

# Tolterodine and Tamsulosin for Treatment of Men With Lower Urinary Tract Symptoms and Overactive Bladder

## A Randomized Controlled Trial

Steven A. Kaplan, MD

Claus G. Roehrborn, MD

Eric S. Rovner, MD

Martin Carlsson, MS

Tamara Bavendam, MD

Zhonghong Guan, MD, PhD

**O**VERACTIVE BLADDER IS A SYNDROME characterized by urinary urgency, with or without urgency urinary incontinence, usually with increased micturition frequency during the day and at night (ie, nocturia).<sup>1</sup> An estimated 10 million men 40 years or older have symptoms consistent with overactive bladder.<sup>2</sup> Overactive bladder symptoms are often attributed to detrusor overactivity, a condition characterized by involuntary detrusor contractions during bladder filling.<sup>1</sup>

In men, detrusor overactivity may coexist with bladder outlet obstruction due to benign prostatic hyperplasia (BPH), or it may be secondary to obstruction, whereby the increased pressure required to void leads to structural changes in the bladder, which in turn, increases the excitability of detrusor smooth muscle cells.<sup>3</sup> Bladder outlet obstruction may also cause urinary hesitancy, intermittency, weak stream, and other lower urinary tract symptoms. Overactive bladder symptoms are reasonably well correlated with detrusor overactivity, but hesitancy, intermittency, and weak stream correlate poorly with bladder outlet obstruction<sup>3</sup>; thus, these urinary symptoms may not be indicative of underlying pathophysiology.

**Context** Men with overactive bladder and other lower urinary tract symptoms may not respond to monotherapy with antimuscarinic agents or  $\alpha$ -receptor antagonists.

**Objective** To evaluate the efficacy and safety of tolterodine extended release (ER), tamsulosin, or both in men who met research criteria for both overactive bladder and benign prostatic hyperplasia.

**Design, Setting, and Participants** Randomized, double-blind, placebo-controlled trial conducted at 95 urology clinics in the United States involving men 40 years or older who had a total International Prostate Symptom Score of 12 or higher and, an International Prostate Symptom Score quality-of-life (QOL) item score of 3 or higher, a self-rated bladder condition of at least moderate bother, and a bladder diary documenting micturition frequency ( $\geq 8$  micturitions per 24 hours) and urgency ( $\geq 3$  episodes per 24 hours), with or without urgency urinary incontinence. Patients were recruited between November 2004 and February 2006, and the study was completed May 2006.

**Interventions** Patients were randomly assigned to receive placebo (n=222), 4 mg of tolterodine ER (n=217), 0.4 mg of tamsulosin (n=215), or both tolterodine ER plus tamsulosin (n=225) for 12 weeks.

**Main Outcome Measures** Patient perception of treatment benefit, bladder diary variables, International Prostate Symptom Scores, and safety and tolerability were assessed.

**Results** A total of 172 men (80%) receiving tolterodine ER plus tamsulosin reported treatment benefit by week 12 compared with 132 patients (62%) receiving placebo ( $P < .001$ ), 146 (71%) receiving tamsulosin ( $P = .06$  vs placebo), or 135 (65%) receiving tolterodine ER ( $P = .48$  vs placebo). Patients receiving tolterodine ER plus tamsulosin compared with placebo experienced significant reductions in urgency urinary incontinence ( $-0.88$  vs  $-0.31$ ,  $P = .005$ ), urgency episodes without incontinence ( $-3.33$  vs  $-2.54$ ,  $P = .03$ ), micturitions per 24 hours ( $-2.54$  vs  $-1.41$ ,  $P < .001$ ), and micturitions per night ( $-0.59$  vs  $-0.39$ ,  $P = .02$ ). Patients receiving tolterodine ER plus tamsulosin demonstrated significant improvements on the total International Prostate Symptom Score ( $-8.02$  vs placebo,  $-6.19$ ,  $P = .003$ ) and QOL item ( $-1.61$  vs  $-1.17$ ,  $P = .003$ ). All interventions were well tolerated. The incidence of acute urinary retention requiring catheterization was low (tolterodine ER plus tamsulosin, 0.4%; tolterodine ER, 0.5%; tamsulosin, 0%; and placebo, 0%).

