

Review Article

Prostate Int 2014;2(2):43-49 • <http://dx.doi.org/10.12954/PI.14045>

Current role of treatment in men with lower urinary tract symptoms combined with overactive bladder

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Lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH) are highly prevalent in older men. The storage subcategory of LUTS is synonymous with overactive bladder (OAB) syndrome, which is an empirical diagnosis. Traditionally, alpha-blockers are widely prescribed to manage the LUTS of BPH, although storage symptoms may persist in many men despite treatment. Therefore, because therapies that target the prostate often fail to alleviate storage symptoms, they may not be the appropriate therapy for OAB. In past years, most physicians appeared to give more weight in elderly men to voiding symptoms than to storage symptoms and to be more concerned with initial treatment with anticholinergics for males with storage symptoms. Considering the recent increase in data on the efficacy and safety of combination treatment with alpha receptor antagonists and antimuscarinic agents, the standard pharmacologic treatment of patients with LUTS combined with OAB should be an alpha receptor antagonist and an antimuscarinic agent. Beta-3 adrenoceptor agonists may also potentially be useful for the treatment of male LUTS combined with OAB.

Keywords: Prostatic hyperplasia, Overactive urinary bladder, Pharmacology

INTRODUCTION

Lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH) are highly prevalent in older men. The prevalence and severity of LUTS increase with age [1]. In the EPIC study, a cross-sectional survey of 19,615 adults in 5 countries, 62.5% of men reported having one or more LUTS [2]. The LUTS of BPH that relate to voiding tend to be most prevalent, and the symptoms related to storage are embarrassing and disruptive to daily life and tend to be more bothersome [3].

The storage subcategory of LUTS is synonymous with overactive bladder (OAB) syndrome, which is defined by the International Continence Society as “urgency, with or without urge incontinence, usually with frequency and nocturia”

[4]. International differences in OAB prevalence have been observed. A multinational study in six European countries demonstrated significant variation in prevalence, with Spain reporting the highest (22%) prevalence and France reporting the lowest (12%) prevalence [5]. However, in Asian samples, the prevalence of OAB has been reported to be even higher. An OAB prevalence of about 30% was observed in the Asian male population (range, 14%–84%). Frequency and urgency were the most commonly reported symptoms, whereas 13% of individuals examined reported urge incontinence [6].

Traditionally, alpha-blockers are widely prescribed to manage the LUTS of BPH, although storage symptoms may persist in many men despite treatment [7]. Therefore, because therapies that target the prostate often fail to alleviate storage symptoms, they may not be the appropriate therapy for OAB. Addi-

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Submitted: 10 March 2014 / Accepted after revision: 7 April 2014

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pISSN: 2287-8882 • eISSN: 2287-903X

tionally, in clinical practice, it is difficult to treat patients who have BPH and OAB symptoms with an anticholinergic agent because of the possibility of acute urinary retention (AUR) [8]. The aim of this article was to provide a contemporary review of the current role of anticholinergic therapy in the treatment of male LUTS combined with OAB.

TREATMENT OPTIONS FOR MEN WITH LUTS AND OAB

LUTS in men are often treated first with agents that target the prostate or bladder outlet obstruction (BOO; dynamic obstruction), such as 5-alpha reductase inhibitors (5-ARIs) and alpha receptor antagonists [9]. Men with LUTS/OAB are usually treated with BPH drugs rather than those specific for OAB, despite the high prevalence of coexistent storage symptoms in men with LUTS [10]. Many physicians are still reluctant to prescribe anticholinergics owing to concern about urinary retention, especially in men with BOO. However, several studies have reported that prescribing anticholinergics to men with LUTS or even BOO does not seem to elevate the risk of AUR [11,12].

