Review Article

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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 adrenoreceptor 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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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 α1-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

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