**Conclusions** These results suggest that treatment with tolterodine ER plus tamsulosin for 12 weeks provides benefit for men with moderate to severe lower urinary tract symptoms including overactive bladder.

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**Author Affiliations:** Department of Urology, Weill Cornell Medical College, New York, NY (Dr Kaplan); Department of Urology, University of Texas Southwestern Medical Center, Dallas (Dr Roehrborn); Department of Urology, Medical University of South Carolina, Charleston (Dr Rovner);

Pfizer Inc, New York, NY (Mr Carlsson and Drs Bavendam and Guan).

**Corresponding Author:** Steven A. Kaplan, MD, Weill Cornell Medical College, New York Presbyterian Hospital, 1300 York Ave, New York, NY 10021 (kaplans@med.cornell.edu).

The current standard of care for men with lower urinary tract symptoms is treatment with  $\alpha$ -adrenergic receptor antagonists, which reduce smooth muscle tone in the prostate and bladder neck and decrease bladder outlet resistance.<sup>5</sup> If the prostate is very large, a 5 $\alpha$ -reductase inhibitor may also be prescribed to reduce prostatic volume.<sup>5</sup> Treatment with these agents is often initiated on the assumption that these urinary tract symptoms are caused by BPH. However, because overactive bladder symptoms may coexist with BPH or bladder outlet obstruction without being caused by the prostatic condition, pharmacotherapies that target only the prostate (and not the bladder) may not alleviate overactive bladder symptoms.<sup>4</sup>

Although antimuscarinic agents, such as tolterodine, reduce detrusor overactivity and are indicated for the treatment of overactive bladder symptoms, many men are only prescribed antimuscarinic agents for overactive bladder symptoms that persist after surgery to remove or shrink the prostate. Some clinicians may elect not to initiate antimuscarinic therapy in men before surgery because of concern that decreasing detrusor contractility could increase the risk of urinary retention in cases of potential outlet obstruction. However, primary studies<sup>6,7</sup> and post hoc analyses<sup>8,9</sup> suggest that tolterodine is not associated with an increased incidence of urinary retention in men with overactive bladder, with or without other lower urinary tract symptoms.

Some men enrolled in overactive bladder studies do not respond to antimuscarinic agents, and some men enrolled in BPH studies do not respond to  $\alpha$ -receptor antagonists,<sup>7,10</sup> 5 $\alpha$ -reductase inhibitors,<sup>11,12</sup> or a combination of both.<sup>13</sup> Treatment failures may be due to the practice of using entry criteria that identify patients with symptoms that are likely to respond to the tested drug based on its mechanism of action: overactive bladder symptoms in the case of antimuscarinic agents and lower urinary tract symptoms associated with BPH in the case of  $\alpha$ -receptor antagonists and 5 $\alpha$ -reductase inhibitors, regardless of whether other lower urinary tract symptoms are present.

Measures used to assess treatment efficacy in each of the 2 types of trials are similarly targeted. Specifically, men with BPH are often identified and enrolled in clinical trials based, in part, on having an International Prostate Symptom Score (IPSS)<sup>14,15</sup> of 12 or higher,<sup>11,16,17</sup> and the change in IPSS is used to assess treatment benefit. However, the IPSS does not include an item for urgency urinary incontinence and does not allow for the quantification of micturition frequency or degree of urgency. Thus, overactive bladder symptoms cannot be assessed appropriately with this instrument. Conversely, bladder diaries, which are often used to qualify patients with overactive bladder for enrollment in studies of antimuscarinic agents, do not capture symptoms, such as hesitancy, intermittency, and weak stream quality that may be present in addition to overactive bladder symptoms. Thus, men with suspected BPH based on IPSS and those who have documented their overactive bladder symptoms in a diary are candidates for enrollment in either type of study and receive therapy that targets only 1 of 2 conditions that may contribute to their symptoms.

Results of several small-scale, non-placebo-controlled studies of men with urodynamically confirmed detrusor overactivity and bladder outlet obstruction have supported the use of combination treatment with an  $\alpha$ -receptor antagonist and an antimuscarinic agent.<sup>10,18</sup> However, treatment of patients based on symptoms rather than urodynamic endpoints would improve the generalizability of the results to clinical practice.

