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Tolterodine Treatment Improves Storage Symptoms Suggestive of Overactive Bladder in Men Treated With α-Blockers

Christopher Chapple [a,*], *Sender Herschorn* [b], *Paul Abrams* [c], *Franklin Sun* [d], *Marina Brodsky* [d], *Zhonghong Guan* [d]

[a] *Sheffield Teaching Hospitals, Sheffield, UK*
[b] *Sunnybrook Health Science Center, Toronto, ON, Canada*
[c] *Bristol Urological Institute, Southmead Hospital, Bristol, UK*
[d] *Pfizer Inc, New York, NY, USA*

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Abstract

Background: Some men receiving α-blocker therapy for lower urinary tract symptoms report persistent storage symptoms suggestive of overactive bladder (OAB).
Objective: To evaluate the efficacy of tolterodine extended release (ER) in men on α-blocker therapy.
Design, setting, and participants: This double-blind trial included men aged ≥40 yr with frequency, urgency, and at least moderate problems reported on the Patient Perception of Bladder Condition (PPBC), despite being on a stable dose of α-blocker for ≥1 mo.
Interventions: Subjects were randomized to tolterodine ER 4 mg per day or placebo for 12 wk while continuing their prescribed α-blocker therapy.
Measurements: At baseline and week 12, subjects completed the PPBC, International Prostate Symptom Score (IPSS), Overactive Bladder Questionnaire (OAB-q), and 5-d bladder diaries using the five-point Urinary Sensation Scale (USS). Frequency–urgency sum was defined as the sum of USS ratings for all micturitions.
Results and limitations: PPBC improvement from baseline to week 12 was reported by 63.6% and 61.6% of subjects receiving tolterodine ER plus α-blocker and placebo plus α-blocker, respectively; this treatment difference, which was the primary end point, was not statistically significant ($p > 0.6699$). At week 12, subjects receiving tolterodine ER plus α-blocker had significantly greater improvements versus placebo plus α-blocker in 24-h micturitions (−1.8 vs −1.2; $p = 0.0079$) and daytime micturitions (−1.3 vs −0.8; $p = 0.0123$); 24-h urgency episodes (−2.9 vs −1.8; $p = 0.0010$), daytime urgency episodes (−2.2 vs −1.4; $p = 0.0017$), and nocturnal urgency episodes (−0.5 vs −0.3; $p = 0.0378$); frequency–urgency sum (−7.8 vs −5.1; $p = 0.0065$); IPSS storage subscale (−2.6 vs −2.1; $p = 0.0370$); and OAB-q symptom bother scale (−17.9 vs −14.4; $p = 0.0086$) and coping domain (15.4 vs 12.4; $p = 0.0491$). Acute urinary retention requiring catheterization occurred in <1% of either group. There were no clinically meaningful changes in postvoid residual volume or maximum urinary flow rate.
Conclusions: Men with bothersome OAB symptoms despite continued α-blocker therapy showed significantly greater improvements in diary variables, IPSS Storage scores, and symptom bother when receiving additional tolterodine ER versus placebo plus α-blocker.

* Corresponding author. Sheffield Teaching Hospitals, Glossop Road, Sheffield S10 2 JF, UK.
Tel. +44 114 271 2559; Fax: +44 114 279 7841.
E-mail address: c.r.chapple@shef.ac.uk (C. Chapple).

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1. Introduction

Overactive bladder (OAB) is defined as urgency, with or without urgency urinary incontinence (UUI), usually with increased daytime frequency and nocturia [1,2]. Prevalence rates range between 12% and 17% in North America and Europe [3–5] and are comparable among men and women [3–5]. OAB syndrome is a chronic condition that impairs health-related quality of life (HRQL) [6].

Lower urinary tract symptoms (LUTS) in men may be associated with prostatic obstruction, typically resulting from benign prostatic hyperplasia (BPH), if it causes benign prostatic enlargement [7]. Urodynamic studies report that only 48%–68% of men with LUTS have bladder outlet obstruction (BOO) [8,9]. However, most treated men are presumed to have benign prostatic obstruction (BPO), and bothersome LUTS in men are usually treated first with pharmacologic agents that target the prostate and/or bladder outlet (eg, α-blockers, 5α-reductase inhibitors) [7].

