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REVIEW

Does anticholinergic medication have a role in treating men with overactive bladder and benign prostatic hyperplasia?

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Abstract This review discusses the available evidence concerning the use of anticholinergic drugs, alone or in combination with α-adrenoceptor antagonists, in men with lower urinary tract symptoms due to benign prostatic hyperplasia, benign prostatic enlargement, or benign prostatic obstruction and concomitant overactive bladder syndrome. We emphasize the safety and efficacy of anticholinergic agents in treating men with benign prostatic obstruction. Several recent studies of men with an overactive bladder suggest that combination therapy of anticholinergic and α-adrenoceptor antagonists improves the symptoms effectively without increasing the incidence of acute urinary retention.

Keywords Prostatic hyperplasia · Bladder · Neurogenic · Cholinergic antagonists

Introduction

Lower urinary tract symptoms (LUTS) are common in elderly men, and benign prostatic obstruction (BPO) is a common cause of LUTS (Abrams 1994). The prevalence of overactive bladder (OAB) increases significantly with age, a pattern similar to the natural history associated with benign prostatic hyperplasia (BPH) (Stewart et al. 2003). Therefore, a substantial proportion of men with LUTS exhibits a combination of both storage and voiding symptoms, which suggests that BPO and detrusor overactivity (DO) may coexist. OAB occurs in 50–75% of men with BPO (Abrams et al. 1979; Chapple et al. 1994; Knutson et al. 2001).

Despite the evidence that LUTS are not disease or condition specific and, hence, are not indicative of BPH or bladder outlet obstruction (BOO), male LUTS are thought to arise from BOO secondary to benign prostatic enlargement (BPE). Therefore, patients with OAB and coexisting BPO are often prescribed pharmacotherapy and surgical intervention that target the prostate rather than the bladder. However, LUTS may result from prostatic pathology, bladder dysfunction, or both, so diagnosis and appropriate treatment of men with OAB symptoms are more complex and difficult. Traditionally, the most widely used pharmacological agents in BPO are α-adrenoceptor (AR) antagonists, and it has been suggested that α-AR antagonists improve LUTS by relaxing prostatic and urethral smooth muscle tone, which decreases outlet resistance, the dynamic component of BPH (Ruggieri et al. 2005). In contrast, patients with OAB without BPO tend to be treated with anticholinergics, which decrease uninhibited bladder contraction.

Many clinicians are reluctant to use anticholinergics to treat OAB with BOO because of the risk of urinary retention, in contrast to the negligible direct effects on detrusor contractility of α-AR antagonists. Several studies suggest that α-AR antagonists and transurethral resection of the prostate fail to improve storage symptoms in some men with BOO and OAB (Lee et al. 2004; Kaplan et al. 2006). Recent studies have reported on the safety of anticholinergics in terms of postvoid residuals (PVR) and acute urinary retention (AUR) in men with BPO (Abrams 2001; Athanasopoulos et al. 2003). Therefore, it is expected that combination therapy with an α_1-AR antagonist and an anticholinergic agent in patients with OAB and BPO should

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significantly alleviate symptoms and improve quality of life.

This review discusses the available evidence concerning the use of anticholinergic drugs, alone or in combination with AR antagonists, in men with LUTS due to BPH, BPE, or BPO and with concomitant OAB syndrome. We emphasize the safety and efficacy of anticholinergics in men with BPO.

Prevalence of lower urinary tract symptom types in adult men

Several population-based studies have estimated the prevalence of LUTS, but the prevalence estimates differ based on the type of LUTS and country surveyed. The Events Preceding Interstitial Cystitis (EPIC) study, a large population-based survey of five countries using the 2002 International Continence Society (ICS) definitions, reported a 62.5% overall prevalence of LUTS in men ≥ 18 years of age (Irwin et al. 2006a). The prevalence of storage LUTS (51.3%) was greater than the combined prevalence for voiding (25.7%) and postmicturition (16.9%) symptoms in men. Storage symptoms were reported nearly twice as often as were voiding symptoms. Nocturia was the most common storage symptom (48.6%), followed by urgency (10.8%).

The prevalence of OAB was comparable in men (10.8%) and women (12.8%) and increased with age in both genders (Milsom et al. 2001; Temml et al. 2005). In the EPIC study, 12.8% of women and 10.8% of men reported the LUTS that define OAB (Irwin et al. 2006a). It is generally accepted that OAB has a profound impact on quality of life (Stewart et al. 2003; Corcos and Schick 2004; Moorthy et al. 2004; Castro et al. 2005; Homma et al. 2005; Temml et al. 2005). Men appear to be bothered more by their storage symptoms than by voiding symptoms (Peters et al. 1997). Irwin et al. (2006b) reported that 32% of men with OAB indicated that these symptoms made them feel depressed. Men with symptoms of OAB report lower health-related quality of life than those without symptoms of OAB (Irwin et al. 2006c). The proportion of men reporting any impairment within each of the EuroQoL Instrument (EQ-5D) domains was higher in men with OAB than in controls. Significantly lower EQ-5D scores were reported for all domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) for men with OAB and urgency urinary incontinence (UUI). In addition, in men, OAB with or without urinary incontinence (UI) was associated with lower employment rate and decreased work productivity than in controls (Abrams et al. 2000; Irwin et al. 2006c).

The prevalence of OAB increases significantly with age, which is similar to the natural history associated with BPO (Stewart et al. 2003). Therefore, a substantial proportion of men with LUTS shows a combination of storage and voiding symptoms, which suggests the possibility of coexisting BPO and OAB. OAB occurs in 50–75% of men with BPO (Abrams et al. 1979; Chapple et al. 1994; Knutson et al. 2001). In the EPIC study, most men with LUTS had both storage and voiding or postmicturition symptoms. Storage and voiding symptoms occurred together most often (17.7%), and all three types of LUTS were reported simultaneously by 8.8% of men (Irwin et al. 2006a).

For many years, LUTS in elderly men were considered to be caused by BPO. However, some studies failed to reveal any significant correlations between LUTS and BPH, BPE, or BOO (Barry et al. 1993; Abrams 1994; Ko et al. 1995). In a study of the relationship between LUTS and BPO or BOO, BOO was evident in 69% of the study population, 33% of whom had BOO as the only cause of symptoms, and 67% had one or more other concomitant urodynamic findings (Fusco et al. 2001). The incidence of involuntary detrusor contractions—the most common concomitant urodynamic finding with BOO—and symptoms of OAB have been estimated as high as 50% of all men with BPO (Fusco et al. 2001). Unfavorable outcomes after surgical therapy to relieve obstruction seem to be associated with persistent DO or OAB symptoms (Robertson et al. 1996; Machino et al. 2002). Therefore, the various causes of LUTS and their prevalence in elderly men should be considered when predicting outcomes of treatments and choosing the best treatment modalities.

