Systematic review of therapy for men with overactive bladder

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Abstract

Lower urinary tract symptoms (LUTS) can have multiple causes in men. Overactive bladder (OAB) is an empirical diagnosis used as the basis for initial management after assessing symptoms, physical findings, urinalysis and other indicated evaluations. In men, the diagnosis is complicated by the potential of benign prostatic hyperplasia (BPH), which is a histological diagnosis. Although storage symptoms (i.e., those associated with OAB) are the most bothersome group of LUTS in men with BPH, these patients are usually treated with BPH rather than OAB drugs. The standard pharmacologic treatment of patients with bothersome voiding and storage LUTS at low risk of progression should be an α1-AR antagonist. The combination α1-AR antagonist + antimuscarinic agent is an appropriate and valid option for male patients with voiding symptoms and persistent storage symptoms.

Overactive bladder (OAB) is an empirical diagnosis used as the basis for initial management after assessing lower urinary tract symptoms (LUTS), physical findings, urinalysis, and other indicated assessments. In men, due to the high prevalence of benign prostatic hyperplasia and the associated urinary symptoms, the diagnosis of OAB may often be overlooked. As a result, effective treatment for OAB symptoms may not be offered. This brief review discusses the symptom profile of LUTS in men and identifies the place in therapy of antimuscarinic agents for the treatment of OAB symptoms.

Lower urinary tract symptoms in men

Benign prostatic hyperplasia (BPH) is a histological diagnosis. The absence of a unifying definition, whose sensitivity and specificity can be defined, has been a major problem with 'BPH'. This is a fundamental problem that still requires resolution. It is important to realize that LUTS in men may not be caused by the prostate. For most men with LUTS, there is an overlap of both obstructive voiding symptoms and storage symptoms (Fig. 1), the latter of which are characteristic of the overactive bladder syndrome (OAB).[1] Indeed, it is these storage symptoms, not the voiding symptoms usually associated with prostate enlargement — they are the most bothersome group of LUTS in men with BPH.[2]

Antimuscarinics for OAB symptoms in men

Despite the high prevalence of storage symptoms in men with LUTS, men are usually treated with BPH drugs rather than those specific for OAB.[3] One of the primary reasons that relatively few men with OAB symptoms are not treated with antimuscarinic agents is the perception that these drugs may cause acute urinary retention (AUR). However, published placebo-controlled, open-label and active-comparator studies show that anticholinergics are not, in fact, associated with a substantial increase in risk of AUR (Table 1).[4-9]

There is now a wealth of published research examining the impact of combined alpha-blocker and antimuscarinic therapy for men with both bladder outlet obstruction (BOO) and detrusor overactivity. Lee and colleagues assessed the efficacy of combined treatment with doxazosin and tolterodine in 144 men with symptomatic BOO, a subset of whom also had OAB symptoms (n = 68).[10] All patients were treated with doxazosin (4 mg/day) for three months and then reassessed. For those who had no symptomatic improvement, tolterodine (2 mg twice daily) was added for an additional three months.

After three months of treatment with doxazosin, only 35% (24/68) of the subset with OAB had a symptomatic improvement (compared to 79% with improvement in the BOO-alone subset). After adding tolterodine, 32 of the remaining 44 patients (73%) improved. Acute urinary retention developed in two of 60 men (3.3%) treated with the combined therapy. These cases resolved after drug discontinuation and overnight catheter.

Subsequent to this study, three well designed, placebo-controlled studies were conducted evaluating the combination of alpha-blockade and antimuscarinic therapy in

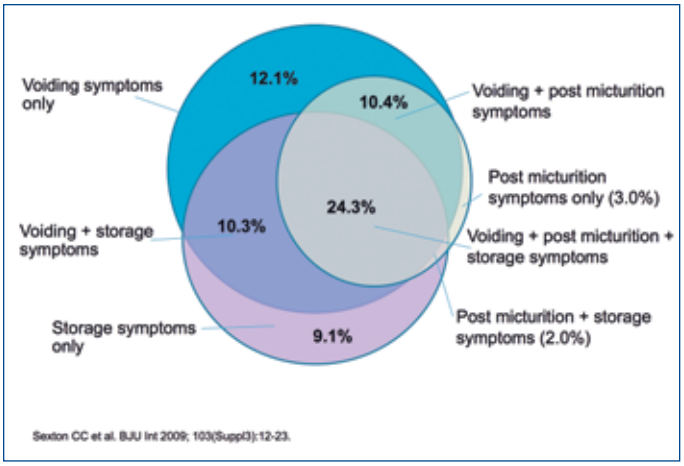

Fig. 1. Most men have **both** voiding and storage symptoms.