For this study, we identified men who reported at least moderate bother due to lower urinary tract symptoms, had symptoms suggestive of BPH (total IPSS  $\geq 12$ ), and diary-documented symptoms of overactive bladder (ie, urgency and micturition frequency, with or without urgency urinary incontinence). These men may be representative of a large population of patients who have not been identified in previous clinical trials and are difficult to treat because they have 2 concomitant conditions (ie, detrusor overactivity and BPH). We evaluated the efficacy and safety of the antimuscarinic

tolterodine extended release (ER), the  $\alpha_1$ -receptor antagonist tamsulosin, and treatment with both agents vs placebo in this population of men. This large-scale trial was designed to investigate the effects of these 2 widely used pharmacotherapies in a population of men who met standard research criteria for both overactive bladder and BPH.

## METHODS

### Patients

Patients were recruited at urology offices and clinics. Eligible patients were men 40 years and older with a total IPSS of 12 or higher; an IPSS quality-of-life (QOL) item score of 3 or higher; and a self-rated bladder condition of "some moderate problems," "severe problems," or "many severe problems" based on the Patient Perception of Bladder Condition question.<sup>19</sup> Additional inclusion criteria were micturition frequency ( $\geq 8$  micturitions per 24 hours) and urgency ( $\geq 3$  micturitions with urgency rating  $\geq 3$  per 24 hours) for 3 or more months.

Men with clinically significant bladder outlet obstruction (defined as a postvoid residual volume  $> 200$  mL and maximum urinary flow rate  $< 5$  mL/s), or serum prostate-specific antigen of more than 10 ng/mL with risk of prostate cancer were excluded. Other exclusion criteria included history of postural hypotension or syncope; significant hepatic or renal disease; some neurologic conditions (eg, multiple sclerosis, spinal cord injury, Parkinson disease); prostate cancer; prostate surgery or other intervention; history of acute urinary retention requiring catheterization; use of an indwelling catheter or self-catheterization program; bladder outlet obstruction due to causes other than BPH; or any condition for which antimuscarinic use was contraindicated. Men treated with an  $\alpha$ -receptor antagonist within 2 weeks; antimuscarinic, antispasmodic, saw palmetto, or electrostimulation within 1 month; any investigational drug within 2 months; or a 5 $\alpha$ -reductase inhibitor within 3 months of screening were also excluded.

Written informed consent was obtained from each patient. Each investi-

gator obtained prospective approval of the trial protocol, protocol amendments, informed consent forms, and other relevant documents from the appropriate institutional review board or independent ethics committee. All correspondence with the institutional review board or independent ethics committee was retained by the investigator and copies of approvals were forwarded to the sponsor.

### Study Design

This was a 12-week, randomized, double-blind, active- and placebo-controlled trial conducted at 95 urology clinics in the United States. At each clinic, patients presenting with lower urinary tract symptoms were screened for eligibility. For assessment of demographics, race (white, black, Asian, or other [categories specified by the sponsor]) was reported by the investigator).

At the end of the baseline period, patients who met all protocol criteria and were eligible to receive study medication were randomly assigned using a 1:1:1:1 randomization ratio. All patient identification numbers and randomization numbers were assigned sequentially in ascending order beginning with the lowest number available. The randomization scheme was prepared by the study biostatistician, applying a block size of 8, and produced by the randomization administrator. Patients were dispensed study medication and randomized numbers were taken from the drug supply kit. All study medication and placebo were similar looking and smelling. Treatment allocations were balanced across the 4 treatment groups and blinded to patients, site investigators, and all study personal directly involved in conduct of the study.

Patients were randomly assigned to receive placebo, 4 mg of tolterodine ER, 0.4 mg of tamsulosin, or tolterodine ER plus tamsulosin once a day for 12 weeks. Patients were instructed to take study medication approximately 30 minutes after dinner. This dosing regimen is consistent with instructions provided in the tamsulosin package insert.<sup>20</sup> The objective of the study was to evaluate the ef-

ficacy and tolerability of these interventions in men with lower urinary tract symptoms including clinically documented overactive bladder who were bothered by their bladder condition. We hypothesized that men who received tolterodine ER plus tamsulosin would perceive greater treatment benefit than would men who received placebo.