Pharmacology of α_1-adrenoceptor antagonists and anticholinergics in lower urinary tract function

Traditionally, the target of α-AR antagonists for LUTS in men with BOO resulting from BPH has been assumed to be the bladder neck and prostatic urethra. Each α-adrenergic subtype is present in the human prostate, bladder neck, and proximal urethra, but the α_1 subtype is responsible for contraction (Andersson 2002). Therefore, α-AR antagonists improve voiding symptoms and flow rate in patients with BPH by relaxing prostatic and urethral smooth muscle tone, which decreases outlet resistance, the dynamic component of BPH (Marshall et al. 1995; Chapple 2006). However, because many men with LUTS without BOO show good responses to α-AR antagonists (Jardin 1998), α-AR antagonists improve LUTS apparently without relieving the obstruction (Rossi et al. 2001), and α-AR antagonists can improve symptoms in women (Kessler et al. 2006). This suggests that the mechanism of their ability to relieve LUTS secondary to BPH does not occur by decreasing outlet obstruction only. In addition, the weak correlation between LUTS and prostatic enlargement, outflow obstruc-

tion, or both has refocused interest on the role of extraprostatic α-AR in the pathogenesis of LUTS and their treatment (Andersson and Gratzke 2007).

Recent studies suggests that α_{1A}-ARs relieve obstruction via relaxation of prostate–bladder neck smooth muscle (Forray et al. 1994; Schwinn and Michelotti 2000), whereas α_{1D}-ARs may be important for relieving irritative symptoms (Michelotti et al. 2000; Malloy et al. 1998; Schwinn and Michelotti 2000). Generally, α_{1D}-AR density is 60–70% and α_{1A}-AR density is 30–40% in the human detrusor (Michel and Vrydag 2006). BOO induces a change in the α-AR subtype composition in the bladder and conversion of normally β-AR-induced relaxation to α-AR-mediated contraction, which correlates with detrusor instability (Perlberg and Caine 1982). However, there are controversies for the role of α_{1D}-AR of the bladder on OAB symptoms in the presence of obstruction. Hampel et al. (2002) reported that there was a change from α_{1A} to α_{1D} predominance (from 70% to 23% for α_{1A}; from 25 to 75% for α_{1D}) in the obstructed bladder model and suggested that targeting α_{1D} may provide a new therapeutic approach for controlling bladder irritative symptoms and possibly DO associated with BOO. However, in humans, there is already an α_{1D}-AR predominance in the normal detrusor. This implies that the change of composition as seen in the rat may have lesser impact in human. Moreover, Nomiya and Yamaguchi (2003) have demonstrated that although predominant, the total expression of α_{1D}-AR mRNA in normal human detrusor was extremely low and that there was no up regulation of any of the ARs with obstruction, including the α_{1D} subtype. They suggested that bladder α_{1D}-ARs did not seem to be responsible for DO and storage symptoms in patients with BPO.

Evidence suggests that the therapeutic mechanism of α_1-AR antagonists seems to be dependent on blockade of both prostatic/urethral and extraprostatic α_1-ARs. Several recent studies show that α-AR antagonists act at extraprostatic sites, such as the bladder, ganglia, and spinal cord. Mechanisms outside the prostate involving α_1-ARs, such as the bladder detrusor or trigonal urothelium, ganglia, and spinal or supraspinal structures within the central nervous system (CNS), are thought to be involved in the pathogenesis of storage symptoms. α_1-ARs in the bladder or spinal cord, especially α_{1D}-ARs, are possible mediators of α-AR-antagonist-induced symptom relief (Kortmann et al. 2003; Roehrborn and Schwinn 2004). Terazosin, an α_1-AR-selective antagonist, improves bladder compliance and continence due to its effect on α-ARs in the detrusor muscle or spinal cord in patients with spinal cord injury. Tamsulosin, which acts at α_{1A}- and α_{1D}-ARs, reduces irritative symptoms in men (Swierzewski et al. 1994; Noble et al. 1997). Naftopidil (a selective α_{1D}-AR inhibitor) monotherapy decreased storage symptoms of International Prostate Symptom Score (IPSS), whereas tamsulosin monotherapy decreased the voiding symptoms of IPSS (Ikemoto et al. 2003). Many studies have shown that α_1-AR mRNA is widely distributed in the brain and spinal cord, including within structures known to be involved in control of micturition. Bladder and urethral activation through these pathways might involve excitatory α_1-ARs, which seem to be tonically active in both the sympathetic and somatic neural control of the lower urinary tract (Andersson and Gratzke 2007). Besides actions on the central or peripheral nervous systems, α-AR antagonists are thought to modulate sensory nerves at the urothelium through their effects on α_1 activation, which evokes release of nitric oxide (Birder et al. 1998; Lee et al. 1998). α_1-ARs are expressed on neurons in the rat urinary tract, and their activation may contribute to the signaling of irritative and nociceptive responses. Tamsulosin has an inhibitory effect on C-fiber urethral afferents, thereby improving bladder storage function (Trevisani et al. 2007; Yokoyama et al. 2007).

Anticholinergics or antimuscarinics were developed to target the main pathway controlling detrusor contraction, in which acetylcholine released from parasympathetic nerves activates muscarinic receptors via M2 and M3, the main subtypes found in the bladder (Sellers and McKay 2007). M2 receptors are the predominant subtype in the bladder (70–80% of the total muscarinic receptor population); however, activation of the minor population of M3 receptors (20–30%) mainly mediate bladder contraction (Chapple 2000). Stimulation of M3 receptors by acetylcholine leads to phosphoinositol hydrolysis and ultimately to accumulation of intracellular calcium and smooth muscle contraction (Harriss et al. 1995). The functional role of the large M2 receptor population in detrusor muscle remains unclear. An investigation using M2, M3, and M2/M3 double knockout mice revealed that the M2 receptor may have a role in indirectly mediating bladder contractions by enhancing the contractile response to M3 receptor activation, and that minor M2-receptor-mediated contractions may also occur (Ehlert et al. 2005). Another rodent study suggested that activation of M2 receptors cause smooth muscle contraction by indirect inhibition of sympathetically (β-adrenoreceptor) mediated augmentation of cyclic adenosine monophosphate (cAMP) levels and bladder relaxation (Hegde et al. 1997). A functional role for M2 receptors in bladder function may emerge in certain disease states, as observed in studies of outflow obstruction in rats (Braverman et al. 1998; Braverman and Ruggieri 2003) and neurogenic human bladder (Pontari et al. 2004). During micturition, it has therefore been suggested that activation of M3 receptors by acetylcholine evokes direct smooth muscle contraction, whereas stimulation of M2 receptors reverses sympathetically mediated smooth muscle relaxation. The end result is more efficient voiding of urine.

