



## Benign Prostatic Enlargement

# Tolterodine Extended Release With or Without Tamsulosin in Men With Lower Urinary Tract Symptoms Including Overactive Bladder Symptoms: Effects of Prostate Size

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### Abstract

**Background:** Some men with lower urinary tract symptoms (LUTS) including overactive bladder (OAB) symptoms may benefit from antimuscarinic therapy, with or without an  $\alpha$ -adrenergic antagonist.

**Objectives:** To evaluate the safety and efficacy of tolterodine extended release (ER), tamsulosin, or tolterodine ER+tamsulosin in men meeting symptom entry criteria for OAB and prostatic enlargement trials, stratified by prostate size.

**Design, setting, and participants:** Subjects with an International Prostate Symptom Score (IPSS)  $\geq 12$ ; frequency and urgency, with or without urgency urinary incontinence; postvoid residual volume (PVR)  $< 200$  mL; and maximum urinary flow rate ( $Q_{max}$ )  $> 5$  mL/s were randomized to receive placebo, tolterodine ER (4 mg), tamsulosin (0.4 mg), or tolterodine ER+tamsulosin for 12 wk. Data were stratified by median baseline prostate volume ( $< 29$  mL vs  $\geq 29$  mL).

**Measurements:** Endpoints included week 12 changes in bladder diary variables, IPSS scores, and safety variables.

**Results and limitations:** Among men with larger prostates, tolterodine ER+tamsulosin significantly improved frequency ( $p = 0.001$ ); urgency ( $p = 0.006$ ); and IPSS total ( $p = 0.001$ ), storage ( $p < 0.001$ ), and voiding scores ( $p < 0.013$ ). Tamsulosin significantly improved IPSS voiding scores ( $p = 0.030$ ). Among men with smaller prostates, tolterodine ER significantly improved frequency ( $p = 0.016$ ), UUI episodes ( $p = 0.036$ ), and IPSS storage scores ( $p = 0.005$ ). Tolterodine ER+tamsulosin significantly improved frequency ( $p = 0.001$ ) and IPSS storage scores ( $p = 0.018$ ). Tamsulosin significantly improved nocturnal frequency ( $p = 0.038$ ) and IPSS voiding ( $p = 0.036$ ) and total scores ( $p = 0.044$ ). There were no clinically or statistically significant changes in  $Q_{max}$  or PVR; incidence of acute urinary retention (AUR) was low in all groups ( $\leq 2\%$ ).

**Conclusions:** Men with smaller prostates and moderate-to-severe LUTS including OAB symptoms benefited from tolterodine ER. Therapy with tolterodine ER+tamsulosin was effective regardless of prostate size. Tolterodine ER, with or without tamsulosin, was well tolerated and not associated with increased incidence of AUR.

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## 1. Introduction

Benign prostatic hyperplasia (BPH) often produces benign prostatic enlargement, which may result in bladder outlet obstruction (BOO) [1]. Lower urinary tract symptoms (LUTS) in men are often attributed to prostatic enlargement and BOO [2]. BPH and LUTS increase dramatically in prevalence among men >40 years old [3–5].

Overactive bladder (OAB) is a syndrome of storage LUTS defined by the International Continence Society (ICS) as urgency, with or without urge urinary incontinence, usually with frequency and nocturia [1]. OAB symptoms are as prevalent as BPH, increasing in prevalence among men >40 years old [5]. OAB symptoms are often caused by detrusor overactivity (DO) [1], which may be secondary to BOO [6]. However, DO and OAB symptoms often occur independently of BOO; DO persists in many men after pharmacologic or surgical treatment of BOO [7], and urodynamic studies report that only 48% to 68% of men with LUTS have BOO [8,9]. Thus, LUTS in men may result from prostatic enlargement or other conditions leading to OAB.

LUTS in men are often treated first with agents that target the prostate and/or bladder outlet, such as  $\alpha$ -adrenergic antagonists and  $5\alpha$ -reductase inhibitors [2]. These agents may have limited efficacy in relieving OAB symptoms that may arise from bladder dysfunction, especially if they are not secondary to BOO [2]. Antimuscarinics, such as tolterodine extended release (ER), are first-line pharmacotherapy for OAB [10] and are effective in men [11–14]. However, antimuscarinics are not widely prescribed for men, because clinicians often associate male LUTS with prostatic pathology rather than with bladder dysfunction and/or fear that acute urinary retention (AUR) may occur [2,6]. Several studies have shown that concerns about increased incidence of AUR may be unwarranted [11–16].