### Clinical Efficacy Assessments

The primary efficacy end point was patient perception of treatment benefit at week 12. The Perception of Treatment Benefit question<sup>21</sup> was administered after weeks 1, 6, and 12 of treatment. At each visit, the investigator asked the patient, "Have you had any benefit from your treatment?" and if so, "Have you had little benefit or much benefit?" Secondary efficacy measures included bladder diary variables. For every voluntary micturition or urgency urinary incontinence episode, the patient recorded the time of day and rated how urgently he needed to pass urine on a 5-point urgency rating scale (1, no urgency, "I felt no need to empty my bladder but did so for other reasons"; 2, mild urgency, "I could postpone voiding as long as necessary without fear of wetting myself"; 3, moderate urgency, "I could postpone voiding for a short time without fear of wetting myself"; 4, severe urgency, "I could not postpone voiding but had to rush to the toilet in order not to wet myself"; 5, urgency urinary incontinence, "I leaked before arriving at the toilet.").<sup>22-24</sup>

The following variables were assessed: the change from baseline in urgency urinary incontinence episodes (urgency rating, 5) per 24 hours, urgency episodes (nonurgency urinary incontinence micturitions with urgency rating, 3 or 4) per 24 hours, total micturitions per 24 hours, and micturitions per night. Patients were instructed to complete bladder diaries for the 5 days preceding visits at baseline and weeks 1, 6, and 12 of treatment. Analyses of urgency urinary incontinence at all time points were based only on patients with urgency urinary incontinence at baseline (urgency urinary incontinence episodes >0 per 24

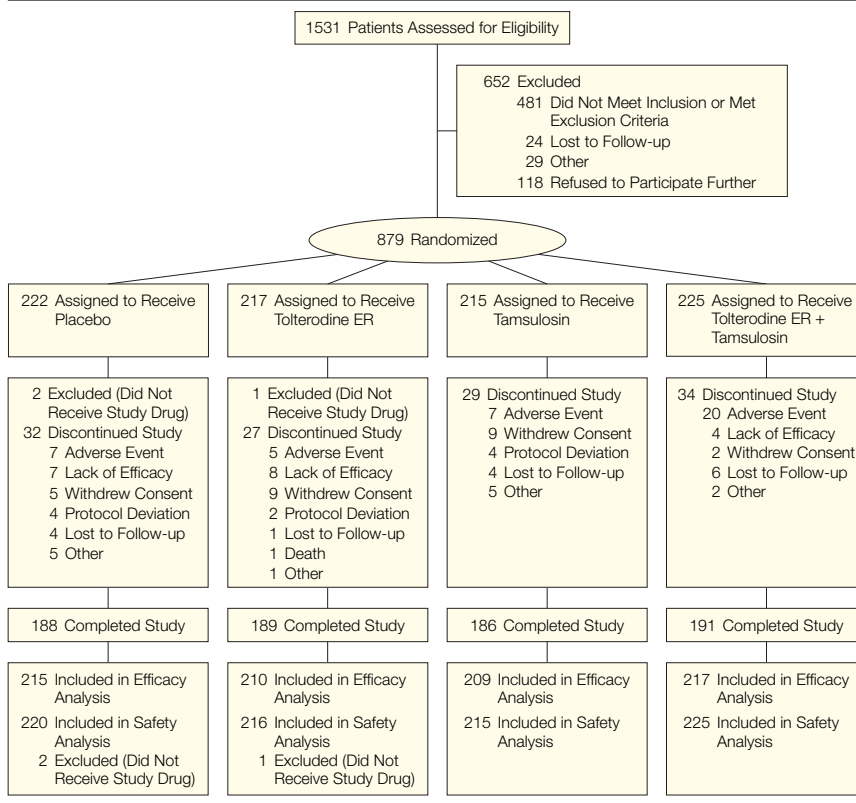
hours). Nighttime was defined as the time a patient went to bed for the night until the time he arose.

Secondary efficacy measures also included the IPSS, which was completed by patients at baseline and weeks 1, 6, and 12 and assessed as the change from baseline. Postvoid residual volume was measured using ultrasound, and maximum urinary flow rate was measured using a flowmeter. Both were assessed at baseline and week 12. All adverse events were recorded.