In addition, a putative sensory mode of action of the anticholinergics on the urothelium or suburothelium has been suggested as a target for antimuscarinics. Yoshida et al. (2004) found that basal acetylcholine release of non-neuronal origin is generated by the urothelium. Intravesical administration of muscarinic receptor agonists can generate DO, which can be inhibited by antimuscarinics via afferent nerves in the suburothelium. At low doses, tolterodine has an inhibitory effect on C-fiber bladder afferent nerves, thereby improving bladder capacity during the storage phase (Yoshida et al. 2004; Yokoyama et al. 2005). However, there are controversies. Hedlund et al. (2007) showed that tolterodine increased the micturition interval and bladder capacity not only in controls but also in resiniferatoxin-treated animals, suggesting that tolterodine effects were exerted independently of resiniferatoxin-sensitive afferents (C fibers). Dickson et al. (2006) reported interesting results about the role of bladder mucosa for urinary symptoms. They showed, in a chronic model of cyclophosphamide-induced cystitis, that the density of both parasympathetic and peptidergic sensory fibers in the bladder mucosa was significantly increased. Based on these results, the authors suggested that peripheral sprouting of parasympathetic and peptidergic fibers could be a mechanism responsible for sensitization of the bladder, leading to urinary symptoms.

Therefore, the effectiveness of antimuscarinic agents in the treatment of OAB syndrome is thought to arise through blockade of bladder muscarinic receptors located on detrusor smooth muscle cells, the urothelium or suburothelium, and afferent nerves that may contribute to the pathophysiology of OAB.

Is it enough to use α_1 antagonists alone in a man with OAB or BPH?

Medical treatment is frequently used as the initial management approach for LUTS in older men. Traditionally, the most commonly prescribed treatments for LUTS, including OAB symptoms, target the prostate; for example, α_1-AR antagonists such as doxazosin, terazosin, alfuzosin, and tamsulosin, although 5α-reductase inhibitors, are often administered concomitantly when there is significant prostate enlargement (Abrams et al. 2006a). A recent prescription database study of men with newly diagnosed OAB suggests that these patients are more likely to be prescribed α_1-AR antagonists or 5α-reductase inhibitors than anticholinergics (Jumadilova et al. 2005). In a review of more than 12,000 men with OAB 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. Thus, 56% of men with OAB and no BPH diagnosis who receive drug treatment are prescribed agents that target the prostate.

Although α_1-AR antagonists and 5α-reductase inhibitors impart reasonable benefit for the obstructive symptoms associated with LUTS by reducing bladder outlet resistance, and α_1-AR antagonists relieve both voiding and storage symptoms in BPO (Chapple et al. 1994), neither class has any known action that directly reduces DO and urgency, the most bothersome symptoms among older men. OAB symptoms result from primary DO or DO secondary to BOO. Therefore, drug therapy that targets only the prostate has limited therapeutic effects on OAB symptoms. α-AR-antagonist monotherapy has had limited success in the treatment of OAB symptoms. Lee et al. (2004) assessed whether there was any benefit from adding an anticholinergic agent in men with BOO plus DO. Of 144 patients, 76 (53%) were diagnosed as having BOO and 68 (47%) BOO plus DO. In men with BOO plus DO, at the end of the initial 3-month treatment period with doxazosin alone, only 35% reported improvement in symptoms (a decrease in IPSS of > 3 points). The remaining 65% were then given tolterodine immediate release (IR) in addition to doxazosin. At the end of the 2-month treatment phase, 73% of those patients assigned to therapy with tolterodine IR plus doxazosin reported improvement in symptoms. These results suggest that α-AR antagonist monotherapy has limited success in the treatment of OAB symptoms and that combination treatment with an α-AR antagonist and anticholinergic is clinically effective when α-AR antagonist therapy fails to resolve the symptoms of OAB.

Men with LUTS have voiding symptoms and bothersome OAB storage symptoms. LUTS may be caused by the bladder, the prostate, or both and may respond differently to drug therapy. Men with LUTS are historically diagnosed with BPH and are treated with α_1-AR antagonists, leaving a subset of patients still bothered by OAB symptoms.

Is it safe to use anticholinergics in men with BPH?

A concern expressed by clinicians in using an anticholinergic agent in men is the risk for AUR. The rationale for prescribing anticholinergics for BPO patients is based on the mechanism of action of the antimuscarinics. The classic view is that antimuscarinics function by blocking muscarinic receptors on the detrusor muscle and that this blocking of activity in turn decreases the contractile ability of the bladder. Therefore, a traditional concern is that an antimuscarinic agent in men with BPO can induce elevated PVR or AUR because of the inhibitory effects of antimuscarinics on bladder contraction. As a result, these drugs tend not to be used in men with BPO, although the

US Food and Drug Administration has approved them for men with OAB.

However, recent research has newly revealed a mechanism of action for antimuscarinic agents with regard to OAB (Andersson and Yoshida 2003). During the storage phase, acetylcholine may be released from both neuronal and nonneuronal sources and then directly or indirectly (by increasing detrusor smooth muscle tone) excite afferent nerves in the suburothelium as well as in the detrusor. This mechanism may be relevant to the pathophysiology of OAB and may also comprise a possible target for antimuscarinic drugs. In addition, most antimuscarinic drugs function as competitive antagonists. Therefore, during the massive release of acetylcholine during micturition, the effects of the antimuscarinics decrease. From a theoretical point of view, unless the dose of antimuscarinics is extremely high, these drugs should not impair bladder contractility and, therefore, should not decrease the voiding pressure and flow rate (Andersson and Yoshida 2003).

The clinical safety of antimuscarinics in men who have OAB and BPO has been demonstrated in several clinical trials. Abrams et al. (2006b) reported on the safety of tolterodine 2 mg twice daily on urodynamic parameters in men who exhibited urodynamically proven BPO and DO. Tolterodine increased PVR (25 mL) when compared with a placebo (0 mL), but this was hardly a substantial clinical change that was not associated with AUR. In the tolterodine group, there was no change of Q_{max} after 12 weeks of treatment (from 8.5ml/s to 8.5ml/s). Lee et al. (2005) reported that propiverine is not associated with any urinary safety concerns. They investigated the safety of propiverine combined with doxazosin in patients with OAB and BPO. They included patients who had at least one episode of urgency daily, average frequency of greater than eight times per 24 h, and urodynamically proven BOO [Abrams–Griffith (AG) score 20 or greater]. Twenty milligrams of propiverine, a lower dosage than used in European countries, ensured, to some degree, the safety and tolerability of this study during 8 weeks of treatment. The change in Q_{max} was not different from doxazosin only group in the combination group. PVR increased significantly by 20.7 mL when propiverine therapy was combined with doxazosin but not for doxazosin only. However, this increase in PVR in men receiving the combined drugs was not accompanied by urinary retention. In a 6-month open-label study, Kaplan et al. (2005) assessed the efficacy and safety of the extended release (ER) formula of tolterodine in men with BPH who had not experienced relief from LUTS with α-AR-antagonist therapy. The patients who had American Urological Association (AUA) symptom score between 8 and 35 and Q_{max} of 4–15 mL/s received 4 mg tolterodine ER daily for 6 months. Tolterodine alone increased Q_{max} from 9.8 at baseline to 11.7 mL/s and decreased PVR from 97 to 75 mL. No incidence of AUR was observed.