Recently, the TIMES (Tolterodine and Tamsulosin In Men with LUTS Including OAB: Evaluation of Efficacy and Safety) study demonstrated that men with symptoms suggestive of both BPH and OAB showed significant improvements in LUTS with tolterodine ER+tamsulosin, an  $\alpha$ -adrenergic antagonist, compared with placebo or tolterodine ER or tamsulosin alone [16]. However, tolterodine ER did not show significant treatment effects over placebo [16], possibly because this study included subjects with both prostate and bladder conditions. Prostate size may be a predictor of responsiveness to therapy and clinical outcomes in men with LUTS [17]. Thus, we conducted a post hoc analysis of data from the TIMES study [16], stratified by prostate size, to assess

efficacy and safety of tolterodine ER, tamsulosin, or tolterodine ER+tamsulosin in men with LUTS including OAB.

## 2. Materials and methods

### 2.1. Subjects and study design

A description of the study design has been published [16]. This trial was conducted at 95 urology clinics in the United States. Eligible men were aged  $\geq 40$  years with a total International Prostate Symptom Score (IPSS)  $\geq 12$ , bladder diary-documented frequency ( $\geq 8$  micturitions per 24 h) and urgency ( $\geq 3$  episodes per 24 h) with or without urgency urinary incontinence (UUI), and at least “some moderate problems” related to their bladder condition reported on the Patient Perception of Bladder Condition [18] at baseline. Subjects with significant BOO (postvoid residual volume [PVR]  $> 200$  mL or maximum urinary flow rate [ $Q_{max}$ ]  $< 5$  mL/s) were excluded. Subjects were randomized to receive double-blind treatment with placebo, tolterodine ER (4 mg), tamsulosin (0.4 mg), or tolterodine ER+tamsulosin for 12 wk. Prostate volume was measured at baseline by transrectal ultrasound. Subjects were stratified by median baseline prostate volume ( $< 29$  mL vs  $\geq 29$  mL).

### 2.2. Assessments

Subjects completed five-day bladder diaries and the IPSS at baseline and week 12. Subjects rated the urgency level of every micturition using the five-point Urinary Sensation Scale (USS; 1 = no urgency, 2 = mild urgency, 3 = moderate urgency, 4 = severe urgency, 5 = UUI) with established content validity [19]. Micturition-related urgency episodes were defined as those with a rating  $\geq 3$  on the USS. Frequency-urgency sum was defined as the sum of USS ratings for all voids [20].

$Q_{max}$  and PVR were assessed at baseline and week 12 using a flowmeter and ultrasound, respectively.

### 2.3. Statistical analysis

All efficacy analyses were conducted using the intent-to-treat (ITT) population, defined as patients who received  $\geq 1$  dose of assigned treatment and had  $\geq 1$  postbaseline assessment. Mean changes from baseline to week 12 in diary variables and the IPSS total, storage, and voiding scores were compared using analysis of covariance (ANCOVA) with terms for center, treatment, smoking status, age, duration of OAB, and baseline score.

Mean changes from baseline to week 12 in  $Q_{max}$  and PVR were compared using ANCOVA with terms for center, treatment, and baseline value for the safety population, which included all subjects who received  $\geq 1$  dose of study medication.

## 3. Results

A total of 879 men were randomized; 851 were included in the ITT population. Baseline demo-

