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

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Abstract
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 syndrome (OAB) which is an empirical diagnosis. Traditionally, alpha-blockers are widely prescribed to manage LUTS of BPH, although storage symptoms may persist in many men despite treatment. Therefore, since therapies that target the prostate often fail to alleviate storage symptoms, they may not be the appropriate therapy for overactive bladder (OAB). In past years, most physicians appear 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. Considering the recent increasing data about the efficacy and safety of combination treatment of alpha receptor antagonists and antimuscarinic agents, the standard pharmacologic treatment of patients with LUTS combined with OAB should be an alpha receptor antagonists and antimuscarinic agent. Beta 3 adreno receptor agonists may potentially also be useful for the treatment of male LUTS combined with OAB.

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 syndrome (OAB), defined by the International Continence Society (ICS) 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, while 13% of individuals examined reported urge incontinence[6].

Traditionally, alpha-blockers are widely prescribed to manage LUTS of BPH, although storage symptoms may persist in many men despite treatment[7]. Therefore, since therapies that target the prostate often fail to alleviate storage symptoms, they may not be the appropriate therapy for overactive bladder (OAB). Additionally, in clinical practice, it is difficult to treat patients who have BPH and OAB symptoms with anticholinergic agent due to the possibility of acute urinary retention (AUR)[8]. The aim of this article is to provide a contemporary review of the current role for anticholinergic therapy in the treatment of male LUTS combined with OAB.
**Treatment options for men with LUTS/OAB**

LUTS in men are often treated first with agents that target the prostate and/or bladder outlet obstruction (dynamic obstruction), such as 5 alpha reductase inhibitors and alpha receptor antagonists[9]. Men with LUTS/OAB are usually treated with BPH drugs rather than those specific for OAB, even though high prevalence of storage symptoms in men with LUTS are coexist [10]. Many physicians are still reluctant to prescribe anticholinergics due to the concern of urinary retention, especially in men with BOO. 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 first-line treatment for LUTS [13]. Alpha receptor antagonists decrease smooth muscle tone in the prostate and bladder neck [14]. As LUTS in men have been traditionally attributed to BPH and obstructed urinary flow, the pharmacological therapies have been aimed at improving urinary flow rates rapidly and optimizing voiding efficiency [15]. According to the European Association of Urology (EAU) guidelines alpha-blockers should be offered to men with moderate-to-severe lower urinary tract symptoms and are considered the first-line drug treatment for these patients [16]. The American Urologic Association (AUA) 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 a1- blockers typically reduce the IPSS by approximately 35-40%. And the maximum urinary flow rate (Qmax) increases by approximately 20-25% [17-19].

The main alpha receptor antagonists used for treating LUTS in men with BPH are alfuzosin, doxazosin, terazocin, tamsulosin, silodosin and more recent drug, naftopidil. In the male prostate and urethra, the alpha 1A receptor subtype is most prevalent. All these drugs 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 post voided 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, afluzosin significantly improved total IPSS (p<0.005), IPSS storage subscore (p<0.001), IPSS voiding subscore (p<0.001), and Qmax (p<0.001) compared to placebo [22]. In the meta-analysis analyzing the outcome of 14 different tamsulosin studies, compared to placebo, tamsulosin was superior to placebo with an IPSS-improvement of 12% (tamsulosin 0.4 mg) and 16% (tamsulosin 0.8 mg) [23]. More recent drug, silodosin had equal efficacy as tamsulosin on endpoints compared to tamsulosin 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 a 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 scores (5.0±0.8 to 3.6±1.3, p<0.001) and storage symptom scores (8.6±2.9 to 5.8± 3.3, p<0.001) from baseline [26].

Several studies reported the 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 would be insufficient to support a recommendation for the alpha 1 mono therapy for the male LUTS combined with OAB.