Most recently, Kaplan et al. (2006) evaluated the efficacy and safety of tolterodine ER alone, tamsulosin alone, and the combination of both in 879 men who met research criteria for both OAB and BPH in a large-scale, multicenter, randomized, double-blind, placebo-controlled trial (the TIMES study). Inclusion criteria were men ≥ 40 years old; total IPSS ≥ 12; IPSS quality-of-life (QOL) item score ≥ 3; micturitions per 24 h ≥ 8; urgency episodes per 24 h ≥ 3 with urgency rating ≥ 3; a self-rated bladder condition of "some moderate problems," "severe problems," or "many severe problems" based on the Patient Perception of Bladder Condition questionnaire. Men with clinically significant BOO (defined as PVR > 200 mL and maximum flow rate < 5 mL/s), or serum prostate-specific antigen ≥ 10 ng/mL showing a risk of prostate cancer were excluded. All study patients were randomly assigned into one of four groups: placebo; 4 mg of tolterodine ER; 0.4 mg of tamsulosin; or tolterodine ER plus tamsulosin once a day.

In the TIMES study, patients treated with tolterodine ER with or without tamsulosin demonstrated a 5- to 6-mL increase in PVR from baseline (placebo –3.61; tolterodine ER 5.27; tamsulosin 0.11; tolterodine ER plus tamsulosin 6.42) (Kaplan et al. 2006). The increase was not statistically or clinically significant, and the change in PVR did not differ significantly between groups. All treatment groups demonstrated slight changes in maximum urinary flow rate compared with baseline (placebo −0.53; tolterodine ER −0.60; tamsulosin −0.22; tolterodine ER plus tamsulosin 0.07). Neither the changes from baseline nor comparisons between any two groups was statistically significant. Table 1 shows safety data from studies on anticholinergic treatment of men with OAB with and without BPO.

Even several clinical results reported the safety of anticholinergics on PVR or AUR; these results came from well-controlled clinical trials. Patients with high PVR and weak flow are usually excluded from the studies. To date, the effects of antimuscarinics have been studied primarily in patients with OAB without BPO, and only a few researchers have formally assessed the safety of antimuscarinics in treating men with BPO. In patients with chronic obstruction, morphological, biochemical, and functional changes together with detrusor denervation make it reasonable to assume that blockage of a damaged bladder with antimuscarinic agents can lead to drug-induced detrusor decompensation.

Few studies have evaluated the risk factors of AUR or elevated PVR during the use of anticholinergics. Meigs et al. (1999) reported the incidence rate of AUR from a health professional follow-up study with 6,100 men aged from 45 to 83 years. During 15,851 person years of follow-up, 82 men reported an episode of AUR. The authors demonstrat-

Table 1 Safety data from studies on anticholinergic treatment for men with lower urinary tract symptoms

Authors	Study design	Patients	Duration	PVR (mL)	AUR rate
Randomized controlled trials published in peer-reviewed journals					
Saito et al. (1999)	RCT: tamsulosin vs. tamsulosin + propiverine	134	1 month	–4.0 (NA)	2.6%
Athanasopoulos et al. (2003)	RCT: tamsulosin vs. tamsulosin + tolterodine	50	3 months	–4.2 (NS)	0%
Lee et al. (2005)	RCT: doxazosin vs. doxazosin + propiverine	21	2 months	+20.7 (p=0.002)	0%
Abrams et al. (2006b)	RCT: tolterodine vs. placebo	221	3 months	+25 (p<0.004)	0% (1 case in placebo)
Kaplan et al. (2006)	RCT: placebo vs. tolterodine vs. tamsulosin vs. tolterodine ER + tamsulosin	879	3 months	+5.3 in tolterodine (NS) +6.4 in combined (NS)	7 patients (3 in placebo, 2 in tolterodine, 0 in tamsulosin, 2 in combined)
Prospective case series published in peer-reviewed journals					
Kaplan et al. (2005)	Case series: tolterodine	43	6 months	–22 (p<0.03)	0%
Lee et al. (2004)	Case series: doxazosin + tolterodine	60	3 months	NR	3.3% (2 patients)

RCT randomized controlled trial, *ER* extended release, *PVR* postvoid residual urine, *AUR* acute urinary retention, *NA* not available, *NR* not reported, *NS* not significant

ed that men with a clinical diagnosis of BPH, AUA symptom score 8 or greater, and use of medication with adrenergic or anticholinergic side effects predicted AUR. Men with moderate or severe LUTS and a clinical diagnosis of BPH had AUR rates nine times greater than those without symptoms or a BPH diagnosis. Although the overall incidence of AUR was low (sampling adjusted incidence rate of 4.5/1,000 person years), data suggest that men with BPH who have moderate or severe LUTS should take care when using anticholinergics.

From the review of literature, Gonzalez and Te (2003) proposed an algorithm for the evaluation and treatment of men with OAB based on the authors' clinical experience. In that study, they recommended the clinical judgment according to the IPSS, flow rate, and PVR. The authors consider a high PVR volume to be = 40% of functional bladder capacity. If the patient has normal flow and a low PVR, they suggest that it is safe to consider a trial of anticholinergics. However, studying patients with OAB with low flow rate (< 12 mL/s) and high PVR suggested that anticholinergics should not be recommended without excluding or treating BOO (Gonzalez and Te 2003). In patients with OAB and a flow rate and high PVR or a history of urinary retention, the authors recommended urodynamics to rule out BOO and appropriate surgical therapy for patients with proven BOO.

Prescribing antimuscarinics for LUTS associated with BPO should lead to different results depending on BOO grade. Lee et al. (2005) evaluated the efficacy and safety of treatment according to BOO grade. The therapeutic efficacy did not differ when patients were grouped by Abrams–Griffith (AG) number (20–40, 41–60, and > 60). However, three of the 16 severely obstructed patients (AG > 60) receiving propiverine treatment discontinued their treatment because of significant PVR (> 50% of voided urine volume). The authors concluded that in patients with severe BOO, anticholinergic therapy requires close supervision to detect increase in PVR.

To support the safety of anticholinergic drugs in patients with OAB with BPO, further research is necessary with a large population of patients and long-term treatment. The optimal dose of anticholinergics to treat patients with BPO should be determined. It is probable that a lower dose of anticholinergics can be used safely in patients with OAB and BPO with the same efficacy.

Clinical results of combination treatment of anticholinergics and α-AR antagonists in men with OAB and coexisting BPH

Recent studies suggest that anticholinergic drugs are effective and safe in treating men with LUTS (Saito et al.

