Management of Overactive Bladder in Men and in Neurogenic Voiding Dysfunction

Yat-Ching Tong, M.D.

Department of Urology, College of Medicine, National Cheng Kung University, Tainan, Taiwan

INTRODUCTION

In its original form, the definition of overactive bladder (OAB) is a medical condition referring to symptoms of frequency and urgency, with or without urge incontinence, when appearing in the absence of local pathologic or metabolic factors that would account for these symptoms. Incontinence is not a necessary condition for diagnosis because roughly half of people with overactive bladder do not have incontinence. Nevertheless, there is a profound impairment in their quality of life due to urgency and frequency symptoms [1]. In 2002, the International Continence Society proposed a revised definition for OAB: Urgency, with or without urge incontinence, usually with frequency and nocturia, can be described as overactive bladder syndrome, urge syndrome or urgency syndrome [2]. The prevalence of OAB is estimated to be around 17% in European countries as well as in the United States [3,4]. In Taiwan, Yu et al reported an age-adjusted OAB prevalence rate of 16.9% among the community-dwelling adult population on Matsu island. Age, diabetes, and benign prostatic hyperplasia in men, and diabetes, hyperlipidemia, stress incontinence, and recurrent lower urinary tract infections in women were independent risk factors associated with OAB [5]. As the population ages and metabolic diseases become more prevalent, the clinical burden of OAB will increase in Taiwan.

TREATMENTS OPTIONS FOR OAB

Currently, treatment modalities for OAB include:

1. Life style interventions: reduction of body weight, cessation of smoking, moderate fluid intake and reduced caffeine consumption.
2. Physical therapies: pelvic floor muscle training, field electric stimulation and neuromodulation.
3. Bladder retraining: patient education, scheduled voiding, urgency control strategies, self-monitoring and positive reinforcement.
4. Pharmacological therapies: antimuscarinic drugs, calcium channel blockers, potassium channel openers, mixed action bladder relaxants, alpha-blockers, beta-agonists, prostaglandin synthesis inhibitors, antidepressants, vasopressin analogues, intravesical capsaicin and resiniferatoxin instillation and intravesical botulinum toxin injection.
5. Surgical treatments: bladder denervation and bladder augmentation.
6. Combination therapy: since OAB often involves multiple etiological and pathological factors, a combination of different treatment modalities can offer the best therapeutic outcome.

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Address correspondence to: Dr. Yat-Ching Tong, Department of Urology, National Cheng Kung University Hospital, 138, Sheng-Li Road, Tainan, 70403, Taiwan
E-mail: yctong@mail.ncku.edu.tw

OAB IN THE MALE POPULATION

Lower urinary symptoms (LUTS) in men have traditionally been ascribed to benign prostatic hyperplasia (BPH). Urologists tend to blame the prostate rather than the bladder for the occurrence of male LUTS. Functionally the bladder and prostate do not work totally independent of each other, and male OAB and BPH are not completely separate entities. From a practical point of view, we can consider these two clinical conditions as part of the "male LUTS complex" (Fig. 1) which is composed of BPH, OAB, bladder outlet obstruction (BOO), and chronic prostatitis (CP) as well as interstitial cystitis (IC).

Considering the epidemiological evidence, we must agree that OAB in the male population is not a rare condition. In Taiwan as well as in western societies, the reported OAB prevalence rates in males and females are similar [3-5]. Thus, if OAB is a major health problem in females, it should not be a minor problem in males.

The EPIC study [6] was a cross-sectional, geographically stratified random sample population (n=19,165) of European adults aged ≥18 years. The primary objectives were (1) to estimate the prevalence of OAB, mixed urinary incontinence (MUI), stress urinary incontinence (SUI), and other LUTS and (2) to evaluate the impact of OAB, MUI, SUI, and their LUTS on bother and quality of life. The results showed the overall LUTS prevalence rate in men was 62.5%. The prevalence of symptoms increased with age, especially after the age of 60 years. Storage symptoms were reported nearly twice as often as voiding symptoms (51.3% vs. 25.7%). In addition, urine storage symptoms were

