duration between both groups.

| Duration (Months) | PV (mL) | | P Value* |
|---|---|---|---|
| | FIN (*n*=37) | DUT (*n*=40) | |
| 0 | 39.78 ± 9.30 | 39.22 ± 12.27 | 0.997 |
| 12 | 30.02 ± 7.58 | 28.97 ± 8.27 | 0.568 |
| 24 | 36.22 ± 10.76 | 34.38 ± 10.72 | 0.435 |
| Change from 0 to 12[†] (%) | −24.51 ± 10.01 | −26.11 ± 5.06 | 0.552 |
| Change from 12 to 24[‡] (%) | +20.69 ± 14.10 | +18.62 ± 7.40 | 0.340 |
| Ratio of 0–24(%) | 91.05 ± 27.04 | 87.62 ± 24.33 | 0.068 |
| P value[§] | <0.001 | <0.001 | – |

Data presented as mean ± SD.
*Analysis between two groups using Student's *t*-test; [†]Reduction rate in PV; [‡]Regrowth rate in PV; [§]Statistical analysis between 0 and 12 months and 12 and 24 months performed with repeated measures analysis of variance.
DUT: dutasteride; FIN: finasteride.

**TABLE 35** Comparison of change in total IPSS according to study duration between both groups.

| Duration (Months) | FIN (*n*=31) | DUT (*n*=30) | *P* Value* |
|---|---|---|---|
| 0 | 18.62 ± 5.97 | 18.77 ± 5.85 | 0.555 |
| 12 | 12.74 ± 4.48 | 12.97 ± 4.51 | 0.058 |
| 24 | 14.17 ± 4.94 | 14.20 ± 4.83 | 0.865 |
| Change from 0 to 12 (%) | −31.57 ± 24.06 | −30.90 ± 22.38 | 0.728 |
| Change from 12 to 24 (%) | +11.22 ± 6.98 | +8.66 ± 5.24 | 0.061 |
| *P* value† | <0.001 | <0.001 | – |

Data presented as mean ± SD; patients receiving alpha-blocker only before enrollment excluded from analysis.
*Analysis between two groups using Student's *t*-test; †Statistical analysis between 0 and 12 months and 12 and 24 months performed with repeated measures analysis of variance.

**TABLE 36** Mean change in PSA level from baseline according to study duration.

| Duration (Months) | FIN (*n*=37) | DUT (*n*=40) | *P* Value* |
|---|---|---|---|
| 0 | 1.83 ± 0.73 | 1.85 ± 1.18 | 0.615 |
| 12 | 0.94 ± 0.36 | 0.91 ± 0.55 | 0.352 |
| 24 | 1.74 ± 0.66 | 1.75 ± 1.06 | 0.655 |
| Change from 0 to 12 (%) | −48.9 ± 8.59 | −50.9 ± 12.1 | 0.493 |
| Ratio of 0–24 (%) | 95.1 ± 7.96 | 94.0 ± 11.3 | 0.852 |

Data presented as mean ± SD.
*Analysis between two groups using Student's *t*-test.

### 8.6.4.5 Prevention of lower urinary tract symptoms/benign prostatic hyperplasia

The PCPT trial has been used to study the potential use of finasteride in the primary prevention of LUTS and BPH (261). After those with a history of BPH diagnosis or treatment, and those with an IPSS ≥8 at study entry were excluded, 9,253 men were eligible for analysis. The primary endpoint was incidence clinical BPH, defined as the initiation of medical treatment, surgery, or sustained, clinically significant urinary symptoms (IPSS >14). The mean length of follow-up was 5.3 years.

The incidence of clinical BPH was 19 per 1000 person-years in the placebo arm and 11 per 1000 person-years in the finasteride arm ($p<0.001$). In a covariate-adjusted model, finasteride reduced the risk of incident clinical BPH by 40% (hazard ratio: 0.60; 95% CI: 0.51 to 0.69; $p<0.001$).

The number needed to treat (NNT) to prevent one case of clinical BPH over 7 years was 58 (95% CI: 35 to 177) for men 55–59 years of age, 42 (95% CI: 25 to 123) for men 60–64 years, and 31 (95% CI: 19 to 83) for men ≥65 years. For men ≥65 years, the 5- and 6-year NNT values were 54 (95% CI: 32 to 152) and 40 (95% CI: 25 to 111), respectively (**Figure 21**).

**FIGURE 21**

Unadjusted cumulative incidence of symptomatic BPH in finasteride and placebo arms among men ≥65 years old at baseline (n=2,912).
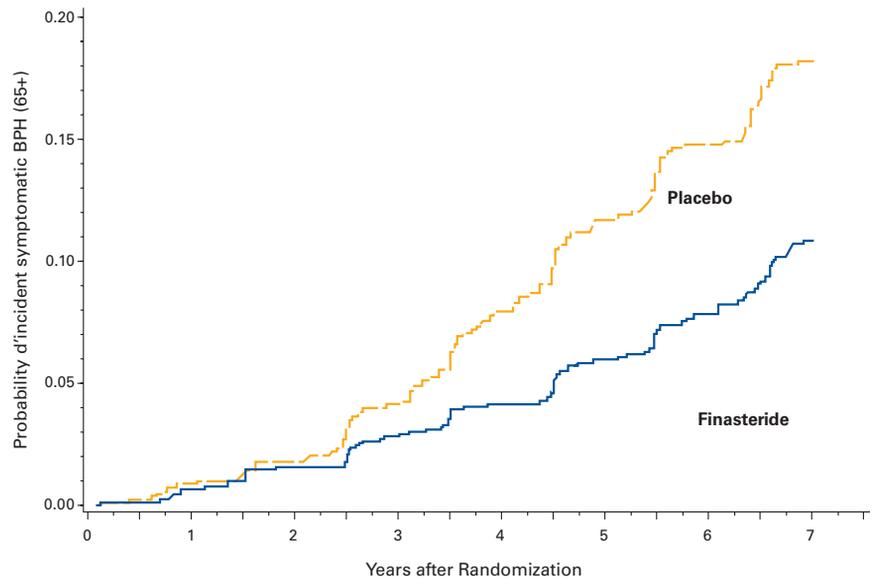


| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 | Year 7 |
|---|---|---|---|---|---|---|---|
| **Finasteride group** | | | | | | | |
| No. at risk | 1391 | 1248 | 1175 | 1077 | 994 | 912 | 813 |
| No. BPH events | 11 | 8 | 15 | 14 | 18 | 18 | 24 |
| **Placebo group** | | | | | | | |
| No. at risk | 1521 | 1408 | 1306 | 1192 | 1079 | 977 | 853 |
| No. BPH events | 9 | 15 | 31 | 45 | 43 | 33 | 32 |

A similar analysis was done using the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study data (262), in 1,617 men randomized to dutasteride or placebo with a PV >40 mL and baseline IPSS <8.

Subjects who took medications for BPO were excluded at study entry. The outcome was a comparison of risk of clinical progression of BPH at 4 years (defined as a ≥4-point worsening on IPSS, AUR, urinary tract infection (UTI), or BPH-related surgery). A total of 464 patients (29%) experienced clinical progression, 297 (36%) of whom were receiving placebo, and 167 (21%) of whom were receiving dutasteride ($p<0.001$).

The RR reduction was 41% and the absolute risk reduction was 15%, with an NNT of 7 (**Figure 22**). Among men who had AUR and BPO-related surgery, the absolute risk reduction with dutasteride was 6.0% and 3.8%, respectively. On multivariable regression analysis adjusting for covariates, dutasteride significantly reduced clinical progression of BPO, with an OR of 0.47 (95% CI: 0.37 to 0.59, $p<0.001$). Analysis of the time to first event yielded a hazard ratio of 0.673 ($p<0.001$) for those taking dutasteride.

**FIGURE 22**

Absolute rates and RR reduction for AUR, BPH-related surgery, and clinical progression of BPH among 1,617 asymptomatic men with enlarged prostate glands who were randomized to treatment with dutasteride or placebo (262).



RRR: relative risk (RR) reduction
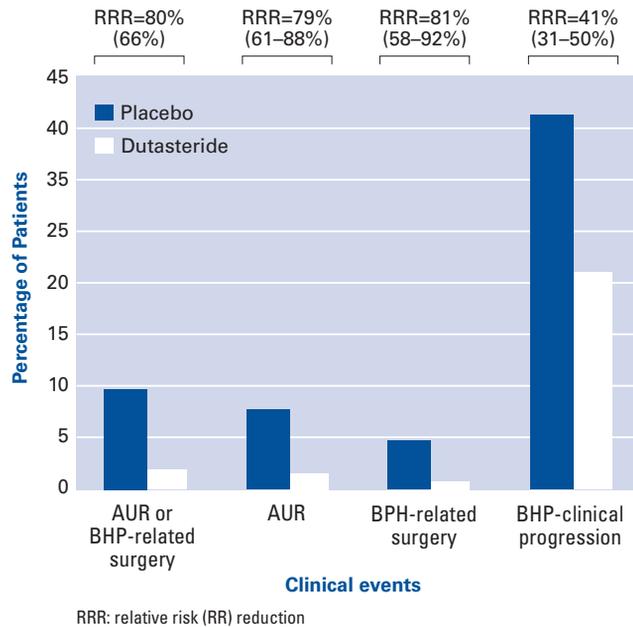
## 8.6.4.6 Meta-analyses and systematic reviews

Several meta-analyses and systematic reviews have been performed reviewing the safety and efficacy of finasteride and dutasteride. The overall conclusions of these reviews are that both drugs have moderate efficacy and are reasonably safe for use in men with LUTS and BPO (263–266).

## 8.6.4.7 Adverse events and adverse reactions

According to their package inserts and scientific studies, both finasteride and dutasteride have some effect on semen parameters, but these effects are not significant, and return back to baseline upon cessation of treatment (202).

Neither drug has been shown to affect bone density over time as LHRH analogues given for 2 years or more have been shown to (256,267,268).

Both dutasteride and finasteride are known to increase serum testosterone by 10%–30% from baseline, with a greater increase in men with lower baseline levels (which could be a regression-to-the-mean phenomenon) (203,269–271).

Finasteride and dutasteride are generally well tolerated, with the most prevalent adverse events being sexual function–related, such as impotence, decreased libido, and abnormal or decreased volume of ejaculation. However, these side effects are rare compared to those associated with traditional anti-androgen treatment, typically appearing in the first year of treatment in 5%–10% of patients.

In later phases of controlled clinical studies and open-label extension arms, the incidence of newly developed sexual adverse events was found to be similar to that in the placebo control group, which in turn is reflective of the incidence of erectile dysfunction (ED) and libido and ejaculatory problems found in aging men in general (**Tables 37–39**) (272–274).

There are several large review articles that report the incidence rates for such events in the peer-reviewed literature (275,276).

**TABLE 37** Incidence of sexually related adverse events in double-blind and open-label extension arms of the phase 3 finasteride trial (209).

| Adverse Event | Year 1 (Double Blind) | | | Open Extension (Finasteride 5 mg) | | | | |
|---|---|---|---|---|---|---|---|---|
| | FIN 5 mg (n=547) | FIN 1 mg (n=552) | PLA (n=558) | Year 2 (n=1,344) | Year 3 (n=1,218) | Year 4 (n=1,085) | Year 5 (n=957) | Year 6 (n=853) |
| Decreased libido | 3.8 | 4.9 | 1.8 | 2.5 | 1.6 | 1.5 | 1.7 | 1.4 |
| Ejaculation disorder | 2.9 | 2.9 | 1.1 | 1.4 | 0.7 | 0.7 | 0.6 | 0.8 |
| Impotence | 3.8 | 4.3 | 1.6 | 3.2 | 2.1 | 1.9 | 2.4 | 1.9 |
| Orgasm dysfunction | 0.5 | 0.2 | 0.2 | 0.3 | 0.1 | 0.1 | 0.2 | 0 |
| Rash | 0.5 | 0.7 | 0.2 | 0.1 | 0 | 0 | 0 | 0 |
| Breast complaint | 0.2 | 0.4 | 0 | 0.4 | 0.4 | 0 | 0.3 | 0.7 |
| Discontinuations due to sexual adverse events | 1.3 | 0.7 | 0.2 | 0.5 | 0.5 | 0.6 | 0.6 | 0.8 |

FIN: finasteride; PLA: placebo

**TABLE 38** Adverse events reported in ≥1% of subjects in dutasteride placebo-controlled clinical trials over a 24-month period (from the dutasteride package insert).

| Adverse Event Dutasteride (n) Placebo (n) | Adverse Event Time of Onset | | | |
|---|---|---|---|---|
| | Months 0–6 (n=2,167) (n=2,158) | Months 7–12 (n=1,901) (n=1,922) | Months 13–18 (n=1,725) (n=1,714) | Months 19–24 (n=1,605) (n=1,555) |
| Impotence Dutasteride Placebo | 4.7% 1.7% | 1.4% 1.5% | 1.0% 0.5% | 0.8% 0.9% |
| Decreased libido Dutasteride Placebo | 3.0% 1.4% | 0.7% 0.6% | 0.3% 0.2% | 0.3% 0.1% |
| Ejaculation disorders Dutasteride Placebo | 1.4% 0.5% | 0.5% 0.3% | 0.5% 0.1% | 0.1% 0.0% |
| Breast disorders* Dutasteride Placebo | 0.5% 0.2% | 0.8% 0.3% | 1.1% 0.3% | 0.6% 0.1% |

*Includes breast tenderness and breast enlargement.

**TABLE 39** Sexually related adverse events in clinical trials with finasteride and dutasteride (275).

| Source | Condition | N Drug | N PLA | Ages | Daily Dosage | Duration | Libido (Drug/PLA) | ED (Drug/PLA) | Ejaculatory Function Disorder or Abnormal Ejaculate Volume (Drug/PLA) |
|---|---|---|---|---|---|---|---|---|---|
| Kaufman *et al.* | Alopecia | 779 | 774 | 18–41 | 1 mg FIN | 1 year + 1 year open | 1.9%/1.3% | 1.4%/0.9% | 1%/0.4% (volume) |
| Leyden *et al.* | Alopecia | 133 | 123 | 18–40 | 1 mg FIN | 1 year + 1 year open | 1.5%/1.6% | 0.75%/0% | 0/0.8% |
| Whiting *et al.* | Alopecia | 286 | 138 | 41–60 | 1 mg FIN | 2 years | 4.9%/4.4% | 3.8%/0.7% | 2.8%/0.7% |
| Byrnes *et al.* | BPH | 1,759 | 583 | ≥45 | 5 mg FIN | 12 months | 2.9%/1.0% | 5.6%/2.2% | 2.1%/0.5% |
| Clark *et al.* | BPH | 60 | 59 | ≥50 | 0.5 mg DUT | 24 weeks | 4%/2% | 11%/3% | N/A |
| Clark *et al.* | BPH | 55 | 59 | ≥50 | 5 mg FIN | 24 weeks | 13%/2% | 11%/3% | N/A |
| Debruyne *et al.* | BPH | 2,166 | 2,158 | ≥50 | 0.5 mg DUT | 2 years | 0.6%/0.3% | 1.7%/1.2% | 0.5%/0.1% |
| Gormley *et al.* | BPH | 297 | 300 | 40–83 | 5 mg FIN | 12 months | 4.7%/1.3% | 3.4%/1.7% | 4.4%/1.7% |
| Hudson *et al.* | BPH | 259 | N/A | 64 (avg) | 5 mg FIN | 1 year + 4 years open | 7.7%/3.3% | 6.7%/4.0% | 4.7%/1.7% |
| Kirby *et al.* | BPH | 264 | 269 | 50–80 | 5 mg FIN | 1 year | 3.4%/1.9% | 4.9%/3.3% | 2.3%/1.5% (volume) |
| Lepor *et al.* | BPH | 310 | 305 | 45–80 | 5 mg FIN | 1 year | 5%/1% | 9.4%/4.6% | 2%/1% |
| Lowe *et al.* | BPH | 547 | 558 | 64 (avg) | 5 mg FIN | 1 year + 5 years open | 3.8%/2.3% | 4.8%/1.8% | 3.1%/1.1% |
| Marberger | BPH | 1,577 | 1,591 | 50–75 | 5 mg FIN | 2 years | 4.0%/2.8% | 6.6%/4.7% | 2.1%/0.6% |
| McConnell *et al.* | BPH | 1,523 | 1,516 | 64 (avg) | 5 mg FIN | 4 years | 2.6%/2.6% | 5.1%/5.1% | 0.2%/0.1% |
| McConnell *et al.* | BPH | 168 | 737 | ≥50 | 5 mg FIN | 4.5 years | 2.4%/1.4% | 4.5%/3.3% | 1.8%/0.8% |
| Nickel *et al.* | BPH | 310 | 303 | 45–80 | 5 mg FIN | 2 years | 10%/6.3% | 15.8%/6.3% | 7.7%/1.7% |
| Roehrborn *et al.* | BPH | 1,128 | 1,123 | ≥50 | 0.5 mg DUT | 2 years | 0.5%/0.4% | 1.3%/1.3% | 0.3%/0.1% |
| Tenover *et al.* | BPH | 1,736 | 579 | ≥45 | 5 mg DUT | 12 months | 5.4%/3.3% | 8.1%/3.8% | 4.0%/0.9% |
| Amory *et al.* | None | 34 | 32 | 18–55 | 5 mg FIN | 1 year + 6-month follow-up | 18%/3% | 3%/6% | 6%/0% |
| Amory *et al.* | None | 33 | 32 | 18–55 | 0.5 mg DUT | 1 year + 6-month follow-up | 6%/3% | 6%/6% | 3%/0% |

DUT: dutasteride; FIN: finasteride; N/A: not applicable; PLA: placebo

It has been suggested that some sexually related adverse events with finasteride–at least when used in younger men for the treatment of alopecia at the 1 mg daily dosage–are irreversible (277). However, most other biochemical, biological, and patient-reported effects of the 5-ARIs are reversible, and it has been suggested that these sexually related adverse events are part of a nocebo phenomenon to some degree, induced by the consent forms given to study patients (278).

### 8.6.4.8 Recommendations: 5-alpha-reductase inhibitors

1. 5-alpha-reductase inhibitors are superior to placebo in high-quality RCTs in terms of symptoms, bother, and QOL in men with clinically enlarged prostates >30 mL secondary to BPH (Level 1, Grade A).
2. 5-alpha-reductase inhibitors are superior to placebo in high-quality RCTs in terms of symptoms, bother, and QOL in unselected men with LUTS (Level 1, Grade B).
3. 5-alpha-reductase inhibitors maintain improvements in symptoms, bother, and QOL over the long term (up to 5 years and longer) in controlled studies and open-label extension studies (Level 1, Grade A).
4. The efficacy and tolerability of finasteride and dutasteride are identical (Level 1, Grade B).
5. Discontinuation of either finasteride or dutasteride leads to a reversal of the beneficial effects on symptoms and PV (and the reduction in serum PSA); intermittent therapy is not recommended (Level 1, Grade B).
6. Other aspects of therapy relating to prevention of progression in PV increase, and reduction of the risk of retention and the development of cancer are considered by other committees (Grade D).

### 8.6.4.9 Hematuria due to benign prostatic enlargement/obstruction

5-alpha-reductase inhibitors have been shown to have an effect on hematuria presumed due to prostatic origin by excluding other causes (279–282). Foley *et al.* studied 57 patients prospectively randomized to finasteride versus placebo (279). In the untreated control group, hematuria recurred in 17 patients (63%) within a year, but in only 4 patients (14%) in the finasteride group, which was a statistically significant difference ($p<0.05$). Surgery was required for bleeding in 7 control patients (26%), while no patient on finasteride required surgery.

A recent Cochrane meta-analysis confirmed this overall effect and reported that compared with the placebo control group, the finasteride group showed a significantly decreased incidence of hematuria during the 12-month follow-up period (OR: 0.11; 95% CI: 0.06 to 0.21, $p<0.05$) (283).

Several investigators have examined the MOAs underlying this effect and have come to similar conclusions (284–286). Pareek *et al.* studied 24 patients undergoing prostatic surgery for benign disease, of whom 12 were given finasteride for a minimum of 6 weeks before surgery, and the remaining 12 served as controls. Sections from the prostatic urothelium and hyperplastic prostate were individually stained for CD34, specific for nascent blood vessels and vascular endothelial growth factor (VEGF). Analysis of each specimen was performed in a blinded fashion. Microvessel density (MVD) was calculated by counting the number of positively stained blood vessels on 10 consecutive, non-overlapping, high-power fields within the suburethral and hyperplastic prostate compartments. Vascular endothelial growth factor expression was examined by immunohistochemistry. Statistical analysis of the results was performed using Student's t-test.

Prostatic suburethral VEGF expression and MVD were significantly lower in the finasteride group compared to controls ($p<0.05$). Differences between the two groups in VEGF expression and MVD at the level of the hyperplastic prostate were not found to be significant.

Hochberg *et al.* found the mean MVD in finasteride-treated patients to be significantly lower in the suburethral portion of the prostate versus in untreated controls (14.0 ± 2.8 versus 20.2 ± 5.3 vessels per high-power field, $p<0.05$ (286). Memis *et al.* found that the mean MVD in the suburethral portion of prostate was significantly lower in patients treated with finasteride compared with controls (9.08 ± 5.6 and 13.94 ± 5.90, respectively, $p<0.05$). The mean MVD for the hyperplastic portion of prostate was similar between the finasteride and control groups (14.21 ± 7.10 and 19.75 ± 9.73, respectively, $p>0.05$) (284).