5 alpha reductase inhibitors

The enzyme 5 alpha reductase converts testosterone to dihydrotestosterone (DHT) [32]. There are two isoforms of 5 alpha reductase type (1 and 2). Two 5 alpha reductase inhibitors (5ARI) are available for clinical use. Dutasteride has a dual mechanism and inhibits type 1 and type 2 5 alpha reductase whereas finasteride inhibits only 5 alpha reductase type 2. These inhibitors induce apoptosis of prostate epithelial cells resulting in a decrease of prostate size by about 18-20% and of PSA levels by about 50% after 6-12 months of duration [33]. Finasteride significantly improved symptom scores (p<0.001 and p<0.015) and Qmax (p<0.001) compared to placebo after 12 months duration of use[34]. A meta analysis of these early study concluded that these improvements were less in patients with smaller prostate [35]. Dutasteride also showed symptom scores from 6 months onward (p<0.001) with a mean improvement in 4.5 points at 24 months[36]. The Qmax improved significantly from 1 months (p<0.01) with an increase of 2.2 mL/sec 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 5ARI mono therapy 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. This 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 while their effects decrease during the voiding phase when a massive release of acetylcholine from cholinergic nerves is present[39].

In a clinical practice many physicians are reluctant to prescribe antimuscarinic agents in male LUTS patients combined with OAB due 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]. Several studies have supported the efficacy and safety of antimuscarinics in treating men with LUTS and OAB [41-44]. Abrams et al. reported the efficacy of tolterodine IR in men with both BOO and OAB [11]. Tolterodine significantly reduced bladder outlet obstruction index (-0.9 vs 0, p<0.02) and increased maximal cystometric capacity (+67 ml, 95% CI 35-103, p<0.003) compared to placebo. No significant differences in the incidence of adverse events were seen while change in PVR was significantly higher among patients treated with tolterodine (+25 ml) than placebo (0 ml, p <0.004). Fesoterodine 4 or 8mg had significantly greater improvements in micturition frequency, urgency episodes, and urgency urinary incontinence episodes versus placebo in men with OAB [45].

Although studies in elderly men with LUTS and overactive bladder symptoms were exclusively carried out with tolterodine or fesoterodine it is likely that similar efficacy and adverse events will also appear with other antimuscarinic agents. Long-term studies on the efficacy of muscarinic receptor antagonists in men with LUTS are still missing, 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 alpha reductase inhibitors, many patients with BPH/LUTS suffer from persistent symptoms of OAB. In recent years, a number of studies have reported the combination treatment of alpha receptor antagonists and antimuscarinic agent [12, 41-47]. In 2006 Kaplan study named TIMES study[48], tolterodine ER (extend release) and tamsulosin combination treatment reported significant improvement in urgency episodes, number of micturitions and nocturia as well as IPSS. The medication was well tolerated with no differences on voiding pattern, PVR or episodes of AUR. A sub-analysis of the TIMES study combination treatment with tamsulosin and tolterodine ER showed significant improvements in IPSS storage symptom scores compared to placebo. In a recent phase II study [49], dose finding solifenacin and tamsulosin in males with LUTS associated with BPH (SATURN) study designed to investigate a combination of tamsulosin and solifenacin versus tamsulosin alone and placebo in the treatment of men with LUTS were reported. Combination therapy was associated with significant improvements in micturition frequency and voided volume versus tamsulosin oral controlled absorption system alone. In addition, a significant improvement was found in the IPSS storage subscore in all the combination groups against tamsulosin alone. In another recent study [50], the combination of solifenacin 6mg and 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 SR had 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 antimuscaritic agents 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 their use as in combination with alpha-blockers for men with BOO mixed with OAB [52]. However, there seems to be a discrepancy between the awareness of urologists and actual practice patterns of treatment of men with BOO mixed with OAB due to fear of AUR [10].

5 alpha reductase inhibitors and antimuscarinic agents

Recently, Chung et al[53]. Reported that combination therapy with 5 alpha reductase inhibitors and antimuscarinic agents is safe and effective in men with LUS/BPH. Tolterodine ER with 0.5mg dutasteride in men with persistent OAB symptoms and LUTS unsuccessfully treated with dutasteride alone. All patients were given 4mg tolterodine ER daily for 12 weeks and maintained dutasteride. Total IPSS had 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 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]. Nitti et al[57]. reported that 40mg mirabegron showed a statistically significant decrease of urgency episodes and micturition frequency without affecting the adverse voiding urodynamics. These findings that show the urodynamic safety of mirabegron in male with LUTS and BOO, are very promising however, more randomized controlled trials are needed for positioning a new therapy for LUTS and OAB.

Conclusions

The treatment of BPH/LUTS combined with OAB is slowly but constantly evolving. In past years, most physicians appear 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 antagonists and antimuscarinic agent. Beta 3 adrenoreceptor agonists may potentially also be useful for the treatment of male LUTS combined with OAB.

Conflict of Interest

None declared.
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