Overactive bladder in males

Alex Gomelsky and Roger R. Dmochowski

Abstract: The prevalence of overactive bladder (OAB) symptoms is considerable in both men and women and the impact on quality of life (QOL) is equally substantial. Ironically, despite nearly equal prevalence, OAB symptoms in men are infrequently treated, and often with medical therapies aimed at bladder outlet obstruction (BOO). In this review, we examine the pathophysiology of OAB and its evaluation in the context of benign prostatic hypertrophy and concomitant BOO. We then consider the efficacy and safety of individual therapeutic options for lower urinary tract symptoms in men, focusing on the mainstays of medical therapy: α -adrenergic blockers, 5- α reductase inhibitors, and antimuscarinic agents. Finally, we aim to comment on new therapeutic strategies and targets that may one day be available for the treatment of male OAB.

Keywords: anticholinergic, benign prostatic hypertrophy, overactive bladder

Introduction

Lower urinary tract symptoms (LUTS) are divided into three categories based on their temporal relationship to the micturition cycle [Abrams *et al.* 2003]. Urinary storage symptoms include urgency, frequency, nocturia, and urinary incontinence, while voiding symptoms include slow stream, splitting or spraying of the stream, intermittency, hesitancy, straining to urinate, and terminal dribbling. Postmicturition symptoms include postmicturition dribbling and a feeling of incomplete emptying. The storage subcategory of LUTS is synonymous with overactive bladder syndrome (OAB), defined by the International Continence Society (ICS) as 'urgency, with or without urge incontinence, usually with frequency and nocturia' [Abrams *et al.* 2003]. The authors state that these symptom combinations are suggestive of urodynamically demonstrable detrusor overactivity (DO). All of these definitions, in turn, rely on the interplay between bladder and outlet.

As the definitions of LUTS and OAB are intimately intertwined, it would be reasonable to expect that both men and women would be offered similar symptom-directed treatment options. It has been found that OAB symptoms in men are frequently attributed to a bladder outlet obstruction (BOO) due to benign prostatic hypertrophy (BPH) and treated accordingly. Conversely, women with similar symptoms

often receive treatment aimed at presumed DO [Rosenberg *et al.* 2007]. The failure of prostate-specific treatments in a significant number of men with OAB symptoms, and the proven benefit and safety of pharmacological treatment of DO in this population, are but two factors that are responsible for the recent 'paradigm shift' in the treatment of male OAB (with or without concomitant outlet obstruction) [Chapple and Roehrborn, 2006].

Epidemiology of OAB

The overall prevalence of OAB is significant. The EPIC study was a population-based cross-sectional survey of adults 18 years of age or older in five countries (Canada, Germany, Italy, Sweden and the UK) [Irwin *et al.* 2006]. Of more than 19,000 participants, nearly 65% reported at least one LUTS. The prevalence of storage symptoms (men, 51.3%; women, 59.2%) was greater than that for voiding (men, 25.7%; women, 19.5%) and postmicturition (men, 16.9%; women, 14.2%) symptoms combined. The overall prevalence of OAB was 11.8% and rates were similar in men and women, increasing with age for both sexes. In a secondary analysis of the EPIC study, Irwin *et al.* found that men with OAB symptoms reported more LUTS and greater severity of symptoms than the general population [Irwin *et al.* 2009]. Symptom bother was related to the number of LUTS and urgency severity.

Ther Adv Urol

(2009) 1(4) 209–221

DOI: 10.1177/

1756287209350383

© The Author(s), 2009.

Reprints and permissions:

<http://www.sagepub.co.uk/journalsPermissions.nav>

Correspondence to:

Roger R. Dmochowski, MD, FACS,

Professor, Department of Urologic Surgery, Vanderbilt University Medical Center, A-1392, Medical Center North, Nashville, TN 37232, USA

roger.dmochowski@vanderbilt.edu

Alex Gomelsky, MD

Associate Professor of Clinical Urology, Louisiana State University Health Sciences Center – Shreveport, Shreveport, LA 71103, USA

In another European population-based survey encompassing nearly 17,000 interviewed men and women, the overall prevalence of OAB symptoms in individuals over 40 years of age was 16.6% [Milsom *et al.* 2001]. Frequency (85%) was the most commonly reported symptom, followed by urgency (54%), and urge incontinence (36%). As in the EPIC study, the prevalence of OAB increased with advancing age for both men and women. Additionally, while 60% of symptomatic respondents had consulted a doctor, only 27% were currently receiving treatment. In the US, the National Overactive Bladder Evaluation (NOBLE) Program was a national telephone survey employing a clinically validated interview of over 5000 adults [Stewart *et al.* 2003]. The overall prevalence of OAB was similar between men (16%) and women (16.9%); OAB without urge incontinence was more common in men than in women across all age groups. The study also revealed that, in relation to chronic health disorders such as diabetes, heart disease, and asthma, OAB was only second to arthritic symptoms in terms of overall prevalence [Stewart *et al.* 2003].

Overactive bladder is known to have a significant impact on quality of life (QOL) in both women and men. In a US online survey of nearly 900 women currently being treated, lapsed in treatment, and never treated for OAB, over one-third of respondents indicated that OAB symptoms interfered with their daily activities and their ability to participate in physical activities [Dmochowski and Newman, 2007]. Additionally, 23% were not able to go on short outings and 12% stayed at home more often. In one EPIC subanalysis, patients with storage, voiding, and postmicturition symptoms reported significantly greater symptom bother, worse health-related QOL, higher rates of depression, and decreased enjoyment of sexual activity than other subgroups [Koyne *et al.* 2008]. Likewise, men in the NOBLE study with OAB (with and without urge incontinence) had clinically and significantly lower SF-36 QOL scores, higher Center for Epidemiologic Studies Depression (CES-D) Scale scores, and poorer quality of sleep than matched controls [Stewart *et al.* 2003]. In another EPIC subanalysis, OAB was found to impact significantly on work productivity [Sexton *et al.* 2009].

The costs of treating OAB are also substantial. Findings from the Urologic Diseases in America

project estimated that the overall economic burden for male urinary incontinence was \$18.8 billion in direct medical costs in year 1998/1999 dollars [Stothers *et al.* 2005]. Medical expenditures for urinary incontinence for male Medicare beneficiaries 65 years and older have doubled since 1992, and, compared to men without incontinence, the presence of incontinence more than doubled the annual expenditures per person yearly (\$3204 *versus* \$7702). A subanalysis of the NOBLE study estimated the total cost of urinary incontinence and OAB to be \$19.5 billion and \$12.6 billion in year 2000 dollars, respectively [Hu *et al.* 2004]. With OAB, \$9.1 and \$3.5 billion was incurred by community and institutional residents, respectively.

While the prevalence of OAB, its impact on QOL, and costs to society appear to be substantial, the actual number of patients receiving treatment is significantly lower [Dmochowski and Newman, 2007]. Reasons for undertreatment may be due to both patient- and practitioner-derived reasons. Of over 160,000 survey respondents with probable OAB, only 45.7% had discussed the symptoms with a medical provider [Benner *et al.* 2009]. Additionally, only 22.5% had previously used prescription medications for OAB, 13.5% had used OAB medications in the last 12 months, and 8.1% were currently undergoing treatment. Similar results were reported in a UK study analyzing the prevalence of LUTS in a database of over a million men [Morant *et al.* 2008]. In the 12-month period before 1 January 2006, only 25% of men diagnosed with OAB and 6–7% of men with storage LUTS received antimuscarinics, whereas 36% of men with a record of LUTS/BOO received α_1 -adrenergic receptor antagonists (α -blockers) and 5 α -reductase inhibitors (5 α RI). Furthermore, although the prevalence of OAB is similar in men and women, treatment is disproportionate; men are treated for OAB less frequently than women. When prescriptions for antimuscarinic medications were assessed over a 12-month period, it was found that women accounted for significantly more prescriptions than men, by a 4:1 ratio [Verispan Patient Longitudinal Data, MAT, 2005].

