Use of anticholinergic therapy in men

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Lower urinary tract symptoms in men usually include symptoms of bladder overactivity such as urinary frequency, urgency or nocturia. These are often the initial presenting symptoms for men seeking medical attention for urinary dysfunction. The prevalence of overactive bladder in men is similar to women and increases with advancing age. While women with these symptoms are treated primarily with anticholinergic therapy, there is reluctance to use these agents in men due to concerns regarding worsening obstructive symptoms or urinary retention exacerbated by a large prostate. For men, alpha blocker monotherapy remains the primary therapy for lower urinary tract symptoms despite the fact that a larger fraction of men continue to experience symptoms of overactive bladder. There is emerging body of evidence that the use of anticholinergic agents may be safe and effective in men. We will discuss the rationale for the use of anticholinergic therapy in men with bladder overactivity, either alone, or in combination with alpha blockers. We will review the current literature on the topic and discuss potential future directions in the management of overactive bladder in men.

Key Words: overactive bladder, anticholinergic, combination therapy, men

Lower urinary tract symptoms (LUTS) are a constellation of both storage and voiding symptoms. The storage symptoms are frequency, urgency, nocturia and urgency incontinence. The voiding symptoms are hesitancy, poor flow, intermittency and straining to void.[1] In practice, the prevalence of obstructive symptoms is much higher, yet the patients are more bothered by their storage symptoms.[2] In this study by Peters et al, questionnaires were provided to 1271 men > 45 years old who presented to urology departments in 12 countries with symptoms of bladder outlet obstruction secondary to benign prostatic hypertrophy (BPH). The instrument contained 22 questions measuring 20 urinary symptoms plus seven condition specific quality of life questions and four questions concerning sexual function. The questionnaire was designed to determine both the prevalence of the symptoms and the degree to which the patient was bothered by the symptom. These men reported a high prevalence of the hallmark symptoms of overactive bladder (OAB), including urgency (75%), frequency (74%), and nocturia (74%), and a lesser prevalence of urge incontinence (48%), at least occasionally. Of those men reporting individual symptoms, those who reported some degree of bother by that symptom included urge incontinence (84%), urgency (80%), frequency (76%), and nocturia (74%). Overall, voiding symptoms were most prevalent, whereas storage symptoms (including those symptoms associated with OAB) were most bothersome. This is evident from the clinical observation that often the initial complaints

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from the patients presenting for evaluation of lower urinary tract function are related to urinary frequency, urgency or nocturia, and less often about decreased flow or hesitancy.

Overactive bladder may be defined as urinary frequency, urgency, nocturia, with or without urgency incontinence. It is equally prevalent in men and women, and in men, it often overlaps with conditions of the prostate. In a study of 5204 participants, Stewart et al noted that the prevalence of OAB symptoms for men was 16.0% and for women was 16.9%. The prevalence increased with age at a similar rate for both sexes.[3] Overactive bladder is a fairly common condition evaluated in the urology office in both men and women. While both men and women can have identical symptoms, women are initially treated with antimuscarinic therapy and men are more likely to be initially treated with alpha blockers alone for the same symptoms. Many men have persistent storage symptoms after treatment for BPH related voiding symptoms. When overactive bladder symptoms are evaluated it is very interesting to note that the prevalence is the same across all age groups in both men and women.[3]

Most men will exhibits symptoms of overactive bladder as well as obstructive symptoms and this is well delineated in the American Urological Association symptom score. Despite the data about similar prevalence, fewer men are treated with anticholinergics than women, a ratio of 80-20.[4] Published data show that many men are often not treated at all for their symptoms. If medical therapy is instituted, it is usually for treatment of obstructive symptoms alone, while a few men are treated for their overactive bladder alone and even fewer are treated with combination therapy. When treatment is focused primarily towards BPH and outlet obstruction, quite frequently the irritative symptoms are not relieved. As many as 65% of men treated for bladder outlet obstruction and lower urinary tract symptoms may not show symptomatic improvement.[5,6] It is instructive to note that even after a transurethral resection of prostate, overactive bladder symptoms may persist or recur in up to one third of the men.

Why is it that we treat men differently then woman when it comes to their bladder symptoms when the symptoms of overactive bladder are the same? This practice pattern likely stems from the fear that use of anticholinergic therapy may lead to worsening of voiding function and may result in urinary retention. Published pharmaceutical reports which will be described later in this review show that anticholinergics do not lead to increased risk of urinary retention.[4,7] We will highlight some of the current published reports with regard to the clinical utility of anticholinergic (or antimuscarinic) therapy in men. A safety study involving 220 men evaluated those who were urodynamically obstructed and determined the impact of utilization of an anticholinergic alone in this population. The study showed that there was no decrease in uroflow rates from baseline to 12 weeks for those receiving anticholinergics compared to those receiving placebo. Urodynamic evaluations from this trial also showed no change in detrusor contractions between the anticholinergic and placebo groups. The postvoid residual urine did show a slight increase in the anticholinergic group but this was not associated with a higher rate of adverse urinary effects.[8]