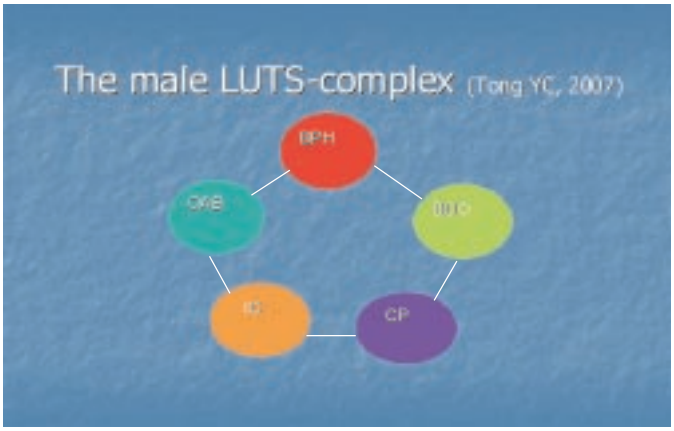

Fig. 1. The male LUTS-complex which is composed of five clinical entities: BPH, OAB, BOO, CP and IC.

more bothersome than emptying symptoms. The most bothersome symptoms were urgency incontinence and urinary urgency. More than 80% of men with urgency incontinence or urgency were bothered by their symptoms. In an earlier survey by Peters et al [7], storage and voiding symptoms were both prevalent and bothersome in men. Men reported a higher incidence of voiding symptoms but were more bothered by storage symptoms, which included the hallmark symptoms of OAB: urgency with or without urgency incontinence, frequency, and nocturia.

On the other hand, it has been demonstrated that 50% to 75% of BPH patients have urodynamic evidence of detrusor overactivity (DO) or clinical symptoms of OAB [8,9]. Thus OAB must be considered and properly dealt with in the management of LUTS in men.

TREATMENT CONSIDERATIONS IN MALE OAB

Prostate-focused treatments are inadequate for male OAB

Currently, men with OAB are predominantly treated with BPH agents rather than OAB agents. In a pharmacy database review [10] of more than 12,000 male OAB patients without baseline BPH, only 11% were prescribed an OAB medication alone, whereas 22% were prescribed an agent for BPH only, and 6% were prescribed combination therapy. The remainder received no prescription for their OAB symptoms.

This prostate-focused treatment approach leaves a subset of LUTS patients with unsatisfactory therapeutic outcomes. In a study of men with BOO and concomitant DO, 65% of patients reported that α-blocker therapy failed to resolve the symptoms of OAB. Addition of tolterodine IR to the treatment regimen resulted in improvement of symptoms in 73% in this combination group [11]. Surgical treatment with transurethral resection of the prostate (TUR-P) can relieve BOO and also OAB symptoms. However it has been reported that 19% patients had persistent OAB symptoms after TUR-P. The rate is even higher in men over 80 years old. Moreover, recurrence of OAB symptoms is common, with a rate of 63% after an average follow-up of 12.6 years [12].

Antimuscarinic agents have been the mainstay of pharmacologic management of OAB for many years. The under-treatment rate with antimuscarinics for male OAB patients is attributed to traditional views on possible side effects. It is generally advised that these drugs as a class should be administered with caution in patients with clinically significant BOO at risk for urinary retention and are contraindicated in patients with urinary retention. The drug information warnings have deterred many physicians from prescribing antimuscarinic agents to male OAB patients. However, recent evidence has demonstrated a positive therapeutic role of antimuscarinics for treatment of OAB in men [13].

Safety of antimuscarinic treatment in male patients without BOO

The efficacy and safety of tolterodine ER in men and women with OAB was established in a multinational, multicenter, randomised, double-blind, placebo-controlled trial; 16% of participants were male [14,15]. Enrolled patients had symptomatic OAB, defined as ≥8 micturition episodes/day, and urgency incontinence. A post hoc analysis was undertaken of these men who were assigned to either placebo or tolterodine ER groups. Patients were excluded from the study if they had clinically relevant BOO. At the end of the 12-week study period, the tolterodine ER group reported a 71% median reduction in urgency incontinence episodes/week, compared with 40% in the placebo group ($P<0.05$). One patient taking tolterodine ER was withdrawn from the study because of symptoms suggestive of urinary retention; no patients reported urinary retention in the placebo arm. Additionally, tolterodine ER was not associated with acute urinary retention (AUR) that necessitated catheterisation.

To determine the effects of tolterodine ER on nocturnal frequency, 2 identical, randomised, double-blind, placebo-controlled studies were conducted in men and women. For the total study cohort, a nighttime regimen of tolterodine ER significantly reduced 24-hour micturition frequency at the 12-week study end point ($P=0.0484$). A subset analysis of the men enrolled in this study was performed post hoc [16]. Three patients taking tolterodine ER and 2 patients in the placebo group were withdrawn from the study because of symptoms suggestive of acute urinary retention. However, tolterodine ER was not associated with AUR that necessitated catheterisation.