Pathophysiology of OAB

To fully appreciate the pathophysiology of OAB, it is first imperative to understand the complex interaction between the various bladder layers, neurotransmitters, and peripheral and central

nerve centers that contribute to normal bladder storage. The outcome of efficient urinary storage is retention of a socially acceptable amount of urine at a low vesical pressure and a competent and closed bladder outlet, in the absence of DO. Urinary storage is achieved mainly by spinal reflex pathways which are under supraspinal control via the periaqueductal grey and the pontine micturition center. The accommodation of urine (compliance) is primarily a passive phenomenon dependent on the intrinsic properties and collagen content of the vesical smooth muscle and the quiescence of the parasympathetic pathway [Yoshimura and de Groat, 1997; de Groat, 2006]. In conditions such as BOO, the collagen content may increase and lead to the loss of bladder distensibility and subsequent loss of compliance. Conversely, a normal bladder stores urine until it is full at intravesical pressures (<10 cm H₂O) significantly lower than urethral resistance pressure [Klevmark, 1974].

Increased wall tension during filling activates bladder afferent nerves that evoke the sensation of bladder filling. A low level of vesical afferent activity (through A δ axons in the pelvic nerve) leads to reflex activation of sympathetic outflow to the lower urinary tract from the lumbosacral spinal cord [de Groat, 2006; de Groat and Theobald, 1976]. Consequently several efferent pathways are activated. There is contraction of the external sphincter and pelvic floor striated musculature via the pudendal nerve (nicotinic receptor) and internal sphincter contraction (α_1 -adrenoceptors). Additionally, there is ganglionic inhibition via the hypogastric nerve. Adrenergic activity may also cause relaxation of the detrusor muscle through the stimulation of β_3 -adrenergic receptors [Igawa *et al.* 1999]. Furthermore, during the storage phase the sacral parasympathetic outflow is quiescent. The end result is detrusor inhibition and outlet excitation, leading to continent storage.

Overactive bladder is often associated with DO, a urodynamic observation characterized by involuntary detrusor contractions during bladder filling [Abrams *et al.* 2004; Ouslander, 2004]. While symptoms of OAB such as urgency and urge urinary incontinence are outcomes of DO, many factors can influence its development. Hormonal changes, BOO, aging, ischemia, and concomitant neurologic and non-neurologic conditions have been cited as factors that may ultimately impact bladder function

[Andersson, 2003]. Mechanisms contributing to OAB symptoms may be sensory or motor, and may be neurogenic, myogenic, mixed, or idiopathic in origin [Andersson, 2004; Ouslander, 2004]. Additionally, various receptors and neurotransmitters associated with the urothelium may have a role in generating OAB symptoms.

Traditionally, DO was thought to result from a decreased capacity to handle increased afferent information or from a loss or decrease of the tonic inhibition of afferent impulses [Andersson, 2004]. During normal bladder filling, suprapontine inhibition can be voluntarily increased in response to bladder contractions. However, in conditions such as stroke, suprapontine inhibition may be affected. Subsequently, involuntary detrusor contractions may be generated from low intensity afferent input and at lower bladder volumes.

Recently, Andersson proposed a cascade of further peripheral events that may result in DO [Andersson, 2004]. An enhanced reaction to heightened wall tension and stretching of the detrusor smooth muscle leads to increased afferent signaling during bladder filling. Additionally, increased afferent activity may result from increased urothelial signaling to suburothelial nerves, as may be seen in BOO and normal aging. One theory is that there is an increased amount of acetylcholine (ACh) released from the urothelium during bladder filling, above and beyond the typical basal ACh release. The increase in ACh release from neuronal and non-neuronal (urothelial) sources increases the sensitivity of the detrusor to neurotransmitters. The resultant micromotion of the detrusor increases the afferent signaling in the suburothelium and detrusor, leading to the sensation of urgency. ACh is released from the urothelium and detrusor. This feedback mechanism to the central nervous system leads to the sensation of urgency. Other functional changes in the detrusor include an increase in the purinergic receptor-mediated contractile response and increase in the expression of purinergic receptors such as P2X₁ [Boselli *et al.* 2001; O'Reilly *et al.* 2001].

The 'myogenic theory' proposes that morphologic changes in the detrusor, brought on by conditions such as BOO, normal aging, and neurogenic insults, may be associated with OAB [Brading, 1997]. Changes seen with these conditions include progressive denervation and

hypertrophy of the bladder wall [Levin *et al.* 1990; Gosling *et al.* 2000; Andersson, 2003]; alterations in nondetrusor components and extracellular matrix composition [Gabella and Uvelius, 1990]; and 'patchy denervation' of the detrusor, leading to potentially increased excitability between detrusor myocytes [Turner and Brading, 1997; Charlton *et al.* 1999; Mills *et al.* 2000]. Additionally, the areas of denervation may correspond to individual muscle 'modules' that develop an increased sensitivity to neurotransmitters such as ACh [Drake *et al.* 2001]. As in denervation supersensitivity, this heightened muscular excitability leads to an increased ability for activity to spread among cells. Local uncoordinated detrusor contractions then lead to an increase in afferent signaling. This pathway may serve as a link between the neurogenic and myogenic theories of OAB.

Bladder outlet obstruction may also contribute to symptoms of OAB through changes in intracellular communication between myocytes. As detrusor cells are believed to be electrically coupled, the involvement of gap junctions has been implicated [Daniel *et al.* 1983; Andersson 1993; Neuhaus *et al.* 2002]. Expression of connexin 43 has not only been localized in human detrusor smooth muscle, but its upregulation in BOO has been demonstrated [Wang *et al.* 2001; Christ *et al.* 2003; Haferkamp *et al.* 2004]. Furthermore, bladders of patients with DO appear to have abnormal gap junctions between cells [Elbadawi *et al.* 1993a; Elbadawi *et al.* 1993b; Elbadawi *et al.* 1997a; Elbadawi *et al.* 1997b; Tse *et al.* 2000]. Thus, increases in receptor-mediated muscle contractility and interaction between smooth muscle cells may result in coordinated myogenic contraction of the entire bladder and DO [Yoshimura *et al.* 2008].

The evaluation of OAB in men

The American Urological Association (AUA) Guideline Panel on the Management of BPH is one of two groups that have made recommendations regarding the initial evaluation of LUTS in men [Roehrborn *et al.* 2003a]. First, all men presenting with LUTS suggestive of BPH should undergo a medical history to identify other causes of voiding dysfunction or comorbidities that may complicate treatment. The medical history should focus on the urinary tract, previous surgical procedures, and medical conditions and symptoms that lead to bladder dysfunction or polyuria. A family history of BPH and prostate

cancer should be elicited, and fitness for possible surgical procedures should be assessed. Second, the presence of locally advanced prostate cancer, which also can produce LUTS, should be excluded by digital rectal examination (DRE). A focused neurologic examination should assess the patient's general mental status, ambulatory status, lower extremity neuromuscular function, and anal sphincter tone. Third, a urinalysis should be performed by dipstick testing or microscopic examination of the sediment to screen for hematuria and urinary tract infection (UTI).