### 8.6.4.10 Recommendation: finasteride for idiopathic prostate-related bleeding

1. Based on cohort studies and one RCT of moderate quality, finasteride is recommended for the treatment of idiopathic and presumably prostate-related hematuria (Level 2, Grade B).

### 8.6.4.11 Idiopathic Hemospermia

There is one placebo-controlled trial in 25 men with idiopathic refractory hemospermia, in which there was remission over 12 month in 66.7% of the finasteride- vs. 25% of the placebo-treated patients (287).

### 8.6.4.12 Recommendation: finasteride for idiopathic hemospermia

1. Based on one low-quality RCT, finasteride is recommended as a possible treatment for idiopathic hemospermia (Level 2, Grade B).

### 8.6.4.13 Prevention of bleeding during trans-urethral surgery

An effect of finasteride and dutasteride on peri-operative bleeding at the time of TURP has been observed by several clinicians (288–293). Not all authors, however, had consistent positive findings (294,295). Many of these studies suffered from methodological shortcomings in terms of the measurement of blood loss, standardization, and the definitions of meaningful endpoint (e.g. transfusion rate instead of drop in hemoglobin–Hb).

Hahn *et al.* conducted perhaps the best and most definite study pertaining to this question (296). They performed a double-blind, randomized, placebo-controlled, multicentre study involved 214 patients with BPO. Placebo was compared with dutasteride 0.5 mg/day 2 weeks before and after TURP, or 4 weeks before and 2 weeks after TURP. Surgical blood loss was measured using an Hb photometer (HemoCue AB, Angelholm, Sweden), and post-operative adverse events were recorded. Microvessel density was calculated by immunostaining and light microscopy of the prostatic chips.

Although dutasteride reduced serum DHT by 86%–89% in 2–4 weeks, and intraprostatic DHT was approximately 10 times lower than in the placebo group, the (adjusted) mean Hb loss during surgery was 2.15–2.55 g Hb/g resectate, with no significant difference in blood loss between the groups either during or after TURP.

Clot retention occurred in 6%–11%, and urinary incontinence in 14%–15% of patients during the 14 weeks after TURP, with no difference between the groups. The authors concluded that there were no significant reductions in blood loss during or after TURP (or complications afterwards) with dutasteride compared with placebo, despite significant suppression of intraprostatic DHT (**Table 40**). Blood loss and transfusion rates in the placebo group were lower than those previously reported in studies where there was a beneficial effect of a 5-ARI, relative to placebo, on bleeding during TURP.

**TABLE 40** Blood loss during or after TURP, complications after TURP, and changes in DHT and testosterone (296).

| Variable | Group 1 PLA (N=70) | Group 2 PLA + DUT (N=72) | Group 3 DUT (N=71) |
|---|---|---|---|
| **Blood loss, g Hb/g resectate** | | | |
| During TURP | | | |
| Adjusted mean (SE) | 2.55 (0.41) | 2.15 (0.40) | 2.55 (0.39) |
| Median (range) | 1.54 (0.24–28.89) | 1.56 (0.14–15.35) | 1.37 (0.11–20.49) |
| After TURP | | | |
| Adjusted mean (SE) | 0.85 (0.25) | 0.98 (0.25) | 0.99 (0.24) |
| Median (range) | 0.31 (0.10–7.92) | 0.40 (0.02–6.70) | 0.38 (0.05–7.12) |
| Total during and after TURP | | | |
| Adjusted mean (SE) | 3.09 (0.44) | 2.84 (0.44) | 3.16 (0.43) |
| Median (range) | 1.94 (0.25–28.89) | 2.17 (0.14–15.35) | 1.75 (0.22–20.71) |
| Total blood loss during TURP, g Hb | | | |
| Adjusted mean (SE) | 54.5 (7.45) | 45.7 (7.33) | 61.1 (7.19) |
| Median (range) | 28.8 (3.53–260.05) | 31.2 (1.35–225.90) | 32.5 (1.05–317.56) |
| Total blood loss during TURP, L | | | |
| Adjusted mean (SE) | 0.37 (0.05) | 0.32 (0.05) | 0.43 (0.05) |
| Median (range) | 0.24 (0.03–1.74) | 0.21 (0.01–1.64) | 0.21 (0.01–2.48) |

*Socially or hygienically unacceptable leakage of urine; [†]Patients could be included in more than one severity level
DUT: dutasteride; PLA: placebo

**TABLE 40** Blood loss during or after TURP, complications after TURP, and changes in DHT and testosterone (296), *Cont'd*

| Variable | Group 1 PLA (N=70) | Group 2 PLA + DUT (N=72) | Group 3 DUT (N=71) |
|---|---|---|---|
| N (%): | | | |
| Excessive/severe bleed after TURP | 4 (6) | 1 (1) | 2 (3) |
| Blood transfusions | 2 (3) | 2 (3) | 1 (1) |
| Clot retention | 4 (6) | 8 (11) | 4 (6) |
| AUR | 8 (11) | 12 (17) | 9 (13) |
| UTI | 14 (20) | 19 (26) | 22 (31) |
| Urinary incontinence* | 10 (14) | 10 (14) | 11 (15) |
| **Mean (SE) highest MVD** | | | |
| Prostatic urethra | 44 (20) | 46 (18) | 48 (21) |
| Nodular hyperplasia | 53 (22) | 50 (21) | 55 (21) |
| **Bleeding after TURP** | | | |
| N | 64 | 67 | 67 |
| Median (range) total days with bleeding | 13 (1–66) | 13 (2–50) | 15 (1–109) |
| Median (range) days to last bleeding event | 26 (3–103) | 25 (5–94) | 25 (1–110) |
| Severity of bleeding†, n (%) | | | |
| Mild | 48 (75) | 53 (79) | 50 (75) |
| Moderate | 56 (88) | 64 (96) | 63 (94) |
| Severe | 7 (11) | 2 (3) | 5 (7) |
| **Changes in DHT and testosterone** | | | |
| N | 70 | 72 | 71 |
| Serum testosterone (adjusted means) | | | |
| % change to TURP | 3.5 | 14.5 | 13.3 |
| % change 4 weeks after TURP | 2.7 | 9.8 | 9.6 |
| Serum DHT (adjusted means) | | | |
| % change to TURP | 0.9 | −85.9 | −88.7 |
| % change 4 weeks after TURP | −10.7 | −87.6 | −87.4 |
| Intra-prostatic hormones, pg/g | | | |
| Adjusted mean testosterone | 43 | 1,414 | 1,644 |
| Adjusted mean DHT | 3,155 | 365 | 290 |

*Socially or hygienically unacceptable leakage of urine; †Patients could be included in more than one severity level
DUT: dutasteride; PLA: placebo

### 8.6.4.14 Recommendation: 5-alpha-reductase inhibitors to prevent bleeding during trans-urethral resection of the prostate

1. Finasteride and dutasteride have been studied in several moderate- to high-quality RCTs in the setting of pre-TURP treatment, to reduce bleeding and related complications during surgery. The evidence is conflicting, but the best-quality RCT fails to show superiority in the relevant clinical outcomes. The use of these drugs in the setting of prevention of bleeding and related complications prior to TURP is not recommended (Level 2, Grade B).

### 8.6.4.15 Prostate cancer chemoprevention

The issue of chemoprevention using 5-ARIs is beyond the scope of this consensus conference on male LUTS and BPO, but is germane to the drug class. Two large placebo-controlled trials using finasteride and dutasteride consistently showed a reduction in the period prevalence of prostate cancer, by approximately 23%–25% (235,297). However, in the same trials, a trend towards identification of higher-grade cancers in the 5-ARI treatment groups was found, which ultimately lead to the FDA not approving a chemoprevention indication, as well as a label change for both drugs, including a warning regarding the potential for higher-grade prostate cancer (298).

A recent Cochrane review found that (a) 5-ARIs reduce the risk of being diagnosed with prostate cancer among men who are screened regularly for prostate cancer (**Table 41**); (b) information is inadequate to assess the effect of 5-ARIs on prostate cancer or all-cause mortality; and (c) 5-ARIs increase sexual dysfunction and ED (299).

**TABLE 41** Prostate cancer period prevalence (299).

| Study | Prostate Cancer Detected 'for Cause' | | | Overall Prostate Cancer Period Prevalence | | |
|---|---|---|---|---|---|---|
| | 5-α-RI, n/N | PLA, n/N | RR (95% CI) | 5-α-RI, n/N | PLA, n/N | RR (95% CI) |
| **Finasteride, mid–term treatment duration (1–2 years)** | | | | | | |
| Cote 1998 | – | – | – | 8/27 | 1/25 | 7.41 (1.00–55.09) |
| PROSPECT 1996 | 3/310 | 6/303 | 0.49 (0.12–1.94) | 3/310 | 6/303 | 0.49 (0.12–1.94) |
| FSG 1992–93 | 7/1,090 | 3/555 | 1.19 (0.31–4.58) | 8/1,090 | 4/555 | 1.02 (0.31–3.37) |
| *Subtotal* | *10/1,400* | *9/858* | *0.74 (0.30–1.82)* | *19/1,427* | *11/883* | *1.29 (0.33–5.02)* |
| **Finasteride, long-term treatment duration (>2 years)** | | | | | | |
| PCPT 2003 | 435/9,423 | 571/9,459 | 0.76 (0.68–0.86) | 803/9,423 | 1,147/9,459 | 0.70 (0.65–0.77) |
| PLESS 1998 | 36/1,524 | 45/1,516 | 0.80 (0.52–1.23) | 72/1,524 | 77/1,516 | 0.93 (0.68–1.27) |
| *Subtotal* | *471/10,947* | *616/10,975* | *0.77 (0.68–0.86)* | *875/10,947* | *1,224/10,975* | *0.78 (0.60–1.01)* |
| **Dutasteride, mid-term treatment duration (1–2 years)** | | | | | | |
| ARIA 2002 | 27/2,167 | 55/2,158 | 0.49 (0.31–0.77) | 27/2,167 | 55/2,158 | 0.49 (0.31–0.77) |
| Total | 508/14,541 | 680/14,016 | 0.75 (0.67–0.83) | 921/14,541 | 1,290/14,016 | 0.74 (0.55–1.00) |
| **Dutasteride for men at increased risk for prostate cancer, long-term treatment duration (>2 years)** | | | | | | |
| REDUCE 2010 | 63/4,105 | 86/4,126 | 0.74 (0.53–1.02) | 659/4,105 | 858/4,126 | 0.77 (0.70–0.85) |
| **Dutasteride vs. combined dutasteride and tamsulosin, long-term treatment duration (>2 years)** | | | | | | |
| CombAT 2010 | 42/1,623 | 37/1,610 | 1.13 (0.73–1.74) | 42/1,623 | 37/1,610 | 1.13 (0.73–1.74) |
| **Dutasteride vs. doxazosin, long-term treatment duration (>2 years)** | | | | | | |
| CombAT 2010 | 42/1,623 | 63/1,611 | 0.66 (0.45–0.97) | 42/1,623 | 63/1,611 | 0.66 (0.45–0.97) |
| **Combined dutasteride and tamsulosin vs. tamsulosin, long-term treatment duration (>2 years)** | | | | | | |
| CombAT 2010 | 37/1,610 | 63/1,611 | 0.59 (0.39–0.88) | 37/1,610 | 63/1,611 | 0.59 (0.39–0.88) |

CombAT: Combination of Avodart and Tamsulosin; PLA: placebo

## 8.6.4.16 Recommendation: 5-alpha-reductase inhibitors for prostate cancer chemoprevention

1. The committee does not make a formal recommendation and refers to other guidelines from authoritative bodies (Grade D).

# 8.7 Phosphodiesterase Type 5 Enzyme Inhibitors

## 8.7.1 Introduction

In 2012, the phosphodiesterase type 5 enzyme (PDE5) inhibitor tadalafil (Cialis) was approved by the FDA in a 5-mg daily dosage for the treatment of men with LUTS/BPH and ED in a comorbid setting. Approval in Europe and other parts of the world is anticipated in coming years. This marks the first approval of an entirely new class of drugs for male LUTS/BPH in some time.

The following sections review the basic science of phosphodiesterase (PDE) isoenzymes, their inhibitors, the developments of the PDE5 inhibitors for the treatment of ED, the basic science and population-based data linking male LUTS and ED, and the MOAs proposed for the use of PDE5 inhibitors in male LUTS/BPH.

## 8.7.2 Phosphodiesterases and their inhibitors

Two cyclic nucleotide monophosphates, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are important endogenous mediators of several processes, including smooth muscle motility (300,301).

Cyclic nucleotides are synthesized from the corresponding nucleoside triphosphates by the activity of adenylyl and guanylyl cyclases. The increase in cAMP or cGMP triggers a signal transduction cascade encompassing the activation of cyclic nucleotide–dependent protein kinases (cAMP-dependent protein kinase–cAK, cGMP-dependent protein kinase–cGK), subsequent phosphorylation of the actin–myosin system, and Ca2+ channels and adenosine triphosphate (ATP)-driven Ca2+ pumps located in the outer cell membrane or the membrane of the sarcoplasmic reticulum. This cascade leads to a reduction in cytosolic Ca2+ and, finally, to smooth muscle relaxation.

Cyclic nucleotides are degraded by PDE isoenzymes, a heterogeneous group of hydrolytic enzymes. Phosphodiesterases are classified according to their preferences for cAMP or/and cGMP, kinetic parameters of cyclic nucleotide hydrolysis, sensitivity to inhibition by various compounds, allosteric regulation by other molecules, and chromatographic behaviour on anion exchange columns.

Eleven families of PDE isoenzymes have been distinguished. The first six of these families are Ca2+/calmodulin–stimulated PDE (PDE1); cGMP-stimulated PDE (PDE2); cGMP-inhibited PDE (PDE3), cAMP-specific PDE (PDE4); cGMP-specific PDE (PDE5); and the cGMP-binding, cGMP-specific PDE of mammalian rods and cones (PDE6). While PDE7 (high cAMP affinity) and PDE8 (3-isobutyl-methylxanthine–insensitive) have preferred selectivity for cAMP, PDE9 exclusively degrades cGMP. Phosphodiesterase isoenzymes 10 and 11 can inactivate both cAMP and cGMP.

Some of these isoenzyme families consist of more than one gene, and some genes are alternatively spliced so that more than 50 isoenzymes or variants have been identified. Some PDE genes are also variably expressed in different tissues (302). Since the distribution and functional significance of PDE isoenzymes can vary in different tissues, isoenzyme-selective inhibitors have the potential to exert specific effects on a target tissue. To date, six out of the 11 PDE isoenzymes have been proven to be of pharmacological importance: PDE1, PDE2, PDE3, PDE4, PDE5, and PDE11 (**Table 42**) (303,304).

**TABLE 42** Overview of the PDE families currently known, their (preferred) substrate(s) (cAMP and/or cGMP), selective inhibitors, and allosteric activators, as well as (potential) clinical indications for the use of isoenzyme-specific PDE inhibitors (303).

| PDE | Substrate | Selective Inhibitor(s) | Activator(s) | (Potential) Clinical Indication(s) |
|---|---|---|---|---|
| PDE1 | cAMP/cGMP | Vinpocetine, calmodulin-antagonists | Ca2+/calmodulin | Hypertension, cerebral arterial insufficiency, OAB |
| PDE2 | cAMP (>>cGMP) | EHNA (MEP1) | cGMP | Diseases of the cardiovascular system |
| PDE3 | cAMP (>>cGMP) | Enoximone, milrinone, amrinone, quazinone, cilostamide, cGMP, SK&F 94120, siguazodan | | Cardiac insufficiency, *asthma bronchiale, claudicatio intermittens,* colon cancer |
| PDE4 | cAMP (>>cGMP) | Rolipram, Ro 20–1724, roflumilast (RP 73401), zardaverine, etazolate, denbufylline (BRL 30982), SB 207499, TVX 2706, ZK 803616 | | Dementia in the elderly, depression, *asthma bronchiale,* colon cancer, chronic colitis, gut hypermotility disorders, COPD, BPH/LUTS, OAB, urolithiasis, FSD/FSAD, premature ejaculation |
| PDE5 | cGMP (>>cAMP) | Sildenafil (citrate), NCX 911 (sildenafil nitrate), vardenafil, tadalafil, zaprinast, dipyridamole, TA 1790 (avanafil), udenafil, lodenafil, MY 5445, E 4021 | | ED, Peyronie disease, vascular arterial thrombosis, pulmonary hypertension, Raynaud disease, BPH/LUTS, OAB, premature ejaculation, FSD/FSAD |
| PDE6 | cGMP (>>cAMP) | | | |
| PDE7 | cAMP (>>cGMP) | | | |
| PDE8 | cAMP (>>cGMP) | | | |
| PDE9 | cGMP (>>cAMP) | BAY 73–6691, SCH 51866 | | Antidiuretic effect, Alzheimer disease |
| PDE10 | cAMP/cGMP | | | |
| PDE11 | cAMP/cGMP | Exisulind, tadalafil | | Prostate carcinoma |

COPD: chronic obstructive pulmonary disease; FSD: female sexual dysfunction; FSAD: female sexual arousal disorder

Clinically, by far the most important of the PDE isoenzymes has proven to be PDE5, because of its role in penile erection. Erection is principally mediated by nitric oxide (NO) released during non-adrenergic, non-cholinergic neurotransmission, and from the endothelium (305). Within the muscle, NO activates a soluble guanylyl cyclase, which raises the intracellular concentration of cGMP. This in turn activates a specific protein kinase, which phosphorylates certain proteins and ion channels, resulting in the opening of potassium channels and hyperpolarization of the muscle–cell membrane,

sequestration of intracellular Ca2+ by the endoplasmic reticulum, and blocking of Ca2+ influx by the inhibition of Ca2+ channels. The consequence is a drop in cytosolic Ca2+ concentrations, and relaxation of the smooth muscle. During the return to the flaccid state, cGMP is hydrolyzed to guanosine monophosphate by PDE5.

Other PDEs are also found in the corpus cavernosum, but they do not appear to have an important role in erection. Inhibition of the PDE5 isoenzyme by the commercially available PDE5 inhibitors sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis) has become the most successful and widespread treatment for a variety of causes of ED in men.

### 8.7.3 Male lower urinary tract symptoms and erectile dysfunction

In the 1990s, numerous publications began to emphasize the common overlap of LUTS and ED in elderly men. Since then, the preponderance of well-designed longitudinal studies has highlighted a cause-and-effect relationship between LUTS and ED (**Table 43**) (306). Together, these studies demonstrate reliable strength of association among study consistency, dose-response effect, and temporality (although further studies are needed). The studies also consistently account for alternative explanations of bias, confounding, and randomness through the use of well-powered multivariate analyses.

**TABLE 43** Summary of epidemiological studies associating LUTS and ED (306).

| Study | Study Design /Name | n | Findings |
|---|---|---|---|
| Braun *et al.* | Cologne Male Survey | 4,000 | LUTS in 72.2% of patients with ED vs. 37.7% without ED; prevalence risk highly significant |
| Blanker *et al.* | Krimpen Community Cohort | 3,924 | ED RR: 1.8–7.5 for increasing urinary complaints; risk of ED greater with LUTS than with smoking or cardiac symptoms |
| Moreira *et al.* | Brazilian Cohort Study | 428 | ED incidence RR: 3.67 if self-reported BPH–2-year follow-up; addresses temporality of BPH → ED |
| Boyle *et al.* | UrEpik Study | 4,800 | IPSS >7 showed an OR of 1.39 of having ED in a weighted multiple regression model, including age; similar ORs: heart attack, hypertension, and smoking |
| Vallancien *et al.* | Cross-Sectional European Survey | 1,274 | 55% of patients with mild LUTS had ED vs. 70% with severe LUTS; significance maintained after multiple regression analyses |
| Rosen *et al.* | Multinational Survey of the Aging Male | 12,815 | RR: 3.7–7.6; IPSS correlated with IIEF, sexual activity, and ejaculatory parameters; controlled for age and comorbidities; older men still sexually active |
| Braun *et al.* | Cologne Male Survey | 4,489 | Prevalence of LUTS in men suffering from ED was about 72.2% (*n*=621) vs. 37.7% (*n*=1,367) in men with normal erections; the OR was 2.11, even after controlling for age |
| Chung *et al.* | Cross-Sectional Community Survey | 2,115 | LUTS correlated with ED; sexual satisfaction and libido inversely correlated with LUTS |

BACH: Boston Area Community Health Survey; DAN-PSS: Danish Prognostic Symptom Score

**TABLE 43** Summary of epidemiological studies associating LUTS and ED (306), *Cont'd*

| Study | Study Design /Name | n | Findings |
|---|---|---|---|
| Ponholzer *et al.* | Austrian Study | 2,858 | RR for ED in men with LUTS (IPSS >7) was 2.2; controlled for age, vascular risk factors, and predominance of obstructive or irritative symptoms |
| Hansen *et al.* | Danish Study | 3,442 | LUTS predicted ED after multiple regression; RR: 2.3–3.4; overall LUTS prevalence 39% and ED prevalence 29% |
| Elliott *et al.* | US Veterans Administration Survey | 181 | ED correlated with obstructive LUTS after controlling for age, depression, hypertension, and coronary artery disease on multivariate analysis |
| Terai *et al.* | Japanese Cross-Sectional Survey | 2,084 | RR: 1.5; ED correlated with LUTS (IIEF vs. IPSS); correlation remained after controlling for age |
| McVary *et al.* | MTOPS Secondary Analysis | 3,000 | AUA-SI score correlated with ED and other domains; included correlation with $Q_{max}$ (multivariate analysis controlled for confounders) |
| Shiri *et al.* | Finish Cohort Study | 1,126 | RR of ED incidence with DAN-PSS score 7–11 was 2.7, RR was 3.1 for DAN-PSS >12 over a 5-year period; addresses temporality of BPH → ED |
| Paick *et al.* | PLESS Study and Questionnaire | 2,981 | 2% increase in ED risk for unit increase in the PLESS LUTS survey, significant after controlling for age |
| Brookes *et al.* | BACH Study Subset Analysis | 2,301 | Multivariable regression model of ED found strong association of AUA-SI score and ED independent of age; nocturia, incontinence, and prostatitis strongest factors; no differences found across race or ethnicity |

BACH: Boston Area Community Health Survey; DAN-PSS: Danish Prognostic Symptom Score

To date, biologically plausible interrelationships between LUTS and ED fall into four categories: alteration in NO levels, autonomic hyperactivity (AH), the alternate pathway through Rho-kinase, and pelvic atherosclerosis.