**Table 1 – Baseline demographic and clinical characteristics**

|                                 | Prostate size $\geq 29$ mL |                    |                  |                           | Prostate size $< 29$ mL |                     |                  |                           |
|---------------------------------|----------------------------|--------------------|------------------|---------------------------|-------------------------|---------------------|------------------|---------------------------|
|                                 | Placebo<br>(n = 107)       | TOL ER<br>(n = 98) | TAM<br>(n = 107) | TOL ER + TAM<br>(n = 112) | Placebo<br>(n = 108)    | TOL ER<br>(n = 112) | TAM<br>(n = 102) | TOL ER +<br>TAM (n = 105) |
| Mean (SD) age, y                | 65 (9)                     | 65 (9)             | 66 (9)           | 64 (9)                    | 60 (10)                 | 59 (9)              | 58 (10)          | 58 (10)                   |
| Race, n (%)                     |                            |                    |                  |                           |                         |                     |                  |                           |
| White                           | 87 (81)                    | 75 (77)            | 89 (83)          | 100 (89)                  | 91 (84)                 | 90 (80)             | 84 (82)          | 88 (84)                   |
| Black                           | 8 (8)                      | 15 (15)            | 8 (8)            | 2 (2)                     | 12 (11)                 | 12 (11)             | 11 (11)          | 7 (7)                     |
| Other                           | 12 (11)                    | 8 (8)              | 10 (9)           | 10 (9)                    | 5 (5)                   | 10 (9)              | 7 (7)            | 10 (10)                   |
| Mean (SD) prostate volume, mL   | 47.2 (17.1)                | 47.8 (20.2)        | 48.5 (18.6)      | 52.8 (23.2)               | 21.5 (5.0)              | 21.4 (5.3)          | 20.2 (5.3)       | 20.7 (5.4)                |
| IPSS, mean (SD)                 |                            |                    |                  |                           |                         |                     |                  |                           |
| Total                           | 20.4 (5.4)                 | 19.3 (5.3)         | 19.9 (4.9)       | 19.8 (5.6)                | 19.7 (5.5)              | 19.6 (5.0)          | 20.1 (5.2)       | 20.4 (5.5)                |
| Storage                         | 10.3 (2.3)                 | 9.8 (2.5)          | 10.1 (2.1)       | 9.9 (2.4)                 | 10.1 (2.2)              | 10.0 (2.3)          | 10.4 (2.3)       | 10.4 (2.4)                |
| Voiding                         | 10.1 (4.4)                 | 9.6 (4.3)          | 9.8 (4.0)        | 9.9 (4.4)                 | 9.6 (4.6)               | 9.6 (4.2)           | 9.7 (4.5)        | 10.0 (4.9)                |
| Diary variables, mean (SD)      |                            |                    |                  |                           |                         |                     |                  |                           |
| Frequency                       | 12.0 (3.5)                 | 11.9 (3.1)         | 11.9 (2.9)       | 11.7 (3.2)                | 11.8 (2.9)              | 11.7 (2.6)          | 12.1 (3.7)       | 12.2 (3.5)                |
| Urgency                         | 7.6 (4.1)                  | 7.7 (3.4)          | 7.3 (3.3)        | 6.2 (3.9)                 | 7.1 (3.6)               | 7.5 (3.6)           | 6.7 (3.7)        | 7.4 (3.9)                 |
| UII                             | 0.9 (1.6)                  | 1.0 (1.0)          | 0.7 (1.0)        | 1.2 (1.6)                 | 1.1 (0.9)               | 0.7 (0.6)           | 0.7 (0.9)        | 1.7 (3.6)                 |
| Nocturia                        | 2.0 (1.2)                  | 1.9 (1.3)          | 1.8 (1.2)        | 2.1 (1.3)                 | 2.0 (1.2)               | 2.0 (1.3)           | 1.7 (1.3)        | 2.1 (1.3)                 |
| Frequency-urgency sum           | 32.8 (11.8)                | 33.5 (10.5)        | 32.7 (10.2)      | 30.9 (12.0)               | 32.3 (10.2)             | 32.3 (9.2)          | 31.6 (10.4)      | 34.0 (14.2)               |
| Urodynamic variables, mean (SD) |                            |                    |                  |                           |                         |                     |                  |                           |
| $Q_{max}$ , mL/s                | 10.9 (4.4)                 | 11.6 (6.3)         | 12.8 (7.2)       | 12.3 (6.9)                | 13.6 (8.0)              | 14.8 (8.6)          | 13.9 (8.0)       | 13.1 (6.8)                |
| PVR, mL                         | 50.7 (49.6)                | 61.9 (60.0)        | 55.8 (57.0)      | 64.5 (57.0)               | 43.2 (45.5)             | 41.2 (50.5)         | 45.7 (52.3)      | 52.8 (49.6)               |

IPSS = International Prostate Symptom Score; PVR = postvoid residual volume;  $Q_{max}$  = maximum urinary flow rate; SD = standard deviation; TAM = tamsulosin; TOL ER = tolterodine extended release; UII = urgency urinary incontinence.

graphic characteristics were similar across groups, except that subjects with higher prostate volumes tended to be older. There were no apparent differences in any endpoint between subjects with prostate volume  $\geq 29$  mL versus  $< 29$  mL at baseline (Table 1). Mean percentage changes in bladder diary variables and IPSS scores from baseline to week 12 are shown in Fig. 1 with LS mean changes in bladder diary variables and IPSS scores shown in Table 2 and described below.