1999; Athanasopoulos et al. 2003; Lee et al. 2004; Kaplan et al. 2005; Lee et al. 2005; Abrams et al. 2006b; Kaplan et al. 2006; MacDiarmid et al. 2006; MacDiarmid and Rogers 2007). Several randomized, controlled trials involving men with OAB and coexisting BPH demonstrated that combined anticholinergic drug—α_1-AR-antagonist treatment is more effective in reducing male LUTS than is α_1-AR antagonist alone (Saito et al. 1999; Athanasopoulos et al. 2003; Lee et al. 2005; Kaplan et al. 2006; MacDiarmid et al. 2006).

Saito et al. (1999) were the first to report the therapeutic benefit of combined anticholinergics (propiverine) and α_1-AR antagonists (tamsulosin) compared with α_1-AR antagonists alone. Patients treated with combination therapy had a more favorable improvement in rates of daytime frequency, UI, and urgency. Athanasopoulos and colleagues (2003) conducted an open-label, randomized, controlled trial in 50 consecutive patients with urodynamically proven mild or moderate BOO according to the Schafer nomogram and concomitant DO who were initially assigned the α-AR antagonist tamsulosin, 0.4 mg once daily. After 1 week of therapy, participants were randomized to single-drug therapy with tamsulosin (0.4 mg once daily) or a combination of tamsulosin and tolterodine (2 mg twice daily). After 3 months of treatment, the patients were reassessed through quality of life questionnaires (the Greek version of the EuroLife BPH Quality of Life 9 questionnaire) and urodynamic studies. Quality of life improved significantly in the group treated with combination therapy (from mean 525.0 to 628.4) but not in those treated with tamsulosin monotherapy (from mean 542.8 to 548.2). Both groups demonstrated significant improvement in flow rate and volume at first contraction, whereas the combined group also showed a significant decrease in maximum detrusor pressure (from 69.5 to 61.3 vs. from 70.0 to 64.9 cmH_2O) and the magnitude of maximum bladder contraction (from 30.9 to 19.8 vs. from 29.0 to 27.8 cmH_2O) after therapy.

Lee et al. (2005) published a prospective, randomized, double-blind, multicenter study that compared the efficacy and safety of combination therapy of propiverine and doxazosin in a cohort of patients with OAB syndrome and urodynamically proven BOO. Two hundred and eleven patients were randomized (1:2) to receive either doxazosin (4 mg once daily) only or propiverine hydrochloride (20 mg once daily) plus doxazosin for 8 weeks. Both groups showed significant improvement in urinary frequency, maximum flow rate, mean micturition volume, and IPSS. However, compared with the doxazosin arm, patients treated with combination therapy experienced higher rates of improvement in urinary frequency (23.5% vs. 14.3%), and average micturition volume (32.3% vs. 19.2%) and IPSS storage subscale (41.3% vs. 32.6%) and urgency score (42.9% vs. 28.0%). Patients' satisfaction with treatment was significantly higher in the combination therapy group, and the odds of a patient reporting a benefit was 2.34 times higher in the combined-treatment group than in the doxazosin-only group. The authors suggested that the difference in patient satisfaction rates might be attributable to differences in the quantity and quality of symptom improvement. For example, the combination treatment group showed greater improvement in daytime frequency and number of voids/24 h. In addition, the combination treatment group had more improvements in storage symptoms and urgency than did the doxazosin monotherapy group, and combination treatment did not attenuate the voiding symptoms. Previous studies show that storage symptoms tend to be more bothersome than voiding symptoms (Jolleys et al. 1994; Witjes et al. 1997). Urgency is the central symptom of OAB and is very bothersome to patients, and any effective OAB treatment must ameliorate this symptom (Chapple et al. 2004).

As mentioned above, Kaplan et al. (2006) evaluated the efficacy and safety of tolterodine ER alone, tamsulosin alone, and the combination of both in 879 men with OAB and BPH in the TIMES study. The primary efficacy endpoint was patient perception of treatment benefit at week 12. Secondary efficacy measures included bladder diary variables such as the change from baseline in UUI episodes (urgency rating 5) per 24 h, urgency episodes (non-UUI micturitions with urgency rating 3 or 4) per 24 h, total micturitions per 24 h, and micturitions per night; IPSS, and PVR. The 5-point urgency rating scale was used to evaluate urgency grade. In the primary efficacy analysis, 172 men (80%) receiving tolterodine ER plus tamsulosin reported treatment benefit by week 12 compared with 132 patients (62%) receiving placebo, 146 (71%) receiving tamsulosin, or 135 (65%) receiving tolterodine ER. In the secondary efficacy analysis, patients receiving tolterodine ER plus tamsulosin compared with placebo experienced significant reductions in UUI (−0.88 vs. −0.31), urgency episodes without incontinence (−3.33 vs. −2.54), micturitions per 24 h (−2.54 vs. −1.41), and micturitions per night (−0.59 vs. −0.39). Patients in the tolterodine ER group experienced significant reduction only in UUI episodes per 24 h at week 12 than placebo. However, at week 12, diary variables did not differ significantly between tamsulosin monotherapy and placebo groups (Table 2). Patients receiving tolterodine ER plus tamsulosin demonstrated significant improvements on the total IPSS (−8.02 vs. placebo −6.19) and QOL item (−1.61 vs. −1.17). Although total IPSS increased significantly in patients who received tamsulosin alone than placebo, this variable did not differ significantly between tolterodine ER and placebo categories at week 12.

These studies suggest that the combination of anticholinergics and α_1-AR antagonists provides the most efficacious initial therapy for men with OAB symptoms in the

Table 2 Randomized controlled trials comparing the efficacy between the combination therapy of α_1-adrenoceptor (AR) antagonist and anticholinergics and α_1-AR antagonist alone in men with overactive bladder (OAB) and coexisting benign prostatic hyperplasia (BPH)