These theories are not mutually exclusive, and may overlap substantially. Risk factors for one are often risk factors for another, and second messenger cascades ultimately leading to smooth muscle contraction and relaxation for either prostatic/bladder neck tissue or erectile tissue may be shared.

**Figure 23** illustrates the interplay of the four theories. It is evident that PDE5 inhibition interacts at various points in the different pathways and may thus improve male LUTS as well as ED.
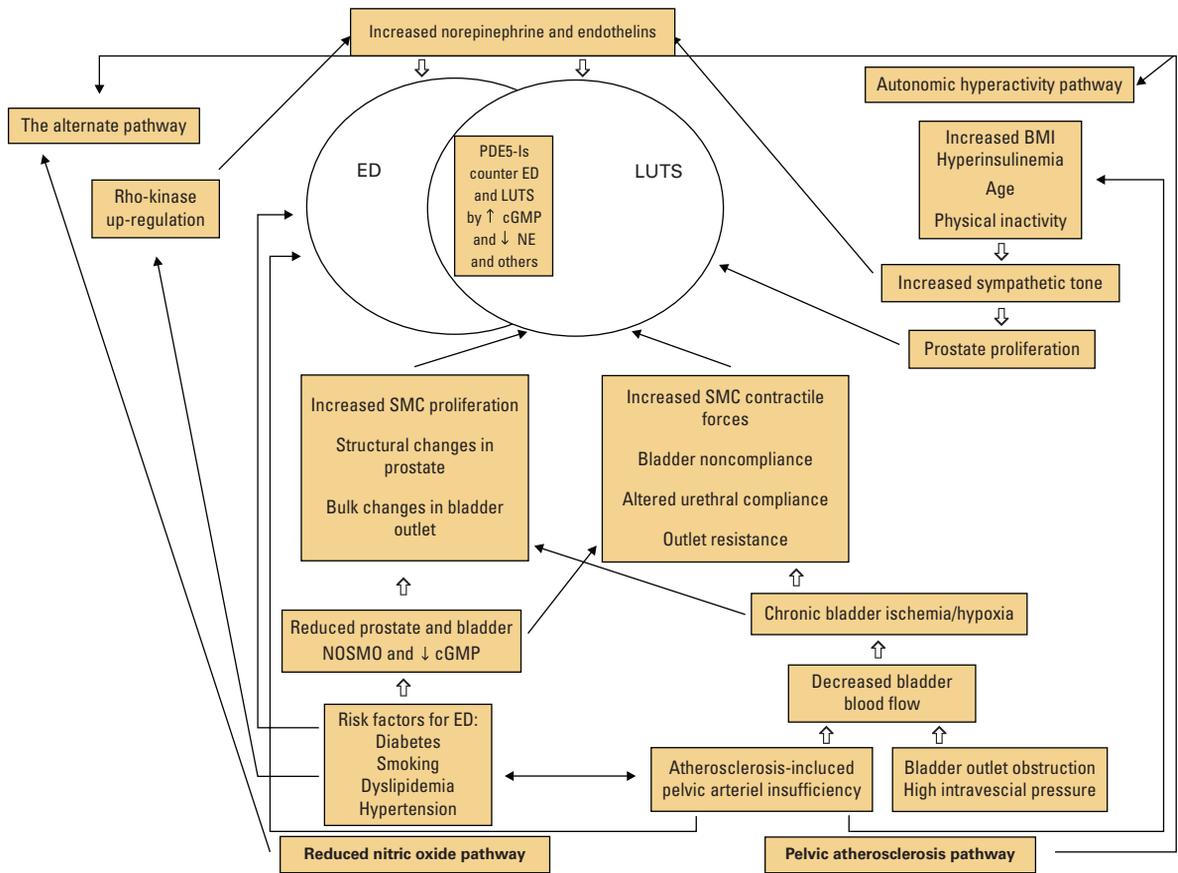
**FIGURE 23**

Four proposed theories linking ED and LUTS. The arrows demonstrate the interplay of the four theories, as they share many common pathways and etiologies. Note that the risk factors for one mechanism are often similar to those for another. The theory of atherosclerosis and pelvic ischemia asserts that risk factors for ED affect pelvic arterial blood flow, resulting in loss of smooth muscle from the bladder detrusor, with loss of bladder compliance. At the same time, prostate fibrosis increases urethral resistance, resulting in LUTS. A similar process results in smooth muscle loss in the penis with resultant ED. Atherosclerosis can lead to reduced NO levels, AH, and Rho-kinase activation. The AH theory asserts that increased AH results from increased body mass index (BMI), hyperinsulinemia, increased age, and decreased physical activity. The resulting increased sympathetic tone encourages BPH growth, LUTS, and vasoconstrictive forces that results in ED through norepinephrine, endothelin, and other secondary messenger systems. The Rho-kinase system, when activated from atherosclerosis or decreased NO, uses similar pathways to result in LUTS and BPH. The theory of pelvic reduction in NO synthase and NO, and decreased cGMP from various systemic diseases that also promote ED, results in increased smooth muscle cell contractile forces at the bladder neck and prostatic urethra. Additionally, the reduced NO synthase/NO results in prostatic smooth muscle cell proliferation and increased outlet resistance. Both forces worsen LUTS. Note that atherosclerosis results in similar smooth muscle cell alterations. Phosphodiesterase type 5 enzyme inhibitors can improve both LUTS and ED by targeting various points in the different pathways by increasing cGMP or blocking the effects of norepinephrine and other secondary messengers (306).

### 8.7.4　**Mechanism of action**

Paramount to an activity of PDE5 inhibition in the male LUT is the presence of PDE isoenzymes. The expression of the cAMP and cGMP PDE isoenzymes PDE1, PDE2, PDE4, PDE5, PDE7, PDE8, PDE9, and PDE10 in the human prostate was shown using molecular biology methods (reverse transcriptase polymerase chain reaction).

In organ bath studies, the tension of prostate strip preparations mediated via the activation of $\alpha$1ARs was dose-dependently reversed by the PDE5 inhibitors sildenafil, tadalafil, and vardenafil. The reversion of tension was accompanied by an enhancement in tissue cAMP or cGMP (307–309).

These results provided evidence of a significance of both the cGMP and cAMP signalling in controlling the function of prostate smooth muscle, and are considered to be of importance as a possible MOA of PDE5 inhibition in male LUTS through muscle relaxation, similar to the proposed MOA of alpha-blockers (304,310).

Diffuse atherosclerosis of the prostate, penis, and bladder serves an additional hypothesis linking LUTS with ED and providing a rationale for an MOA for PDE5 inhibition by way of improving vascularity (311). The theory asserts that known risks for ED (hypertension, smoking, hypercholesterolemia, and diabetes mellitus) also affect LUTS.

In a recent epidemiological study that supports this theory, both men and women who had two risk factors of atherosclerosis (diabetes mellitus, hypertension, hyperlipidemia, or nicotine use) had a statistically significantly higher IPSS compared with subjects with one or no risk factors (312,313).

Smooth muscle alterations in the bladder, prostate, and penis of animal models of hypercholesterolemia and pelvic ischemia show similarities. Hypoxia-induced overexpression of TGF-$\beta$1 and altered prostanoid production have been proposed as potential mechanisms. Penile ischemia leads to smooth muscle loss in the penis, resulting in ED. Loss of smooth muscle in the bladder would decrease compliance and worsen LUTS. Similarly, bladder ischemia from either BOO or pelvic vascular disease can induce bladder smooth muscle loss, with resultant replacement of collagen deposition and fibrosis, as well as loss of compliance, hyperactivity, and impaired contractility. Loss of smooth muscle in the prostate would result in a less distensible urethra, increased flow resistance, decreased urinary flow rate, and worsening LUTS. Pelvic atherosclerosis ties in elegantly with all the previously described theories, as pelvic ischemia/atherosclerosis is a component of the metabolic syndrome/AH, up-regulates Roh-kinase activity, and reduces NO synthase expression (306,311,312).

In summary, these two proposed MOAs suggest that PDE5 isoenzymes are highly expressed in human LUT tissues and PDE5 inhibition may relax the smooth muscles in these tissues, restore blood perfusion and oxygenation of the impacted bladder and prostatic tissue, and modulate sensory signalling, thus improving male LUTS (**Figure 24**).

**FIGURE 24**

Phosphodiesterase type 5 isoenzymes in the LUT.
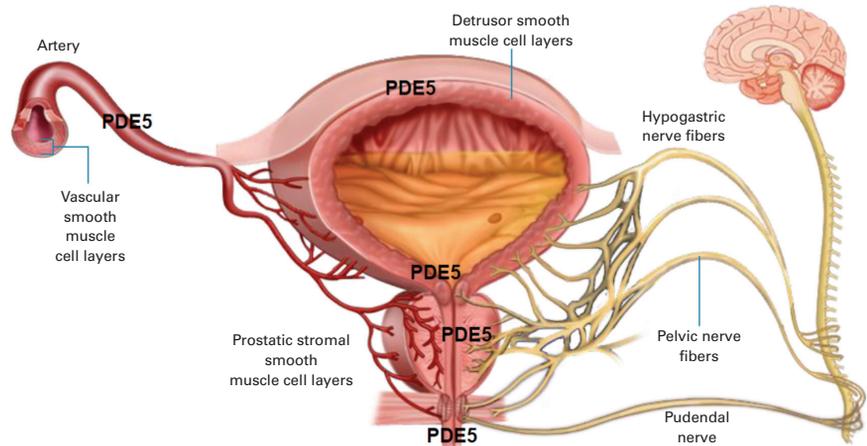
## 8.7.5   Clinical studies

### 8.7.5.1   Single-arm studies

Serendipity and astute observations on the part of physicians treating men in an ED clinic initiated a series of studies resulting ultimately in the approval of tadalafil 5 mg daily for men with BPO and men with LUTS/BPH and ED.

In 2002, a small, uncontrolled study of 112 men who were taking on-demand sildenafil for ED over a 3-month period demonstrated an improvement in IPSS from baseline that failed to reach statistical significance (314).

In 2006, another small uncontrolled study of 48 men on on-demand sildenafil for ED over a 3-month period with a baseline IPSS score >10 noted a reduction in AUA-SI score of 4.6 points ($p=0.013$) (315). In total, 60% of men improved their IPSS score, and 35% had at least a 4-point improvement in their score. The mean number of uses of sildenafil per week was 2.0 ±0.6.

### 8.7.5.2   Placebo-controlled studies

The placebo-controlled studies of PDE5 inhibitors are summarized in **Table 44**, and discussed in more detail in the following subsections.

**TABLE 44** Mean changes from baseline to endpoint in total IPSS, IPSS subscores, and $Q_{max}$ in double-blind, randomized, placebo-controlled clinical studies of PDE5 inhibitors.

| Study Authors | Duration | Treatment | N | Total IPSS[a] | IPSS Storage Subscore[a] | IPSS Voiding Subscore[a] | $Q_{max}$ (mL/s) |
|---|---|---|---|---|---|---|---|
| **Tadalafil** | | | | | | | |
| McVary et al. (316) | 12 weeks | Placebo<br>Tadalafil 5/20 mg | 143<br>138 | −1.7<br>−3.8* | −1.0<br>−2.2* | −0.7<br>−1.7* | 0.9[a]<br>0.5[a] |
| Roehrborn et al. (317) | 12 weeks | Placebo<br>Tadalafil 2.5 mg<br>Tadalafil 5 mg<br>Tadalafil 10 mg<br>Tadalafil 20 mg | 210<br>208<br>212<br>216<br>208 | −2.3<br>−3.9*<br>−4.9*<br>−5.2*<br>−5.2* | −1.0<br>−1.6<br>−1.9*<br>−2.0*<br>−2.1* | −1.3<br>−2.2*<br>−2.9*<br>−3.1*<br>−3.1* | 1.2[a]<br>1.4[a]<br>1.6[a]<br>1.6[a]<br>2.0[a] |
| Porst et al. (318) | 12 weeks | Placebo<br>Tadalafil 5 mg | 164<br>161 | −3.6<br>−5.6* | −1.3<br>−2.3* | −2.3<br>−3.3* | 1.1[a]<br>1.6[a] |
| Egerdie et al. (319) | 12 weeks | Placebo<br>Tadalafil 2.5 mg<br>Tadalafil 5 mg | 200<br>198<br>208 | −3.8<br>−4.6<br>−6.1* | −1.6<br>−1.9<br>−2.5* | −2.2<br>−2.7<br>−3.6* | 1.2[a]<br>1.7*,[a]<br>1.6[a] |
| Oelke et al. (320) | 12 weeks | Placebo<br>Tadalafil 5 mg<br>Tamsulosin 0.4 mg | 172<br>171<br>165 | −4.2<br>−6.3*<br>−5.7* | −1.6<br>−2.2<br>−2.2 | −2.6<br>−4.1*<br>−3.5* | 1.2[a]<br>2.4*,[a]<br>2.2*,[a] |
| **Sildenafil** | | | | | | | |
| McVary et al. (321) | 12 weeks | Placebo<br>Sildenafil 50/100 mg | 162<br>179 | −1.9<br>−6.3* | VNR[d]<br>VNR*,[d] | VNR[d]<br>VNR*,[d] | 0.2[a]<br>0.3[a] |
| **Vardenafil** | | | | | | | |
| Stief et al. (322) | 8 weeks | Placebo<br>Vardenafil 10 mg[c] | 110<br>104 | −3.6<br>−5.9* | −1.6<br>−2.7* | −1.9<br>−3.2* | 1.0[b]<br>1.6[b] |

VNR = value not reported

[a]Mean change from baseline to endpoint; [b]Change calculated by subtracting results reported at 8 weeks from baseline; [c]Twice daily; [d]Subscores were reported graphically without actual values

*$p<0.05$

## Sildenafil

In a 12-week prospective, multicentre, double-blind, randomized, placebo-controlled trial, the effect of treatment with daily sildenafil on ED (IIEF ≤25) and LUTS (IPSS ≥12) was examined in 189 men as compared with 180 men treated with placebo (321).

Sildenafil (50 mg) or placebo was administered daily, either before bedtime or sexual activity. After 2 weeks, the sildenafil dose was increased to 100 mg daily, being well tolerated by 90% of patients. Patients were instructed to attempt sexual activity at least weekly.

Decreases in IPSS scores were greater in the sildenafil group (6.3 points; 95% CI: 4.5 to 8.1) than in the placebo group (1.9 points; 95% CI, 0.2–3.7) ($p<0.0001$). Sildenafil patients with severe and moderate LUTS experienced greater improvement in IPSS than did patients receiving placebo (−8.6 vs. −2.4 for severe LUTS; −2.4 vs. −1.7 for moderate LUTS). IPSS QOL scores were statistically ($p<0.0001$) and clinically improved with sildenafil (0.97; 95% CI, 0.62 to 1.32 vs. 0.29; 95% CI, 0.05 to 0.64). Small, insignificant increases in $Q_{max}$ were seen in both groups.

These findings are important, as the first prospective controlled trial of a PDE5 inhibitor used for treatment of LUTS in men with ED and LUTS at baseline, supporting the concept that daily sildenafil may improve LUTS outcomes in addition to ED.

## Vardenafil

In a randomized, placebo-controlled study, vardenafil 10 mg taken twice daily was used as a treatment for LUTS (IPSS >12) in men with BPH (322). A total of 247 men were randomized, and 225 completed the 8-week intention-to-treat study.

The mean changes in total IPSS in this study were 5.9 in the vardenafil arm and 3.6 in the placebo arm. Although the difference in total score was statistically significant, it is of interest that the placebo arm experienced what would be considered a clinically significant improvement in total IPSS score. There were neither significant changes in flow rate nor changes in PVR urine volume.

In another study, 80 men with LUTS (IPSS ≥12), and without concomitant ED were randomized to receive 10 mg vardenafil or placebo twice a day. In this study, significant improvements were observed in the IPSS total score (−6.14 vs. −3.2; $p=0.001$), the irritative and obstructive IPSS subscores, and QOL, without observable difference in urinary flow (323). Significant improvements on IIEF domain scores in the vardenafil group as compared with placebo were also observed, as in previous studies.

## Tadalafil

Daily tadalafil for BPH-related LUTS (IPSS ≥13), regardless of ED, was studied in a prospective double-blind, placebo-controlled, multicentre parallel-arm trial (316). Patients were randomized to receive either tadalafil 5 mg (*n*=138) or placebo (*n*=143) daily; patients were stratified by IPSS (<20 or ≥20), prior alpha-blocker therapy, and geographic distribution. Patients were evaluated after 6 weeks of treatment, and the tadalafil dose was increased to 20 mg daily.

The IPSS was <20 in 64% of patients. The IPSS change at 6 weeks was significantly greater in the tadalafil 5 mg group than in the placebo group ($2.8 \pm 0.5$ vs. $1.2 \pm 0.5$; *p*=0.003). More patients taking tadalafil reported a clinically relevant improvement in IPSS than did those receiving placebo (49.3% vs. 36.4%; *p*=0.03). Patients receiving placebo and dose-escalated tadalafil tended to experience further LUTS improvement during weeks 6–12. At week 12, the IPSS improvement was greater in the tadalafil group than in the placebo group ($3.8 \pm 0.5$ vs. $1.7 \pm 0.5$; *p*<0.001), and more tadalafil-treated patients experienced a perceptible IPSS improvement (60.9% vs. 42.7%; *p*<0.01).

Similar results were reported in a phase 2 dose-ranging randomized double-blind, placebo-controlled, parallel-group, multinational study, in which 1,058 men were randomly assigned to placebo or one of four tadalafil daily dosing regimens (2.5, 5, 10, or 20 mg) for 12 weeks (317).

At baseline, patients had IPSS >12 due to BPO for 6 months and a $Q_{max}$ of 4–15 mL/s. After a 4-week single-blind placebo run-in phase, men were stratified by baseline IPSS (<20 vs. ≥20), baseline uroflow parameters, ED history (<3 vs. ≥3 months), and geographic region.

The study's main endpoint revealed a significant improvement of the IPSS in the 5-mg tadalafil group, with a change of 4.9 versus 1.8 points (*p*<0.05). Mean IPSS QOL score, BII, and LUTS Global Assessment Question all significantly improved with at least a 5-mg daily dose. The $Q_{max}$ of the tadalfil treatment group was not significantly different from that of the placebo treatment group for any treatment arm. An increase in tadalafil dose >5 mg showed similar improvements in IPSS but had a higher incidence of adverse events. The subset of men who were sexually active (55%) showed a significant improvement in the erectile function domain of the IIEF (IIEF-EF) (+2.38 with placebo vs. +7.15 in the 5-mg tadalafil treatment group; *p*=0.001).

A recent post-hoc analysis in men with LUTS secondary to BPH with (*n*=716) or without (*n*=340) comorbid ED at baseline showed that changes in IPSS score after 12 weeks of treatment with placebo or various doses of once-daily tadalafil were similar (324).

One additional RCT with 2.5- and 5-mg tadalafil daily is of importance, as it enrolled men who had both BPH and ED at baseline (comorbid study population) (319). Men were ≥45 years old, sexually active, and had experienced ED for ≥3 months and BPH-LUTS for >6 months.

Randomization (baseline) followed a 4-week placebo lead-in; changes from baseline were assessed via analysis of covariance and compared to placebo. The co-primary measures were the IIEF-EF and IPSS; key secondary measures were the Sexual Encounter Profile Question 3 (SEP Q3) and BII.

Tadalafil 2.5 mg ($n$=198) and 5 mg ($n$=208) significantly improved IIEF-EF domain scores (both $p<0.001$) vs. placebo ($n$=200) at endpoint. For IPSS, improvements were significant with tadalafil 5 mg ($p<0.001$), but not 2.5 mg, for observations from 2 weeks through endpoint (least-squares mean ± SE change from baseline at endpoint, placebo $-3.8 \pm 0.5$, tadalafil 2.5 mg $-4.6 \pm 0.4$, and 5 mg $-6.1 \pm 0.4$). Tadalafil 5 mg significantly improved SEP Q3 and BII ($p<0.001$). Overall, tadalafil was well tolerated, with no clinically adverse changes in orthostatic vital signs or uroflowmetry parameters.

### 8.7.5.3  Direct comparator studies

One direct comparator trial was conducted using tadalafil. A randomized, double-blind, international, placebo-controlled, parallel-group study assessed men ≥45 years of age with LUTS/BPH, IPSS ≥13, and $Q_{max}$ of 4–15 mL/s. Following screening and washout, if needed, subjects completed a 4-week placebo run-in before randomization to placebo ($n$=172), tadalafil 5 mg ($n$=171), or tamsulosin 0.4 mg ($n$=168) once daily for 12 weeks.