A trial of long acting tolterodine was performed by Kaplan et al in men who had failed initial alpha blocker therapy for benign prostatic hyperplasia. This was a small study of 43 men with a mean age of 61. All the men had failed alpha blocker therapy for at least 1 month and these men were given anticholinergic monotherapy for 6 months. The parameters studied were symptom score, voiding diaries, and adverse events. Men with a history of surgical or medical intervention for their BPH, and those with a PSA over 10 ng/ml were excluded. The study population had post void residual urine of 100 ml at the start of the study, a symptom score of 17 and uroflow rate in the obstructive range. Anticholinergic therapy resulted in an improvement in the symptom scores and uroflow rate (9.8 to 11.7), and a decrease in the postvoid residual volume (97 cc to 75 cc). The study also found a decrease in urinary frequency (9.8 to 6.3) and nocturia (4.1 to 2.9). Finally, none of these patients experienced urinary retention.[9]

Acute urinary retention has been reported in 2.4% to 2.9% of men receiving placebo in the Medical Therapy of Prostate Symptoms MTOPS and Veterans Administration Cooperative studies, respectively. It appears from open label as well as randomized trials that the use of anticholinergics does not increase the risk of acute urinary retention and appears to be safe in this regard.[8,10-12]

Lee et al studied the use of doxazosin with or without an antimuscarinic agent in men with both symptomatic BPH and overactive bladder. This was a prospective controlled study of 144 men and all had obstruction by urodynamics. The patients were subdivided into obstruction only or obstruction with detrusor over activity groups. Detrusor overactivity was defined as an involuntary detrusor contraction $\geq$ 10 cm H_2O. Symptomatic improvement was defined as > 3 point decrease in IPSS score. Mean age was 68,

symptom score was 25, prostate volume about 35 cc, bladder capacity of 304, uroflow rate in the obstructive range at 10.7 cc/sec, and modest postvoid residual of 42 cc. With alpha blocker therapy alone, only 35% of the patients demonstrated an improvement in the IPSS score. The remaining 65% who did not improve were given a combination of antimuscarinic agent and an alpha blocker. Of these, 73% noted an improvement with the addition of anticholinergic therapy.[13] The study also found that the combination of an anticholinergic agent with an alpha blocker did not increase the incidence of acute urinary retention.[13]

Another randomized study from evaluated the usefulness of combination therapy with alpha blocker with anticholinergic therapy versus alpha blocker alone. All men had urodynamics prior to the start of the study confirming mild to moderate bladder outlet obstruction. These men received 1 week of an alpha blocker and then were randomized to either the addition of an anticholinergic or continued on the alpha blocker alone. They all had urodynamic studies again at 12 weeks. Results from the combination group showed a slight decrease in detrusor contractions, an increase in flow rate, and no increase in residual volume.[14] This small study confirms the findings of previous studies that adding an anticholinergic agent in urodynamically proven obstruction is very safe and effective in relieving symptoms of obstruction and overactive bladder.

In 2006, the first large randomized, double blind, placebo controlled trial was reported which evaluated the effects of an anticholinergic (tolterodine) in addition to an alpha blocker (tamsulosin) in male patients with symptoms of overactive bladder and benign prostatic hypertrophy. The study included 800 men, but in this study, urodynamics were not performed. The inclusion criteria required that the patients be bothered by their symptoms, and have an IPSS $\geq$ 12, IPSS QOL $\geq$ 3, urinary frequency ($\geq$ 8 episodes/24 hrs), and urinary urgency ($\geq$ 3 episodes/24 hrs). Patients were treated with placebo, alpha blocker alone, anticholinergic alone, or combination anticholinergic and alpha blocker. A validated patient reported outcomes measure was used as the primary endpoint to evaluate patient perception of treatment benefit at the end of the 12 weeks. Results showed that most patients in the trial perceived a benefit from treatment. At 12 weeks, the combination therapy group had the best improvement with regard to frequency and urgency. Those patients with urge incontinence benefited with either monotherapy with the anticholinergic or combination therapy. Improvements in symptoms score were seen with alpha blocker alone or combination therapy. Either drug therapy was beneficial for urge incontinence. Improvements in IPSS score were seen with either alpha blocker or combination. To summarize, there was a significant improvement in the combination arm as a whole and combination was better than either monotherapy alone. For patient perceived outcomes, combination therapy was the best. Finally, there was no significant increase in postvoid residual or significant decrease in uroflow rate, or any increased risk of urinary retention with the use of anticholinergic therapy.[15]

At present, there are several anticholinergic agents in the market. Kaplan et al presented a study at the annual meeting of the American Urological Association in 2008 comparing three commonly used agents including solifenacin, darifenacin and tolterodine. All of the men in this study were on alpha blockers and had persistent frequency and/or urgency. Men were randomized to one of these three anticholinergics, in addition to the alpha blocker, and various outcome measures were analyzed. The results showed that darifenacin was not as effective as tolterodine or solifenacin with regard to urgency, IPSS storage symptoms and postvoid residual. Furthermore, nearly half the men receiving darifenacin experienced urinary retention in this trial. This study, albeit small, points out the possibility that not all anticholinergic agents are equivalent in treating men with LUTS and caution must be exercised before selecting any anticholinergic for a use in men.