The Panel also recommended a symptom assessment instrument (AUA Symptom Score (AUASS); International Prostate Symptom Score (IPSS)) in the initial assessment of each patient presenting with BPH, as this scale has been found to be superior to an unstructured interview in quantifying symptom frequency and severity [Barry *et al.* 1992]. Using seven questions that relate to associated symptoms, classification ranges from mild (0–7) to moderate (8–19) or severe (20–35). Based on Panel expert opinion, other validated assessment instruments addressing the frequency or severity of LUTS in men with BPH, bother due to symptoms, interference with daily activities, urinary continence, sexual functioning and health-related general or disease-specific quality of life have been deemed optional. Optional tests following the initial evaluation include urinary flow rate recording and measurement of postvoid residual urine (PVR). These tests were not felt to be necessary prior to the institution of watchful waiting or medical therapy; however, they were felt to be helpful in patients with a complex medical history (e.g. neurologic or other diseases known to affect bladder function or prior failure of BPH therapy) and in those desiring invasive therapy.

The 6th International Consultation on New Developments in Prostate Cancer and Prostate Disease also recently published its recommendations regarding the initial evaluation of LUTS in men [Abrams *et al.* 2008]. The recommended tests (history, physical examination, assessment of symptom bother, and urinalysis) were the same as those recommended by the AUA BPH Guidelines Panel. The International Panel also recommended a serum prostate specific antigen (PSA) in those men with a life expectancy exceeding 10 years or when a diagnosis of prostate cancer can modify the management, as well as a frequency–volume chart in

those men with nocturia as a predominant symptom. Additionally, the International Panel recommended validated questionnaires, frequency–volume charting, urinary flow rate recording, and PVR, for those men with persistent bothersome LUTS after basic management. Furthermore, pressure–flow studies were recommended prior to invasive therapy, unless the maximum flow rate on noninvasive flow recording is <10 cc/sec. Previous studies have likewise suggested that a flow rate <8 cc/sec is highly predictive of BOO [Ockrim *et al.* 2001]. Optional tests include imaging of the prostate with transabdominal or transrectal ultrasound, upper urinary tract imaging with ultrasound or intravenous urography, and endoscopy of the lower urinary tract.

Treatment

Treatments for the symptoms of OAB include pharmacological and nonpharmacological options, with the latter category divided into simple and complex interventions. Lifestyle interventions, such as modifying excessive fluid intake, engaging in regular exercise, and smoking cessation, may be helpful. Additionally, judicious limitation of caffeine and increasing dietary intake of vegetables, beta carotene, lutein, and vitamin C may lower the risk of BPH [Suzuki *et al.* 2002; Rohrmann *et al.* 2007]. Additional conservative interventions include bladder retraining (i.e. scheduled voiding, double voiding, judicious limitation of fluids at night) and pelvic floor muscle training (PFMT) with the addition of biofeedback. While PFMT and biofeedback have been shown to be effective in women, the role of these interventions in the male population is unclear. As the incidence of OAB is high in men with obstructive sleep apnea, addressing this comorbidity may offer additional symptom relief [Kemmer *et al.* 2009]. The mainstay of therapy is pharmacologic, with a combination of behavioral intervention and pharmacologic therapy potentially producing better outcomes than either intervention alone [Burgio *et al.* 2000]. More invasive nonpharmacologic options, such as neuromodulation and intravesical botulinum toxin injection, are typically reserved for refractory cases.

The AUA Guideline Panel on the Management of BPH also made recommendations regarding the treatment of LUTS in men [Roehrborn *et al.* 2003a]. As a standard, the Panel recommended a strategy of watchful waiting for men

with mild symptoms of BPH (AUASS <7) and men with moderate or severe symptoms (AUASS >8) who are not bothered by their symptoms (i.e. they do not interfere with the daily activities of living). For men with bothersome moderate to severe symptoms of BPH (AUASS >8), therapeutic options include watchful waiting, medical therapy, minimally invasive, or surgical therapies. Pharmacological treatment of LUTS in men often presents a therapeutic challenge, as differentiating BPH from OAB may be difficult, especially in the absence of data from advanced testing, such as uroflow measurement, PVR determination, and pressure–flow studies.

There are two main approaches to pharmacologic therapy of male LUTS: ‘prostate-centered’ and ‘symptom-centered’. As LUTS in men have been traditionally attributed to BPH and obstructed urinary flow, the pharmacological therapies have been aimed at improving urinary flow rates and optimizing voiding efficiency. The two principal classes of drugs targeting the prostate are α -blockers and 5 α RI. Alpha-blockade leads to relaxation of prostatic and bladder neck smooth musculature. The AUA Guidelines Panel determined that alfuzosin, doxazosin, tamsulosin, and terazosin are all appropriate treatment options for patients with LUTS secondary to BPH [Roehrborn *et al.* 2003a]. Although there are slight differences in the adverse-event profiles of these agents, the Panel concluded that all four agents have equal clinical effectiveness. As alfuzosin and tamsulosin are clinically uroselective, their use results in fewer vasodilatory cardiac adverse events [Lowe, 2004]. The data were insufficient to support a recommendation for the use of prazosin or the nonselective α -blocker phenoxybenzamine as treatment options for LUTS secondary to BPH.

5 α RI inhibit the conversion of testosterone to dihydrotestosterone, slowing prostate growth. The AUA Panel determined that both finasteride and dutasteride are appropriate and effective treatments for patients with LUTS associated with demonstrable prostatic enlargement [Roehrborn *et al.* 2003a]. The Panel also concluded that men with symptomatic prostatic enlargement but without signs of bother may be offered a 5 α RI to prevent progression of the disease. Both drugs in this class have been noted to reduce the risk of acute urinary retention (AUR) and the need for surgical intervention to relieve AUR [Kaplan, 2006]. However, the Panel

cautioned that the disadvantages of this therapeutic option (e.g. side effects such as sexual dysfunction and the need for long-term daily therapy) should be presented to the patient in comparison to a reasonable estimate of his baseline risk of progression (i.e. AUR and the risks associated with BPH-related surgery) so that an informed decision can be made [Roehrborn *et al.* 2003a]. Furthermore, the Panel concluded that 5 α RI are not appropriate treatments for men with LUTS who do not have evidence of prostatic enlargement and that the combination of an α -blocker and a 5 α RI (combination therapy) is an appropriate and effective treatment for patients with LUTS associated with demonstrable prostatic enlargement [Roehrborn *et al.* 2003a]. It has been shown that combination therapy may decrease the incidence of complications such as AUR in those men most at risk (prostate volume >30 ml or a PSA >1.4 ng/ml) [McConnell *et al.* 2003].

The 'prostate-centered' approach to treating LUTS in men is contingent on the assumption that urinary frequency and urgency result solely from incomplete emptying due to partial BOO. Unfortunately, this assumption fails to consider the role of the bladder, and failure to do so may leave a proportion of men undertreated. Several findings support the role of the bladder in male LUTS and subsequently a 'symptom-centered' treatment approach. First, it has been demonstrated that up to 75% of men with clinical BPH have concomitant urodynamic DO or clinical symptoms of OAB [Bates *et al.* 1970; Abrams, 1985]. Second, in a study of men with BOO and DO, 65% reported inadequate control of their symptoms (defined as an IPSS reduction of <3 points) after treatment with an α -blocker for three months [Lee *et al.* 2004]. However, 73% of nonresponders reported an improvement in their symptoms after tolterodine immediate-release (IR) was added. Third, 19% of men will have persistent OAB symptoms after undergoing transurethral resection of the prostate (TURP) [Gormley *et al.* 1993]. This effect appears more marked in men over 80 years of age and a significant number of these men are often retreated with surgical therapy. Fourth, over 80% of men whose OAB symptoms resolve after TURP may experience a recurrence of their symptoms at long-term mean follow-up of 12.6 years after surgery [Thomas *et al.* 2004]. The authors also observed that 39 of 82 (48%) men who were

free of OAB symptoms preoperatively developed *de novo* OAB in the postoperative period. Additionally, it appears that urinary storage symptoms are more bothersome to men than voiding symptoms, as over 80% of men with urgency with or without incontinence were bothered by their symptoms [Irwin *et al.* 2006]. Likewise, while voiding symptoms were more prevalent in more than 1200 men with LUTS, storage symptoms such as urgency, urge incontinence, frequency, and nocturia were more bothersome [Peters *et al.* 1997].