The IPSS significantly improved versus placebo through 12 weeks with tadalafil ($-2.1$; $p$=0.001; primary efficacy outcome) and tamsulosin ($-1.5$; $p$=0.023), and as early as 1 week (tadalafil and tamsulosin both $-1.5$; $p<0.01$). The BII significantly improved versus placebo at first assessment (week 4) with tadalafil ($-0.8$; $p<0.001$) and tamsulosin ($-0.9$; $p<0.001$), and through 12 weeks (tadalafil $-0.8$, $p$=0.003; tamsulosin $-0.6$, $p$=0.026). The IPSS QOL Index and the Treatment Satisfaction Scale-BPH improved significantly versus placebo with tadalafil (both $p<0.05$) but not with tamsulosin (both $p>0.1$). The IIEF-EF improved versus placebo with tadalafil (4.0; $p<0.001$) but not with tamsulosin ($-0.4$; $p$=0.699); $Q_{max}$ increased significantly versus placebo with both tadalafil (2.4 mL/s; $p$=0.009) and tamsulosin (2.2 mL/s; $p$=0.014). This study was limited in not being powered to directly compare tadalafil versus tamsulosin (320). **Table 45** summarizes the key efficacy results of the study, and **Table 46** summarizes the adverse events data..

**TABLE 45** Total IPPS, storage and voiding subscores, and nocturia question (320).

| | Placebo (*n*=172) | Tadalafil (*n*=171) | Tamsulosin 0.4 mg (*n*=167) |
|---|---|---|---|
| IPSS total: | *n*=172 | *n*=171 | *n*=165 |
| Change from baseline, LS mean ± SE | −4.2 ± 0.5 | −6.3 ± 0.5 | −5.7 ± 0.5 |
| Change vs. placebo, LS mean ± SE (95% CI) | – | −2.1 ± 0.6 (−3.3 to −0.8) | −1.5 ± 0.6 (−2.8 to −0.2) |
| *p* value | – | 0.001 | 0.023 |
| Storage subscore* | *n*=172 | *n*=171 | *n*=165 |
| Change from baseline, LS mean ± SE | −1.6 ± 0.2 | −2.2 ± 0.2 | −2.2 ± 0.2 |
| Change vs. placebo, LS mean ± SE (95% CI) | – | −0.6 ± 0.3 (−1.1 to 0.0) | −0.6 ± 0.3 (−1.1 to 0.0) |
| *p* value | – | 0.055 | 0.055 |
| Voiding subscore** | *n*=172 | *n*=171 | *n*=165 |
| Change from baseline, LS mean ± SE | −2.6 ± 0.3 | −4.1 ± 0.3 | −3.5 ± 0.3 |
| Change vs. placebo, LS mean ± SE (95% CI) | – | −1.5 ± 0.4 (−2.4 to −0.7) | −1.0 ± 0.4 (−1.8 to −0.1) |
| *p* value | – | <0.001 | 0.026 |
| Nocturia question[†] | *n*=172 | *n*=171 | *n*=165 |
| Change from baseline, LS mean ± SE | −0.3 ± 0.1 | −0.5 ± 0.1 | −0.5 ± 0.1 |
| Change vs. placebo, LS mean ± SE (95% CI) | – | −0.2 ± 0.1 (−0.4 to 0.0) | −0.2 ± 0.1 (−0.4 to 0.0) |
| *p* value | – | 0.080 | 0.118 |

LS: least squares
*IPSS questions 2 + 4 + 7; **IPSS questions 1 + 3 + 5 + 6; [†]IPSS question 7.

**TABLE 46** Adverse events (320).

| | Placebo (*n*=172) No. (%) | Tadalafil 5 mg (*n*=171) No. (%) | Tamsulosin 0.4 mg (*n*=168) No. (%) | *P* Value* Tadalafil vs. Placebo | *P* Value* Tamsulosin vs. Placebo |
|---|---|---|---|---|---|
| Subjects with ≥1 TEAE | 35 (20.3) | 40 (23.4) | 40 (23.8) | 0.516 | 0.513 |
| TEAEs: | | | | | |
| Headache | 2 (1.2) | 5 (2.9) | 7 (4.2) | 0.283 | 0.101 |
| Nasopharyngitis | 8 (4.7) | 5 (2.9) | 3 (1.8) | 0.574 | 0.219 |
| Back pain | 1 (0.6) | 4 (2.3) | 2 (1.2) | 0.215 | 0.619 |
| Dizziness | 3 (1.7) | 4 (2.3) | 6 (3.6) | 0.723 | 0.332 |
| Dyspepsia | 0 | 4 (2.3) | 3 (1.8) | 0.061 | 0.120 |
| Subjects discontinuing due to an AE | 2 (1.2) | 2 (1.2) | 1 (0.6) | 1.00 | 1.00 |
| Subjects with ≥1 serious AE | 0 | 2 (1.2) | 2 (1.2) | 0.248 | 0.243 |

TEAE: treatment-emergent adverse event; AE: adverse event
*$p$ values are from the Fisher exact test.

### 8.7.5.4 Long-term studies

There are data from only one long-term, open-label extension study available for review. In that study, 427 men who completed the 12-week, placebo-controlled, dose-finding study assessing once-daily tadalafil (2.5, 5, 10, or 20 mg) or placebo (317) elected to continue into an open-label extension period of 1 year. In total, 299 patients (69.9%) completed the 1-year, open-label extension period (325).

Changes in the total IPSS, IPSS irritative and obstructive subscores, IPSS health-related QOL, and BII were maintained after 1 year. In sexually active patients with ED, improvements in the IIEF-EF were maintained after 1 year. **Figure 25** shows that the patients switched from placebo and from 2.5-mg tadalafil experienced further improvement; those previously on 5 mg experienced no change; and those previously on 10 and 20 mg experienced very minor deterioration only. This suggests and verifies that 5 mg is the correct dosage for daily treatment in the LUTS indication.

**FIGURE 25**

Changes in total IPSS from baseline (BL) to week 12 and to endpoint (325).
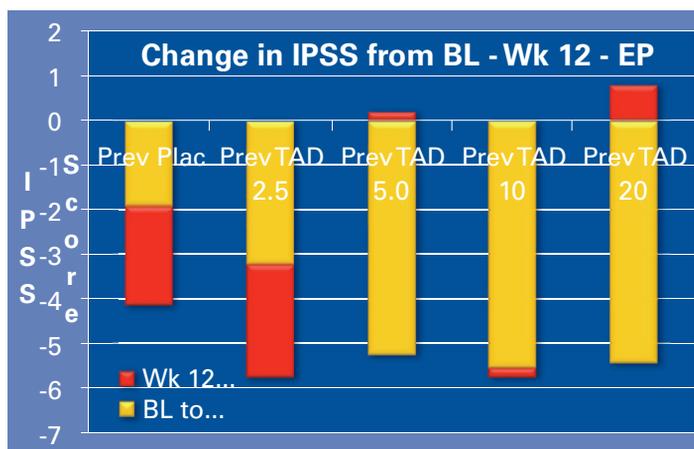


Adverse events in the open-label extension study were similar to those reported in the shorter trials, with an overall rate of 4.7 serious adverse events and a 5.2% rate of discontinuation as a result of adverse events (**Table 47**).

**TABLE 47** Overview of the adverse events reported in the open-label extension (325).

| Variable | Previous PLA (N=92) | Previous TAD 2.5 mg (N=96) | Previous TAD 5 mg (N=83) | Previous TAD 10 mg (N=85) | Previous TAD 20 mg (N=71) | Total (N=427) |
|---|---|---|---|---|---|---|
| TEAEs, n (%)* | | | | | | |
| Dyspepsia | 4 (4.3) | 3 (3.1) | 4 (4.8) | 3 (3.5) | 3 (4.2) | 17 (4.0) |
| Gastro-esophageal reflux disease | 2 (2.2) | 4 (4.2) | 2 (2.4) | 5 (5.9) | 4 (5.6) | 17 (4.0) |
| Back pain | 4 (4.3) | 5 (5.2) | 2 (2.4) | 3 (3.5) | 2 (2.8) | 16 (3.7) |
| Headache | 3 (3.3) | 0 (0.0) | 0 (0.0) | 6 (7.1) | 4 (5.6) | 13 (3.0) |
| Sinusitis | 0 (0.0) | 2 (2.1) | 2 (2.4) | 5 (5.9) | 3 (4.2) | 12 (2.8) |
| Hypertension | 0 (0.0) | 3 (3.1) | 3 (3.6) | 3 (3.5) | 2 (2.8) | 11 (2.6) |
| Cough | 1 (1.1) | 3 (3.1) | 1 (1.2) | 2 (2.4) | 2 (2.8) | 9 (2.1) |
| One or more TEAE, n (%) | 50 (54.3) | 52 (54.2) | 47 (56.6) | 49 (57.6) | 48 (67.6) | 246 (57.6) |
| One or more SAE, n (%) | 5 (5.4) | 3 (3.1) | 6 (7.2) | 4 (4.7) | 2 (2.8) | 20 (4.7) |
| Discontinuations due to AEs, n (%) | 6 (6.5) | 4 (4.2) | 4 (4.8) | 5 (5.9) | 3 (4.2) | 22 (5.2) |

AE: adverse event; N: number of subjects enrolled in the open-label extension and received at least one dose of tadalafil; n: number of subjects in each category; PLA: placebo; SAE: serious AE; TAD: tadalafil; TEAE: treatment-emergent AE
*Treatment-emergent adverse events reported in ≥2% of patients.

### 8.7.5.5 Urodynamic effects

In none of the RCTs conducted with the PDE5 inhibitors was there a significant change in $Q_{max}$ compared with placebo, an observation that led to the request on the part of the FDA to demonstrate the safety of the class of drug in terms of urodynamic parameters, and specifically the detrusor muscle.

A total of 200 patients were enrolled in a multicentre RCT and randomized to 20 mg tadalafil daily vs. placebo over 12 weeks. To answer the question of safety, a stratified enrollment was done, such that one third of each treatment arm were not obstructed, one third were equivocal, and one third were obstructed based on the Abrams-Griffiths nomogram (326). Additionally, one third had to be moderately and two thirds severely symptomatic based on the IPSS (327,328). All assessments, including standardized invasive pressure-flow studies with central reader, were done at baseline and repeated at 12 weeks. There were no differences found in any of the non-invasive or the invasive pressure-flow study parameters, although the IPSS improvement was significant in the tadalafil- vs. placebo-treated patients (**Table 48**).

**TABLE 48** Changes in pressure-flow and free flow urodynamic parameters from baseline to endpoint (327).

| | Mean ± SD PLA Baseline (N=89) | Mean ± SD PLA Change (N=89) | Mean ± SD TAD Baseline (N=83) | Mean ± SD TAD Change (N=83) | Mean ± SE Difference of Change (TAD – PLA) | P Value |
|---|---|---|---|---|---|---|
| **Pressure-flow parameters:** | | | | | | |
| $P_{det}.Q_{max}$ (cm $H_2O$) | 54.9 ± 27.6 | 0.1 ± 15.5 | 56.2 ± 29.2 | 2.1 ± 13.8 | 2.2 ± 2.2 | 0.33 |
| $Q_{max}$ (mL/s) | 9.5 ± 4.9 | 0.5 ± 2.9 | 10.3 ± 4.5 | 0.4 ± 2.9 | 0.1 ± 0.5 | 0.79 |
| Qave (mL/s)* | 4.6 ± 2.4 | 0.5 ± 1.6 | 5.5 ± 2.7 | 0.6 ± 1.9 | 0.1 ± 0.3 | 0.68 |
| Vcomp (mL) | 294.5 ± 148.1 | 4.1 ± 141.9 | 297.9 ± 143.7 | 13.6 ± 100.2 | 15.1 ± 18.9 | 0.43 |
| Max $P_{det}$ (cm $H_2O$)* | 67.3 ± 31.9 | 3.4 ± 20.6 | 71.6 ± 38.6 | 3.2 ± 22.0 | 0.6 ± 3.4 | 0.87 |

*Number of patients with data for placebo and tadalafil was different from total number of randomized patients, with $Q_{ave}$ placebo 85, tadalafil 80; maximum $P_{det}$ placebo 81, tadalafil 77; †$Q_{max}$ at baseline not significantly different between arms, $p>0.05$; ‡Number of patients with baseline and change data, respectively, for $Q_{max}$ placebo 82 and 76, tadalafil 72 and 67; $Q_{ave}$ placebo 67 and 67, tadalafil 55 and 55; $V_{comp}$ placebo 81 and 75, tadalafil 72 and 67; $PVR_{cath}$ placebo 73 and 68, tadalafil 69 and 64; and for bladder capacity and voiding efficiency placebo 72 and 67, tadalafil 68 and 63.
PLA: placebo; TAD: tadalafil

**TABLE 48** Changes in pressure-flow and free flow urodynamic parameters from baseline to endpoint (327), *Cont'd*

| | Mean ± SD PLA Baseline (N=89) | Mean ± SD PLA Change (N=89) | Mean ± SD TAD Baseline (N=83) | Mean ± SD TAD Change (N=83) | Mean ± SE Difference of Change (TAD – PLA) | *P* Value |
|---|---|---|---|---|---|---|
| Bladder contractility index | 102.2 ± 33.0 | 2.8 ± 17.8 | 107.7 ± 31.8 | 0.2 ± 19.0 | 2.8 ± 2.9 | 0.33 |
| BOOI | 36.0 ± 31.2 | 0.9 ± 18.2 | 35.6 ± 32.7 | 2.8 ± 15.6 | 1.9 ± 2.5 | 0.45 |
| **Non-invasive uroflow parameters:** | | | | | | |
| $Q_{max}$ (mL/s)[†,‡] | 13.3 ± 7.5 | 0.5 ± 8.0 | 15.5 ± 11.1 | 0.1 ± 9.3 | 0.6 ± 1.5 | 0.67 |
| $Q_{ave}$ (mL/s)[‡] | 7.1 ± 4.5 | 0.1 ± 4.1 | 7.4 ± 4.3 | 0.9 ± 3.0 | 1.0 ± 0.7 | 0.13 |
| $V_{comp}$ (mL)[‡] | 262.6 ± 138.0 | 15.6 ± 147.4 | 270.8 ± 154.8 | 1.4 ± 153.6 | 7.9 ± 24.6 | 0.75 |
| PVR (mL)[‡] | 62.1 ± 68.0 | 1.8 ± 86.6 | 52.6 ± 68.9 | 10.4 ± 78.1 | 13.0 ± 14.7 | 0.38 |
| Bladder capacity (mL)[‡] | 333.1 ± 169.0 | 29.0 ± 180.7 | 323.1 ± 195.1 | 12.3 ± 196.4 | 3.5 ± 32.0 | 0.91 |
| Voiding efficiency (%)[‡] | 83.5 ± 14.8 | 0.6 ± 17.2 | 85.1 ± 13.7 | 1.9 ± 17.6 | 2.7 ± 3.2 | 0.39 |

*Number of patients with data for placebo and tadalafil was different from total number of randomized patients, with $Q_{ave}$ placebo 85, tadalafil 80; maximum $P_{det}$ placebo 81, tadalafil 77; [†]$Q_{max}$ at baseline not significantly different between arms, $p>0.05$; [‡]Number of patients with baseline and change data, respectively, for $Q_{max}$ placebo 82 and 76, tadalafil 72 and 67; $Q_{ave}$ placebo 67 and 67, tadalafil 55 and 55; $V_{comp}$ placebo 81 and 75, tadalafil 72 and 67; $PVR_{cath}$ placebo 73 and 68, tadalafil 69 and 64; and for bladder capacity and voiding efficiency placebo 72 and 67, tadalafil 68 and 63.
PLA: placebo; TAD: tadalafil

The answer to the FDA question is therefor that there is no detrimental effect demonstrable on any urodynamic parameter, and thus indirectly on detrusor function itself. The only study in which a statistically significant improvement from baseline was achieved was the tadalafil direct comparator trial versus tamsulosin and placebo (320).

### 8.7.5.6 Meta-analysis and systematic review

Several systematic reviews and meta-analyses have been published quite recently (329,330). Gacci *et al.* retrieved 107 articles, of which 12 were included in the meta-analysis: seven on PDE5 inhibitors versus placebo (with 3,214 men) and five on the combination of PDE5 inhibitors with alpha1-blockers versus alpha1-blockers alone (with 216 men).

The median follow-up of all RCTs was 12 weeks. Combining the results of those trials, the use of PDE5 inhibitors alone was associated with a significant improvement in IIEF score (+5.5; $p<0.0001$) and IPSS ($-2.8$; $p<0.0001$), but not $Q_{max}$ (0.00; $p=$ not significant), at the end of the study compared with placebo.

The combination of PDE5 inhibitors and alpha1-blockers improved IIEF score (+3.6; $p<0.0001$), IPSS score ($-1.8$; $p=0.05$), and $Q_{max}$ (+1.5; $p<0.0001$) at the end of the study compared with alpha-blockers alone.

### 8.7.5.7 Adverse events and adverse reactions

Perhaps the most relevant compilations of side effects can be found in the meta-analysis by Gacci *et al.* (**Table 49**) (329). In general, the adverse events reported are similar to those found in the very large body of literature regarding PDE5 inhibitor treatment for ED. In studies comparing the effect of PDE5 inhibitors versus placebo, events were reported in 301 of 1,879 men (16%) treated with PDE5 inhibitors, versus 52 of 870 men (6.0%) treated with placebo. This meta-analysis of adverse events demonstrates that flushing, gastroesophageal reflux, headache, and dyspepsia have a higher risk of occurrence after PDE5 inhibitor administration (**Table 50**).

**TABLE 49** Odds ratio, lower limit (LL), upper limit (UL), and *p* value of the meta-regression of adverse events reported in at least two papers comparing the effect of PDE5 inhibitor alone versus placebo (329).

| Side Effect | OR | LL | UL | P Value |
|---|---|---|---|---|
| Flushing | 4.888 | 1.546 | 15.459 | 0.007 |
| Gastroesophageal reflux | 2.214 | 0.556 | 5.123 | 0.063 |
| Headache | 1.876 | 1.181 | 2.980 | 0.008 |
| Dyspepsia | 1.850 | 1.064 | 3.216 | 0.029 |
| Back pain | 1.177 | 0.731 | 1.897 | 0.503 |
| Sinusitis | 1.376 | 0.428 | 4.426 | 0.552 |

# TABLE 50 Most commonly reported treatment-related adverse events stratified by trial and treatment arm (329).

| | Arm | McVary et al. Sildenafil 100 mg | McVary et al. Tadalafil 100 mg | Stief et al. Vardenafil 10 mg | Roehrborn et al. Tadalafil 2.5 mg | 5 mg | 10 mg | 20 mg | Porst et al. Tadalafil 2.5 mg | 5 mg | 10 mg | 20 mg | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Headache | D | 21 (11.0) | 4 (2.9) | 14 (13.0) | 0 | 0 | 6 (7.1) | 4 (5.6) | 4 (3.5) | 4 (3.4) | 6 (5.0) | 2 (1.7) | |
| | P | 6 (3.0) | 1 (0.7) | 2 (1.8) | 3 (3.3) | | | | 4 (3.5) | | | | |
| Dyspepsia | D | 12 (6.0) | 6 (4.3) | 8 (7.4) | 3 (3.1) | 4 (4.8) | 3 (3.5) | 3 (4.2) | 1 (0.9) | 5 (4.3) | 2 (1.7) | 3 (2.6) | |
| | P | 2 (1.0) | 0 | 0 | 4 (4.3) | | | | 0 | 0 | 0 | 0 | |
| Back pain | D | | 5 (3.6) | 3 (2.8) | 5 (5.2) | 2 (2.4) | 3 (3.5) | 2 (2.8) | 2 (1.8) | 1 (0.9) | 5 (4.2) | 6 (5.2) | |
| | P | | 2 (1.4) | 0 | 4 (4.3) | | | | 1 (0.9) | | | | |
| Flushing | D | 9 (5.0) | | 7 (6.5) | | | | | | | | | |
| | P | 1 (1.0) | | 1 (0.9) | | | | | | | | | |
| Gastro-esophageal reflux | D | | | 3 (2.8) | 4 (4.2) | 2 (2.4) | 5 (5.9) | 4 (5.6) | | | | | |
| | P | | | 0 | 2 (2.2) | | | | | | | | |
| Sinusitis | D | | | | 2 (2.1) | 2 (2.4) | 5 (5.9) | 3 (4.2) | | | | | |
| | P | | | | 0 | 0 | 0 | 0 | | | | | |
| Rhinitis | D | 8 (4.0) | 3 (2.2) | | | | | | | | | | |
| | P | 3 (2.0) | 0 | | | | | | | | | | |
| Hypertension | D | | | | 3 (3.1) | 3 (3.6) | 3 (3.5) | 2 (2.8) | | | | | |
| | P | | | | 0 | 0 | 0 | 0 | | | | | |
| Myalgia | D | | | | | | | | 1 (0.9) | 5 (4.3) | 2 (1.7) | 3 (2.6) | |
| | P | | | | | | | | 0 | 0 | 0 | 0 | |
| Cough | D | | | | 3 (3.1) | 1 (1.2) | 2 (2.4) | 2 (2.8) | | | | | |
| | P | | | | 1 (1.1) | | | | | | | | |

C: combined therapy (i.e. a PDE5 inhibitor plus an alpha-blocker); D: drug (i.e. PDE5 inhibitor); P: placebo; α: alpha-blocker alone
*Data are reported as number of events and percentage (%).

| Tamimi et al. UK-369003 | | | | Porst et al. Tadalafil | Overall | Arm | Kaplan et al. Sildenafil | Bechara et al. Tadalafil | Liguori et al. Tadalafil | Tuncel et al. Sildenafil | Gacci et al. Vardenafil | Overall |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 mg | 25 mg | 50 mg | 100 mg | 5 mg | | | 25 mg | 20 mg | 20 mg | 25 mg | 10 mg | |
| 5 (9.0) | 2 (4.0) | 4 (8.0) | 5 (6.0) | 6 (3.7) | 87 (4.6) | C | | 1 | | | 2 | 3 (2.9) |
| 1(3.0) | | | | 1 (0.6) | 18 (2.1) | α | | 1 | | | 1 | 2 (2.0) |
| 1 (2.0) | 1 (2.0) | 4 (8.0) | 3 (3.0) | | 59 (3.1) | C | 2 | | | | 1 | 3 (2.9) |
| 1 (3.0) | | | | | 7 (0.8) | α | | | | | 1 | 1 (1.0) |
| 0 | 2 (4.0) | 2 (4.0) | 4 (4.0) | 5 (3.1) | 47 (2.5) | C | | | | | | 0 |
| 2 (5.0) | | | | 4 (2.4) | 13 (1.5) | α | | | | | | 0 |
| 1 (2.0) | 0 | 1 (2.0) | 2 (2.0) | | 20 (1.2) | C | | | | | | 0 |
| 0 | 0 | 0 | 0 | | 2 (0.2) | α | | | | | | 0 |
| | | | | | 18 (1.0) | C | | | | | | 0 |
| | | | | | 2 (0.2) | α | | | | | | 0 |
| 0 | 0 | 1 (2.0) | 1 (1.0) | | 14 (0.7) | C | | | | | | 0 |
| 2 (5) | | | | | 2 (0.2) | α | | | | | | 0 |
| | | | | | 11 (0.6) | C | | | | | | 0 |
| | | | | | 3 (0.3) | α | | | | | | 0 |
| | | | | | 11 (0.6) | C | | | | | | 0 |
| | | | | | 0 | α | | | | | | 0 |
| | | | | | 11 (0.6) | C | | | | | | 0 |
| | | | | | 0 | α | | | | | | 0 |
| | | | | | 8 (0.4) | C | | | | | | 0 |
| | | | | | 1 (0.1) | α | | | | | | 0 |

C: combined therapy (i.e. a PDE5 inhibitor plus an alpha-blocker); D: drug (i.e. PDE5 inhibitor); P: placebo; α: alpha-blocker alone
*Data are reported as number of events and percentage (%).