At present, there are a few ongoing clinical trials to further elucidate the safety and efficacy of anticholinergics in men with LUTS. One of the limiting factors in the clinical use of anticholinergic drugs are the significant side effects. Using the active metabolite of the drug is thought to produce similar efficacy at a lower dose and with fewer side effects. There are studies examining the effects of 5HMP, which is the active metabolite of tolterodine. There are beta receptors present in the detrusor muscle of men with obstructive and irritative symptoms. Beta blockers have been shown to cause relaxation of the detrusor muscle, with minimal to no systemic side effects. Tachycardia is usually not noted, and since its mechanism of action is different than the anticholinergics, dry mouth is also not very common.[16-18] There is an ongoing trial of YM-178, a beta agonist, in men with LUTS.[18] These are just a few of the interesting directions that the treatment for overactive bladder may take in the future.

In conclusion, using anticholinergic agents in men with bladder overactivity is effective, safe and without any undue risk of incomplete emptying or urinary retention. These agents may be used as monotherapy

in men with mostly irritative and minimal obstructive symptoms. These agents also provide improved efficacy when used in combination with alpha blockers for men with persistently overactive bladder following monotherpay with an alpha blocker. The anticholinergic agents can be used safely in men without severe obstructive symptoms such as significantly diminished uroflow or very high postvoid residual volumes. In addition to the newer agents with improved efficacy and side effect profile, the role of various currently available anticholinergics in men with overactive bladder warrants further study.

Disclosure

None declared. □

References

1. Abrams P et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002.;21(2):167-178.
2. Peters TJ et al. The International Continence Society "Benign Prostatic Hyperplasia" Study: the botherosomeness of urinary symptoms. J Urol 1997;157(3):885-889.
3. Irwin DE et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *Eur Urol* 2006;50(6):1306-1314;discussion 1314-1315.
4. Stewart WF et al. Prevalence and burden of overactive bladder in the United States. *World J Urol* 2003;20(6):327-336.
5. Dmochowski RR, Staskin D. Overactive bladder in men: special considerations for evaluation and management. *Urology* 2002;60(5 Suppl 1):56-62;discussion 62-63.
6. Thomas AW et al. The natural history of lower urinary tract dysfunction in men: minimum 10-year urodynamic followup of transurethral resection of prostate for bladder outlet obstruction. *J Urol* 2005;174(5):1887-1891.
7. Machino R et al. Detrusor instability with equivocal obstruction: A predictor of unfavorable symptomatic outcomes after transurethral prostatectomy. *Neurourol Urodyn* 2002;21(5):444-449.
8. Abrams PKS, Millard R. Tolterodine treatment is safe in men with bladder outlet obstruction (BOO) and symptomatic detrusor overactivity (DO). *Neurourol Urodyn* 2001;(20):547-548.
9. Kaplan SA, Walmsley K, Te AE. Tolterodine extended release attenuates lower urinary tract symptoms in men with benign prostatic hyperplasia. *J Urol* 2005;174(6):2273-2275;discussion 2275-2276.
10. McConnell JD, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003;349(25):2387-2398.
11. Wasson JH et al. A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. The Veterans Affairs Cooperative Study Group on Transurethral Resection of the Prostate. *N Engl J Med* 1995;332(2):75-79.
12. Gonzalez RR, Te AE. Overactive bladder and men: indications for anticholinergics. *Curr Urol Rep* 2003;4(6):429-435.
13. Lee JY et al. Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and an overactive bladder. *BJU Int* 2004;94(6):817-820.
14. Athanasopoulos A et al. Combination treatment with an alpha-blocker plus an anticholinergic for bladder outlet obstruction: a prospective, randomized, controlled study. *J Urol* 2003;169(6):2253-2256.
15. Kaplan SA et al. Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. *JAMA* 2006;296(19):2319-2328.
16. Chapple CR et al. Comparison of fesoterodine and tolterodine in patients with overactive bladder. *BJU Int* 2008.
17. Nitti VW et al. Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome. *J Urol* 2007;178(6):2488-2494.
18. Takasu T et al. Effect of (R)-2-(2-aminothiazol-4-yl)-4'-{2-[(2-hydroxy-2-phenylethyl)amino]ethyl} acetanilide (YM178), a novel selective beta3-adrenoceptor agonist, on bladder function. *J Pharmacol Exp Ther* 2007;321(2):642-647.