With the abundance of data supporting the prevalence and bother of OAB symptoms in men, it is unusual that more men are not actively treated for OAB. Indeed, if men with LUTS are treated with any medications, they appear to be predominantly treated with agents for BPH rather than agents aimed at OAB. Of over 12,000 male OAB patients without BPH identified from a claims database of over 30 managed care plans, 11% of men received OAB agents only, 22% received BPH agents only, 6% received both, and 61% received neither [Jumadilova *et al.* 2005]. Some of the reluctance to initiate OAB treatment with an antimuscarinic agent likely stems from the concern regarding the development of AUR in men with BOO. Although included in the package insert of every antimuscarinic medication, this warning specifies neither the PVR nor degree of BOO that would place a man at risk of developing a clinically significant deterioration of his bladder emptying [Rosenberg *et al.* 2007].

Antimuscarinic medications inhibit DO through their antagonistic action at cholinergic receptors on the detrusor muscle, thereby preventing unwanted muscle contraction resulting from the parasympathetic ACh release [Rosenberg *et al.* 2007]. As these agents are competitive antagonists, their effects may be blunted during the significant release of ACh during normal micturition [Andersson, 2004]. Anticholinergic medications may exert their effects through two potential routes: on a motor pathway via central and peripheral actions that block a facilitatory mechanism and stimulate an inhibitory mechanism, and on the sensory pathway via central and peripheral actions that modulate afferent innervations [Rosenberg *et al.* 2007]. Of the five oral anticholinergics available for OAB treatment, tolterodine has been the most extensively studied in terms of efficacy and safety.

After taking tolterodine extended-release (ER) for 12 weeks, men with OAB symptoms without BOO experienced a significant reduction in weekly incontinence episodes when compared with placebo (-71% versus -40% , $p < 0.05$) [Roehrborn *et al.* 2006]. Men receiving tolterodine ER also had fewer micturitions per day, but this was not significantly different from placebo (median % change, -12% versus -4% , $p = 0.22$). Significantly more men treated with tolterodine ER (63%) than placebo-treated men (46%) reported a benefit of treatment after 12 weeks ($p = 0.04$). Tolterodine ER has been also evaluated as monotherapy in men who had previously failed α -blocker therapy. This open-label, 6-month study included 43 men with BPH and LUTS who discontinued an α -blocker due to adverse events (11 patients) or lack of efficacy (32 patients) [Kaplan *et al.* 2005]. Daytime frequency decreased from 9.8 to 6.3 micturitions per day and night-time frequency decreased from 4.1 to 2.9. Furthermore, the AUASS decreased from 17.3 to 11.2. A significant increase in maximum flow rate ($Q_{\max}$, from 9.8 ml/s to 11.7 ml/s; $p < 0.001$) and decrease in PVR was observed (from 97 ml to 75 ml; $p < 0.03$).

Several studies have evaluated a combination of α -blocker and antimuscarinic in treating men with concomitant OAB symptoms and BOO. Yang *et al.* randomized 69 men on terazosin to continue on terazosin or a combination regimen consisting of terazosin and tolterodine IR [Yang *et al.* 2007]. While the IPSS improved significantly for both groups at 6 weeks, the reduction in the combination group was significantly greater. A decrease in urgency, frequency and nocturia were the main contributory factors causing the reduction of IPSS in the combination group. Improvement in $Q_{\max}$ and PVR from baseline values were noted in both groups after treatment, but were not significantly different between the two groups. The incidence of adverse effects in the combination group was higher than that in the terazosin group, owing mostly to dry mouth. Kaplan *et al.* conducted a randomized, double-blind, placebo-controlled trial conducted at 95 urology clinics in the United States, enrolling men with IPSS ≥ 12 , IPSS QOL ≥ 3 and significant urgency and frequency from a voiding diary [Kaplan *et al.* 2006]. A total of 172 men (80%) receiving tolterodine ER plus tamsulosin reported treatment benefit by week 12 compared with 132 men (62%)

receiving placebo ($p < 0.001$), 146 (71%) receiving tamsulosin alone ($p = 0.06$ versus placebo), or 135 (65%) receiving tolterodine ER ($p = 0.48$ versus placebo). Men receiving tolterodine ER plus tamsulosin compared with placebo experienced significant reductions in urgency urinary incontinence (-0.88 versus -0.31 ; $p = 0.005$), urgency episodes without incontinence (-3.33 versus -2.54 ; $p = 0.03$), micturitions per 24 hours (-2.54 versus -1.41 ; $p < 0.001$), and micturitions per night (-0.59 versus -0.39 ; $p = 0.02$). When compared with men taking placebo, men receiving tolterodine ER plus tamsulosin demonstrated significant improvements in IPSS (-8.02 versus -6.19 ; $p = 0.003$) and IPSS QOL (-1.61 versus -1.17 ; $p = 0.003$). In a *post hoc* analysis of data from the aforementioned study, men with a PSA level < 1.3 ng/ml, tolterodine ER alone and tolterodine ER plus tamsulosin significantly improved the 24-hour frequency, daytime frequency, frequency–urgency sum, and IPSS storage scores compared with those receiving placebo [Roehrborn *et al.* 2008]. Tamsulosin alone was ineffective.

In another prospective study, 144 consecutive men with BOO were subdivided into BOO or BOO + OAB groups, based on presence of DO and results of the Abrams–Griffiths nomogram [Lee *et al.* 2004]. All men were treated with doxazosin for 3 months and tolterodine IR was added for an additional 3 months in men with no symptomatic improvement. Of the 144 men, 76 (53%) were diagnosed as having BOO and 68 (47%) BOO + OAB. After 3 months of treatment with doxazosin, 60 men with BOO (79%) and 24 men with BOO + OAB (35%) reported symptomatic improvement. In those men with no improvement, six of 16 men with BOO (37.5%) and 32 of 44 men with BOO+OAB (73%) improved after adding tolterodine. A fourth study included 50 consecutive men with uroynamically proven mild or moderate BOO and concomitant DO [Athanasopoulos *et al.* 2003]. All men were treated with tamsulosin for a week and then randomized to tamsulosin only and tamsulosin and tolterodine IR. At 3 months, men who added tolterodine to their regimen had a statistically significant improvement in QOL scores (mean score 525.0 and 628.4 before and after treatment, respectively, 2-sided *t* test $p = 0.0003$). A significant difference was noted in both groups after treatment for $Q_{\max}$ and volume at first contraction.

Other antimuscarinic agents have also been studied. Men with an IPSS ≥ 8 and significant urgency and frequency by bladder diary were randomized to naftopidil (α -blocker), propiverine (antimuscarinic), or combination for a 4-week treatment regimen [Yokoyama *et al.* 2009]. Fifty-eight of 66 men (87.9%) completed the 4 weeks of treatment. IPSS improved significantly in men taking naftopidil or combination therapy, while urinary frequency improved significantly in men taking naftopidil or combination therapy. PVR volume increased significantly in men taking propiverine and combination therapy and significant improvements in urgency episodes were noted for each group of men.