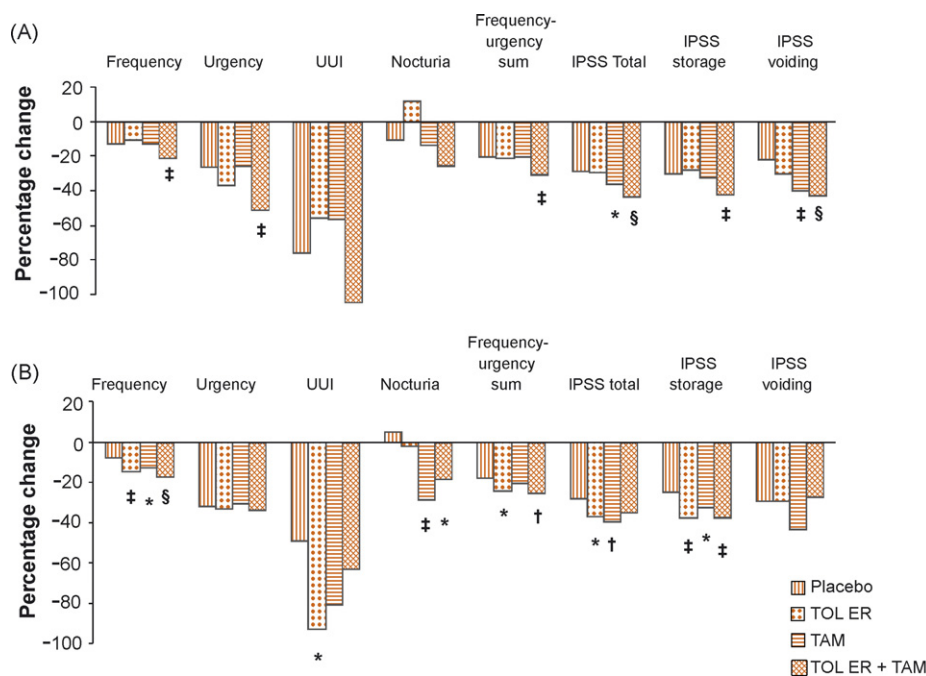
### 3.1. Bladder diary variables

Subjects receiving tolterodine ER+tamsulosin reported significantly reduced frequency per 24 h regardless of prostate volume ( $\geq 29$  mL,  $p = 0.001$ ;  $< 29$  mL,  $p = 0.001$ ) versus placebo (Table 2). Men with prostate volumes  $< 29$  mL receiving tolterodine ER alone also reported significantly decreased frequency ( $p = 0.016$  vs placebo), whereas subjects receiving tamsulosin alone did not ( $p = 0.105$  vs placebo). Frequency was not reduced in men with prostate volumes  $\geq 29$  mL receiving tolterodine ER ( $p = 0.468$ ) or tamsulosin alone ( $p = 0.766$ ) compared with placebo.

The number of men experiencing UII was low among all treatment groups in subjects with prostate volumes  $\geq 29$  mL and  $< 29$  mL (Table 2). UII episodes were not significantly reduced compared with placebo by any active treatment in men with prostate volumes  $\geq 29$  mL (tolterodine ER,  $p = 0.211$ ; tamsulosin,  $p = 0.199$ ; tolterodine ER+tamsulosin,  $p = 0.978$ ). UII episodes were significantly reduced in men with prostate volumes  $< 29$  mL receiving tolterodine ER ( $p = 0.036$ ) but not tamsulosin ( $p = 0.082$ ) or tolterodine ER+tamsulosin ( $p = 0.153$ ).

Micturition-related urgency episodes per 24 h were significantly reduced versus placebo in men with prostate volumes  $\geq 29$  mL receiving tolterodine ER+tamsulosin ( $p = 0.006$ ; Table 2) but not tolterodine ER ( $p = 0.966$ ) or tamsulosin ( $p = 0.531$ ) alone. Urgency episodes were not reduced relative to placebo in men with prostate volumes  $< 29$  mL receiving any active treatment (tolterodine ER,  $p = 0.444$ ; tamsulosin,  $p = 0.704$ ; tolterodine ER+tamsulosin,  $p = 0.506$ ).

Nocturnal frequency was not reduced compared with placebo for any active treatment (tolterodine ER,  $p = 0.322$ ; tamsulosin,  $p = 0.807$ ; tolterodine ER+tamsulosin,  $p = 0.095$ ) in men with prostate



**Fig. 1 – Percentage change from baseline to week 12 in efficacy variables in patients with baseline prostate volume (A)  $\geq 29$  mL and (B)  $< 29$  mL. IPSS = International Prostate Symptom Score; TAM = tamsulosin, TOL ER = tolterodine extended release; UII = urgency urinary incontinence. \* $0.05 < p < 0.1$ ; † $p \leq 0.05$ ; ‡ $p \leq 0.01$ ; § $p \leq 0.001$  vs placebo.**

volumes  $\geq 29$  mL (Table 2). Nocturnal frequency was significantly reduced compared with placebo in men with prostate volumes  $< 29$  mL receiving tamsulosin ( $p = 0.038$ ), but not in men receiving tolterodine ER ( $p = 0.763$ ) or tolterodine ER+tamsulosin ( $p = 0.100$ ).

Frequency-urgency sum per 24 h was significantly reduced versus placebo in men with prostate volumes  $\geq 29$  mL ( $p = 0.001$ ) or  $< 29$  mL ( $p = 0.022$ ) who received tolterodine ER+tamsulosin. Frequency-urgency sum was not reduced relative to placebo

for men with prostate volumes of either  $\geq 29$  mL (tolterodine ER,  $p = 0.625$ ; tamsulosin,  $p = 0.903$ ) or  $< 29$  mL (tolterodine ER,  $p = 0.059$ ; tamsulosin,  $p = 0.528$ ) who received monotherapy (Table 2).