ALPHA RECEPTOR ANTAGONISTS

Alpha receptor antagonists are considered the first-line treatment for LUTS [13]. Alpha receptor antagonists decrease smooth muscle tone in the prostate and bladder neck [14]. Because LUTS in men have traditionally been attributed to BPH and obstructed urinary flow, pharmacological therapies have been aimed at improving urinary flow rates rapidly and optimizing voiding efficiency [15]. According to the European Association of Urology guidelines, alpha-blockers should be offered to men with moderate to severe LUTS and are considered the first-line drug treatment for these patients [16]. The American Urologic Association Clinical Practice Guidelines Committee determined that alfuzosin, doxazosin, tamsulosin, and terazosin are all appropriate treatment options for patients with LUTS secondary to BPH [13]. Placebo-controlled studies have shown that α 1-blockers typically reduce the International Prostate Symptom Score (IPSS) by approximately 35% to 40%. Furthermore, the maximum urinary flow rate (Qmax) increases by approximately 20% to 25% [17-19].

The main alpha receptor antagonists used for treating LUTS in men with BPH are alfuzosin, doxazosin, terazosin, tamsulosin, silodosin, and the more recent drug, naftopidil. In the male prostate and urethra, the alpha-1A receptor subtype is most prevalent. These drugs are all selective for the

alpha-1 receptor subtype present in prostatic tissue. Silodosin and tamsulosin are the alpha-1A-selective alpha receptor antagonists and naftopidil is the alpha-1D-predominant receptor antagonist.

Direct head-to-head comparisons between alpha receptor antagonists are limited. In a randomized double-blind placebo-controlled study, terazosin significantly increased Qmax ($P < 0.001$) and did not alter postvoided residual volume (PVR) at 24 weeks. In a pooled analysis of three double-blind placebo-controlled trials, there was also significant improvement in total IPSS [20]. Doxazosin produced a significantly greater improvement than placebo in Qmax ($P = 0.0017$), symptom severity ($P < 0.0001$), and bother caused by symptoms ($P < 0.0001$) [21]. Another alpha-1 receptor antagonist, alfuzosin, was reported to significantly improve total IPSS ($P < 0.005$), IPSS storage subscore ($P < 0.001$), IPSS voiding subscore ($P < 0.001$), and Qmax ($P < 0.001$) compared with placebo [22]. In a meta-analysis of the outcome of 14 different tamsulosin studies, compared with placebo, tamsulosin was superior to placebo with an IPSS improvement of 12% (tamsulosin, 0.4 mg) and 16% (tamsulosin, 0.8 mg) [23]. A more recent drug, silodosin, showed efficacy equal to tamsulosin on study endpoints, but only silodosin significantly reduced nocturia versus placebo (change from baseline was -0.9, -0.8, and -0.7 for silodosin, tamsulosin, and placebo, respectively; $P < 0.013$ for silodosin vs. placebo) [24]. Naftopidil, most recently approved in Korea, has distinct characteristics because it has three times greater affinity for the alpha-1D adrenergic receptor subtype than for the alpha-1A subtype [25]. Naftopidil significantly improved the overall IPSS (from 19.2 ± 7.9 to 11.7 ± 5.8 , $P < 0.001$), QoL score (5.0 ± 0.8 to 3.6 ± 1.3 , $P < 0.001$), and storage symptom score (8.6 ± 2.9 to 5.8 ± 3.3 , $P < 0.001$) from baseline [26].

Several studies have reported that alpha adrenergic receptor antagonists can improve the storage symptoms in male BPH patients [27-29]. Tamsulosin [27,28] and silodosin [29] showed significant improvement in IPSS storage scores. Naftopidil also demonstrated a significant response to improve storage symptoms including daytime frequency and nocturia [30,31]. However, until now, the data were insufficient to support a recommendation for alpha-1 monotherapy for male LUTS combined with OAB.