As there is concern that antimuscarinics may exacerbate voiding dysfunction in men with OAB and BOO, the effect of tolterodine on urodynamic indices and incidence of AUR in men has been widely studied. None of the 221 men with urodynamically-proven BOO and DO enrolled in a multinational, double-blind study had undergone prior therapy for BPH [Abrams *et al.* 2006]. After 12 weeks of treatment, $Q_{\max}$ and detrusor pressure at $Q_{\max}$ were not significantly different between men taking tolterodine and placebo. While men on tolterodine had a significant mean increase in PVR (27 ml), it is unclear whether this increase was clinically relevant. Furthermore, the incidence of AUR requiring catheterization was not significantly different between men taking tolterodine and placebo. In fact, the overall incidence of AUR in men taking antimuscarinics has been minimal. At a follow up of 3–6 months, only one of 269 men in three studies developed AUR during tolterodine monotherapy [Abrams *et al.* 2006; Kaplan *et al.* 2005; Roehrborn *et al.* 2006]. When tolterodine was combined with an α -blocker, one of 85 men in two studies developed AUR at a follow-up of 3 months [Athanasopoulos *et al.* 2003; Lee *et al.* 2004]. Additionally, no men out of 142 developed AUR while being treated with propiverine and an α -blocker at 2 months of follow-up [Lee *et al.* 2005].

Pharmacologic treatment in men with nocturia and pelvic pain

Using the ICS definition, the prevalence of nocturia in adult males is estimated to be 9–14%, and higher rates are seen in elderly men and those with LUTS/BPH [Abrams, 2005; Irwin *et al.* 2006]. While the etiology of nocturia is often multifactorial, the two main mechanisms

are polyuria and diminished bladder capacity, with the latter occurring in the context of both OAB and BOO [Abrams, 2005]. As for daytime storage symptoms, the majority of studies for pharmacologic treatment of nocturia have been conducted with α -blockers and antimuscarinic agents. Using responses to question 7 of the IPSS as a surrogate for treatment success, several immediate- and extended release formulations of α -blockers have exhibited beneficial effects on nocturia in placebo-controlled, double-blinded trials (doxazosin, terazosin, tamsulosin, alfuzosin, naftopidil) [Chapple *et al.* 1994; Johnson *et al.* 2003; Debruyne *et al.* 1996; Paick *et al.* 2006; Abrams *et al.* 1995; Jardin *et al.* 1991; Roehrborn *et al.* 2003b; Nishino *et al.* 2006; Schneider *et al.* 2009]. Finasteride was not shown to improve nocturia in a placebo-controlled trial [Johnson *et al.* 2003]. Likewise, an improvement in nocturia episodes was also found in double-blinded trials including several antimuscarinic agents (tolterodine, darifenacin, solifenacin, trospium, fesoterodine) [Schneider *et al.* 2009]. Although these benefits were typically moderate in nature, they were felt to be too weak to be considered as specific treatments for isolated nocturia [Michel and de la Rosette, 2005].

Category III chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is another condition with prominent LUTS. These are typically accompanied by pain with ejaculation or in the perineal area. As there is no gold standard diagnostic test for CP/CPPS, and because its etiology is largely unknown, this entity remains a diagnosis of exclusion. As with BPH, the symptoms of CP/CPPS can be present during the storage phase, voiding phase, or can occur postmicturition. It is not surprising then that among seven secondary conditions evaluated by the NIH Chronic Prostatitis Collaborative Research Network, it was BPH that was most commonly diagnosed concomitantly with prostatitis [Pontari *et al.* 2005]. Likewise, as smooth muscle contraction in the bladder and prostate mediated by α_1 -adrenoceptors has been proposed as a possible etiology for CP/CPPS, there may be a role for α_1 -blockers in the treatment of this entity [Nickel, 2008]. A recent systematic review identified 10 clinical trials evaluating α_1 -blocker therapy for men with CP/CPPS [Lee *et al.* 2007]. Encouraging results in five uncontrolled, open-label, and small prospective clinical trials, led to the development of five reasonably-powered,

double-blinded, placebo controlled, randomized trials evaluating terazosin, doxazosin, tamsulosin, and alfuzosin. The data suggests that treatment-naïve and newly-diagnosed patients appear more likely to respond to α_1 -blocker therapy than long-term or refractory patients. Longer courses of treatment (12 weeks to 6 months) appear to be superior to shorter courses, and less selective agents appear superior to more selective α_1 -blockers.

Emerging options for OAB

Although antimuscarinics currently comprise the bulk of the medical therapeutic options for OAB in men, their use may be limited by side effects. Furthermore, in some men, antimuscarinics alone may not attain the desired therapeutic effect. In recent years, calcium antagonists, selective β -adrenoceptor agonists, and potassium channel openers have emerged as potential targets *in vitro* for the treatment of OAB. L-type calcium channel blockers, such as verapamil and nifedipine, have been shown to be very potent relaxants of human detrusor muscle *in vitro* [Badawi *et al.* 2006]. To date, however, *in vivo* results have been conflicting. Eighty-six men with a mean age of 73.4 years were randomized in a double-blind fashion to nimodipine or placebo for 3 weeks [Naglie *et al.* 2002]. For the 76 men (88.4%) completing the study, there was no significant difference in the number of incontinence episodes with nimodipine compared with placebo, which included a difference of 0.03 incontinent episodes during a 5-day period ($p=0.98$, 95% CI $-2.7-2.8$). Scores on the modified incontinence impact questionnaire and the AUASS were not significantly different in the nimodipine group and placebo group ($p=0.07$ and 0.22 , respectively). Conversely, Liu *et al.* randomized 355 men with hypertension and LUTS to receive terazosin, amlodipine, or a combination [Liu *et al.* 2009]. At the end of 28 days, men in the combination group demonstrated comparable efficacy in lowering the total IPSS and significant improvement in the presence of overactive bladder compared with the terazosin group ($p < 0.05$) and significant improvement in QOL compared with the amlodipine group ($p < 0.05$). The amlodipine plus terazosin group also achieved the greatest blood pressure control compared with either the terazosin group ($p < 0.01$) or amlodipine group ($p < 0.05$). While not available clinically, potassium channel openers of ATP-sensitive potassium channels or BK channels are thought to be selective for the

urinary bladder, thus theoretically reducing the possibility of cardiovascular side effects.

The β_3 -adrenergic receptor is the most abundant of the AR subtypes in human detrusor muscle, suggesting that this subtype mediates detrusor relaxation. The mechanism by which β -AR agonists induce relaxation of smooth muscles is not fully understood, but it is believed that an intracellular pathway for smooth muscle relaxation is activated by cAMP. Some animal studies of β_3 -adrenoceptor agonist have revealed increased bladder capacity, no change in micturition pressure and no change in residual volume [Fujimura *et al.* 1999; Takeda *et al.* 2000]. Selective β_3 -AR agonists should have a theoretical advantage over non-selective β -AR agonists, as the latter may exhibit serious cardiovascular side effects like tachycardia or decrease of blood pressure by stimulating β_1 - and β_2 -adrenoceptors [Badawi and Langbein, 2006].