Authors	Patients	Duration	Medication	Outcome measures			
				IPSS	QoL	Voiding diary	Urodynamics
Saito et al. (1999)	134	1 month	Tams vs. Tams + Prop	NR	NR	In Tams only and combination groups, daytime frequency (29.6%, 44.7%), nocturia (22.5%, 44.4%), UUI (42.9%, 57.1%), urgency (18.2%, 22.2%) improved The change of nocturia was more prominent in combination group (NA)	Q_{max} increased from 11.5 to 14.4 mL/s in Tams only group but not in combination group (from 11.3 to 11.8 mL/s) NA
Athanasopoulos et al. (2003)	50	3 months	Tams vs. Tams + Tolt	NR	Improved in only combination therapy group (p=0.0003 vs. p=0.836 in Tams only group)	NR	Q_{max} increased in both groups (p=0.0001; p=0.002) Maximum detrusor pressure during micturition and unstable contraction decreased only in combination therapy group (p=0.0082; p<0.0001)
Lee et al. (2005)	211	2 months	Doxa vs. Doxa + Prop	Improved in both groups (p<0.05) Storage and urgency IPSS improved more in combination group (p=0.029; p=0.019)	IPSS-QoL item score improved in both groups (p<0.05) Similar improvement in both groups	24-h frequency and mean micturition volume improved in both groups (p<0.05) but more in combination therapy group (both p=0.004).	Q_{max} improved in both groups (p<0.05) but no difference between groups PVR increased only in combination therapy group (p<0.05)
Kaplan et al. (2006)	879	3 months	Placebo vs. Tolt vs. Tams vs. Tolt + Tams	Improved in combination and Tams only group (p=0.003; p=0.007 vs. placebo) No changes in Tolt alone group	Improved in combination group (p=0.003 vs. placebo) No changes in Tams only and Tolt only groups	UUI and urgency episodes, 24-h frequency, and nighttime frequency improved in combination group (p<0.005; p=0.03; p < 0.001; p=0.02 vs. placebo) UUI episodes improved in Tolt only group (p < 0.008 vs. placebo) No changes in any variable in Tams only group	No changes from baseline or between any 2 groups in Q_{max} or PVR
MacDiarmid et al. (2006)	409	3 months	Tams + placebo vs. Tams + Oxyb	Greater improvement in combination group than in Tams only group (p=0.006)	Greater improvement in combination group than in Tams only group (p=0.001).	NR	Occurrence of reduced Q_{max} (< 5 mL/s) was 3.8% in combination group and 5.7% in Tams only group (p=0.493)

RCT randomized controlled trial, *IPSS* International Prostate Symptom Score, *QoL* quality of life, Q_{max} maximum flow rate, *UUI* urgency urinary incontinence, *Tams* tamsulosin, *Doxa* doxazosin, *Tolt* tolterodine, *Prop* propiverine, *Oxyb* Oxybutynin, *NA* not available, *NR* not reported, *NS* not significant, *PVR* postvoid residuals

presence of BPH or BPO. Table 2 summarizes data of selected studies on the efficacy of combination therapy of α_1-AR antagonists and anticholinergic drugs.

Future directions

Although the current studies of the safety of anticholinergics suggest that anticholinergics do not increase the incidence of AUR in men with or without BOO, most of these findings were the results of secondary analyses of larger studies, small or open-label trials, or well-designed, randomized, controlled trials. The study populations were selected by strict inclusion and exclusion criteria, and the patients with severe BOO or large PVR were excluded. Therefore, in real-life practice, when treating patients with elevated PVR, detrusor underactivity, or myogenic failure from the aging bladder, the efficacy and safety of anticholinergics may not be comparable with well-controlled studies. In addition, these studies reported short-term data. OAB symptoms often require long-term treatment, and BOO due to BPH tends to progress with time. Although these reports suggest that anticholinergic treatment safely ameliorates OAB symptoms in men with LUTS, prospective studies should include larger populations, longer duration of therapy, and other anticholinergic agents (e.g., oxybutynin, trospium, darifenacin, solifenacin) and should simulate clinical practice. This would provide us with a more complete understanding of the safety of anticholinergic treatment in this patient population. The optimal treatment regimen that considers factors such as adequate dose and duration, patient characteristics, and clinically significant adverse effects other than AUR, especially in older patients, must be determined through large-scale, placebo-controlled studies.

Conclusion

LUTS in men may arise from variable causes, including BOO, DO, or both; in other words, LUTS may result from prostatic pathology, bladder dysfunction, or both. LUTS are divided into storage and voiding symptoms, and OAB symptoms are a subset of storage LUTS. The prevalence of OAB symptoms is similar in men and women, and the adverse effects on quality of life and costs associated with the condition have been well described.

Men with LUTS, including those with OAB symptoms, are treated predominantly with agents such as α-AR antagonists or 5α-reductase inhibitors or prostate surgery that targets the prostate. Some of these patients experience persistent OAB symptoms, especially men with bladder pathology. When an α-AR antagonist is not effective in treating a man with LUTS, the clinician should consider the possibility that LUTS may be caused by bladder dysfunction (e.g., DO) rather than prostatic enlargement. Results from several recent studies of men with OAB symptoms and other LUTS (with or without some degree of BOO) suggest that anticholinergic and α-AR antagonist combination therapy improves OAB symptoms effectively without increasing the incidence of AUR. However, most of these studies have a few limitations; for example, short study duration, strict inclusion criteria that do not reflect real clinical situations, and exclusion of the high AUR risk group. Further, many long-term studies involving larger numbers of men who are enrolled based on symptoms rather than urodynamic criteria will provide newer insights into the diagnosis and management of this bothersome condition. These studies should help determine the standard regimen (dose and duration), indications, safety, and efficacy of anticholinergic agents in men.

References

Abrams P (1994) In support of pressure-flow studies for evaluating men with lower urinary tract symptoms. Urology 44:153–155

Abrams P (2001) Evidence for the efficacy and safety of tolterodine in the treatment of overactive bladder. Expert Opin Pharmacother 2:1685–1701

Abrams PH, Farrar DJ, Turner-Warwick RT, Whiteside CG, Feneley RC (1979) The results of prostatectomy: a symptomatic and urodynamic analysis of 152 patients. J Urol 121:640–642

Abrams P, Kelleher CJ, Kerr LA, Rogers RG (2000) Overactive bladder significantly affects quality of life. Am J Manag Care 6: S580–S590

Abrams P, Andersson KE, Buccafusco JJ, Chapple C, de Groat WC, Fryer AD, Kay G, Laties A, Nathanson NM, Pasricha PJ, Wein AJ (2006a) Muscarinic receptors: their distribution and function in body systems, and the implications for treating overactive bladder. Br J Pharmacol 148:565–578

Abrams P, Kaplan S, De Koning Gans HJ, Millard R (2006b) Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. J Urol 175:999–1004; discussion 1004

Andersson KE (2002) Alpha-adrenoceptors and benign prostatic hyperplasia: basic principles for treatment with alpha-adrenoceptor antagonists. World J Urol 19:390–396

Andersson KE, Gratzke C (2007) Pharmacology of alpha1-adrenoceptor antagonists in the lower urinary tract and central nervous system. Nat Clin Pract Urol 4:368–378

Andersson KE, Yoshida M (2003) Antimuscarinics and the overactive detrusor—which is the main mechanism of action? Eur Urol 43:1–5

Athanasopoulos A, Gyftopoulos K, Giannitsas K, Fisfis J, Perimenis P, 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

Barry MJ, Cockett AT, Holtgrewe HL, McConnell JD, Sihelnik SA, Winfield HN (1993) Relationship of symptoms of prostatism to commonly used physiological and anatomical measures of the severity of benign prostatic hyperplasia. J Urol 150:351–358

Birder LA, Apodaca G, De Groat WC, Kanai AJ (1998) Adrenergic- and capsaicin-evoked nitric oxide release from urothelium and afferent nerves in urinary bladder. Am J Physiol 275:F226–F229

Braverman AS, Ruggieri MR Sr (2003) Hypertrophy changes the muscarinic receptor subtype mediating bladder contraction from M3 toward M2. Am J Physiol Regul Integr Comp Physiol 285: R701–R708