5-ALPHA REDUCTASE INHIBITORS

The enzyme 5-alpha reductase converts testosterone to dihydrotestosterone [32]. There are two isoforms of 5-alpha reductase: type 1 and type 2. Two 5-ARIs are available for clinical

use. Dutasteride has a dual mechanism and inhibits type 1 and type 2 5- α reductase, whereas finasteride inhibits only 5- α reductase type 2. These inhibitors induce apoptosis of prostate epithelial cells, which results in a decrease of prostate size by about 18% to 20% and of prostate-specific antigen levels by about 50% after 6 to 12 months of treatment [33]. Finasteride significantly improves symptom scores ($P < 0.001$ and $P < 0.015$) and Qmax ($P < 0.001$) compared with placebo after 12 months of use [34]. A meta-analysis of these early studies concluded that these improvements were less in patients with a smaller prostate [35]. Dutasteride also showed symptom scores from 6 months onward ($P < 0.001$) with a mean improvement of 4.5 points at 24 months [36]. The Qmax improved significantly from 1 month ($P < 0.01$) with an increase of 2.2 mL/s reported at 24 months ($P < 0.001$). In a head-to-head trial of the two drugs, Qmax, prostate volume, and LUTS variation were similar for both drugs [37]. However, it remains to be elucidated whether 5-ARI monotherapy can improve the storage component of male LUTS, particularly male OAB symptoms.

ANTIMUSCARINIC AGENTS

Antimuscarinic agents are considered the first-line treatment for patients with OAB. These agents act by blocking acetylcholine binding at muscarinic receptors on the detrusor muscle, thereby reducing the ability of the detrusor to contract during the voiding phase [38]. Antimuscarinic agents improve the storage symptom of urgency and increase bladder capacity, whereas their effects decrease during the voiding phase when a massive release of acetylcholine from cholinergic nerves is present [39].

In clinical practice, many physicians are reluctant to prescribe antimuscarinic agents in male patients with LUTS combined with OAB owing to the concern of urinary retention. However, several studies have reported that prescribing antimuscarinic agents to men with LUTS or even BOO does not seem to elevate the risk of AUR [11,40]. The results of several studies support the efficacy and safety of antimuscarinics in treating men with LUTS and OAB [41-44]. For example, Abrams et al. [11] reported the efficacy of tolterodine immediate-release in men with both BOO and OAB. Tolterodine significantly reduced the BOO index (-0.9 vs. 0 , $P < 0.02$) and increased maximal cystometric capacity ($+67$ mL; 95% confidence interval, 35-103; $P < 0.003$) compared with placebo. No significant differences in the incidence of adverse events were seen, whereas the change in PVR was significantly higher among patients treated with tolterodine ($+25$ mL)

than in those given placebo (0 mL, $P < 0.004$). In another study, fesoterodine 4 or 8 mg resulted in significantly greater improvements in micturition frequency, urgency episodes, and urgency urinary incontinence episodes compared with placebo in men with OAB [45].

Although studies in elderly men with LUTS and OAB symptoms were exclusively carried out with tolterodine or fesoterodine, it is likely that similar efficacy and adverse events will also be shown with other antimuscarinic agents. Long-term studies on the efficacy of muscarinic receptor antagonists in men with LUTS are still lacking; therefore, these drugs should be prescribed with caution, and regular re-evaluation of IPSS and PVR urine is advised [13,16].