Conclusions

The prevalence of OAB is similar in men and women and increases with age. In both sexes, urinary storage symptoms are more bothersome than voiding symptoms and impact significantly on many facets of everyday life. Many symptomatic men do not receive treatment and physicians are more likely to use BPH agents to improve emptying rather than OAB agents as a first-line therapy for OAB symptoms in men. Many of these men will not respond to α -blockers or 5 α RI, and will have persistent storage symptoms that will continue to affect their quality of life. Early evidence suggests that antimuscarinics are efficacious both as first-line therapy for male OAB and as second-line treatment for those men who have previously failed other medications. Additional data supports the combination of α -blockers and antimuscarinics in those men with concomitant BOO and OAB. The concern regarding antimuscarinic use leading to an increased incidence of urinary retention appears to be unfounded; however, as in women, the utility of antimuscarinic use is limited by side effects such as dry mouth. While the data is certainly encouraging, enthusiasm must be tempered by the short-term results reported in the majority of trials. Long-term outcomes in well-designed, randomized trials are imperative to further our understanding of LUTS in men.

Conflict of interest statement

None declared.

References

- Abrams, P. (1985) Detrusor instability and bladder outlet obstruction. *Neurourol Urodyn* 4: 317–328.
- Abrams, P. (2005) Nocturia: the major problem in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction (LUTS/BPO). *Eur Urol Suppl* 3: 8–16.
- Abrams, P., Schulman, C.C. and Vaage, S. (1995) Tamsulosin, a selective α_{1c} -adrenoceptor antagonist: a randomized, controlled trial in patients with benign prostatic 'obstruction' (symptomatic BPH). *Br J Urol* 76: 325–336.
- Abrams, P., Cardozo, L., Fall, M., Griffiths, D., Rosier, P., Ulmsten, U. *et al* (2003) The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology* 61: 37–49.
- Abrams, P., Kaplan, S.A., De Koning Gans, H.J. and Millard, R. (2006) Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. *J Urol* 175: 999–1004.
- Abrams, P., Chapple, C., Khoury, S., Roehrborn, C. and de la Rosette, J. (2008) Evaluation and treatment of lower urinary tract symptoms in older men. *J Urol* 181: 1779–1787.
- Andersson, K.E. (1993) Pharmacology of lower urinary tract smooth muscle and penile erectile tissues. *Pharmacol Rev* 45: 253–308.
- Andersson, K.E. (2003) Storage and voiding symptoms: pathophysiological aspects. *Urology* 62(Suppl 5B): 3–10.
- Andersson, K.E. (2004) Antimuscarinics for treatment of overactive bladder. *Lancet Neurol* 3: 46–53.
- Athanasopoulos, A., Gyftopoulos, K., Giannitsas, K., Fisis, J., Perimenis, P. and Barbalias, G. (2003) Combination treatment with an alpha blocker plus an anticholinergic for bladder outlet obstruction: a prospective, randomized, controlled study. *J Urol* 169: 2253–2256.
- Badawi, J.K. and Langbein, S. (2006) Selective beta-adrenoceptor agonists, calcium antagonists and potassium channel openers as a possible medical treatment of the overactive bladder and urge incontinence. *Pharmazie* 61: 175–178.
- Badawi, J.K., Li, H., Langbein, S., Kwon, S.T., Kamp, S. and Bross, S. (2006) Inhibitory effects of L- and T-type calcium antagonists on contractions of human detrusor muscle. *Eur J Clin Pharmacol* 62: 347–354.
- Barry, M.J., Fowler Jr, F.J., O'Leary, M.P., Bruskewitz, R.C., Holtgrewe, H.L., Mebust, W.K. *et al* (1992) The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 148: 1549–1557.
- Bates, C.P., Whiteside, C.G. and Turner-Warwick, R. (1970) Synchronous cine-pressure-flow-cystourethrography with special reference to stress and urge incontinence. *Br J Urol* 42: 714–723.
- Benner, J.S., Becker, R., Fanning, K., Jumadilova, Z., Bavendam, T. and Brubaker, L. (2009) Bother related to bladder control and health care setting behavior in adults in the United States. *J Urol* 181: 2591–2598.
- Boselli, C., Govoni, S., Condino, A.M. and D'Agostino, G. (2001) Bladder instability: a re-appraisal of classical experimental approaches and development of new therapeutic strategies. *J Auton Pharmacol* 21: 219–229.
- Brading, A.F. (1997) A myogenic basis for the overactive bladder. *Urology* 50(6A Suppl): 57–67.
- Burgio, K.L., Locher, J.L. and Goode, P.S. (2000) Combined behavioral and drug therapy for urge incontinence in older women. *J Am Geriatr Soc* 48: 370–374.
- Chapple, C.R. and Roehrborn, C.G. (2006) A shifted paradigm for the further understanding, evaluation, and treatment of lower urinary tract symptoms in men: focus on the bladder. *Eur Urol* 49: 651–659.
- Chapple, C.R., Carter, P., Christmas, T.J., Kirby, R.S., Bryan, J., Milroy, E.J. *et al* (1994) A three month double-blind study of doxazosin as treatment for benign prostatic bladder outlet obstruction. *Br J Urol* 74: 50–56.
- Charlton, R.G., Morley, A.R., Chambers, P. and Gillespie, J.I. (1999) Focal changes in nerve, muscle and connective tissue in normal and unstable human bladder. *BJU Int* 84: 953–960.
- Christ, G.J., Day, N.S., Day, M., Zhao, W., Persson, K., Pandita, R.K. *et al* (2003) Increased connexin 43-mediated intercellular communication in a rat model of bladder overactivity in vivo. *Am J Physiol Regul Integr Comp Physiol* 284: R1241–R1248.
- Daniel, E.E., Cowan, W. and Daniel, V.P. (1983) Structure bases for neural and myogenic control of human detrusor muscle. *Can J Physiol Pharmacol* 61: 1247–1273.
- Debruyne, F.M.J., Witjes, W.P.J., Fitzpatrick, J., Kirby, R., Kirk, D. and Prezioso, D. (1996) The international terazosin trial: a multicentre study of the long-term efficacy and safety of terazosin in the treatment of benign prostatic hyperplasia. *Eur Urol* 30: 369–376.
- de Groat, W.C. (2006) Integrative control of the lower urinary tract: preclinical perspective. *Br J Pharmacol* 147: S25–S40.
- de Groat, W.C. and Theobald, R.J. (1976) Reflex activation of sympathetic pathways to vesical smooth muscle and parasympathetic ganglia by electrical stimulation of vesical afferents. *J Physiol* 259: 223–237.