**TABLE 50** Most commonly reported treatment-related adverse events stratified by trial and treatment arm (329), *Cont'd*

| | Arm | McVary *et al.* Sildenafil 100 mg | McVary *et al.* Tadalafil 100 mg | Stief *et al.* Vardenafil 10 mg | Roehrborn *et al.* Tadalafil 2.5 mg | 5 mg | 10 mg | 20 mg | Porst *et al.* Tadalafil 2.5 mg | 5 mg | 10 mg | 20 mg | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diarrhea | D | | | 5 (4.6) | | | | | | | | | |
| | P | | | 1 (0.9) | | | | | | | | | |
| UTI | D | | 3 (2.2) | | | | | | | | | | |
| | P | | 1 (0.7) | | | | | | | | | | |
| Priapism | D | | 7 (5.1) | | | | | | | | | | |
| | P | | 2 (1.4) | | | | | | | | | | |
| Extremity pain | D | | | | | | | | | | | | |
| | P | | | | | | | | | | | | |
| Dizziness | D | | | | | | | | | | | | |
| | P | | | | | | | | | | | | |
| Hypo-tension | D | | | | | | | | | | | | |
| | P | | | | | | | | | | | | |
| Overall | D | 50 (29.8) | 28 (22.2) | 40 (38.1) | 20 (11.0) | 14 (7.7) | 27 (15.4) | 20 (12.3) | 7 (6.2) | 15 (12.8) | 15 (12.5) | 14 (12.1) | |
| | P | 12 (7.7) | 6 (4.8) | 4 (3.6) | 14 (7.6) | | | | 5 (4.3) | | | | |

C: combined therapy (i.e. a PDE5 inhibitor plus an alpha-blocker); D: drug (i.e. PDE5 inhibitor); P: placebo; α: alpha-blocker alone
*Data are reported as number of events and percentage (%).

## 8.7.6 Recommendations: phosphodiesterase type 5 inhibitors

Phosphodiesterase type 5 inhibitors have been studied in men with LUTS. Sildenafil and vardenafil were studied in moderate-quality RCTs. Tadalafil was studied in several high-quality RCTs. A 5-mg daily dosage was found to be superior to placebo in RCTs of up to 12 weeks and open-label extension studies of up to 52 weeks, in terms of symptoms, bother, and QOL improvement. The safety profile is acceptable. Tadalafil 5 mg daily is recommended for men with LUTS with no selection criteria (Level 1a).

There are no urodynamic effects different from those seen with placebo noted in any of the studies using PDE5 inhibitors (Level 1b).

Tadalafil 5 mg daily has a reasonable safety profile for the treatment of men with LUTS (Level 1a).

| Tamimi et al. | | | | Porst et al. | Overall | Arm | Kaplan et al. | Bechara et al. | Liguori et al. | Tuncel et al. | Gacci et al. | Overall |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| UK-369003 | | | | Tadalafil | | | Sildenafil | Tadalafil | Tadalafil | Sildenafil | Vardenafil | |
| 10 mg | 25 mg | 50 mg | 100 mg | 5 mg | | | 25 mg | 20 mg | 20 mg | 25 mg | 10 mg | |
| | | | | | 5 (0.3) | C | | | | | | 0 |
| | | | | | 1 (0.1) | α | | | | | | 0 |
| | | | | | 3 (0.2) | C | | | | | | 0 |
| | | | | | 1 (0.1) | α | | | | | | 0 |
| | | | | | 7 (0.4) | C | | | | | | 0 |
| | | | | | 2 (0.2) | α | | | | | | 0 |
| | | | | | 0 | C | | | | | | 0 |
| | | | | | 0 | α | | | | | | 0 |
| | | | | | 0 | C | 1 | | | | | 1 (0.97) |
| | | | | | 0 | α | 2 | | | | | 2 (2.0) |
| | | | | | 0 | C | | | | | | 0 |
| | | | | | 0 | α | | | | | | 0 |
| 8 (15.4) | 5 (8.9) | 12 (23.5) | 15 (17.2) | 11 (7.4) | 301 (16.0) | C | 3 (15.8) | 1 (7.1) | – | – | 3 (10.0) | 7 (6.8) |
| 6 (16.2) | | | | 5 (3.3) | 52 (6.0) | α | 2 (11.1) | 1 (7.7) | – | – | 2 (6.9) | 5 (5.1) |

C: combined therapy (i.e. a PDE5 inhibitor plus an alpha-blocker); D: drug (i.e. PDE5 inhibitor); P: placebo; α: alpha-blocker alone
*Data are reported as number of events and percentage (%).

# 8.8 Combination Medical Therapy

## 8.8.1 Alpha-blockers + 5-alpha-reductase inhibitors

A recent systematic review and associated tables (**Tables 51–53**) serve as the basis for this chapter (331).

**TABLE 51** Alpha1-adrenoceptor antagonists and 5-ARI combination trial characteristics and subjective outcome measures (14).

| Trial | Drug (Dose) | Trial Duration, Months | Primary End Point(s) | Age; PV at Baseline, Mean ± SD | Inclusion Criteria | |
|---|---|---|---|---|---|---|
| VA COOP 1992–1995 (*N*=1,229) | Terazosin (10 mg) finasteride (5 mg) | 12 | AUA-SI $Q_{max}$ | 65 ± 7 y; 37 ± 1 mL | ▪ Age 45–80 y<br>▪ AUA-SI >8<br>▪ PSA ≤10 ng/mL<br>▪ $Q_{max}$ 4–15 mL/s<br>▪ Any PV | |
| ALFIN 1994–1996 (*N*=1,051) | Alfuzosin (2×5 mg) finasteride (5 mg) | 6 | IPSS $Q_{max}$ | 63 ± 6 y; 41 ± 24 mL | ▪ Age 50–75 y<br>▪ IPSS >7<br>▪ PSA ≤10 ng/mL<br>▪ $Q_{max}$ 5–15 mL/s<br>▪ Any PV | |
| PREDICT 2001–2007 (*N*=1,095) | Doxazosin (4–8 mg) finasteride (5 mg) | 12 | IPSS $Q_{max}$ | 63 ± 7 y; 36 ± 14 mL (by DRE) | ▪ Age 50–80 y<br>▪ IPSS >12<br>▪ PSA ≤10 ng/mL<br>▪ $Q_{max}$ 5–15 mL/s<br>▪ Prostatic enlargement assessed by DRE | |
| MTOPS 1995–2001 (*N*=3,047) | Doxazosin (4–8 mg) finasteride (5 mg) | 54–72 | Clinical progression | 62 ± 7 y; 36 ± 20 mL | ▪ Age >50 y<br>▪ AUA-SI 8–30<br>▪ PSA ≤10 ng/mL<br>▪ $Q_{max}$ 4–14 mL/s<br>▪ Any PV | |
| CombAT 2003–2009 (*N*=3,195–3,822) | Tamsulosin (0.4 mg) dutasteride (0.5 mg) | 24–48 | Time to first AUR or BPH-related surgery | 66 ± 7 y; 55 ± 23 mL | ▪ Age >50 y<br>▪ IPSS >12<br>▪ PSA 1.5–10 ng/mL<br>▪ $Q_{max}$ 5–15 mL/s<br>▪ PV >30 mL | |

ALFIN: Alfuzosin, Finasteride, and Combination in the Treatment of BPH; na: not assessed; PREDICT: Prospective European Doxazosin and Combination Therapy; y: years

| | Change of Symptom Score from Baseline (IPSS or AUA-SI Score) | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | α1-Blocker | | 5-ARI | | Placebo | | Combination | |
| | −6.1 | Significant vs. baseline vs. 5-ARI vs. placebo | −3.2 | Significant vs. baseline | −2.6 | Significant vs. baseline | −6.2 | Significant vs. baseline vs. 5-ARI vs. placebo |
| | −6.3 | Significant vs. baseline vs. 5-ARI | −5.2 | Significant vs. baseline | na | na | −6.1 | Significant vs. baseline vs. 5-ARI |
| | −8.3 | Significant vs. baseline vs. 5-ARI vs. placebo | −6.6 | Significant vs. baseline | −5.7 | Significant vs. baseline | −8.5 | Significant vs. baseline vs. 5-ARI vs. placebo |
| | −6.6 | Significant vs. baseline vs. placebo vs. 5-ARI | −5.6 | Significant vs. baseline vs. placebo | −4.9 | Significant vs. baseline | −7.4 | Significant vs. baseline vs. 5-ARI vs. placebo vs. α1-blocker |
| | −3.8 | Significant vs. baseline | −5.3 | Significant vs. baseline vs. α1-blocker | na | na | −6.3 | Significant vs. baseline vs. 5-ARI vs. α1-blocker |

ALFIN: Alfuzosin, Finasteride, and Combination in the Treatment of BPH; na: not assessed; PREDICT: Prospective European Doxazosin and Combination Therapy; y: years

**TABLE 52** Alpha-blocker and 5-ARI combination objective outcome measures (331).

| Trial | Change in $Q_{max}$ from Baseline (mL/s) | | | | | | | |
| | $\alpha$1-Blocker | | 5-ARI | | Placebo | | Combination | |
|---|---|---|---|---|---|---|---|---|
| VA COOP Terazosin/ finasteride | +2.7 | Significant vs. baseline vs. 5-ARI vs. placebo | +1.6 | Significant vs. baseline | +1.4 | Significant vs. baseline | +3.2 | Significant vs. baseline vs. 5-ARI vs. placebo |
| ALFIN Alfuzosin/ finasteride | +1.8 | Significant vs. baseline | +1.8 | Significant vs. baseline | na | na | +2.3 | Significant vs. baseline |
| PREDICT Doxazosin/ finasteride | +3.6 | Significant vs. baseline vs. 5-ARI vs. placebo | +1.8 | Significant vs. baseline | +1.4 | Significant vs. baseline | +3.8 | Significant vs. baseline vs. 5-ARI vs. placebo |
| MTOPS Doxazosin/ finasteride | +2.5 | Significant vs. baseline vs. placebo | +2.2 | Significant vs. baseline vs. placebo | +1.4 | Significant vs. baseline | +3.7 | Significant vs. baseline vs. 5-ARI vs. placebo vs. $\alpha$1-blocker |
| CombAT Tamsulosin/ dutasteride | +0.7 | Significant vs. baseline | +2.0 | Significant vs. baseline vs. $\alpha$1-blocker | na | na | +2.4 | Significant vs. baseline vs. 5-ARI vs. $\alpha$1-blocker |

ALFIN: Alfuzosin, Finasteride, and Combination in the Treatment of BPH; na: not assessed; nr: not reported; ns: not significant; PREDICT: Prospective European Doxazosin and Combination Therapy

| Change in PV from Baseline (mL, unless otherwise specified) | | | | | | | |
|---|---|---|---|---|---|---|---|
| α1-Blocker | | 5-ARI | | Placebo | | Combination | |
| +0.5 | Significant vs. baseline | −6.1 | Significant vs. baseline vs. 5-ARI vs. placebo | +0.5 | Significant vs. baseline | −7 | Significant vs. baseline vs. 5-ARI vs. placebo |
| −0.2 | ns | −4.3 | Significant vs. baseline vs. α1-blocker | na | na | −4.9 | Significant vs. baseline vs. α1-blocker |
| na | na | na | na | na | na | na | na |
| +24% | nr | −19% | nr | +24% | nr | −19% | nr |
| +4.6% | Significant vs. baseline | −28− | Significant vs. baseline vs. α1-blocker | na | na | −27.3% | Significant vs. baseline vs. 5-ARI vs. α1-blocker |

ALFIN: Alfuzosin, Finasteride, and Combination in the Treatment of BPH; na: not assessed; nr: not reported; ns: not significant; PREDICT: Prospective European Doxazosin and Combination Therapy

**TABLE 53** Alpha-blocker and 5-ARI combination selected side effects (331).

| | | VA COOP Terazosin/ Finasteride | ALFIN Alfuzosin/ Finasteride | PREDICT Doxazosin/ Finasteride | MTOPS Doxazosin/ Finasteride | CombAT Tamsulosin/ Dutasteride |
|---|---|---|---|---|---|---|
| **Alpha1-Blocker, %** | Headache | 6 | 2 | nr | nr | nr |
| | Dizziness and hypotension | 26 | 1.7 | 15.6 | 4.4* | 2 |
| | Loss of libido | 3 | 0.6 | 3.6 | 1.5* | 2 |
| | Impotence | 6 | 2.2 | 5.8 | 3.5* | 5 |
| | Side effects, total | nr | 27 | nr | 27 | 19 |
| | Severe side effects | nr | 1.7 | nr | nr | <1 |
| | Discontinuation rate due to AEs | 7.0 | 7.8 | 11.6 | nr | 4 |
| | AUR | nr | 0.6 | 0.4 | 1 | 6.8 |
| **5-ARI, %** | Headache | 6 | 1.2 | nr | nr | nr |
| | Dizziness and hypotension | 8 | 1.2 | 8 | 2.3* | <1 |
| | Loss of libido | 5 | 1.7 | 3.4 | 2.3* | 3 |
| | Impotence | 9 | 6.7 | 4.9 | 4.5* | 7 |
| | Side effects, total | nr | 26 | nr | 24 | 21 |
| | Severe side effects | nr | 2.9 | nr | nr | <1 |
| | Discontinuation rate due to AEs | 6.1 | 5.9 | 13.6 | nr | 4 |
| | AUR | nr | 0.3 | 1.9 | <1 | 2.7 |
| **Placebo, %** | Headache | 3 | na | nr | nr | na |
| | Dizziness and hypotension | 7 | na | 7.4 | 2.2* | na |
| | Loss of libido | 1 | na | 1.9 | 1.4* | na |
| | Impotence | 5 | na | 10.5 | 3.3* | na |
| | Side effects, total | nr | na | nr | nr | na |
| | Severe side effects | nr | na | nr | nr | na |
| | Discontinuation rate due to AEs | 1.9 | na | 11.9 | nr | na |
| | AUR | nr | na | 2.6 | 2 | na |

AE: adverse event; ALFIN: Alfuzosin, Finasteride, and Combination in the Treatment of BPH; na: not assessed; nr: not reported; PREDICT: Prospective European Doxazosin and Combination Therapy
* Rate per 100 person-years of follow-up

**TABLE 53** Alpha-blocker and 5-ARI combination selected side effects (331), *Cont'd*

| | | VA COOP Terazosin/ Finasteride | ALFIN Alfuzosin/ Finasteride | PREDICT Doxazosin/ Finasteride | MTOPS Doxazosin/ Finasteride | CombAT Tamsulosin/ Dutasteride |
|---|---|---|---|---|---|---|
| **Combination, %** | Headache | 5 | 1.4 | nr | nr | nr |
| | Dizziness and hypotension | 21 | 2.3 | 13.6 | 5.3* | 2 |
| | Loss of libido | 5 | 2 | 2.1 | 2.5* | 4 |
| | Impotence | 9 | 7.4 | 3.3 | 5.1* | 9 |
| | Side effects, total | nr | 26 | nr | 18 | 28 |
| | Severe side effects | nr | 2.3 | nr | nr | <1 |
| | Discontinuation rate due to AEs | 9.4 | 8.1 | 12.6 | nr | 6 |
| | AUR | nr | 0.3 | 0 | <1 | 2.2 |

AE: adverse event; ALFIN: Alfuzosin, Finasteride, and Combination in the Treatment of BPH; na: not assessed; nr: not reported; PREDICT: Prospective European Doxazosin and Combination Therapy
* Rate per 100 person-years of follow-up

### 8.8.1.1 Introduction and mechanisms of action

Alpha-blockers presumably work by relaxation of the smooth muscle at the bladder neck, the prostate and its capsule, and perhaps in the central nervous system and spinal cord, where there are also alpha receptors (109,115,124,332). 5-alpha-reductase inhibitors work by addressing the underlying condition of BPO, preferentially shrinking the glandular epithelial component of the prostate and thereby presumably improving the outflow condition, leading to symptom improvement (204,243,332).

There is no alternative mechanism proposed, although effects on VEGF has been reported, but not linked to male LUTS per se (284,285). Since alpha-blockers begin to be effective within a week, while the 5-ARIs usually require at least 3 months to become effective, the combination of these two drug classes has generated considerable interest.

### 8.8.1.2 Small studies of short duration

Pushkar *et al.* have published data from a series of studies in which patients received combination therapy with finasteride and terazosin (333,334). The investigators reported superior outcomes with combination therapy. The studies, however, lacked placebo control, and outcome assessment was inconsistent.

Another study compared the efficacy of terazosin, finasteride, and a combination of both in 195 men with enlarged prostate glands (335). All patients–those receiving terazosin (*n*=64), finasteride (*n*=65), or combination therapy (*n*=66)–were well matched at baseline.

Decreases in symptom score of 4.9, 4.1, and 6.4 points from baseline were realized at 12 months for the terazosin, finasteride, and combination therapy arms, respectively; the differences between the combination therapy group and both the finasteride and terazosin groups were significant, whereas

the difference between the terazosin and finasteride groups was not. Improvements in flow rate of 1.2 mL/s, 4.0 mL/s, and 4.9 mL/s were realized for the terazosin, finasteride, and combination therapy groups, respectively.

The authors provided information on study patients with prostates of 40 mL or larger ($n$=33). In the finasteride group, these patients had greater improvement in symptom score compared with those with prostates <40 mL ($n$=32) (−6.3 points vs. −1.6 points; $p$<0.01). However, PV did not influence the change in symptom score in the terazosin or combination therapy groups. Similarly, improvement in $Q_{max}$ was greater for the patients in the finasteride group who had PV ≥40 mL (5.4 mL/s vs. 3.2 mL/s; $p$<0.05). Although this study also lacked a placebo group, it differed from the previous studies in that it enrolled patients with particularly large prostates (average: 46.8 mL by TRUS).

### 8.8.1.3 Placebo-controlled and direct comparator studies

In 1998, Debruyne *et al.* (336) reported results on behalf of the ALFIN Study Group. This randomized, double-blind, multicentre trial compared the effects of 6 months of therapy with a sustained-release formulation of the alpha1-blocker alfuzosin, 5 mg twice daily ($n$=358); finasteride, 5 mg once daily ($n$=344); or both drugs in combination ($n$=349) (336).

Patients in the alfuzosin, finasteride, and combination therapy groups had decreases from baseline symptom score of 6.3, 5.2, and 6.1 points, respectively. The difference in score reduction was significant between the alfuzosin and finasteride groups ($p$=0.01), as well as between the combination therapy and finasteride groups ($p$=0.03). Improvements in $Q_{max}$ (alfuzosin: 1.8 mL/s; finasteride: 1.8 mL/s; combination therapy: 2.3 mL/s) were not significantly different among treatment groups. Reductions in PV of slightly more than 10% were realized in the finasteride and combination therapy arms. Prostate-specific antigen levels also decreased significantly in these two treatment arms, whereas no change was observed in the alfuzosin arm. This trial, like the previously mentioned studies, lacked a placebo group, and therefore did not allow systematic analysis of the effect of PV on response to treatment.