### 3.2. International Prostate Symptom Score

IPSS scores were significantly improved compared with placebo among men with prostate volumes  $\geq 29$  mL receiving tolterodine ER+tamsulosin ( $p = 0.001$ ) but not tolterodine ER ( $p = 0.628$ ) or

**Table 2 – Least square mean changes from baseline in efficacy variables at week 12**

| Efficacy variable                                         | Prostate size $\geq 29$ mL |        |                    |                     | Prostate size $< 29$ mL |                    |                    |                    |
|-----------------------------------------------------------|----------------------------|--------|--------------------|---------------------|-------------------------|--------------------|--------------------|--------------------|
|                                                           | Placebo                    | TOL ER | TAM                | TOL ER + TAM        | Placebo                 | TOL ER             | TAM                | TOL ER + TAM       |
| Number of subjects, n                                     | 107                        | 99     | 110                | 108                 | 107                     | 111                | 99                 | 109                |
| Number of subjects with $> 0$ UII episodes at baseline, n | 23                         | 29     | 27                 | 30                  | 25                      | 24                 | 23                 | 22                 |
| Micturitions per 24 h                                     | -1.68                      | -1.43  | -1.79              | -2.80 <sup>§</sup>  | -1.10                   | -1.93 <sup>†</sup> | -1.67              | -2.29 <sup>§</sup> |
| UII episodes per 24 h <sup>#</sup>                        | -0.87                      | -0.65  | -0.65              | -0.87               | 0.02                    | -0.90 <sup>†</sup> | -0.85 <sup>*</sup> | -0.66              |
| Urgency episodes per 24 h                                 | -2.70                      | -2.72  | -2.37              | -4.09 <sup>‡</sup>  | -2.63                   | -3.03              | -2.43              | -2.99              |
| Micturitions per night                                    | -0.45                      | -0.33  | -0.48              | -0.66 <sup>*</sup>  | -0.33                   | -0.37              | -0.59 <sup>†</sup> | -0.54 <sup>†</sup> |
| Frequency-urgency sum per 24 h                            | -7.65                      | -7.04  | -7.50              | -11.76 <sup>§</sup> | -6.21                   | -8.68 <sup>*</sup> | -7.06              | -9.33 <sup>†</sup> |
| IPSS total                                                | -6.20                      | -5.79  | -7.64 <sup>*</sup> | -8.88 <sup>§</sup>  | -6.10                   | -7.82 <sup>*</sup> | -8.06 <sup>†</sup> | -6.99              |
| IPSS storage                                              | -3.01                      | -2.86  | -3.33              | -4.38 <sup>§</sup>  | -2.85                   | -4.08 <sup>†</sup> | -3.55              | -3.97 <sup>†</sup> |
| IPSS voiding                                              | -3.19                      | -2.94  | -4.35 <sup>†</sup> | -4.48 <sup>†</sup>  | -3.24                   | -3.78              | -4.50 <sup>†</sup> | -2.98              |

IPSS = International Prostate Symptom Score; TAM = tamsulosin; TOL ER = tolterodine extended release; UII = urgency urinary incontinence.

\* $0.05 < p < 0.1$ ; † $p \leq 0.05$ ; ‡ $p \leq 0.01$ ; § $p \leq 0.001$  vs placebo.

<sup>#</sup>Includes only subjects who were incontinent at baseline.

Table 3 – Safety parameters

|                                        | Prostate size $\geq 29$ mL |                    |                  | Prostate size $< 29$ mL |                     |                  |
|----------------------------------------|----------------------------|--------------------|------------------|-------------------------|---------------------|------------------|
|                                        | Placebo<br>(n = 107)       | TOL ER<br>(n = 98) | TAM<br>(n = 107) | Placebo<br>(n = 108)    | TOL ER<br>(n = 112) | TAM<br>(n = 102) |
| Urinary retention, n                   | 1                          | 2                  | 0                | 2                       | 0                   | 0                |
| Urinary flow decreased, n              | 1                          | 1                  | 0                | 0                       | 1                   | 0                |
| Discontinuations due to urinary AEs, n | 1                          | 1                  | 0                | 1                       | 0                   | 0                |
| Catheterization required, n            | 0                          | 1                  | 0                | 0                       | 0                   | 0                |
| Mean change (SE) in PVR, mL            | -2.18 (7.0)                | 5.59 (7.8)         | -6.53 (6.3)      | 0.47 (6.2)              | 6.26 (5.1)          | 4.17 (7.0)       |
| Mean change (SE) in $Q_{max}$ , mL/s   | 0.16 (0.6)                 | -0.03 (0.6)        | -0.91 (0.8)      | -0.74 (0.7)             | -1.44 (0.7)         | 0.19 (0.7)       |

AE = adverse events; PVR = postvoid residual volume;  $Q_{max}$  = maximum urinary flow rate; SE = standard error; TAM = tamsulosin; TOL ER = tolterodine extended release.

tamsulosin ( $p = 0.086$ ) (Table 2). IPSS scores were significantly improved compared with placebo for men with prostate volumes  $< 29$  mL who received tamsulosin ( $P = 0.044$ ) but not tolterodine ER ( $p = 0.063$ ) or tolterodine ER+tamsulosin ( $p = 0.373$ ).