- Dmochowski, R.R. and Newman, D.K. (2007) Impact of overactive bladder on women in the United States: results of a national survey. *Curr Med Res Opin* 23: 65–76.
- Drake, M.J., Mills, I.W. and Gillespie, J.I. (2001) Models of peripheral autonomous modules and a myovesical plexus in normal and overactive bladder function. *Lancet* 358: 401–403.
- Elbadawi, A., Yalla, S.V. and Resnick, N.M. (1993a) Structural basis of geriatric voiding dysfunction. I. Methods of a prospective ultrastructural/urodynamic study and an overview of the findings. *J Urol* 150: 1650–1656.
- Elbadawi, A., Yalla, S.V. and Resnick, N.M. (1993b) Structural basis of geriatric voiding dysfunction. II. Aging detrusor: normal versus impaired contractility. *J Urol* 150: 1657–1667.
- Elbadawi, A., Hailemariam, S., Yalla, S.V. and Resnick, N.M. (1997a) Structural basis of geriatric voiding dysfunction. VI. Validation and update of diagnostic criteria in 71 detrusor biopsies. *J Urol* 157: 1802–1813.
- Elbadawi, A., Hailemariam, S., Yalla, S.V. and Resnick, N.M. (1997b) Structural basis of geriatric voiding dysfunction. VII. Prospective ultrastructural/urodynamic evaluation of its natural evolution. *J Urol* 157: 1814–1822.
- Fujimura, T., Tamura, K., Tsutsumi, T., Yamamoto, T., Nakamura, K., Koibuchi, Y. *et al* (1999) Expression and possible functional role of the beta 3-adrenoceptor in human and rat detrusor muscle. *J Urol* 161: 680–685.
- Gabella, G. and Uvelius, B. (1990) Urinary bladder of rat: fine structure of normal and hypertrophic musculature. *Cell Tissue Res* 262: 67–79.
- Gormley, E.A., Griffiths, D.J., McCracken, P.N., Harrison, G.M. and McPhee, M.S. (1993) Effect of transurethral resection of the prostate on detrusor instability and urge incontinence in elderly males. *Neurourol Urodyn* 12: 445–453.
- Gosling, J.A., Kung, L.S., Dixon, J.S., Horan, P., Whitbeck, C. and Levin, R.M. (2000) Correlation between the structure and function of the rabbit urinary bladder following partial outlet obstruction. *J Urol* 163: 1349–1356.
- Haferkamp, A., Mundhenk, J., Bastian, P.J., Reitz, A., Dorsam, J., Pannek, J. *et al* (2004) Increased expression of connexin 43 in the overactive neurogenic detrusor. *Eur Urol* 46: 799–805.
- Hu, T.W., Wagner, T.H., Bentkover, J.D., LeBlanc, K., Zhou, S.Z. and Hunt, T. (2004) Costs of urinary incontinence and overactive bladder in the United States: a comparative study. *Urology* 63: 461–465.
- Igawa, Y., Yamazaki, Y., Takeda, H., Hayakawa, K., Akahane, M., Ajisawa, Y. *et al* (1999) Functional and molecular biological evidence for a possible beta 3-adrenoceptor in the human detrusor muscle. *Br J Pharmacol* 126: 819–825.
- Irwin, D.E., Milsom, I., Hunskaar, S., Reilly, K., Kopp, Z., Herschorn, S. *et al* (2006) Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *Eur Urol* 50: 1306–1314.
- Irwin, D.E., Milsom, I., Kopp, Z., Abrams, P., Artibani, W. and Herschorn, S. (2009) Prevalence, severity, and symptom bother of lower urinary tract symptoms among men in the EPIC study: impact of overactive bladder. *Eur Urol* (e-published 3 March 2009).
- Jardin, A., Bensadoun, H., Delauche-Cavallier, M.C. and Attali, P. (1991) The BPH-ALF Group. (1991) Alfuzosin for treatment of benign prostatic hypertrophy. *Lancet* 337: 1457–1461.
- Johnson II, T.M., Jones, K., Williford, W.O., Kutner, M.H., Issa, M.M. and Lopor, H. (2003) Changes in nocturia from medical treatment of benign prostatic hyperplasia: secondary analysis of the Department of Veterans Affairs Cooperative Study trial. *J Urol* 170: 145–148.
- Jumadilova, Z., Harris, H., del Aguila, M., Wagner, S., Boccuzzi, S., Bavendam, T. (2005) Agent selection for overactive bladder patients with and without documented comorbid benign prostatic hyperplasia. 2005 Annual ICS Meeting, Abstract #486.
- Kaplan, S.A. (2006) Update on the American Urological Association guidelines for the treatment of benign prostatic hyperplasia. *Rev Urol* 8(Suppl 4): S10–S17.
- Kaplan, S.A., Walmsley, K. and Te, A. (2005) Tolterodine extended release attenuates lower urinary tract symptoms in men with benign prostatic hyperplasia. *J Urol* 174: 2273–2276.
- Kaplan, S.A., Roehrborn, C.G., Rovner, E.S., Carlsson, M., Bavendam, T. and Guan, Z. (2006) Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder. *JAMA* 296: 2319–2328.
- Kemmer, H., Mathes, A.M., Dilk, O., Groschel, A., Grass, C. and Stockle, M. (2009) Obstructive sleep apnea syndrome is associated with overactive bladder and urgency incontinence in men. *Sleep* 32: 271–275.
- Klevmark, B. (1974) Motility of the urinary bladder in cats during filling at physiological rates. I. Intravesical pressure patterns studies by a new method of cystometry. *Acta Physiol Scand* 90: 565–577.
- Koyne, K.S., Sexton, C.C., Irwin, D.E., Kopp, Z.S., Kelleher, C.J. and Milsom, I. (2008) The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. *BJU Int* 101: 1388–1395.

- Lee, J.Y., Kim, H.W., Lee, S.J., Koh, J.S., Suh, H.J. and Chancellor, M.B. (2004) Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and overactive bladder. *BjU Int* 94: 817–820.
- Lee, K.S., Choo, M.S., Kim, D.Y., Kim, J.C., Kim, H.J., Min, K.S. *et al* (2005) Combination treatment with propiverine hydrochloride plus doxazosin controlled release gastrointestinal therapeutic system formulation for overactive bladder and coexisting benign prostatic obstruction: a prospective, randomized, controlled multicenter study. *J Urol* 174: 1334–1338.
- Lee, S.W., Liong, M.L., Yuen, K.H., Liong, Y.V. and Krieger, J.N. (2007) Chronic prostatitis/chronic pelvic pain syndrome: role of alpha blocker therapy. *Urol Int* 78: 97–105.
- Levin, R.M., Longhurst, P.A., Monson, F.C., Kato, K. and Wein, A.J. (1990) Effect of bladder outlet obstruction on the morphology, physiology, and pharmacology of the bladder. *Prostate Suppl* 3: 9–26.
- Liu, H., Liu, P., Mao, G., Chen, G., Wang, B., Qin, X. *et al* (2009) Efficacy of combined amlodipine/terazosin therapy in male hypertensive patients with lower urinary tract symptoms: a randomized, double-blind clinical trial. *Urology* April 14[Epub ahead of print].
- Lowe, F.C. (2004) Role of the newer alpha-adrenergic receptor antagonists in the treatment of benign prostatic hyperplasia-related lower urinary tract symptoms. *Clin Ther* 26: 1701–1713.
- McConnell, J.D., Roehrborn, C.G., Bautista, O.M., Andriole Jr, G.L., Dixon, C.M., Kusek, J.W. *et al* (2003) for the Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. (2003) The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 349: 2387–2398.
- Michel, M.C. and de la Rosette, J.J.M.C.H. (2005) Role of muscarinic receptor antagonists in urgency and nocturia. *BjU Int* 96(Suppl 1): 37–42.
- Mills, I.W., Greenland, J.E., McMurray, G., McCoy, R., Ho, K.M., Noble, J.G. *et al* (2000) Studies of the pathophysiology of idiopathic detrusor instability: the physiological properties of the detrusor smooth muscle and its pattern of innervation. *J Urol* 163: 646–651.
- Milsom, I., Abrams, P., Cardozo, L., Roberts, R.G., Thuroff, J. and Wein, A.J. (2001) How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BjU Int* 87: 760–766.
- Morant, S.V., Reilly, K., Bloomfield, G.A. and Chapple, C. (2008) Diagnosis and treatment of lower urinary tract symptoms suggestive of overactive bladder and bladder outlet obstruction among men in general practice in the UK. *Int J Clin Pract* 62: 688–694.
- Naglie, G., Radomski, S.B., Brymer, C., Mathiasen, K., O'Rourke, K. and Tomlinson, G. (2002) A randomized, double-blind, placebo controlled crossover trial of nimodipine in older persons with detrusor instability and urge incontinence. *J Urol* 167: 586–590.
- Neuhaus, J., Weimann, A., Stolzenburg, J.U., Dawood, W., Schwalenberg, T. and Dorschner, W. (2002) Smooth muscle cells from human urinary bladder express connexin 43 in vivo and in vitro. *World J Urol* 20: 250–254.
- Nickel, J.C. (2008) Role of alpha1-blockers in chronic prostatitis syndromes. *BjU Int* 101(Suppl): 11–16.
- Nishino, Y., Masue, T., Miwa, K., Takahashi, Y., Ishihara, S. and Deguchi, T. (2006) Comparison of two α_1 -adrenoceptor antagonists, naftopidil and tamsulosin hydrochloride, in the treatment of lower urinary tract symptoms with benign prostatic hyperplasia: a randomized crossover study. *BjU Int* 97: 747–751.
- Ockrim, J.L., Laniado, M.E., Patel, A., Tubaro, A. and St Clair Carter, S. (2001) A probability based system for combining simple office parameters as a predictor of bladder outflow obstruction. *J Urol* 166: 2221–2225.
- O'Reilly, B.A., Kosaka, A.H., Chang, T.K., Ford, A.P., Popert, R. and McMahon, S.B. (2001) A quantitative analysis of purinoceptor expression in the bladders of patients with symptomatic outlet obstruction. *BjU Int* 87: 617–622.
- Ouslander, J.G. (2004) Management of overactive bladder. *N Engl J Med* 350: 786–799.
- Paick, J-S., Ku, J.H., Shin, J.W., Yang, J.H. and Kim, S.W. (2006) α -Blocker monotherapy in the treatment of nocturia in men with lower urinary tract symptoms: a prospective study of response prediction. *BjU Int* 97: 1017–1023.
- Peters, T.J., Donovan, J.L., Kay, H.E., Abrams, P., de la Rosette, J.J., Porru, D. *et al* (1997) The International Continence Society 'Benign Prostatic Hyperplasia' Study: the bothersomeness of urinary symptoms. *J Urol* 157: 885–889.
- Pontari, M.A., McNaughton-Collins, M., O'Leary, M.P., Calhoun, E.A., Jang, T., Kusek, J.W. *et al*; CPCR Study Group (2005) A case-control study of risk factors in men with chronic pelvic pain syndrome. *BjU Int* 96: 559–565.
- Roehrborn, C.G., McConnell, J.D., Barry, M.J., Benaïm, E., Bruskewitz, R.C., Blute, M.L. *et al* (2003a) Guidelines on the Management of Benign Prostatic Hyperplasia. American Urological Association Education and Research, Inc: Linthicum, MD.
- Roehrborn, C.G., van Kerrebroeck, P. and Nordling, J. (2003b) Safety and efficacy of alfuzosin 10 mg once-daily in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a pooled analysis of three double-blind, placebo-controlled studies. *BjU Int* 92: 257–261.