The VA COOP BPH Study Group conducted a 1-year, double-blind, placebo-controlled trial in men with BPH (238,337–341). A total of 1,229 men were randomized to receive placebo ($n$=305); finasteride, 5 mg/day ($n$=10); terazosin at a forced titration to 10 mg/day, with permission to reduce the dosage to 5 mg/day in the event of an adverse event ($n$=305); or a combination of finasteride and terazosin ($n$=309).

At 52 weeks, symptom scores in the terazosin and combination groups were significantly lower than at baseline, and lower than those in the placebo and finasteride groups. Changes in symptom score from baseline in the finasteride and placebo groups were also significant, but the difference between those groups was not. The same was true for improvement in $Q_{max}$. As expected, PV reduction and a decrease in PSA level (by nearly 50%) were noted in the finasteride and combination arms only (340).

Several secondary analyses of the VA COOP study were published. An analysis of bother and QOL measures found that group mean differences in symptom problem and BPH impact scores between the finasteride versus placebo, and terazosin versus combination groups were not statistically or clinically significant. Group mean differences in all outcome measures were highly statistically

significant between the terazosin and finasteride groups and the combination and finasteride groups. The percentages of subjects who rated improvement as marked or moderate with placebo, finasteride, terazosin, and combination were 39%, 44%, 61%, and 65%, respectively (341). There was no difference in those patients enrolled with a baseline PV ≥50 mL (341). Filling and voiding subscores of the IPSS were analyzed, but found not to be clinically useful (338).

Johnson reported on nocturia episodes in the VA COOP study (337). Of the 1,078 men available for analysis, 1,040 (96.5%) had at least one episode of nocturia at baseline and 38 (3.5%) had less than one episode (baseline nocturia is an average of two measures). Of those 1,040 men, 788 (75.8%) had two or more nocturia episodes. Overall, nocturia decreased from a baseline mean of 2.5 to 1.8, 2.1, 2.0, and 2.1 episodes in the terazosin, finasteride, combination, and placebo groups, respectively. Among the men with two or more episodes of nocturia, a 50% reduction in nocturia was seen in 39%, 25%, 32%, and 22% in the terazosin, finasteride, combination, and placebo groups, respectively. Changes in nocturia were correlated with changes in reported bother from nocturia (Pearson correlation: 0.48), BII (0.32), and overall satisfaction with urinary symptoms (0.33).

The PREDICT study group recently published data from a similar European multicentre, randomized, placebo-controlled trial, also lasting 52 weeks (239). The study included 1,095 patients with LUTS and BPH, aged 50 to 80 years, each with an IPSS≥12, a $Q_{max}$ between 5 mL/s and 15 mL/s with a total voided volume of greater than 150 mL, and an enlarged prostate as determined by DRE. Patients were randomized to receive placebo; finasteride 5 mg; doxazosin titrated to response based on an IPSS improvement of 30% or more and an improvement of 3 mL or greater in $Q_{max}$; or a combination of finasteride and doxazosin.

Similar to the results of the VA COOP Trial, both doxazosin and the combination of doxazosin and finasteride produced statistically significant improvements in all outcome parameters (IPSS, $Q_{max}$, QOL score, and BII score) compared with placebo and finasteride alone ($p<0.05$). Finasteride alone did not differ from placebo with respect to $Q_{max}$ or QOL score, and only marginally differed with respect to BII score and total IPSS ($0.05 \le p<0.10$).

There are two trials comparing the combination of alpha-blockers and 5-ARIs against alpha-blocker monotherapy (and in the case of the MTOPS study, against placebo) over a period of 4 (Combination of Avodart and Tamsulosin–CombAT) and 5.5 years (MTOPS) (208,342,343).

The MTOPS trial is not only the largest but also the longest study ever undertaken in the field of LUTS and clinical BPH (344). Participants were men aged 50 years or older with an AUA-SI score of 8 to 30 and a $Q_{max}$ between 4 mL/s and 15 mL/s with a voided volume of at least 125 mL. A total of 3,047 patients were enrolled from 1993 through 1998 at 17 academic centres, and were followed for 4 to 5 years (average: 4.5 years). Patients with a previous medical or surgical intervention for LUTS or BPH, a supine blood pressure lower than 90/70 mm Hg, or a serum PSA level of greater than 10 ng/mL were excluded from the study.

Subjects were randomly assigned in a double-blind fashion to one of four treatment groups: placebo, doxazosin, finasteride, or combination therapy. Finasteride was administered as a 5-mg daily dose. The dosage of doxazosin was increased weekly from 1 mg daily to 2-, 4-, and 8-mg daily doses. Participants unable to tolerate the 8-mg dose of doxazosin were given a 4-mg dose; those unable to tolerate both the 8-mg and 4-mg doses were counted as having discontinued doxazosin therapy.

Quarterly assessments were conducted in the research centres; DREs, serum PSA measurements, and urinalyses were performed annually. Prostate volume was assessed at baseline and at the end of year 5 or end of study, whichever came first.

In contrast with previous trials, the primary outcome in the MTOPS trial was overall clinical progression, defined as the occurrence of one of the following five events: an increase in the AUA-SI score of 4 or more points from baseline, AUR, renal insufficiency, recurrent UTI, or urinary incontinence. An increase in the AUA-SI score of 4 or more points was measured relative to the score at the time of randomization and confirmed by re-administration of the symptom index within 4 weeks. Acute urinary retention was defined as the inability to urinate following a trial without catheter. Renal insufficiency had to be attributable to BPO and was defined as a serum creatinine level of at least 1.5 mg/dL and an increase relative to baseline of 50% or more. Recurrent UTI was defined as two or more infections within 1 year, separated by a negative urine culture, or urosepsis. Urinary incontinence was defined as self-reported socially or hygienically unacceptable involuntary loss of urine. All outcomes were reviewed by a clinical review committee unaware of treatment assignments. Secondary outcomes were longitudinal change in AUA-SI score and $Q_{max}$. All analyses were conducted using the intention-to-treat principle, with life table methods used to estimate the cumulative incidence of outcome events.

Of the 4,391 men screened for eligibility, 3,747 were enrolled and randomly assigned to one of the four treatment groups. Among the treatment groups, the mean age at baseline ranged from 62.5 to 62.7 years, and the mean AUA-SI score ranged from 16.8 to 17.6 points. Maximum flow rate ranged from 10.3 to 10.6 mL/s, and TRUS-measured PV ranged from 35.2 to 36.9 mL. Over a mean follow-up period of 4.5 years, 351 primary outcome events occurred, distributed as follows: approximately 78% due to a rise in the AUA-SI score of 4 or more points; 12% due to AUR; 9% due to urinary incontinence; and 1% due to recurrent UTI.

In this well-controlled study, which included quarterly visits and yearly laboratory checks, renal insufficiency due to BPO did not develop in any patient. The rate of overall clinical progression in the subjects who received placebo was 4.5 per 100 person-years. Compared with placebo, doxazosin reduced the risk of progression by 39%; finasteride, by 34%; and combination therapy, by 66%. The risk reduction for both single and combination therapy compared with placebo was highly significant ($p<0.01$), and the risk reduction for combination therapy was significant compared with either drug alone ($p<0.001$).

The risk of AUR was significantly reduced in the finasteride and combination therapy groups compared with placebo. However, although doxazosin therapy delayed the time to AUR, it did not ultimately reduce the cumulative incidence compared with placebo. Similarly, finasteride and combination therapy significantly reduced the cumulative incidence of crossover to invasive therapy

for BPO, whereas doxazosin slightly delayed but did not ultimately reduce crossover to invasive therapy. The rates of urinary incontinence and UTI were too low in the treatment groups to perform meaningful analyses between treatments or with placebo.

Longitudinal changes in AUA-SI score and $Q_{max}$ were recorded following the intention-to-treat principle. Combination therapy produced the greatest improvements in symptom score (7.4 points) and $Q_{max}$ (5.1 mL/s). When interpreting the improvements in symptom score and flow rate for the placebo group (4.9 points and 2.8 mL/s, respectively), it is important to keep in mind that in the intention-to-treat analysis, subjects who crossed over to active known therapy and/or had a surgical intervention for BPO were counted as being in the placebo group. Thus, taking into account the prolonged duration of this clinical trial, the estimation of changes in symptom score and flow rate may be overly optimistic, particularly in the placebo group, in which more patients than in any of the other treatment groups crossed over to active known therapy or had surgical intervention for their disease. A protocol analysis eliminating patients who did not continue on placebo throughout the entirety of the study would help elucidate the actual natural history of the disease in this group of patients.

An NNT analysis was performed, and the NNT to prevent a case of overall clinical progression was 8.4 with combination therapy, 13.7 with doxazosin, and 15.0 with finasteride. In men with serum PSA levels higher than 4.0 ng/mL (20% of the randomized patients) or baseline TRUS PVs greater than 40 mL (30% of the randomized patients), the NNT was reduced in the combination therapy group (4.7 and 4.9, respectively) and the finasteride group (7.2 for both subgroups).

The initial results of the MTOPS trial have answered several important questions regarding the use of combination therapy for BPO. It has become clear that combination therapy is of significant value in the long-term management of patients with LUTS and BPO, particularly those presenting at onset with enlarged prostates or slightly elevated serum PSA levels, who are at risk for progression. Monotherapy with an alpha-blocker (in this case, doxazosin) is effective in treating LUTS associated with BPO and preventing symptomatic progression of the disease; however, it is less effective in preventing AUR, and not at all effective in preventing crossover to surgical therapy.

The second large combination study of sufficient duration is the CombAT trial, a 4-year study randomizing over 4,500 patients to treatments with tamsulosin, dutasteride, or a combination of both (343,345–348). The absence of a placebo group is explained by ethical considerations, since the fate of prolonged placebo treatment had been demonstrated in the MTOPS trial.

Men ≥50 years of age with a clinical diagnosis of BPH based on medical history and physical examination, an IPSS ≥12 points, PV ≥30 mL by TRUS, total serum PSA ≥1.5 ng/mL, and $Q_{max}$ of 5–15 mL/s with a minimum voided volume ≥125 mL were eligible for inclusion. The principal exclusion criteria were total serum PSA >10.0 ng/mL, history or evidence of prostate cancer, previous prostatic surgery, history of AUR within 3 months prior to study entry, 5-ARI use within 6 months (or dutasteride within 12 months) prior to entry, or use of an alpha-blocker or phytotherapy for BPH within 2 weeks prior to entry.

The importance of the inclusion criteria requiring a PV ≥30 mL by TRUS and a total serum PSA ≥1.5 ng/mL cannot be overstated, since it created baseline parameters quite different from those of MTOPS, resulting in different and more severe outcomes. While age, IPSS, and $Q_{max}$ were similar, the average PV was 55.0 vs. 36.3 mL (CombAT vs. MTOPS) and the serum PSA, 4.0 vs. 2.4 ng/mL (CombAT vs. MTOPS).

The improvements in IPSS from baseline were −3.8 (tamsulosin), −5.3 (dutasteride), and −6.3 (combination). The difference from baseline was significant for all three treatment arms. Combination was superior vs. tamsulosin from 9 months and vs. dutasteride from 3 months on. Dutasteride–and this is the only study where a 5-ARI is superior to any alpha-blocker in this regard–was numerically superior to tamsulosin starting after 18 months (342).

The adjusted mean increase in $Q_{max}$ from baseline at month 48 followed a very similar pattern, with an improvement of 0.7 mL/s with tamsulosin, 2.0 mL/s with dutasteride, and 2.4 mL/s with combination therapy. Again, dutasteride proved numerically superior to tamsulosin starting after 6 months.

At month 48, the adjusted mean percentage change from baseline in PV was −27.3% with combination therapy, +4.6% ($p<0.001$) with tamsulosin, and −28.0% ($p=0.42$) with dutasteride. At month 48, the adjusted mean percentage change from baseline in TZV in a subset of 656 men was −17.9% for combination therapy, +18.2% ($p<0.001$) for tamsulosin, and −26.5% ($p=0.053$) for dutasteride (342).

The time to first AUR or BPH-related surgery was significantly lower with combination therapy than with tamsulosin ($p<0.001$); there was no significant difference between combination therapy and dutasteride ($p=0.18$). Combination therapy reduced the RR of AUR or BPH-related surgery by 65.8% compared with tamsulosin, and by 19.6% compared with dutasteride. The cumulative incidence of AUR or BPH-related surgery during the study is shown in **Figure 26**. Starting at 8 months, a higher incidence of AUR or BPH-related surgery was seen in the tamsulosin arm compared with the combination and dutasteride arms; the margin of this difference increased with time to month 48 (342).

**FIGURE 26**

Incidence of AUR or BPH-related surgery for three treatment groups in CombAT, stratified by baseline PV, by tertiles (unpublished data on file at GSK).



*$p < 0.001$ vs. combination therapy

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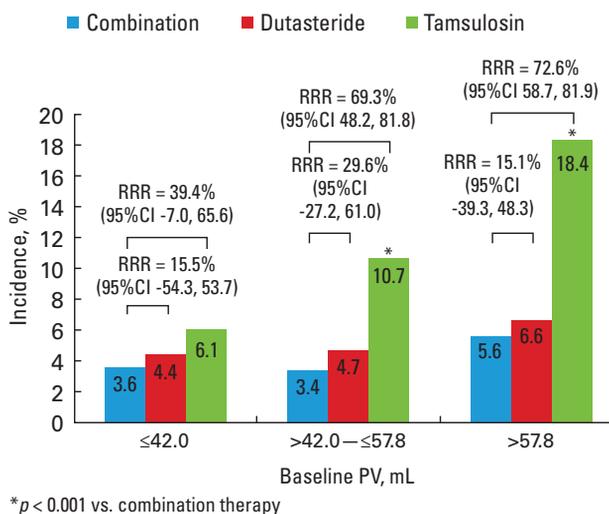
The time to first BPO clinical progression was significantly different in favour of combination therapy versus tamsulosin and dutasteride ($p$<0.001 for both comparisons). Combination therapy reduced the RR of BPO clinical progression by 44.1% compared with tamsulosin, and by 31.2% compared with dutasteride. Symptom deterioration was the most common progression event in each treatment group. The time to first symptom deterioration was significantly different in favour of combination therapy compared with tamsulosin and dutasteride ($p$<0.001 for both comparisons). Combination therapy reduced the RR of symptom deterioration of IPSS ≥4 points by 41.3% versus tamsulosin, and by 35.2% versus dutasteride (342).

The CombAT study allows the examination of outcomes stratified by baseline parameters such as PV and serum PSA to determine at what level of PV or serum PSA there is a measurable benefit of combination therapy or at what level dutasteride becomes superior to tamsulosin.

**Figure 27** demonstrates that with increasing PV there is an increase in the benefit of combination therapy over tamsulosin, as well as dutasteride over tamsulosin; however, the benefit of combination therapy over dutasteride diminishes. Very similar observations can be made for $Q_{max}$ stratified by PV, and for both IPSS and $Q_{max}$ stratified by tertiles of serum PSA.

Similarly, when assessing the risk reduction for either AUR or BPO-related surgery, there is a statistically superior risk reduction comparing tamsulosin versus combination in the upper two tertiles of PV, but not in the lowest tertile (**Figure 27**).

**FIGURE 27**

IPSS score over time for three treatment groups in CombAT, stratified by baseline PV, by tertiles (unpublished data on file at GSK).
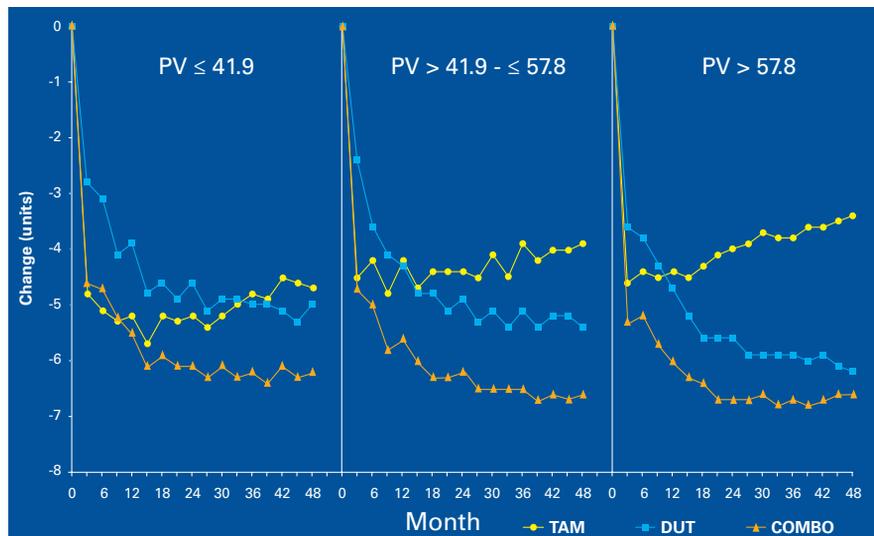


Crawford *et al.* (349) studied the placebo group in MTOPS and found that the risk of various definitions of progression was related to baseline median PV (< ≥31 mL) and baseline median serum PSA (< ≥1.6 ng/mL) (**Figure 28**).

**FIGURE 28**

Incidence rates of overall symptomatic progression, AUR, and invasive therapy in MTOPS, by baseline median PV and serum PSA (350).
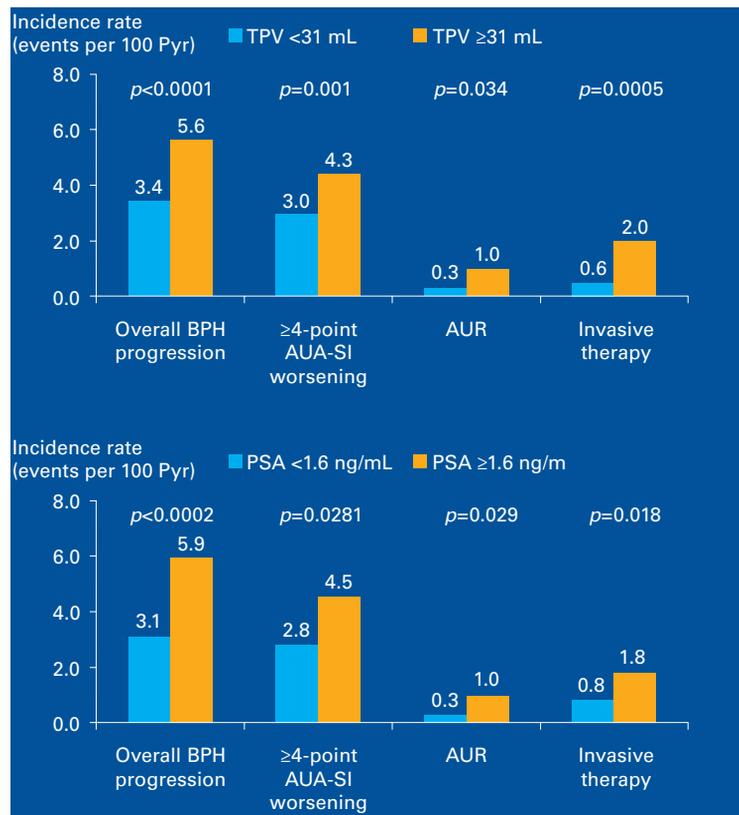
These data allow the drafting of recommendations regarding the appropriateness of combination medical therapy to prevent symptomatic progression and/or progression to AUR and surgery in men with larger glands and/or higher serum PSA values.

### 8.8.1.4 Adverse events with alpha-blocker + 5-alpha-reductase inhibitor combination therapy

As shown earlier, in **Table 53**, alpha1-adrenergic receptor–specific adverse events, such as dizziness, hypotension, and rhinitis, occurred significantly more frequently with alpha1-blocker and combination therapy than with 5-ARI therapy. Anti-androgenic adverse events, such as impotence, decreased libido, and reduction of semen volume, occurred significantly more often with 5-ARI and combination treatments than in alpha1-blocker therapy groups (208,238,239).

Consequently, adverse events were more prevalent in patients receiving combination therapy than in any monotherapy group. Adverse events seem to be additive and not synergistic. Severe adverse events were not observed in either group (208,238,239). Discontinuation rates were similar between treatment groups (11.6%–13.6%) (239).

Within 2 years of treatment, drug-related adverse events occurred more often in the combination therapy group (24%) than in either the tamsulosin (16%) or dutasteride (18%) group. However, the occurrence of serious drug-related adverse events (<1% in each treatment arm) or withdrawal from

the trial (<5% in each treatment arm) was similar between the groups (343). After 4 years of treatment, 6% of patients receiving combination therapy, 4% receiving tamsulosin, and 4% receiving dutasteride discontinued the study due to drug-related adverse events (342).

However, it should not be forgotten that 60%–80% of BPH/LUTS patients are sexually active (351). Both drugs (5-ARI as well as alpha-blockers) might have sexual-related side effects (e.g. loss of libido with 5-ARIs and retrograde ejaculation with alpha-blockers). When an alpha1-blocker and a 5-ARI are combined, these potential side effects might add up and affect the sexual life of the patient. This should not be overlooked in discussing potential side effects with individual patients.