COMBINATION TREATMENT: ALPHA RECEPTOR ANTAGONISTS + ANTIMUSCARINIC AGENTS

Even after treatment with alpha receptor antagonists and 5-ARIs, many patients with BPH/LUTS suffer from persistent symptoms of OAB. In recent years, a number of studies have reported on the combination treatment of alpha receptor antagonists and antimuscarinic agents [12,41-47]. In a 2006 study by Kaplan et al. [48] named the TIMES study, tolterodine extend release (ER) and tamsulosin combination treatment resulted in significant improvement in urgency episodes, number of micturitions, nocturia, and IPSS. The medication was well tolerated with no significant differences in voiding pattern, PVR, or episodes of AUR. A subanalysis of the TIMES study combination treatment with tamsulosin and tolterodine ER showed significant improvements in IPSS storage symptom scores compared with placebo. A recent phase II study [49], a dose-finding study of solifenacin and tamsulosin in males with LUTS associated with BPH (the SATURN study), was designed to investigate the combination of tamsulosin and solifenacin versus tamsulosin alone and placebo in the treatment of men with LUTS. Combination therapy was associated with significant improvements in micturition frequency and voided volume versus the tamsulosin oral controlled absorption system alone. In addition, significant improvement was found in the IPSS storage subscore in all the combination groups compared with tamsulosin alone. In another recent study [50], the combination of solifenacin 6 mg and the tamsulosin oral controlled absorption system significantly improved storage and voiding symptoms, as well as QoL parameters, over placebo. In the ADAM study [51], combination therapy with alpha receptor antagonists and tolterodine sustained release resulted in significantly

greater improvements versus placebo plus alpha-blocker in 24-hour micturitions, daytime micturitions, 24-hour urgency episodes, daytime urgency episodes, nocturnal urgency episodes, frequency-urgency sum, IPSS storage subscale, OAB-q symptom bother scale, and OAB-q coping domain at week 12.

Lee et al. [43,44] recently reported that initial combined treatment with alpha receptor antagonists plus an antimuscarinic agent showed improvement in not only storage symptoms but also QoL scores without increasing the risk of AUR. In recognition of the growing body of evidence for the use of antimuscarinics for storage symptoms in men, the 6th International Consultation on New Developments in Prostate Cancer and Prostate Disease recommended the use of combination therapy with alpha-blockers for men with BOO mixed with OAB [52]. However, there seems to be a discrepancy between the awareness of urologists and their actual practice patterns in the treatment of men with BOO mixed with OAB owing to fear of AUR [10].

5-ARIS AND ANTIMUSCARINIC AGENTS

Recently, Chung et al. [53] reported that combination therapy with 5-ARIs and antimuscarinic agents is safe and effective in men with LUS/BPH. Tolterodine ER with 0.5 mg dutasteride was given to men with persistent OAB symptoms and LUTS that were unsuccessfully treated with dutasteride alone. All patients were given 4 mg tolterodine ER daily for 12 weeks and maintained on dutasteride. The total IPSS decreased with dutasteride treatment from 19.3 to 14.3 and further decreased with the addition of tolterodine to 7.1 ($P < 0.001$). Storage symptoms decreased from 9.8 to 4.5 after tolterodine ($P < 0.001$). In this study, the combination of tolterodine ER and dutasteride was effective, safe, and well-tolerated in men with large prostates (≥ 30 mL) with persistent OAB symptoms and LUTS/BPH.

BETA-3 ADRENORECEPTOR AGONISTS

The beta-3 adrenoreceptor subtype is the predominant form of beta adrenoceptor in the bladder [54]. Its stimulation is associated with increased bladder capacity without a change in micturition pressure, PVR, or voiding contraction [55,56]. Nit-ti et al. [57] reported that 40 mg mirabegron showed a statistically significant decrease in urgency episodes and micturition frequency without adversely affecting voiding urodynamics. Although these findings showing the urodynamic safety of mirabegron in men with LUTS and BOO are very promising, more randomized controlled trials are needed for positioning

a new therapy for LUTS and OAB.

CONCLUSION

The treatment of BPH/LUTS combined with OAB is slowly but constantly evolving. In past years, most physicians appeared to give more weight in elderly men to voiding symptoms than to storage symptoms, and they are more concerned with initial treatment with anticholinergics for males with storage symptoms. However, antimuscarinic therapy alone or in combination with alpha receptor antagonists improves OAB symptoms in men with or without BOO. The concern regarding antimuscarinic use leading to an increased incidence of urinary retention appears to be unfounded. Therefore, the standard pharmacologic treatment of patients with LUTS combined with OAB should be an alpha receptor antagonist and an antimuscarinic agent. Beta-3 adrenoreceptor agonists may also be potentially useful for the treatment of male LUTS combined with OAB.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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