- Roehrborn, C.G., Abrams, P., Rovner, E.S., Kaplan, S.A., Herschorn, S. and Guan, Z. (2006) Efficacy and safety of tolterodine extended-release in men with overactive bladder and urinary urgency incontinence. *BjU Int* 97: 1003–1006.
- Roehrborn, C.G., Kaplan, S.A., Kraus, S.R., Wang, J.T., Bavendam, T. and Guan, Z. (2008) Effects of serum PSA on efficacy of tolterodine extended release with or without tamsulosin in men with LUTS, including OAB. *Urology* 72: 1061–1067.
- Rohrmann, S., Giovannucci, E., Willett, W.C. and Platz, E.A. (2007) Fruit and vegetable consumption, intake of micronutrients, and benign prostatic hyperplasia in US men. *Am J Clin Nutr* 85: 523–529.
- Rosenberg, M.T., Staskin, D.R., Kaplan, S.A., MacDiarmid, S.A., Newman, D.K. and Ohl, D.A. (2007) A practical guide to the evaluation and treatment of male lower urinary tract symptoms in the primary care setting. *Int J Clin Pract* 61: 1535–1546.
- Schneider, T., de la Rosette, J.J.M.C.H. and Michel, M.C. (2009) Nocturia: a non-specific but important symptom of urological disease. *Int J Urol* 16: 249–256.
- Sexton, C.C., Coyne, K.S., Vats, V., Kopp, Z.S., Irwin, D.E. and Wagner, T.H. (2009) Impact of overactive bladder on work productivity in the United States: results from EpiLUTS. *Am J Manag Care* 15: S98–S107.
- Stewart, W.F., Van Rooyen, J.B., Cundiff, G.W., Abrams, P., Herzog, A.R., Corey, R. *et al* (2003) Prevalence and burden of overactive bladder in the United States. *World J Urol* 20: 327–336.
- Stothers, L., Thom, D. and Calhoun, E. (2005) Urologic Diseases in America project: urinary incontinence in males – demographics and economic burden. *J Urol* 173: 1302–1308.
- Suzuki, S., Platz, E.A., Kawachi, I., Willett, W.C. and Giovannucci, E. (2002) Intakes of energy and macro-nutrients and the risk of benign prostatic hyperplasia. *Am J Clin Nutr* 75: 689–697.
- Takeda, H., Yamazaki, Y., Akahane, M., Igawa, Y., Ajisawa, Y. and Nishizawa, O. (2000) Role of the beta (3)-adrenoceptor in urine storage in the rat: comparison between the selective beta (3)-adrenoceptor agonist, CL316, 243, and various smooth muscle relaxants. *J Pharmacol Exp Ther* 293: 939–945.
- Thomas, A.W., Cannon, A., Bartlett, E., Ellis-Jones, J. and Abrams, P. (2004) The natural history of voiding dysfunction in men: a study of the prevalence of detrusor instability. *BjU Int* 93(6): 745–750.
- Tse, V., Wills, E., Szonyi, G. and Khadra, M.H. (2000) The application of ultrastructural studies in the diagnosis of bladder dysfunction in a clinical setting. *J Urol* 163: 535–539.
- Turner, W.H. and Brading, A.F. (1997) Smooth muscle of the bladder in the normal and the diseased state: pathophysiology, diagnosis, and treatment. *Pharmacol Ther* 75: 77–110.
- Verispan Patient Longitudinal Data, MAT, 2005.
- Wang, H.Z., Lee, S.W. and Day, N.S. (2001) Gap junction channel activity in cultured human smooth muscle cell pairs: gating and unitary conductances. *Urology* 57(Suppl 1): 111–112.
- Yang, Y., Zhao, X.F., Li, H.Z., Wang, W., Zhang, Y., Xiao, H. *et al* (2007) Efficacy and safety of combined therapy with terazosin and tolterodine for patients with lower urinary tract symptoms associated with benign prostatic hyperplasia: a prospective study. *Chin Med J (Engl)* 120: 370–374.
- Yokoyama, T., Uematsu, K., Watanabe, T., Sasaki, K., Kumon, H. and Nagai, A. (2009) Naftopidil and propiverine hydrochloride for treatment of male lower urinary tract symptoms suggestive of benign prostatic hyperplasia and concomitant overactive bladder: a prospective randomized controlled study. *Scand J Urol Nephrol* April 24: [Epub ahead of print].
- Yoshimura, N. and de Groat, W.C. (1997) Neural control of the lower urinary tract. *Int J Urol* 4: 111–125.
- Yoshimura, N., Kaiho, Y., Miyazato, M., Yunoki, T., Tai, C., Chancellor, M.B. *et al* (2008) Therapeutic receptor targets for lower urinary tract dysfunction. *Naunyn Schmiedebergs Arch Pharmacol* 377: 437–448.

Visit SAGE journals online
<http://tau.sagepub.com>

SAGE JOURNALS
 Online