### 8.8.1.5 Recommendation: combination therapy with alpha-blockers + 5-alpha-reductase inhibitors

1. The combination of alpha-blockers and 5-ARIs has been studied in high-quality RCTs of durations varying from <1 year to 5 years. Alpha-blocker + 5-ARI combination therapy is superior to placebo in terms of symptoms, bother, QOL, and urodynamic parameters. Alpha-blocker + 5-ARI combination therapy is superior to monotherapy with an alpha-blocker or a 5-ARI in terms of symptoms, bother, QOL, and urodynamic parameters. Superiority over alpha-blockers is achieved after treatment periods of >12 months and depends on baseline PV. Superiority over 5-ARIs is achieved early and is maintained except in patients with exceptionally large prostates. Alpha-blocker + 5-ARI combination therapy is superior to placebo and monotherapy with an alpha-blocker or a 5-ARI in terms of overall prevention of progression. Alpha-blocker + 5-ARI combination therapy is superior to placebo and monotherapy with an alpha-blocker in terms of prevention of progression to urinary retention and surgery. Alpha-blocker + 5-ARI combination therapy is recommended for the treatment of men with LUTS and BPE as measured by either a PV >30 mL by TRUS/magnetic resonance imaging, or a serum PSA of >1.5 ng/mL (Level 1a).

## 8.8.2 Alpha-blockers + antimuscarinics

The first clinical study on alpha1-blocker/antimuscarinic combination therapy was published by Saito *et al.* in 1999 (352). They administered tamsulosin and propiverine to patients with enlarged prostates and increased frequency of any cause (including neurogenic bladders). Following this landmark study, clinical studies with more homogeneous study populations were performed on alpha1-blocker/antimuscarinic combinations (**Tables 54** and **55**) (162–165,353–362). The majority are add-on studies, where an antimuscarinic is added to alpha1-blocker therapy. Only one study included from the beginning on, next to the alpha1-blocker and alpha1-blocker/antimuscarinic groups, an antimuscarinics-only group (163). All studies defined an upper limit of PVR and a lower limit of $Q_{max}$ as study inclusion criteria. As such, statements concerning the safety of the combination are only valid for patients with a PVR <200 mL and a $Q_{max}$ >5 mL/s.

All studies on alpha1-blocker/antimuscarinic combination therapy have only a short follow-up time, usually 12 weeks, and no study assessed this combination for more than 4 months. Therefore, it is currently unknown whether long-term alpha1-blocker/antimuscarinic combination is useful, safe, and/or effective.

**TABLE 54** Alpha-blocker and antimuscarinics trial characteristics and IPSS outcomes (331).

| Trial | Drug (Dose) | Trial Duration, Months | Inclusion Criteria | Weeks during which an $\alpha$1-Blocker was Given Prior to Add-on Antimuscarinic | |
|---|---|---|---|---|---|
| **Studies in which $\alpha$1-blocker, antimuscarinic, or a combination of both was tested from the start** | | | | | |
| TIMES (*N*=879) Level 1b | Tamsulosin (0.4 mg) tolterodine (4 mg) | 3 | • Age >40 y<br>• $Q_{max}$ >5 mL/s<br>• **PVR <200 mL**<br>• IPSS >12<br>• >8 voids/24 h<br>• PSA ≤ 10 ng/mL | | |
| **Studies in which $\alpha$1-blocker/antimuscarinic or $\alpha$1-blocker/placebo was tested from the start** | | | | | |
| Lee *et al.* (*N*=228) Level 1b | Doxazosin (4 mg) propiverine (20 mg) | 2 | • Age 50–80 y<br>• >8 voids/24 h<br>• Urodynamically obstructed<br>• (A-G >20)<br>• **PVR <30% bladder capacity** | | |
| **Studies in which antimuscarinic or placebo was tested as add-on to an $\alpha$1-blocker** | | | | | |
| MacDiarmid *et al.* (*N*=409) Level 1b | Tamsulosin (0.4 mg) oxybutynin (10 mg) | 3 | • Age >45 y<br>• $Q_{max}$ >8 mL/s<br>• **PVR <150 mL**<br>• IPSS >13<br>• IPSS storage subset >8<br>• PSA ≤ 4 ng/mL | ≥4 | |
| VICTOR (*N*=397) Level 1b | Tamsulosin (0.4 mg) solifenacin (5mg) | 4 | • Age >45 y<br>• $Q_{max}$ >5 mL/s<br>• **PVR <100 mL**<br>• IPSS >13<br>• >8 voids/24 h<br>• PSA ≤ 10 ng/mL | ≥4 | |
| ADAM (*N*=652) Level 1b | Any $\alpha$1-blocker tolterodine (4mg) | 3 | • Age >45 y<br>• Any $Q_{max}$<br>• **PVR <200 mL**<br>• >8 voids/24 h<br>• >1 urgency episode/24 h<br>• PSA ≤ 10 ng/mL | ≥4 | |
| ASSIST (*N*=638) Level 1b | Tamsulosin (0.2 mg) solifenacin (2.5–5 mg) | 3 | • Age >50 y<br>• $Q_{max}$ >5 mL/s<br>• **PVR <50 mL**<br>• >8 voids/24 h<br>• >2 urgency episodes/24 h | ≥6 | |

A-G: Abrams-Griffiths; ADAM: Add-on study of Detrol LA to Alpha-blockers in men; ASSIST: Add-on therapy of Solifenacin Succinate in men for BPH with OAB symptoms treated by Tamsulosin; TAABO: Trial of combination treatment of an Alpha-blocker plus an Anticholinergic for BPH with OAB; TIMES: tolterodine and amsulosin in men with LUTS; VICTOR: Vesicare in combination with Tamsulosin in OAB residual symptoms; y: years.

| | Total IPSS Reduction from Baseline (IPSS Storage Symptom Reduction, Where Assessed Separately) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Alpha1-Blocker** | | **Antimuscarinic** | | **Placebo** | | **Combination** | |
| | 7.8 (3.4) | Significant vs. baseline vs. placebo | 6.8 (3.4) | Significant vs. baseline | 6.2 (2.8) | Significant vs. baseline | 8.0 (4.2) | Significant vs. baseline vs. placebo |
| | | | 7.4 (3.8) | Significant vs. baseline | 7.3 (2.9) | Significant vs. baseline | | |
| | | | 6.9 (3.7) | Significant vs. baseline vs. placebo | 5.2 (2.4) | Significant vs. baseline | | |
| | | | 5.4 (2.8) | Significant vs. baseline | 4.9 (2.3) | Significant vs. baseline | | |
| | | | 4.8 (2.7) | Significant vs. baseline vs. placebo | 4.3 (2.2) | Significant vs. baseline | | |
| | | | 3.5 (2.4) | Significant vs. baseline vs. placebo | 3.1 (1.8) | Significant vs. baseline | | |

A-G: Abrams-Griffiths; ADAM: Add-on study of Detrol LA to Alpha-blockers in men; ASSIST: Add-on therapy of Solifenacin Succinate in men for BPH with OAB symptoms treated by Tamsulosin; TAABO: Trial of combination treatment of an Alpha-blocker plus an Anticholinergic for BPH with OAB; TIMES: tolterodine and amsulosin in men with LUTS; VICTOR: Vesicare in combination with Tamsulosin in OAB residual symptoms; y: years.

**TABLE 54** Alpha-blocker and antimuscarinics trial characteristics and IPSS outcomes (331), Cont'd

| Trial | Drug (Dose) | Trial Duration, Months | Inclusion Criteria | Weeks during which an $\alpha$1-Blocker was Given Prior to Add-on Antimuscarinic | |
|---|---|---|---|---|---|
| TAABO (*N*=214) Level 1b | Tamsulosin (0.2 mg) propiverine (10–20 mg) | 3 | <ul><li>Age >50 y</li><li>$Q_{max}$ 5–15 mL/s</li><li>**PVR <100 mL**</li><li>IPSS >8</li><li>>8 voids/24 h</li><li>>1 urgency episode/24 h</li></ul> | 8 | |
| Oelke *et al.* (*N*=1,849) Level 1b | Propiverine (30 mg) ± any $\alpha$1-blocker | 3 | <ul><li>Age >40 y</li><li>$Q_{max}$ >10 mL/s</li><li>**PVR <100 mL**</li><li>IPSS <20</li><li>>8 voids/24 h</li><li>PV <40 mL</li></ul> | Unknown<br><br>Unknown | |

A-G: Abrams-Griffiths; ADAM: Add-on study of Detrol LA to Alpha-blockers in men; ASSIST: Add-on therapy of Solifenacin Succinate in men for BPH with OAB symptoms treated by Tamsulosin; TAABO: Trial of combination treatment of an Alpha-blocker plus an Anticholinergic for BPH with OAB; TIMES: tolterodine and amsulosin in men with LUTS; VICTOR: Vesicare in combination with Tamsulosin in OAB residual symptoms; y: years.

| Total IPSS Reduction from Baseline (IPSS Storage Symptom Reduction, Where Assessed Separately) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Alpha1-Blocker | | Antimuscarinic | | Placebo | | Combination | |
| | | (2.2) | Significant vs. baseline | (1.1) | Significant vs. baseline | | |
| ≥15 mL/s | | 5.1 | Significant vs. baseline | 4.6 | Significant vs. baseline | | |
| <15 mL/s | | 5.3 | Significant vs. baseline | 3.7 | Significant vs. baseline | | |

A-G: Abrams-Griffiths; ADAM: Add-on study of Detrol LA to Alpha-blockers in men; ASSIST: Add-on therapy of Solifenacin Succinate in men for BPH with OAB symptoms treated by Tamsulosin; TAABO: Trial of combination treatment of an Alpha-blocker plus an Anticholinergic for BPH with OAB; TIMES: tolterodine and amsulosin in men with LUTS; VICTOR: Vesicare in combination with Tamsulosin in OAB residual symptoms; y: years.

**TABLE 55** Alpha-blocker and antimuscarinic combination adverse events, PVR increase, and AUR (331).

| | | TIMES | Lee *et al.* | MacDiarmid *et al.* | VICTOR | ADAM | ASSIST | TAABO |
|---|---|---|---|---|---|---|---|---|
| **Alpha1-Blocker, %** | AEs (dry mouth) | 27.9 (6.9) | | | | | | |
| | Clinically significant* increase in PVR (mean increase, mL) | 0 (0.1) | | | | | | |
| | AUR | 0 | | | | | | |
| | Study discontinuation due to AEs | 3.2 | | | | | | |
| **Antimuscarinic, %** | AEs (dry mouth) | 19.9 (7.4) | | | | | | |
| | Clinically significant* increase in PVR (mean increase, mL) | 0 (5.2) | | | | | | |
| | AUR | 1.8 | | | | | | |
| | Study discontinuation due to AEs | 2.3 | | | | | | |
| **Placebo, %** | AEs (dry mouth) | 16.8 (2.2) | | | | | | |
| | Clinically significant* increase in PVR (mean increase, mL) | 0 (−3.6) | | | | | | |
| | AUR | 1.8 | | | | | | |
| | Study discontinuation due to AEs | 3.1 | | | | | | |
| **Combination, %** | AEs (dry mouth) | 47.1 (20.8) | 42.7 (18.3) | 42.6 (15.3) | 45 (7) | 34.7 (9.7) | 55.9 (11.3) | 13.1 (3.2) |
| | Clinically significant* increase in PVR (mean increase, mL) | 0 (6.4) | 1.4 (20.7) | 2.9 (18) | nr (−13.5) | 0 (13.6) | 6.1 (22.6) | 2.4 (nr) |
| | AUR | 0.8 | 0 | 0 | 3 | 0.9 | 1.9 | 0.8 |
| | Study discontinuation due to AEs | 8.8 | 4.9 | 10.3 | 7 | 4 | 4.7 | 7.4 |

ADAM: Add-on study of Detrol LA to Alpha-blockers in men; AE: adverse event; ASSIST: Add-on therapy of Solifenacin Succinate in men for BPH with OAB symptoms treated by Tamsulosin; nr: not reported; TAABO: Trial of combination treatment of an Alpha-blocker plus an Anticholinergic for BPH with OAB; TIMES: tolterodine and amsulosin in men with LUTS; VICTOR: Vesicare in combination with Tamsulosin in OAB residual symptoms.

* Clinically significant increase in PVR depending on the study, defined as increase requiring catheterization or increase >300 mL or increase >50% of initial PVR or over the initially defined PVR threshold for exclusion.

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| | | TIMES | Lee *et al.* | MacDiarmid *et al.* | VICTOR | ADAM | ASSIST | TAABO |
|---|---|---|---|---|---|---|---|---|
| **Alpha1-Blocker /Placebo, %** | AEs (dry mouth) | | 18.9 (5.8) | 42.6 (4.8) | 39 (3) | 27.6 (5.6) | 42.1 (2.8) | 0 (0) |
| | Clinically significant* increase in PVR (mean increase, mL) | | 0 (nr) | 0.5 (7) | nr (0) | 0 (1) | 0.9 (5.9) | 0 (nr) |
| | AUR | | 0 | 0 | 0 | 0.6 | 0 | 0 |
| | Study discontinuation due to AEs | | 1.4 | 9.7 | 4 | 2.5 | 2.8 | 0 |
| | PVR (mL) & $Q_{max}$ (mL/s) limitations of study patients | <200; >5 | <30% bladder capacity | <150; >8 | <100; >5 | <200; any $Q_{max}$ | <50; >5 | <100; 5–15 |

ADAM: Add-on study of Detrol LA to Alpha-blockers in men; AE: adverse event; ASSIST: Add-on therapy of Solifenacin Succinate in men for BPH with OAB symptoms treated by Tamsulosin; nr: not reported; TAABO: Trial of combination treatment of an Alpha-blocker plus an Anticholinergic for BPH with OAB; TIMES: tolterodine and amsulosin in men with LUTS; VICTOR: Vesicare in combination with Tamsulosin in OAB residual symptoms.

\* Clinically significant increase in PVR depending on the study, defined as increase requiring catheterization or increase >300 mL or increase >50% of initial PVR or over the initially defined PVR threshold for exclusion.

### 8.8.2.1 Subjective outcomes of alpha-blocker + antimuscarinic combination therapy

Add-on studies have reported significant IPSS reductions when patients were treated with alpha1-blocker or alpha1-blocker/antimuscarinic combination therapy, especially reductions of the IPSS subscore, which determines storage symptoms (questions 2, 4, and 7) (165,358,361,362).

A mean reduction of 3 IPSS points was observed in 74.4% of patients when oxybutynin was given as an add-on, but in only 65% of patients receiving placebo add-ons (164). Reports on antimuscarinics as add-on therapy regarding the patients' QOL are controversial; but most studies state that add-on therapy does not significantly improve QOL compared with placebo (165,358,361,362). However, different inclusion criteria in the studies and different durations of previous alpha1-blocker use make outcome parameters difficult to compare (**Table 54**).

The effects of add-on tolterodine were, regardless of initial PSA values, dependant on PV (359). Another study reported that IPSS reduction with propiverine was more pronounced in patients with $Q_{max}$ <15 mL/s at baseline (360). However, data on specific patient groups that might benefit from add-on treatment are scarce. Low case numbers and high patient heterogeneity in existing trials make it difficult to determine which LUTS patients benefit most from an add-on antimuscarinic therapy.

The tolterodine and amsulosin in men with LUTS (TIMES) study was the only trial in which an antimuscarinic monotherapy treatment arm was included. The TIMES study reported that only patients treated with combination therapy showed a significant treatment benefit, as defined by patient perception, while patients treated with tamsulosin, tolterodine, or placebo alone did not (80% vs. 71%, 65%, and 62%, respectively) (163).

Similarly, following the 12 weeks of treatment, only combination therapy significantly improved total IPSS and QOL, whereas tolterodine alone did not differ from placebo. Interestingly, after the same treatment period, tamsulosin alone did improve total IPSS but without significant effects on the IPSS QOL item (163). The IPSS storage subscore was only significantly reduced in the combination group (356). However, in men with a PSA<1.3 ng/mL or a PV <29 mL, tolterodine alone was also able to significantly reduce storage symptoms (355,357). The TIMES study therefore indicates that over the short-term, men with enlarged prostates in particular benefit from alpha1-blocker/antimuscarinic combination therapy. In men with small prostates, antimuscarinics alone are also sufficient.

### 8.8.2.2 Objective outcomes of alpha-blocker + antimuscarinic combination therapy

Studies in which antimuscarinics were assessed as add-ons to alpha1-blockers showed no significant difference in $Q_{max}$ increase between treatment groups (162,165,361,362). Add-on combination therapy, when compared to alpha1-blockers alone, showed a significantly higher reduction in 24-hour voiding frequency (162,165,358,360,361,362)–for example, 23.5% vs. −14.3% (162)–and urgency episodes per day (165,353,358,360)–for example, 2.9 vs. 1.8 (165).

The TIMES study reported that in patients with a PV >29 mL, only combination therapy significantly reduced 24-hour voiding frequency (2.8 vs. 1.7 with tamsulosin alone; 1.4 with tolterodine alone; and 1.6 with placebo). In patients with a PV <29 mL, tolterodine alone also reduced 24-hour voiding frequency (tamsulosin/tolterodine 2.2, tolterodine 1.9, vs. placebo 1.1, and tamsulosin 1.6) (357). The significant frequency reduction began 1 week after the start of treatment (163).

The alpha1-blocker/antimuscarinic combination does not seem to influence $Q_{max}$ but improves other objective outcome parameters, such as 24-hour frequency and urgency episodes. Combination therapy appears to be as efficacious as antimuscarinics alone in men with small prostates (<30 mL).

### 8.8.2.3 Adverse events associated with alpha-blocker + antimuscarinic combination therapy

Although several studies found a significant increase in PVR with antimuscarinics (alone or in combination), most studies did in fact not find a significant increase in AUR with antimuscarinics (**Table 55**) (162–165,360–362).

When, for example, oxybutynin was given to patients who had already received tamsulosin, mean PVR increased by 18.2 mL, whereas placebo increased PVR by 7.8 mL. No AUR occurred either in the oxybutynin/tamsulosin or in the placebo/tamsulosin group (164). Only a few studies reported a higher frequency of AUR in patients treated with antimuscarinic add-on compared to placebo add-on, ranging from 1.9%–3% (353,358). However, studies including a placebo-only group (in which patients did not receive any active compounds) also reported an occurrence of AUR around 1.8% (**Table 55**). Considering the natural rate of AUR in patients with LUTS, the AUR rate with antimuscarinics seems even more irrelevant. But it should not be forgotten that all studies used an upper PVR limit of 200 mL and a $Q_{max}$ above 5 mL/s at the time of inclusion (**Table 54**).

Men with increased risk of AUR were excluded from the trials. Therefore, the results of these trials and subsequent recommendations can only be applied to and made for patients with a similarly low risk profile. In general, caution (regular evaluation of PVR) is recommended when prescribing antimuscarinics to patients with increased risk of developing AUR. Interestingly, PV and serum PSA concentration at study initiation had no influence on AUR development during antimuscarinic treatment (357,359).

Study discontinuation occurred more frequently in patients who received add-on combination therapy than in those who received placebo add-on (4.7%–7% and 1.5%–4%, respectively) (162,353,353). Other studies found no difference in discontinuation rates due to drug-related adverse events (**Table 55**) (163,164). Antimuscarinic adverse events such as dry mouth and constipation occurred in the combination therapy group more often than with alpha1-blocker monotherapy (162,163,165,353,358). For example, dry mouth occurred in 15.3% of patients taking oxybutynin and tamsulosin, but in only 4.8% of patients taking tamsulosin and placebo (164). However, in most studies, side effects were mild and improved on drug discontinuation (162,353).

As with alpha1-blocker/5-ARI combination therapy, adverse events do not seem not to be a decisive criterion, since the type of adverse events are identical with either monotherapy and do not potentiate.

Astellas Pharma has sponsored a 12-week randomized trial using different dosages of solifenacin with 0.4 mg tamsulosin versus placebo. This study, called the SATURN trial (NCT00510406) was conducted in men 45 years or older with LUTS associated with BPH diagnosed more than 3 months prior, IPSS score >13, voiding and storage symptoms, $Q_{max}$ of 4–15 mL/s. Exclusion criteria include PVR >200 mL and symptomatic UTI. The trial was followed by an optional 52-week open-label extension called the NEPTUNE study (NCT01021332), which included men who participated in SATURN trial and had completed 12 weeks double-blind treatment. Exclusion criteria for the extension included any significant PVR volume (>150 mL). If these trials yield positive results, it may mark the introduction of a combination tablet of tamsulosin plus flexible dosing of solifenacin to the market, the second combination tablet in the area of male LUTS and BPH.

#### 8.8.2.4 Recommendations: combination therapy with alpha-blockers + antimuscarinics

1. There are cohort studies exploring the addition of antimuscarinics to the treatment regimen of men with moderate to severe LUTS and OAB demonstrating improved efficacy over alpha-blocker treatment alone over relatively short treatment periods. Adding an antimuscarinic to an alpha-blocker in men with LUTS/OAB with insufficient symptom relief is a recommended treatment option (Level 2b).

2. There is a high-quality RCT comparing alpha-blocker + antimuscarinic vs. placebo vs. alpha-blocker vs. antimuscarinic. This study found the combination therapy to be superior to placebo (not tested against monotherapies). There are additional RCTs not yet published. Combination therapy with an alpha-blocker + an antimuscarinic in men with moderate to severe LUTS/OAB is recommended (Level 2a).

### 8.8.3 Alpha-blockers + phosphodiesterase type 5 enzyme inhibitors

#### 8.8.3.1 Clinical Studies

There are five studies employing a combination of a PDE5 inhibitor (sildenafil, tadalafil, or vardenafil) with an alpha-blocker (tamsulosin or alfuzosin) (363–367). These studies do not feature a placebo control arm, are of short duration, and have a limited number of patients enrolled. Sample size and power calculations are often missing (**Table 56**).