Braverman AS, Luthin GR, Ruggieri MR (1998) M2 muscarinic receptor contributes to contraction of the denervated rat urinary bladder. Am J Physiol 275:R1654–R1660

Castro D, Espuna M, Prieto M, Badia X (2005) [Prevalence of overactive bladder in Spain: a population-based study]. Arch Esp Urol 58:131–138

Chapple CR (2000) Muscarinic receptor antagonists in the treatment of overactive bladder. Urology 55:33–46

Chapple C (2006) Alpha antagonists-from initial concept to routine clinical practice. Eur Urol 50:635–642

Chapple CR, Carter P, Christmas TJ, Kirby RS, Bryan J, Milroy EJ, Abrams P (1994) A three month double-blind study of doxazosin as treatment for benign prostatic bladder outlet obstruction. Br J Urol 74:50–56

Chapple CR, Rechberger T, Al-Shukri S, Meffan P, Everaert K, Huang M, Ridder A (2004) Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. BJU Int 93(3):303–310

Corcos J, Schick E (2004) Prevalence of overactive bladder and incontinence in Canada. Can J Urol 11:2278–2284

Dickson A, Avelino A, Cruz F, Ribeiro-da-Silva A (2006) Peptidergic sensory and parasympathetic fiber sprouting in the mucosa of the rat urinary bladder in a chronic model of cyclophosphamide-induced cystitis. Neuroscience 141:1633–1647

Ehlert FJ, Griffin MT, Abe DM, Vo TH, Taketo MM, Manabe T, Matsui M (2005) The M2 muscarinic receptor mediates contraction through indirect mechanisms in mouse urinary bladder. J Pharmacol Exp Ther 313:368–378

Forray C, Bard JA, Wetzel JM, Chiu G, Shapiro E, Tang R, Lepor H, Hartig PR, Weinshank RL, Branchek TA et al (1994) The alpha 1-adrenergic receptor that mediates smooth muscle contraction in human prostate has the pharmacological properties of the cloned human alpha 1c subtype. Mol Pharmacol 45:703–708

Fusco F, Groutz A, Blaivas JG, Chaikin DC, Weiss JP (2001) Videourodynamic studies in men with lower urinary tract symptoms: a comparison of community based versus referral urological practices. J Urol 166:910–913

Gonzalez RR, Te AE (2003) Overactive bladder and men: indications for anticholinergics. Curr Urol Rep 4:429–435

Hampel C, Dolber PC, Smith MP, Savic SL, Throff JW, Thor KB, Schwinn DA (2002) Modulation of bladder alpha1-adrenergic receptor subtype expression by bladder outlet obstruction. J Urol 167:1513–1521

Harriss DR, Marsh KA, Birmingham AT, Hill SJ (1995) Expression of muscarinic M3-receptors coupled to inositol phospholipids hydrolysis in human detrusor smooth muscle cells. J Urol 154:1241–1245

Hedlund P, Streng T, Lee T, Andersson KE (2007) Effects of tolterodine on afferent neurotransmission in normal and resiniferatoxin treated conscious rats. J Urol 178:326–331

Hegde SS, Choppin A, Bonhaus D, Briaud S, Loeb M, Moy TM, Loury D, Eglen RM (1997) Functional role of M2 and M3 muscarinic receptors in the urinary bladder of rats in vitro and in vivo. Br J Pharmacol 120:1409–1418

Homma Y, Yamaguchi O, Hayashi K (2005) An epidemiological survey of overactive bladder symptoms in Japan. BJU Int 96:1314–1318

Ikemoto I, Kiyota H, Ohishi Y, Abe K, Goto H, Kishimoto K, Miki K (2003) Usefulness of tamsulosin hydrochloride and naftopidil in patients with urinary disturbances caused by benign prostatic hyperplasia: a comparative, randomized, two-drug crossover study. Int J Urol 10:587–594

Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, Coyne K, Kelleher C, Hampel C, Artibani W, Abrams P (2006a) 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; discussion 1314–1315

Irwin DE, Milsom I, Reilly K, Hunskaar S, Coyne KS, Kopp Z, Herschorn S, Kelleher C, Hampel C, Artibani W, Abrams P (2006b) Men and women with overactive bladder symptoms report higher prevalence for depression and lower quality of life: results from the EPIC study. ICS 2006 Abstract 433

Irwin DE, Milsom I, Kopp Z, Abrams P, Cardozo L (2006c) Impact of overactive bladder symptoms on employment, social interactions and emotional well-being in six European countries. BJU Int 97:96–100

Jardin A (1998) Alpha-blockers in the treatment of BPH. Health Publication, Plymouth, pp 599–632

Jolleys JV, Donovan JL, Nanchahal K, Peters TJ, Abrams P (1994) Urinary symptoms in the community: how bothersome are they? Br J Urol 74:551–555

Jumadilova Z, Harris H, del Aguilla M, Wagner S, Boccuzzi S, Bavendam T (2005) Agent selection for overactive bladder patients with and without documented comorbid benign prostatic hyperplasia. Presented at: the 35th Annual Meeting of the International Continence Society; August 28-September 2, 2005; Montreal, Canada

Kaplan SA, Walmsley K, Te AE (2005) Tolterodine extended release attenuates lower urinary tract symptoms in men with benign prostatic hyperplasia. J Urol 174:2273–2275

Kaplan SA, Roehrborn CG, Rovner ES, Carlsson M, Bavendam T, Guan Z (2006) Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. JAMA 296:2319–2328

Kessler TM, Studer UE, Burkhard FC (2006) The effect of terazosin on functional bladder outlet obstruction in women: a pilot study. J Urol 176:1487–1492

Knutson T, Edlund C, Fall M, Dahlstrand C (2001) BPH with coexisting overactive bladder dysfunction—an everyday urological dilemma. Neurourol Urodyn 20:237–247

Ko DS, Fenster HN, Chambers K, Sullivan LD, Jens M, Goldenberg SL (1995) The correlation of multichannel urodynamic pressure-flow studies and American Urological Association symptom index in the evaluation of benign prostatic hyperplasia. J Urol 154:396–398

Kortmann BB, Floratos DL, Kiemeney LA, Wijkstra H, de la Rosette JJ (2003) Urodynamic effects of alpha-adrenoceptor blockers: a review of clinical trials. Urology 62:1–9

Lee JZ, Tillig B, Perkash I, Constantinou CE (1998) Effect of alpha1 adrenoceptor antagonist on the urodynamics of the upper and lower urinary tract of the male rat. Neurourol Urodyn 17:213–229

Lee JY, Kim HW, Lee SJ, Koh JS, Suh HJ, Chancellor MB (2004) Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and an overactive bladder. BJU Int 94:817–820