The prevalence of storage symptoms that define OAB increase with age in men [5]. These symptoms usually coexist with detrusor overactivity (DO), in contrast to voiding symptoms, for which there is a much poorer correlation with BOO [2]. It is debated whether DO resulting in OAB symptoms may develop secondary to BOO in men [10]. However, DO and/or storage symptoms often occur independently of BOO and persist in many men despite pharmacologic or surgical treatment of BOO [11,12]. Antimuscarinics are the first-line pharmacotherapy for OAB symptoms [13] and effectively and safely treat OAB symptoms in men [14–17]. Significant improvements in OAB symptoms and other LUTS have been demonstrated in men with symptoms consistent with BPO and DO when treated with tolterodine extended release (ER) plus the α-blocker tamsulosin versus placebo (subjects had not received α-blocker treatment within 2 wk or antimuscarinic treatment within 1 mo of randomization) [18].

The objective of this study was to evaluate the additional efficacy and safety of tolterodine ER (4 mg daily) versus placebo in men with bothersome OAB symptoms of frequency and urgency despite adequate (stable dose for ≥1 mo) and continued α-blocker therapy for their LUTS.

2. Methods

This was a double-blind, randomized, multinational trial conducted at 75 centers across North America, Asia, Europe, and South Africa between March 2006 and May 2007. The study was conducted in accordance with International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was approved by the appropriate Institutional Review Boards and/or Independent Ethics Committees. All subjects provided written informed consent. The data from this study have been posted online at www.clinicalstudyresults.org (Unique ID NCT00282932) in compliance with governmental regulations.

2.1. Subject selection

Eligible subjects were men aged ≥40 yr with OAB symptoms (mean urinary frequency ≥8 times per 24 h including ≥1 micturition-related urgency episode per 24 h with or without UUI in 5-d bladder diaries at baseline) who had been on a stable dose of an α-blocker for ≥1 mo as a treatment for LUTS. Eligible subjects also reported at least "some moderate" bladder-related problems on the Patient Perception of Bladder Condition (PPBC) [19,20]. Men were excluded for the following reasons: postvoid residual volume (PVR) ≥200 ml, a history of acute urinary retention (AUR) requiring catheterization, poor detrusor function or presumed clinically significant BOO as judged by the investigator based on flow rate and residual volume measurements at screening as well as other clinical information or medical history available to the investigator at screening (such as voiding symptoms or prostate size), prostatic surgery, history of prostate cancer or prostate-specific antigen (PSA) level >10 ng/ml, urinary tract infection (UTI), recurrent UTI (>3 episodes in the past year), neurologic disease or injury, or treatment with an anticholinergic ≤30 d before screening.

2.2. Study design

Eligible subjects were randomized to receive tolterodine ER 4 mg per day or placebo within 4 h of going to bed for 12 wk and were instructed to continue their prescribed α-blocker medication for the duration of the study. Study drug and placebo capsules were similar in size, color, smell, and appearance and were labeled with sequentially assigned computer-generated randomization numbers that were recorded by blinded investigators when allocated to subjects. Allocation to groups was concealed, and randomization codes were not released until after the study was completed.

2.3. Clinical assessments

Subjects rated their bladder-related problems at baseline and week 12 using the self-administered, six-point, single-item, validated PPBC (1 = no problems at all, 2 = some very minor problems, 3 = some minor problems, 4 = some moderate problems, 5 = severe problems, 6 = many severe problems) [20]. The percentage of subjects reporting improvement from baseline on the PPBC (≥1 point) at week 12 was the primary end point.

OAB symptoms were evaluated at baseline and at week 12 using 5-d bladder diaries. Subjects rated the urgency sensation associated with each micturition using the five-point Urinary Sensation Scale (USS; 1 = no urgency, 2 = mild urgency, 3 = moderate urgency, 4 = severe urgency, 5 = UUI), which has demonstrated construct validity in subjects with OAB [19]. Micturition-related urgency episodes were defined as those with a USS rating ≥3. Frequency–urgency sum was defined as the sum of USS ratings for all recorded micturitions.

Subjects completed the International Prostate Symptom Score (IPSS) at baseline and week 12. IPSS total index, storage subscale, voiding subscale, and quality of life (QoL) items were assessed.

At baseline and week 12 subjects also completed the validated Overactive Bladder Questionnaire (OAB-q), which consists of an 8-item symptom bother scale and a 25-item HRQL scale with four domains (coping, concern, sleep, and social interaction) [21]. All scale and domain scores were transformed to range from 1 to 100. Higher scores on the symptom bother scale represented greater symptom bother; higher scores on the HRQL scale and domains represented better HRQL.

Adverse events (AEs) were classified by the investigator according to severity and relationship to the study treatment. PVR was assessed by ultrasound, and the maximum urinary flow rate (Q_{max}) was assessed by uroflowmetry at baseline and week 12.

2.4. Statistical analysis

The percentage of subjects reporting improvement in PPBC scores at week 12 was evaluated using Cochran-Mantel-Haenszel test