Compared with placebo, IPSS storage scores were significantly improved in men with prostate volumes  $\geq 29$  mL receiving tolterodine ER+tamsulosin ( $p < 0.001$ ), but not tolterodine ER ( $p = 0.714$ ) or tamsulosin alone ( $p = 0.417$ ) (Table 2). IPSS storage scores were significantly improved compared with placebo in men with prostate volumes  $< 29$  mL receiving tolterodine ER+tamsulosin ( $p = 0.018$ ) and tolterodine ER ( $p = 0.005$ ), but not tamsulosin ( $p = 0.133$ ).

IPSS voiding scores were significantly reduced relative to placebo in men with prostate volumes  $\geq 29$  mL receiving tolterodine ER+tamsulosin ( $p = 0.013$ ) or tamsulosin alone ( $p = 0.030$ ), but not tolterodine ER alone ( $p = 0.654$ ) (Table 2). IPSS voiding scores were significantly reduced relative to placebo in men with prostate volumes  $< 29$  mL receiving tamsulosin ( $p = 0.036$ ) but not tolterodine ER ( $p = 0.344$ ) or tolterodine ER+tamsulosin ( $p = 0.670$ ).

### 3.3. Safety

The incidence of AUR was low across all treatment groups, regardless of prostate volume (Table 3). No clinically or statistically significant changes in PVR or  $Q_{max}$  were observed at week 12 in any treatment group in subjects with prostate volumes  $\geq 29$  mL or  $< 29$  mL (all  $P > 0.10$ ; Table 3).

## 4. Discussion

Tolterodine ER+tamsulosin was efficacious in men with prostate volumes  $\geq 29$  mL. Compared with the placebo group, subjects in the tolterodine ER+tamsulosin group reported significant improvements in 24-h micturition frequency, urgency episodes, frequency-urgency sum, and IPSS total and subscale scores. Subjects with prostate volumes  $\geq 29$  mL receiving tamsulosin alone reported a significant improvement in IPSS voiding scores compared with men receiving placebo. Efficacy variables in men with prostate volumes  $\geq 29$  mL were not improved by tolterodine ER alone.

Tolterodine ER was efficacious in men with prostate volumes  $< 29$  mL. Significant improvements were observed in 24-h micturition frequency and IPSS storage scores relative to placebo. Therapy with tolterodine ER+tamsulosin was also effective in men with prostate volumes  $< 29$  mL. Compared with

placebo, 24-h micturition frequency, frequency-urgency sum, and IPSS storage scores were significantly improved. Nocturnal frequency and IPSS total scores were significantly reduced in men with prostate volumes <29 mL who received tamsulosin alone.

Notably, tolterodine ER, with or without tamsulosin, was well tolerated. No evidence of AUR and no clinically significant changes in PVR or  $Q_{\max}$  were observed in any treatment group among subjects with higher or lower prostate volumes. One reason that antimuscarinic therapy may be well tolerated with a low rate of AUR could be the reduction in the number of muscarinic receptors in the male detrusor with aging [21].

These results are consistent with previous studies in men with LUTS including OAB symptoms and/or DO and show that the administration of tolterodine ER and an  $\alpha$ -adrenergic antagonist is well tolerated and, in certain patients, more efficacious than treatment with an  $\alpha$ -adrenergic antagonist alone. For example, one randomized active-controlled study found that tamsulosin alone and tolterodine ER+tamsulosin improved  $Q_{\max}$  and volume at first contraction in men with OAB symptoms and urodynamically proven BOO and DO [22]. However, only patients treated with tolterodine ER+tamsulosin showed improvement in maximum detrusor pressure and maximum unstable contraction pressure [22]. No instances of AUR were observed, and PVR was not affected in men receiving tolterodine ER+tamsulosin. However, we did not observe improvements in  $Q_{\max}$  in any group in the current study. This discrepancy may be due to the differences in study population characteristics. For instance, men with  $Q_{\max}$  <5 mL/s were excluded from the current study. In another study, men whose LUTS did not resolve after 1 wk of treatment with terazosin were randomized to terazosin alone or tolterodine ER+terazosin for 6 wk [23]. Subjects in the tolterodine ER+terazosin group demonstrated greater improvements in IPSS scores compared with scores from subjects in the terazosin groups with no differences in  $Q_{\max}$  or PVR between groups.