The Improvement in Patients: Assessing Symptomatic Control with Tolterodine (IMPACT) study [17] was a phase 4, open-label, singl-earm trial of tolterodine ER. The goal of the study was to determine the impact of use of the antimuscarinic agent on the symptoms of OAB among patients presenting in a primary care setting. All subjects enrolled in this trial completed a 3-day voiding diary. Men and women displayed significant improvement from baseline in measures of OAB, including urgency, urgency incontinence, daytime frequency, and nocturnal frequency. There was no difference between men and women in the degree of improvement. These data show that, in men with OAB without clinically significant BOO, tolterodine ER provides significant relief of symptoms. Patients enrolled in the IMPACT study also completed questionnaires regarding their perception of their bladder condition. Men and women reported substantial improvement from baseline. No cases of AUR that necessitated use of a catheter were reported. Two men were withdrawn from the study because of symptoms suggestive of urinary retention.

Safety of antimuscarinic treatment in male patients with BOO

In a Korean study, 144 consecutive men with symptoms of BOO and urodynamically proven BOO and DO were enrolled from a single tertiary care center [11]. Patients were subclassified into those with pure BOO and those with BOO plus DO, based on presence of involuntary detrusor contractions. Seventy-six (53%) of these men had BOO alone and 68 (47%) had BOO plus DO. All patients were treated initially with the α-blocker doxazosin in escalating doses up to 4 mg/day for 3 months. At that time, patient symptoms were evaluated using the International Prostate Symptom Score (IPSS). The primary efficacy outcome measure was a change of >3 points in the IPSS. Patients from both groups who reported no improvement in symptoms were then assigned to combination therapy, which included tolterodine IR 2 mg twice daily for an additional 2 months. At the end of the initial 3-month treatment period with doxazosin alone, only 35% of men in the BOO+DO group reported improvement in symptoms. The remainder (65%) were then provided with combination therapy. At the end of the 2-month combination-treatment phase, 73% reported symptomatic improvement. Tolterodine IR in combination with doxazosin was well tolerated. There was one case each of AUR in men taking doxazosin monotherapy and combination therapy. Other adverse events were typical of the treatment regimens patients were assigned to. Patients

taking doxazosin reported dizziness (2%), postural hypotension (1.3%), and abnormal ejaculation (1.3%). Patients assigned to tolterodine IR reported dry mouth (27%), the majority of which was mild to moderate. Only two patients withdrew from combination therapy because of severe dry mouth.

Another open-label study designed to determine the safety and efficacy of tolterodine ER monotherapy was undertaken in 43 men with LUTS because of BPH, and failed α-blocker treatment [18]. The α-blocker therapy had previously been ineffective in 11 patients because of adverse events and in 32 because of lack of efficacy. At baseline, patients had an average post-void residual volume (PVR) of 97 mL, an American Urological Association symptom score (AUA-SS) of 17.3, and a Qmax of 9.8 mL/s, indicating moderate BOO. Use of tolterodine ER in this patient population resulted in statistically significant objective and subjective improvements. The AUA-SS improved to 11.2 at 6 months (-6.1, P<0.001) and the Qmax increased 11.7 mL/s (+1.9 mL/s, P<0.001). PVR volumes decreased to 75 mL (-22 mL, P<0.03). Urinary frequency decreased from 9.8 to 6.3 micturition episodes/day (P <0.03). Nocturia episodes decreased from 4.1 to 2.9 episodes/night (P<0.01). The incidence of adverse events was low. There was no instance of urinary retention. Four men withdrew from therapy because of dry mouth.

In a multinational, multicentre, double-blind placebo-controlled study [19], the safety of tolterodine IR was evaluated in 221 over 40 years of age with urodynamically confirmed DO and concomitant mild, moderate, or severe BOO diagnosed by pressure-flow study. Patients had to exhibit ≥8 micturition episodes/24 hours, urinary urgency, urgency incontinence (≥1 episode/24 hours), or all symptoms. DO was defined as phasic detrusor contractions with an amplitude of ≥10 cm H_2O and a volume of <350 mL at the first contraction. More than half the enrolled men had moderate to severe BOO. The primary objective of the study was to determine the safety of tolterodine in men with OAB and coexisting BOO as measured by the Qmax and Pdetmax. At 12 weeks, changes in the Qmax were comparable between patients assigned to the placebo and tolterodine IR groups. The difference was not statistically significant and not clinically meaningful, which was defined in the protocol as ≥3 mL/s. At the end of the 12-week study, the median change in the PVR was significantly larger statistically in the tolterodine IR group than in the placebo group (P=0.0038). The median PVR at week 12 was 27 mL in the placebo group and 60 mL in the tolterodine IR group. AUR was reported by one patient in each treatment group, and urinary adverse events occurred with similar rates in the tolterodine IR (12.8%) and placebo (12.5%) groups.

