Safety and Tolerability of Tolterodine for the Treatment of Overactive Bladder in Men With Bladder Outlet Obstruction

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Purpose: Antimuscarinic therapy for men with OAB and BOO is perceived as a potential risk for urinary retention. Using pressure flow urodynamics, we evaluated the safety of tolterodine vs placebo in men with OAB and BOO.

Materials and Methods: Men (older than 40 years) with BOO and confirmed detrusor overactivity were randomized to tolterodine (2 mg twice daily in 149) or placebo (in 72) for 12 weeks. Primary end points were Qmax and pdetQmax.

Results: Median treatment differences in Qmax (−0.7 ml per second, 95% CI −1.6 to 0.4) and pdetQmax (−7 cm H_2O, 95% CI −3 to 11) were comparable. Tolterodine significantly reduced the BOOI vs placebo (−9 vs 0, $p < 0.02$). There were significant treatment differences in volume to first detrusor contraction (+59 ml, 95% CI 19–100) and maximum cystometric capacity (+67 ml, 95% CI 35–103), favoring tolterodine over placebo ($p < 0.003$). Change in PVR was significantly greater among patients treated with tolterodine (+25 ml) than placebo (0 ml, $p < 0.004$). There were no significant between-group differences in the incidence of adverse events. Urinary retention was reported by 1 patient treated with placebo.

Conclusions: Tolterodine did not adversely affect urinary function in men with OAB and BOO. Urinary flow rate was unaltered, and there was no evidence of clinically meaningful changes in voiding pressure and PVR or urinary retention. Tolterodine was well tolerated. These results suggest that antimuscarinics can be safely administered in men with BOO.

Key Words: safety, tolterodine, urodynamics

As men age there is an increasing prevalence of LUTS, including those that characterize OAB and those attributed to DO.[1–3] LUTS and DO in men are associated with BOO resulting from BPE.[1] These conditions are typically diagnosed using urine flow and pressure flow studies.[1,4] DO and associated OAB symptoms often resolve after prostatic surgery, which has led to an assumed direct association between DO and BPE/BOO that has been disputed.[5] Interestingly long-term studies have shown that DO returns to its expected age prevalence after 10 to 20 years in the absence of recurrent BOO.[6]

Overactive bladder symptoms may be exacerbated by BOO that results from BPE. The supposed mechanisms by which BOO leads to DO include ischemia induced denervation and BOO induced physiological changes in the bladder wall or changes in neuronal mechanisms that control bladder contraction.[7] However, because muscle and nerve are functionally cooperative, it is likely that myogenic and neurogenic mechanisms are operative in BOO associated DO.

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The most bothersome symptoms of BOO are those associated with storage symptoms typical of DO (ie the OAB symptoms of frequency, urgency and urgency incontinence), although voiding symptoms such as slow stream hesitancy and intermittency are more prevalent.[8–10] Thus, treating these bothersome symptoms is an important goal for the management of comorbid symptomatic DO and BOO.

Drug treatment is frequently used as the initial management approach for LUTS in older men. Traditionally α-adrenergic receptor blockers have been used, although 5α-reductase inhibitors are often administered concomitantly when there is significant BPE (greater than 40 cc). Both classes of drug reduce bladder outlet resistance by different mechanisms. Neither class has any known action that directly reduces DO. Thus, the most bothersome symptoms among older men—whether or not they have BOO—are not usually targeted.

In the primary care setting, men who are treated for LUTS are not usually evaluated with urodynamics to determine the presence of prostatic obstruction. Primary care physicians do not routinely assess prostate size beyond small, medium or large. Therefore, treatment in this setting is for LUTS that are assumed to be secondary to BOO. The validity of this assumption will vary according to age and is more reliable among older men because the prevalence of BOO increases with age. Kaplan et al have shown that most symptomatic men younger than 50 years do not have BOO and, therefore, their symptoms are likely attributable to another cause.[11] Prevalence studies suggest that OAB may

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TABLE 1. *Summary of reasons for withdrawal*

	No. (%)		
	No. Placebo (%)	No. Tolterodine (%)	Total (%)
Adverse event	5 (7)	9 (6)	14 (6)
Consent withdrawn	3 (4)	5 (3)	8 (4)
Protocol violation	3 (4)	3 (2)	6 (3)
Lost to followup	1 (1)	0 (0)	1 (0.5)
Totals	12 (17)	17 (11)	29 (13)

account for the LUTS observed in men without prostatic obstruction. Of European men 50 to 59 years old 10% to 13%, and of American men 45 to 54 years old 18% have been reported to have OAB symptoms of urgency, urgency incontinence and frequency.[2,3]

The American Urological Association has recommended treating LUTS according to the level of symptoms as defined by the International Prostatic Symptom Score. The American Urological Association recommends that no treatment is needed if symptoms are mild (0 to 7 points).[12] Although symptoms are important, the patient's view of the impact of symptoms on quality of life matters most. Most men are unlikely to take regular medication if their symptoms are not bothersome.