The current results extend our understanding of previously published findings from this study. Kaplan et al reported that tolterodine ER+tamsulosin significantly increased the percentage of subjects reporting treatment benefit and improved OAB symptoms and IPSS scores [16]. Both medications were safe and well tolerated in men who met symptom entry criteria for BPH and OAB trials. This post hoc analysis demonstrates that treatment with tolterodine ER+tamsulosin was effective and well tolerated with no increases in AUR in these subjects,

regardless of baseline prostate volume. These results are consistent with another post hoc analysis of this data set showing that tolterodine ER+tamsulosin was effective and well tolerated, regardless of subjects' baseline serum level of prostate-specific antigen (PSA) [24]. Concordance of results of these two post hoc analyses is not unexpected, given that PSA has been shown to be a predictor of prostate volume [25]. Indeed, baseline serum PSA level was significantly correlated ( $r = 0.50$ ,  $p < 0.0001$ ) with prostate volume among these subjects [23].

Notably, this post hoc analysis demonstrated that treatment with tolterodine ER alone improved OAB/storage symptoms in men with lower prostate volumes. As shown previously, tolterodine ER alone improved OAB symptoms and IPSS scores selectively in subjects with lower (<1.3 ng/mL) baseline median PSA levels; tamsulosin demonstrated little efficacy in these subjects [24]. These findings are clinically important because storage LUTS appear to be more bothersome than voiding LUTS [26]. Moreover, although an older study reported that voiding LUTS are more prevalent among men than are storage LUTS [25], a recent study using current ICS definitions found that storage LUTS are more prevalent among men [5].

Current data are consistent with the view that LUTS in men may result from conditions causing OAB symptoms, independent of prostatic enlargement and BOO. BOO associated with BPH and prostatic enlargement may or may not be accompanied by secondary bladder conditions [2,6]. Differences in treatment responsiveness between these two groups would be expected. Men with LUTS due to primary bladder conditions may respond favorably to antimuscarinic therapy alone, whereas those with LUTS due to prostatic enlargement with concomitant or secondary bladder dysfunction may require antimuscarinic and  $\alpha$ -blocker therapy to achieve comparable benefits. This interpretation is supported by findings that a larger percentage of men with BOO only (79%) reported improvement in IPSS voiding scores (>3 points) after 3 mo of treatment with doxazosin alone compared with men with BOO and OAB (35%) [27]. Among men who did not respond to doxazosin, 73% of those with BOO and DO and 38% of those with BOO only reported improvement when tolterodine was added to their ongoing doxazosin therapy.

It is notable that all subjects in the current study met symptom-entry criteria for both OAB and prostatic enlargement trials, and there were no apparent differences in baseline severity of LUTS between subjects with higher versus lower prostate

volumes as measured by bladder diary variables and IPSS scores. Thus, it is likely that men with LUTS will benefit most from therapeutic interventions that are individually adjusted for maximum efficacy, rather than therapy based on generic treatment algorithms. Urodynamic measurements may help guide the choice of therapy for individual patients.

Muscarinic receptors in bladder smooth muscle play an important role in mediating bladder contraction; this is widely believed to be the primary therapeutic site of action of antimuscarinics [10]. However, the benefit of dual therapy in both groups may be explained in part by synergistic effects on prejunctional  $\alpha_{1a}$  adrenoreceptors [28] and norepinephrine [29]. Blockade of prejunctional adrenoreceptors in the bladder by tamsulosin may enhance the action of tolterodine; conversely, tolterodine may reduce norepinephrine release in the prostate or urethra and enhance the action of tamsulosin. Alternatively, antimuscarinics may exert therapeutic effects via actions on bladder afferents [10].

The results of this study should be interpreted within the context of its limitations. This study was not powered for a post hoc subgroup analysis; thus, results should be interpreted carefully. It is known that urodynamic obstruction (BOO) does not correlate well with prostate volume. We can therefore only state whether the interventions given were or were not effective in men with prostates  $<29$  mL or  $\geq 29$  mL, not if they were effective in men with or without BOO. A treating physician would more often know a patient's prostate size than BOO status, which requires formal invasive urodynamics.

Finally, this analysis did not assess impact of age, body mass index, duration of LUTS, and  $Q_{max}$  on treatment responsiveness. Future analyses will evaluate the impact of these factors and whether there are differences in long-term impact (eg, prevention of symptom progression and need for invasive therapy) of treatments assessed.