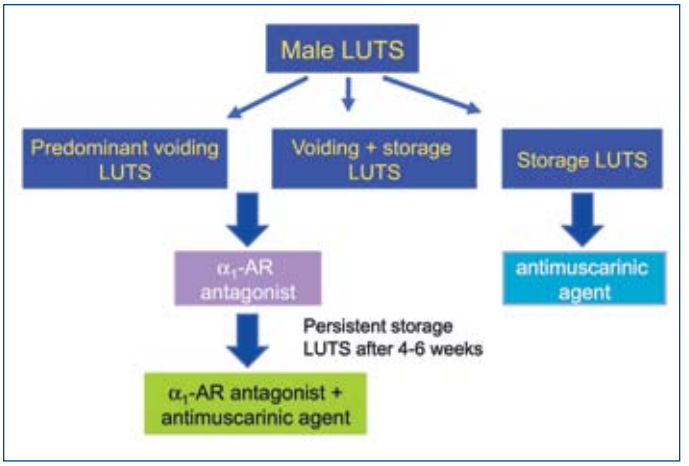

Fig. 2. Simplified treatment algorithm for male lower urinary tract symptoms.

men.[11-13] In the TIMES study, the investigators randomized 879 men with LUTS including OAB symptoms to one of four treatment arms: placebo, tamsulosin, tolterodine SR or tolterodine SR + tamsulosin.[12] For the primary endpoint of patient perception of treatment benefit, 80% of those receiving the combination reported treatment benefit by week 12, compared to 62% in the placebo arm ($p < 0.001$). The combination was also significantly superior to the tamsulosin and tolterodine monotherapy arms (71% and 65%, respectively), which were not significantly different from placebo. The combination was also associated with significant improvements relative to placebo in urgency urinary incontinence, urgency episodes without incontinence, micturitions per 24 hours, micturitions per night, total International Prostate Symptom Score (IPSS) and the IPSS quality-of-life item. In terms of tolerability, dry mouth was the most significant adverse event, occurring in 21% of those in the combination group, compared to 7% in each of the monotherapy groups and 2% in the placebo arm. Acute urinary retention was experienced by 1.8% of the placebo group, 1.9% of the tolterodine monotherapy group, none of the patients in the alpha-blocker monotherapy group and 0.9% of the combination group.

The ADAM study also evaluated alpha-blocker/antimuscarinic combination therapy, but had a different design.[13] This study included 652 men with persistent OAB symptoms who were already on stable α-blocker therapy and randomized them to placebo or tolterodine SR. In this study, there was no significant difference reported in the primary endpoint of Patient Perception of Bladder Condition (PPBC). However, at week 12, subjects receiving the combination therapy 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. The urinary retention rates were the same (1.8%) in both the combination and alpha-blocker monotherapy arms.

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 monotherapy for men with OAB or in combination with alpha-blockers for men with bladder outlet obstruction (BOO) mixed with OAB.[14] However, it must be emphasized that in all of these studies, patients with a post-voiding residual of >200 mL were excluded from the study. For the purposes of the present review, the algorithm proposed by these authors has been simplified and is presented in Figure 2.

Conclusions

It is evident that male LUTS can have multiple causes. The standard pharmacological treatment of patients with bothersome voiding and storage LUTS at low risk of progression is an alpha-blocker. The combination of an alpha-blocker and an antimuscarinic agent is an appropriate and valid option for male patients with voiding symptoms and persistent storage symptoms, providing their post-voiding residual is ≤200 mL.

Competing interests: Dr. Chapple has been a consultant and/or speaker/researcher for Allergan, Astellas, GlaxoSmithKline, Lilly, Pfizer and Recordati.

This paper has been peer-reviewed.

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