A paradigm shift in male LUTS

Antimuscarinic agents are often used with caution in men because of a risk of increased residual urine and urinary retention. However, some recent reports demonstrated both the effectiveness and safety of antimuscarinic therapy alone or in combination with alpha-1 receptor antagonisits in treating male LUTS [20,21]. The reported risks of acute urinary retention associated with antimuscarinic treatment in male patients with or without BOO were minimal. However patients should still be warned about the possible side effects of difficulty in urination and increased PVR. The definite role of antimuscarinic agents in male LUTS should still be verified in large-scale, well designed clinical trials. Additionally, since most studies up to this point have reported on tolterodine, and because the pharmacological effects of different recommended antimuscarinic agents (Table 1) are not identical, the efficacy and safety of other agents will need independent investigations.

Table 1. International Consultation on Incontinence (ICI) recommendations for antimuscarinic agents (Monaco, 2004)

ICI recommendations for antimuscarinic agents		
Drugs	**Evidence level**	**Recommendation level**
Tolterodine	**1**	**A**
Trospium	1	A
Darifenacin	1	A
Propiverine	1	A
Solifenacin	1	A
Oxybutynin	1	A

Other treatment options for male OAB

There are other treatment options for male OAB. However, evidence supporting their effectiveness is mostly inadequate. These treatment options include:

- Smooth muscle relaxants: flavoxate (level C)
- Tricyclic antidepressants: imipramine (level C)
- Life style modification
- Bladder retraining
- Pelvic floor exercise
- Neuromodulation
- Phytotherapy

OAB IN NEUROPATHIC PATIENTS

The occurrence of OAB symptoms in neuropathic lower urinary tract dysfunction (LUTD) may be complicated and can be related to both storage dysfunction and emptying dysfunction. For example, in patients with suprasacral cord lesions (upper motor neuron type neuropathic bladder), LUTS is often associated with neurogenic DO and concomitant DSD. Special considerations need to be kept in mind when dealing with patients with neuropathic LUTD:

1. Neuropathic LUTD changes and progresses with time. Periodic urodynamic studies are mandatory to follow-up the functional status of the lower urinary tract.
2. Neuropathic LUTD is often associated with bladder pathological changes such as bladder wall hypertrophy, trabeculation and pseudodiverticulum. Anatomical evaluation of the urinary tract is crucial.
3. The likelihood of upper urinary tract damage and renal function impairment is increased in neuropathic patients. Renal function evaluation should be performed.

As such, treatment strategies for OAB in neuropathic patients need to be tailored individually. Standard recommended treatments include life style intervention, physical therapy, bladder retraining and intermittent catheterization. Antimuscarinic agents (oxybutynin, propiverine) have been shown to be effective against neurogenic DO and even low bladder compliance [22,23]. Intravesical administration of antimuscarinic agents has been reported in some non-controlled studies [24]. Invasive treatment options include neuromodulation and bladder augmentation for small functional capacity and low compliance (level 5).

Evidence for the role of alpha-blockers in neurogenic DO combined with DSD is inadequate (level 5). Regular follow-up studies at 3-6 months are mandatory in patients with neurogenic OAB as the functional status may change over time and the probability of upper urinary tract damage is substantial.

CONCLUSIONS

1. OAB, BPH and BOO are elements of the male LUTS complex. The problem of OAB in the male is as prominent as that in the female.
2. Placebo-controlled trials have shown the use of antimuscarinic agents in men with OAB but not BOO to be effective and safe.
3. Alpha blockers are the first line treatment in men with OAB plus BOO. The efficacy and safety of antimuscarinics alone or in combination will need further study.
4. OAB due to neuropathic LUTD often accompanies other conditions such as DSD, decreased compliance and upper urinary tract damage.
5. The treatment strategy for neurogenic OAB needs to be tailored to individual patients.
6. Urodynamic study should be used to follow-up the shift in functional status; periodic upper tract evaluation is mandatory.

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