**TABLE 56** Studies of alpha-blocker and PDE5 inhibitors in the treatment of male LUTS.

| Study | Baseline Characteristics | | | Treatment | | |
|---|---|---|---|---|---|---|
| | Age, Years | BMI | IPSS | Drug | Dosage, mg | Pills / Week |
| Kaplan *et al.* 2007 (363) | 63.4 | 25.4 | 17.3 | *N*=67; 12 weeks Sildenafil vs. alfuzosin vs. combination | 25 | 7 |
| Bechara *et al.* 2008 (364) | 63.7 | – | 19.4 | *N*=30; 45 days + 45 days Tadalafil vs. tamsulosin; Cross-over design | 20 | 7 |
| Liguori *et al.* 2009 (367) | 61.3 | – | 15 | *N*=66; 12 weeks Tadalafil vs. alfuzosin vs. combination | 20 | 7 |
| Tuncel *et al.* 2010 (365) | 58.8 | – | 15.4 | *N*=60; 8 weeks Sildenafil vs. tamsulosin vs. combination | 25 | 4 |
| Gacci *et al.* 2012 (362) | 68.0 | 25.7 | 19.6 | *N*=60; 12 weeks Vardenafil vs. tamsulosin | 10 | 7 |

In the Kaplan *et al.* study, IPSS improved significantly in all groups (alfuzosin: $17.3 \pm 4.3$ vs. $14.6 \pm 3.7$ points; $p=0.01$; sildenafil: $16.9 \pm 4.1$ vs. $14.9 \pm 4.2$ points; $p=0.03$; combination: $17.8 \pm 4.7$ vs. $13.5 \pm 4.2$; $p=0.002$). Mean IPSS remained in the moderate LUTS category for all groups. Alfuzosin significantly ($p<0.05$) improved $Q_{max}$ (11.7%), whereas sildenafil alone did not. Combination therapy produced near-additive improvements in IPPS (24.1%), $Q_{max}$ (21.1%), and ED measures (363).

Bechara *et al.* noted significant improvements in IPSS and IPSS QOL with both treatments, but greater improvements with the drug combination. Both regimens similarly improved $Q_{max}$ and decreased the PVR volume from baseline, with no significant differences between tamsulosin alone versus tamsulosin and tadalafil. The IIEF domain score improved with tamsulosin and tadalafil, but not with tamsulosin alone (364).

In the Liguori *et al.* study, IIEF-EF scores were improved in all groups (by 15%, 36%, and 37% from baseline in the alfuzosin, tadalafil, and combination groups, respectively). All groups had an increase in $Q_{max}$ (of 22%, 10%, and 29.6% from baseline in the alfuzosin, tadalafil, and combination groups, respectively), as well as a significant decrease in IPSS score (of 27%, 8%, and 42% from baseline, respectively). All changes were statistically significant compared with baseline values ($p<0.05$), with the exception of the change in IPSS score in the tadalafil-only group (367).

In the small study by Truncel *et al.*, IPSS, $Q_{max}$, PVR volume, Sexual Health Inventory for Men (SHIM) scores, and questions number 3 and 4 of the IIEF significantly improved in each group. Improvement in the symptom score was more evident in both the combination (40.1%) and the tamsulosin-only (36.2%) groups compared with the sildenafil-only group (28.2%) ($p<0.001$). Improvements in $Q_{max}$ and PVR volume were greater in both the tamsulosin-only and the combination group compared with the sildenafil-only group. Sexual Health Inventory for Men scores had a significantly greater improvement in both the sildenafil-only (65%) and the combination (67.4%) groups than in patients who received tamsulosin only (12.4%) ($p<0.001$), and increases in the IIEF scores were greater in the sildenafil-only and combination group than with tamsulosin only. This study showed that treatment with the combination of tamsulosin and sildenafil was not superior to monotherapy with tamsulosin (365).

Gacci *et al.* found a between-group significant difference from baseline to 12 weeks in the following: $Q_{max}$ (placebo: +0.07, vardenafil: +2.56, $p=0.034$); Qave (placebo: −0.15, vardenafil: +1.02, $p=0.031$); irritative IPSS subscores (placebo: −1.67, vardenafil: −3.11, $p=0.039$); and IIEF (placebo: +0.06, vardenafil: +2.61, $p=0.030$). No patient reported any serious (grade ≥2) adverse event. There were no differences in the incidence of common, treatment-related adverse events between men undergoing combined therapy and those receiving tamsulosin alone (366).

### 8.8.3.2 Meta-Analysis

In the meta-analysis performed by Gacci *et al.*, the combination of the two medications significantly improved IPSS (−1.8; 95% CI: −3.7 to 0.0; $p=0.05$) and IIEF score (+3.6; 96% CI: +3.1 to +4.1; $p<0.0001$), as well as $Q_{max}$ (+1.5 mL/s; 95% CI: +0.9 to +2.2; $p<0.0001$), compared with the use of alpha-blockers alone (**Figure 29**) (329).

**FIGURE 29**

IPPS and $Q_{max}$ changes in studies combining alpha-blockers and PDE5 inhibitors (329).
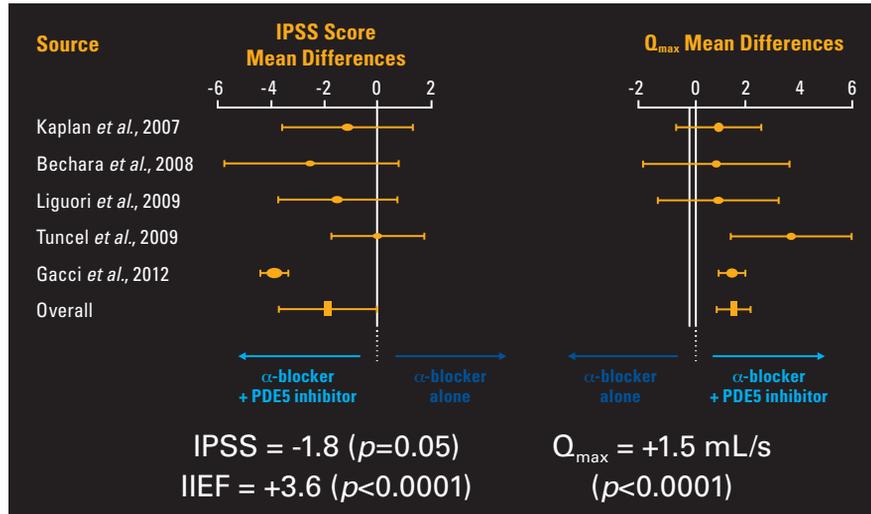


In studies comparing the effect of PDE5 inhibitor plus alpha-blocker combination therapy versus an alpha-blocker alone, seven out of the 103 men treated with combination therapy (6.8%) experienced an adverse event, versus five out of the 99 men treated with alpha-blocker alone (5.1%).

### 8.8.3.3 Recommendation: combination therapy with alpha-blockers + phosphodiesterase type 5 enzyme inhibitors

1. There are several randomized trials without placebo control of low to moderate quality and cohort studies demonstrating the superiority of alpha-blocker + PDE5 inhibitor combination treatment vs. alpha-blocker monotherapy. The combination of an alpha-blocker + a PDE5 inhibitor has been found to be safe. Additional higher-quality controlled studies are needed before recommendations can be made (Grade D).

# 8.9 **References**

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**EVALUATION OF MAN WITH CPPS**

↓

**MANDATORY**
*History*
*Physical Examination (DRE and Pelvic Floor)*
*Urinalysis, Midstream culture*

↓

Recurrent UTIs ⟶ **Cat II Chronic Bacterial Prostatitis**
Positive culture

↓

**RECOMMENDED**
*NIH-CPSI/Sexual history*
*2-glass test*
*Cytology*
*Flow rate/Residual urine*

↓

**OPTIONAL**
**(NOT RECOMMENDED for routine evaluation of typical patient diagnosed with CPPS)**

↓

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Hematuria, Suspicious cytology, Obstruction | Obstruction (Symptoms, Flow rate, Residual urine) | Urethral symptoms (discharge dysuria, penile pain) | Abnormalities suggested by other tests | Semen abnormalities (discolored "foul semen") | Abnormal DRE, >45 years, Family history or risk factors | Major Psychopathology (depression, suicidal) | Bacteria localized in 2-glass test |
| ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |
| *Cystoscopy* | *Urodynamics* | *STI Assessment* | *TRUS, CAT, MRI* | *Semen culture* | *Serum PSA* | *Psychological Evaluation* | *4-glass test?* |

**CPPS Diagnosis**

↓

**Evaluation Algorithm**

| **Urinary** | **Psychosocial** | **Organ Specific** | | **Infection** | **Neuropathic/** Extra-pelvic | **Tenderness** | **Sexual** |

*Voiding Storage*

*Depression Catastrophizing Depression*

*Prostate Tenderness Inflammation*

*Bladder Improvement with voiding*

*Positive cultures Antibiotic response*

*Pelvic floor muscle pain or spasm*

*Dysfunction or pain*

Alpha-blockers
Anti-muscarinics
Diet modification

Antibiotics

Sexual dysfunction therapy (eg. PDE-5 Inhibitors)

Cognitive Behavioral Therapy
Anti-depression Medication
Appropriate referral

Gabapentinoids
Amitriptyline
Neuromodulation
Acupuncture
Pain clinic

Cernilton
Quercetin
Anti-Inflammatories

Pentosanpolysulfate
Quercetin
Intravesical Therapy
(see BPS guidelines)

Pelvic Floor Physical Therapy
Biofeedback
ESWT

```
                    ┌─────────────────────┐
                    │      Nocturia       │
                    └──────────┬──────────┘
                               │
                               ▼
                    ┌─────────────────────┐
     NO             │  Is it bothersome?  │           YES
  ┌────────────────◄│                     │►────────────────┐
  │                 └─────────────────────┘                 │
  ▼                                                         ▼
┌──────────┐                                        ┌──────────────────┐
│  Active  │                                        │ Establish cause  │
└────┬─────┘                                        └────────┬─────────┘
```

| Sleep disturbance | Bladder storage probleme | Polyuria | Psychological | Behavioural |

| Nocturnal polyuria | 24-hour polyuria |

Nocturia

Frequency-volume chart

- Low nocturnal/global bladder capacity
- Nocturnal polyuria: NPi >33%
- Polyuria: 24-hour volume >40 ml/kg
- Mixed

Low nocturnal/global bladder capacity →

Look for urological cause:
- prostatic obstruction
- nocturnal detrusor overactivity
- neurogenic bladder
- pharmacologic agents
- bladder/ureteral calculi

Nocturnal polyuria: NPi >33% →
- Congestive heart failure → Refer to cardiology
- Diabetes mellitus
- Peripheral edema due to venous disease
- Excessive PM fluid intake
- Obstructive sleep apnea suspected (snoring, obesity, short neck) → Sleep studies

Polyuria: 24-hour volume >40 ml/kg →
- Overnight water deprivation
  - Urine >800 mOsm/kg → Primary polydipsia
  - Urine <800 mOsm/kg → Renal concentrating capacity test
    - Normal → Dx central diabetes insipidus → Refer to endocrinology
    - Abnormal → Dx nephrogenic diabetes insipidus → Chronic renal failure, lithium, tetracycline, hypercalcemia, hypokalemia

Mixed →
Multiple incremental etiologies as per individual nocturia categories

**Post MLUTS Tx Sexual Assessment for Bothersome SD**

**Repeat Recommended Evaluations**
Medical and psychosocial history, Physical exam
Sexual history: EF, EJD Libido
Testosterone, prolactin*, lipids, glucose
Validated questionnaire for EF and EJD

**Standard**: identification of organic comorbidities and psychosexual dysfunctions. Both should be appropriately treated/triaged

Bothersome SD

Withdrawal of putative agent

Bothersome SD Persists

Resolution of SD

**ART**
Oral therapies: PDE5i
Regional drug therapies: intra-urethal supp., ICI,
Vacuum constriction device
Surgical therapies**

1. Standard: Discuss MLUTS Treatments impact on sexual function
2. Choose alternate MLUTS Treatment

# Management of Sexual Dysfunction in MLUTS Patients

**Recommended Evaluations at time of MLUTS evaluation**

Medical and psychosocial history, physical exam

Sexual history: EF, EJD libido

Testosterone, prolactin*, lipids, glucose

Validated questionnaire for EF/EJD

**Post-Tx Bothersome SD?**
**Proceed to Post Tx Reassessment**

**No Bothersome SD**
**Watchful wait/Reassess**

**MLUTS Treatment**

Post MLUTS Tx Sexual Assessments

**Bothersome SD**
Standard: identification of organic comorbidities and psychosexual dysfunctions. Both should be appropriately treated/triaged

**Resolution of SD**

**Persistence of ED**

**Oral therapies: PDE5i**

**No Resolution of ED?**

**Regional drug therapies: intra-urethal supp., ICI, Vacuum constriction device**

**No Resolution of ED?**

**Persistence of SD?**

**Appropriately treated/triaged**

**Surgical therapies**

## DIAGNOSTIC TESTS

### A. BASIC EVALUATION

#### Recommended

1. History
2. Assessment of Symptoms and Bother
3. Physical and Digital Rectal Examination
4. Urinalysis
5. Consideration of Serum Prostate-Specific Antigen (PSA)
6. Frequency - Volume Chart (Voiding Diary)

### B. SPECIALIZED EVALUATION

#### I. Recommended Test

1. Detailed Quantification of Symptoms by Standardized Questionnaires
2. Flow Rate Recording
3. Residual Urine
4. Pressure Flow Studies (PFS)

#### II. Optional Testing

1. Imaging of the Prostate by Transabdominal or Transrectal Ultrasound (TRUS)
2. Imaging of the Upper Urinary Tract by Ultrasonography or Intravenous Urography (IUV)
3. Endoscopy of the Lower Urinary Tract

**Basic Management of male LUTS**

**Recommended Tests**
1. Medical Hystory
2. LUTS frequency, severity and bother assessment (questionnaires)
3. Physical Examination incl DRE
4. Urinalysis
5. Serum PSA (what exceptions??)
6. Frequency Volume Chart???

**Complicated LUTS**
1. DRE suspicious for cancer
2. Hematuria
3. Abnormal PSA
4. Pain
5. Infection by UA
6. Bladder palpable
7. Neurological disorder suspected
8. Failed prior medical therapy??
9. Failed prior surgical therapy???

**Uncomplicated LUTS**
1. Mild to moderate symptoms
2. No to little bother
3. No QoL interference

**Reassurance and Follow up in annual inter-**

**LUTS with either or:**
1. Moderate to severe symptoms
2. More than mild bother
3. QoL interference

Nocturia is dominant symptom

Frequency Volume Chart for Three 24 hrs period

No Polyuria

**Polyuria**
     24 hrs output > 3 liters
     Lifestyle alterations
     Reduce fluid intake

**Nocturnal Polyuria**
     >33% output at night
     Reduce fluid intake in evening
     Consider desmopressin

**Non-Drug Treatment**

• Alter modifiable risk factors
     • Drugs
     • Fluid and food intake
• Lifestyle advice
• Bladder training

**Treatment Success**

**Treatment Failure**

**Drug Treatment (see next page)**

**Treatment Success**

**Treatment Failure**

**Continue Treatment**
Reassessment

**Specialized Management of LUTS**

## Specialized Management for Persistent Bothersome Male Luts after Basic Management

**Storage symptoms**
- c/w Overactive bladder (OAB)
- No evidence of Bladder Outlet Obstruction

**Recommended Tests**
1. Validated questionnaires
2. Frequency Volume Charts (FCV)
3. Flowrate recording (FRR)
4. Postvoid Residual check (PVR)
5. Additional optional tests
6. Urethrocystoscopy
7. Transrectal ultrasound (TRUST)
8. Urodynamic studies (UDS)

1. Lifestyle intervention
2. Behavioral therapy
3. Antimuscarinics monotherapy

**Treatment Failure**

**Success: Reassurance and Follow up in annual interval**

Consider:
- Botulinum toxin
- Neuromodulation
- Other invasive therapies

**Evidence of BOO Discuss Rx Options Share Decision**

**MIST or Surgical Intervention**

**Medical Therapy**

**Mixed OAB And BOO**

**Mixed BOO And ED**

**Predominant BOO**

**Antimuscarinics And Alpha Blocker**

**PDE 5 Inhibitors Alone or with Alpha Blocker**

**Small Gland Low PSA Alpha blocker**

**Larger Gland Higher PSA Alpha blocker + 5 alpha Red Inhibitor**

**Success: Reassurance and Follow up in annual intervals**

**Treatment Failure**

Offer MIST or Surgical Intervention to Patient

Evaluation clearly indicative of Obstruction (Qmax < 10 mL/sec)

Yes

No

Urodynamic Pressure Flow Studies (UDS)

Obstruction absent

Obstruction present

Yes

Treat appropriately. If MIST or surgery is pursued, patient must be informed of higher rate of treatment failure

Proceed with planned MIST or Surgical Technique

Glossary

| | |
|---|---|
| PVR | Post-void Residual Urine (mL) |
| FRR | Flow Rate Recording |
| Qmax | Maximum urinary flow rate (mL/sec) |
| OAB | Overactive Bladder |
| MIST | Minimally Invasive Surgical Treatment |
| UDS | Urodynamic Study / Pressure flow Study |
| TRUS | Trans Rectal Ultrasound Study |
| BOO | Bladder Outlet Obstruction |
| ED | Erectile Dysfunction |
| PDE5 | Phosphodiesterace type 5 inhibitor |
| 5 ARI | 5-alpha reductase inhibitor |
| PSA | Prostate Specific Antigen |
| Polyuria | Urine output > 3 liters per 24 hrs period |
| Nocturnal polyuria | >33% of total urine output at night |

# Advancing Urology Worldwide

**SIU**
SOCIÉTÉ INTERNATIONALE D'UROLOGIE

www.**siu-urology**.org

# The Société Internationale d'Urologie

The Société Internationale d'Urologie is the world's only truly international professional organization serving the global urological community. Founded in Paris in 1907, the SIU now serves its members from its Central Office in Montreal, Canada.

SIU members represent the full spectrum of clinicians and investigators from all subspecialties that come together to diagnose, treat and support patients with urological disease.

The Society's mission is to enable urologists in all nations, through international cooperation in education and research, to apply the highest standards of urological care to their patients. The SIU is unique in its international scope and its commitment to effecting positive and sustainable change in nations across the world.

The SIU promotes its mission objectives through annual world congresses, training scholarships, equipment donation and maintenance in training centres, donation of teaching materials, and support of the International Consultation on Urological Diseases (ICUD).

Previous ICUD Consultations have addressed the following topics: Urogenital Trauma (2002), Bladder Cancer (2004), Congenital Genital Anomalies (2006), Stone Disease (2007), Penile Cancer (2008, Testicular Cancer (2009), Vesicovaginal Fistula (2010), Urethral Strictures (2010), Prostate Cancer (2011) , Male Lower Urinary Tract Symptoms (2012), Congenital Anomalies in Children and Upper Tract Urothelial Carcinoma (both 2013). Future Consultations include Stone Disease (2014).

The SIU continues to support its guest lecturer series in conjunction with national urological associations who are interested in hosting an SIU lecture. *Urology – the Gold Journal* is the official journal of the SIU.

## Why Join the SIU?

The Société Internationale d'Urologie is an international democratic body whose first objective is to promote cooperation, education and exchange among urologists of all nations and cultures.

Joining the SIU raises funds for Society activities, heightens awareness of the important work that the Society undertakes in the interest of patient health and welfare, particularly in underserved countries, and provides a truly international forum for specialists active in this area.

Active members of each National Section elect a National Delegate and Deputy Delegate to liaise with the Society and to represent them at the National Delegates' Meeting held during each SIU Congress.

All SIU members have a voice in this inclusive organization, which is committed to building increasingly far-reaching educational and endowment activities.

## Benefits for SIU Members

**Education**

Access to the SIU's eLearning platform–SIU Academy–that features clinical case studies, electronic annotated publications, eSeries, live surgery broadcasts, and Congress webcasts.

**Publications**

- Access to ICUD (International Consultation on Urological Diseases) publications, such as those on Male LUTS (2012), Prostate Cancer (2011), Urethral Strictures (2010), and Vesicovaginal Fistula (2010).
- A monthly subscription to *Urology – The Gold Journal*, the official journal of the SIU (international non-member price: $494 US).
- The quarterly SIU newsletter.

**SIU Congress**

Receive a significant discount off non-member registration fees at SIU Congresses, depending on the registration category.

**Prestige and Recognition**

Peer recognition and membership in an internationally-recognized society, serving urologists since 1907.

**Networking**

Online access to the SIU members-only section to view the SIU membership directory, network with  international members and training centres, and pay dues online.

# MALE LOWER URINARY TRACT SYMPTOMS (LUTS)

Lower urinary tract symptoms (LUTS) are common in men and women, especially in aged populations. Lower urinary tract symptoms negatively affect health-related quality of life (HRQOL) of afflicted individuals and are associated with high healthcare costs. The adoption of the term LUTS has led to some shift in focus when managing men with bothersome symptoms that were historically attributed to their prostate.

This work represents a huge effort by a large international faculty, working in eight committees, as part of the SIU-ICUD Consultation on Male Urinary Tract Symptoms held in Fukuoka, Japan in September 2012, chaired by Drs Christopher Chapple, Kevin McVary, and Claus Roerhborn. This compilation details the consensus statements on patient care and reviews other topics, including epidemiology. The Consultation committees reflect the change in emphasis as they assess not only prostatic obstruction, but also other important causes of male LUTS, such as detrusor overactivity. For the first time, there is also a committee reporting on nocturia.

This work attempts to complete the paradigm shift from "prostatism" to LUTS/BPO. It is hoped that we have been consistent in the correct use of these terms. We hope that you enjoy the content herein and find it a vital and dependable source of data on male LUTS.