## 5. Conclusions

Among men who met symptom-entry criteria for prostate enlargement and OAB trials, tolterodine ER alone effectively improved OAB and storage symptoms in men with lower baseline prostate volumes. Therapy with tolterodine ER+tamsulosin effectively improved LUTS, including OAB symptoms in this population, regardless of baseline prostate volume. Tolterodine ER, with or without tamsulosin, did not alter  $Q_{max}$  or produce clinically significant changes in PVR in men with higher or lower baseline prostate volume. Thus, men with LUTS including OAB who

have lower prostate volumes may benefit from tolterodine ER alone for their OAB symptoms. Men with moderate to severe LUTS including OAB with higher prostate volumes may require therapy with an  $\alpha$ -receptor antagonist and tolterodine ER to achieve treatment benefit.

**Author contributions:** Claus G. Roehrborn had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Roehrborn, Kaplan, Jones, Wang, Bavendam, Guan

**Acquisition of data:** None.

**Analysis and interpretation of data:** Roehrborn, Kaplan, Jones, Wang, Bavendam, Guan.

**Drafting of the manuscript:** Roehrborn, Kaplan, Jones, Wang, Bavendam, Guan.

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**Statistical analysis:** Roehrborn, Kaplan, Jones, Wang, Bavendam, Guan.

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### Editorial Comment on: Tolterodine Extended Release With or Without Tamsulosin in Men With Lower Urinary Tract Symptoms Including Overactive Bladder Symptoms: Effects of Prostate Size

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Millions of men suffer from overactive bladder (OAB) and lower urinary tract symptoms (LUTS). We now possess knowledge regarding the adverse effects on quality of life and costs associated with the condition. In men, the pathophysiology of LUTS may result from a number of causes including bladder outlet obstruction, detrusor overactivity, or both. Increasing data and clinical experience support the efficacy and safety of anticholinergics in men, and the rate of urinary retention has been equal to that of placebo in short-term studies. Urodynamics play a vital role in defining the bladder and/or outlet dysfunction and help direct one's therapy; however, they are time-consuming, require adequate cooperation from patients, and are strongly recommended mainly in case a surgical approach has to be considered. Even before complete assessment is performed, tolterodine ER plus tamsulosin may prove efficacious in relieving symptoms in prostates of bigger size, whereas tolterodine ER alone can be recommended in men with prostates of smaller size.

It may happen that symptoms persist even after  $\alpha$ -blocker therapy. Do we really know the barriers to using antimuscarinics in order to gain additional benefit? Should these men be treated primarily with antimuscarinics considering that storage LUTS appear to be more bothersome than voiding LUTS?

The authors conducted a post hoc analysis of data from the TIMES study [1], stratified by prostate size, to assess efficacy and safety of tolterodine ER,

tamsulosin, or tolterodine ER plus tamsulosin in men with LUTS including OAB [2]. The study was funded by Pfizer Inc.

In line with the results obtained in other studies [3–6], patients with LUTS in this study (eligible men were aged  $\geq 40$  yr with a total International Prostate Symptom Score  $\geq 12$ ) could be safely treated with efficacy using a combination of  $\alpha$ -blocker and antimuscarinic.

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### Editorial Comment on: Tolterodine Extended Release With or Without Tamsulosin in Men With Lower Urinary Tract Symptoms Including Overactive Bladder Symptoms: Effects of Prostate Size

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This post hoc evaluation on an actual and interesting topic used data from a previously published study stratified on prostate size [1,2]. It is clearly and correctly stated that the study was sponsored by a pharmaceutical company, which explains the choice of drugs. The conclusion is that men with smaller prostates and moderate to severe lower urinary tract symptoms (LUTS) including overactive bladder (OAB) benefited from tolterodine ER. Therapy with tolterodine ER plus tamsulosin was effective regardless of prostate size.

Combination therapy has been used before and was shown to be both effective and safe. Combining tolterodine with doxazosin was effective in three-quarters of men with bladder outlet obstruction (BOO) plus OAB [3]. Tolterodine plus tamsulosin improved quality of life in patients with BOO and concomitant detrusor instability [4]. Tolterodine plus terazosine proved an effective and safe treatment for LUTS and benign prostatic hyperplasia (BPH) patients with relatively small prostate volume (<50 ml), no median lobe, moderate impaired  $Q_{max}$ , and dominant storage symptoms [5].

Can one conclude that prostate size is predominantly important in treatment decision making? Probably not to a high extent. The clinical significance of benign prostatic enlargement depends on whether OAB symptoms and/or outflow obstruction are present. Prostate size is not correlated with either condition; large prostates can be unobstructed and asymptomatic, and small prostates can present with both obstruction and symptoms. Rather, the symptoms would guide treatment decisions.

The conclusions of this study, though interesting, cannot be incorporated into flow charts or guidelines because the management of such a population of patients should be chosen on a personal basis. From this and other studies, use of a combined antimuscarinic and an  $\alpha$ -blocker does seem to be safe.

It is unclear as yet whether both drugs in a combination treatment should be started at the same time or whether one could first administer the drug related to the worst symptoms and add the other if initial treatment is unsuccessful. Further study is needed.

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