Among men who desire treatment, general practice prescribing data have shown that antimuscarinics are not often given to elderly men. There is theoretical concern that the inhibitory effect of antimuscarinics on detrusor contraction could aggravate voiding difficulties or cause urinary retention in patients with BOO. To date, this outcome has not been documented in the clinical setting or evaluated in well controlled trials examining the safety of antimuscarinic drugs in older men with BOO. In this study, we evaluated the effects of tolterodine vs placebo using pressure flow urodynamics in men with DO and BOO. The primary objective was to demonstrate equivalence in urinary flow/detrusor function between tolterodine and placebo after 12 weeks of treatment. Results of this study have been previously published in abstract form.[13]

MATERIALS AND METHODS

Patient population and study design. Eligible men (age 40 years or older) were required to have urinary frequency (8 or more micturitions per 24 hours) and urgency, with or without urgency incontinence (1 or more episodes per 24 hours). Men were also required to have urodynamically confirmed DO (involuntary detrusor contraction of 10 or more cm H_2O) and volume to first contraction less than 350 ml, and to be diagnosed with mild, moderate or severe urinary obstruction (BOOI, formerly the Abrams Griffith number, 20 or greater).[14] Key exclusion criteria included previous surgical or outpatient procedures for BOO, PVR greater than 40% of maximum cystometric capacity, urinary retention in the preceding 12 months, indwelling catheter/self-catheterization, bladder training within 10 days preceding randomization, acute urinary tract infection, treatment with 5α-reductase inhibitors or hormones within 6 months of randomization, or treatment with any investigational drug preceding randomization. After screening, patients entered a 7 to 18-day washout/run-in period followed by a 3-day run-in. At visit 2, eligible men were randomized using a computerized list to double-blind treatment with tolterodine (2 mg twice daily) or placebo (2:1 ratio) for 12 weeks.

Urodynamics. A complete urodynamic evaluation including determination of maximum cystometric capacity, voided volume, Qmax and pdetQmax was performed at baseline and at week 12. The final urodynamic investigation was performed within 2 to 6 hours after the last morning dose of medication. PVR was measured via urethral catheter and values were based on a central reading after pressure flow study. At visit 2, men with a PVR greater than 40% of the maximum cystometric capacity could be retested, and the average of the 2 values was used to assess eligibility. Men who experienced symptoms of significant incomplete bladder emptying or urinary retention between visits 2 and 4 were assessed according to the routine used at the investigation center. The BOOI was used to measure the degree of ob-

TABLE 2. *Patient demographics and disease characteristics*

	Placebo	Tolterodine	p Value
No. ethnicity (%):			
White	69 (96)	145 (97)	0.163
Black	2 (3)	1 (0.7)	
Asian or Pacific	0 (0)	3 (2)	
Mixed	1 (1)	0 (0)	
Mean pt age (SD)*	65 (9)	63 (9)	0.275
Mean kg/m^2 body mass index (SD)	28 (4.2)	28 (5)	0.746
No. previous medical therapy for urinary symptoms (%):	36 (50)	57 (38)	0.097
Good response	8 (22)	15 (26)	0.622
Unacceptable side effects	11 (31)	8 (14)	0.060
No. severity of obstruction (%):†			
Unobstructed	7 (10)	8 (5)	0.491
Equivocal	23 (32)	49 (33)	
Moderate	25 (35)	62 (42)	
Severe	14 (19)	23 (15)	
Missing	3 (4)	7 (5)	
No. micturition chart variables (%):			
8 or More micturitions/24 hrs	72 (100)	146 (98)	0.553
1 or More incontinence episodes/24 hrs	27 (38)	46 (31)	0.326
200 Ml or less voided/micturition	59 (82)	108 (73)	0.125

* Age is years between date at visit 2 and date of birth.
† Based on the assessment of the central reviewer.