Lee KS, Choo MS, Kim DY, Kim JC, Kim HJ, Min KS, Lee JB, Jeong HJ, Lee T, Park WH (2005) Combination treatment with propiverine hydrochloride plus doxazosin controlled release gastrointestinal therapeutic system formulation for overactive bladder and coexisting benign prostatic obstruction: a prospec-

tive, randomized, controlled multicenter study. J Urol 174:1334–1338

MacDiarmid S, Rogers A (2007) Male overactive bladder: the role of urodynamics and anticholinergics. Curr Urol Rep 8:66–73

MacDiarmid S, Chen A, Tu N, Peters KM (2006) Effects of tamsulosin and extended-release oxybutynin on lower urinary tract symptoms in men [abstract 1638]. Program and abstracts of the American Urological Association 2006 Annual Meeting. May 20–25, 2006; Atlanta, GA

Machino R, Kakizaki H, Ameda K, Shibata T, Tanaka H, Matsuura S, Koyanagi T (2002) Detrusor instability with equivocal obstruction: A predictor of unfavorable symptomatic outcomes after transurethral prostatectomy. Neurourol Urodyn 21:444–449

Malloy BJ, Price DT, Price RR, Bienstock AM, Dole MK, Funk BL, Rudner XL, Richardson CD, Donatucci CF, Schwinn DA (1998) Alpha1-adrenergic receptor subtypes in human detrusor. J Urol 160:937–943

Marshall I, Burt RP, Chapple CR (1995) Noradrenaline contractions of human prostate mediated by alpha 1A-(alpha 1c-) adrenoceptor subtype. Br J Pharmacol 115:781–786

Meigs JB, Barry MJ, Giovannucci E, Rimm EB, Stampfer MJ, Kawachi I (1999) Incidence rates and risk factors for acute urinary retention: The health professionals followup study. J Urol 162:376–382

Michel MC, Vrydag W (2006) Alpha1-, alpha2- and beta-adrenoceptors in the urinary bladder, urethra and prostate. Br J Pharmacol 147(Suppl 2):S88–S119

Michelotti GA, Price DT, Schwinn DA (2000) Alpha 1-adrenergic receptor regulation: basic science and clinical implications. Pharmacol Ther 83:281–309

Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ (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

Moorthy P, Lapitan MC, Quek PL, Lim PH (2004) Prevalence of overactive bladder in Asian men: an epidemiological survey. BJU Int 93:528–531

Noble AJ, Chess-Williams R, Couldwell C, Furukawa K, Uchyiuma T, Korstanje C, Chapple CR (1997) The effects of tamsulosin, a high affinity antagonist at functional alpha 1A- and alpha 1D-adrenoceptor subtypes. Br J Pharmacol 120:231–238

Nomiya M, Yamaguchi O (2003) A quantitative analysis of mRNA expression of alpha 1 and beta-adrenoceptor subtypes and their functional roles in human normal and obstructed bladders. J Urol 170:649–653

Perlberg S, Caine M (1982) Adrenergic response of bladder muscle in prostatic obstruction. Its relation to detrusor instability. Urology 20:524–527

Peters TJ, Donovan JL, Kay HE, Abrams P, de la Rosette JJ, Porru D, Thuroff JW (1997) The International Continence Society "Benign Prostatic Hyperplasia" Study: the bothersomeness of urinary symptoms. J Urol 157:885–889

Pontari MA, Braverman AS, Luthin GR, Ruggieri MR Sr (2004) The M2 muscarinic receptor mediates in vitro bladder contractions from patients with neurogenic bladder dysfunction. Am J Physiol Regul Integr Comp Physiol 286:R874–R880

Robertson AS, Griffiths C, Neal DE (1996) Conventional urodynamics and ambulatory monitoring in the definition and management of bladder outflow obstruction. J Urol 155:506–511

Roehrborn CG, Schwinn DA (2004) Alpha1-adrenergic receptors and their inhibitors in lower urinary tract symptoms and benign prostatic hyperplasia. J Urol 171:1029–1035

Rossi C, Kortmann BB, Sonke GS, Floratos DL, Kiemeney LA, Wijkstra H, de la RJ (2001) Alpha-blockade improves symptoms suggestive of bladder outlet obstruction but fails to relieve it. J Urol 165:38–41

Ruggieri MR Sr, Braverman AS, Pontari MA (2005) Combined use of alpha-adrenergic and muscarinic antagonists for the treatment of voiding dysfunction. J Urol 174:1743–1748

Saito H, Yamada T, Oshima H, Morita T, Mizuo T, Takeuchi S, Ando M, Sekine H (1999) A comparative study of the efficacy and safety of tamsulosin hydrochloride alone and combination of propiverine hydrochloride and tamsulosin hydrochloride in the benign prostatic hypertrophy with pollakisuria and/or urinary incontinence. Jpn J Urol Surg 12:525–536

Schwinn DA, Michelotti GA (2000) alpha1-adrenergic receptors in the lower urinary tract and vascular bed: potential role for the alpha1d subtype in filling symptoms and effects of ageing on vascular expression. BJU Int 85:6–11

Sellers DJ, McKay N (2007) Developments in the pharmacotherapy of the overactive bladder. Curr Opin Urol 17:223–230

Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, Hunt TL, Wein AJ (2003) Prevalence and burden of overactive bladder in the United States. World J Urol 20:327–336

Swierzewski SJ 3rd, Gormley EA, Belville WD, Sweetser PM, Wan J, McGuire EJ (1994) The effect of terazosin on bladder function in the spinal cord injured patient. J Urol 151:951–954

Temml C, Heidler S, Ponholzer A, Madersbacher S (2005) Prevalence of the overactive bladder syndrome by applying the International Continence Society definition. Eur Urol 48:622–627

Trevisani M, Campi B, Gatti R, Andre E, Materazzi S, Nicoletti P, Gazzieri D, Geppetti P (2007) The influence of alpha(1)-adrenoreceptors on neuropeptide release from primary sensory neurons of the lower urinary tract. Eur Urol 52(3):901–908

Witjes WP, de la Rosette JJ, Donovan JL, Peters TJ, Abrams P, Kay HE, Hofner K, Kinn AC, Walter S (1997) The International Continence Society "Benign Prostatic Hyperplasia" Study: international differences in lower urinary tract symptoms and related bother. J Urol 157:1295–1300

Yokoyama O, Yusup A, Miwa Y, Oyama N, Aoki Y, Akino H (2005) Effects of tolterodine on an overactive bladder depend on suppression of C-fiber bladder afferent activity in rats. J Urol 174:2032–2036

Yokoyama O, Yusup A, Oyama N, Aoki Y, Miwa Y, Akino H (2007) Improvement in bladder storage function by tamsulosin depends on suppression of C-fiber urethral afferent activity in rats. J Urol 177:771–775

Yoshida M, Miyamae K, Iwashita H, Otani M, Inadome A (2004) Management of detrusor dysfunction in the elderly: changes in acetylcholine and adenosine triphosphate release during aging. Urology 63:17–23