### Statistical Analyses

As specified in the study protocol, efficacy analyses were based on the intent-to-treat (ITT) population, defined as those patients who received at least 1 dose of study medication and who had a baseline assessment and at least 1 postbaseline assessment. Sample size determinations were based on a projected treatment difference of 15% between the tolterodine ER plus tamsulosin group and placebo group with respect to the proportion of patients who reported treatment benefit by week 12. It was assumed that the percentage of patients with treatment benefit would be no less than 58% in the tolterodine ER and tamsulosin group and no more than 43% in the placebo group. This assumption was based on data collected from men enrolled in a previous study of tolterodine ER.<sup>25</sup> Using a 2-tailed  $\alpha$ -level of .05 with 80% power and assuming the true response rates of 58% vs 43%, 178 patients per group were required. Allowing for an approximate 15% dropout rate, we aimed to enroll 832 men (208 per group).

Between-group differences for the percentage of patients answering "yes" to the questions related to treatment benefit at weeks 1, 6, and 12 were analyzed with a 2-sided Fisher exact test. Missing data for patient perception of treatment benefit were handled using the last observation carried forward technique. Diary values were averaged for all available diary days, but completion of 3 or more days of a 5-day diary period was required for the data to be included in the analysis. If fewer than 3 days of the diary period were completed, postbaseline data were imputed

**Figure 1.** Study Flow Diagram

using the last observation carried forward. Changes in diary variables were analyzed using an analysis of covariance model with terms for center, treatment, postvoid residual volume, maximum urinary flow rate, and baseline value of the variable being analyzed. Changes on the IPSS total and QOL item were analyzed using an analysis of covariance model with terms for smoking status, age, center, duration of overactive bladder, and baseline score.

Missing postbaseline data for total IPSS and QOL item scores were also imputed using the last observation carried forward. In additional post hoc analysis, patients with missing data for perception of treatment benefit at week 12 were assigned to the no-benefit group, ie, assuming no change from baseline values. The results of this analysis were comparable with those reported herein.

Assessments of safety and tolerability were based on all patients who received at least 1 dose of study medica-

tion. Changes in maximum urinary flow rate and postvoid residual volume were analyzed using an analysis of covariance model with terms for center, treatment, and baseline value of the variable being analyzed. Adverse events were summarized descriptively. Patients who ingested 80% or more of the study medication during the treatment period (as assessed by the investigator at the end of the trial) were considered adherent. Fisher exact tests were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC). Exact 95% confidence intervals for between-group differences were calculated using STATXACT version 4.0 (Cytel, Inc, Cambridge, Mass).

Blinded sample size re-estimation was conducted on treatment benefit using the Friede and Kieser<sup>26</sup> approach for binary data when approximately 50% of the required ITT population had been entered into the database. The sample size re-estimation results indicated sufficient sample size. Consequently, there

were no changes in the preplanned sample size.

## RESULTS

### Patients

Patients were recruited between November 2004 and February 2006. The study was completed May 8, 2006. A total of 879 patients were randomly assigned to 1 of the 4 treatment groups. Patient disposition is summarized in FIGURE 1, and demographic and baseline clinical characteristics are summarized in TABLE 1. At least 85% of patients in each treatment group completed the study. Few patients discontinued because of lack of efficacy (0%-4%) or adverse events (2%-9%). There was no significant difference between the 4 treatment groups with regard to the proportions of discontinuations ( $P = .87$ , Pearson  $\chi^2$  test) nor the timing of discontinuation ( $P = .79$ , overall log-rank test) suggesting that the last observation carried forward analysis of efficacy was not biased in favor of the active treatment groups.

The mean (SD) age of the ITT population was 62 (10) years (range, 40-92 years). Eighty-three percent of patients were white. At baseline, 24% of patients reported urgency urinary incontinence (1.0[1.6] episodes per 24 hours). Baseline values for other bladder diary variables were 7.2 (3.8) urgency episodes per 24 hours, 11.9 (3.2) micturitions per 24 hours, and 2.0 (1.3) micturitions per night. Mean (SD) IPSS total and QOL item scores were 19.9 (5.3) and 4.6 (0.9), respectively. Maximum urinary flow rate at baseline was 12.9 (7.2) mL/s and postvoid residual volume was 53.1 (53.2) mL. More than 95% of patients in the ITT population had adhered to study medication regardless of group assignment.

As stipulated in the study protocol, 17 patients (1.9% of those randomized: 4 tolterodine ER plus tamsulosin, 5 tolterodine ER, 3 tamsulosin, 5 placebo) were excluded from the primary efficacy analysis because they either did not receive study drug ( $n = 3$ ) or did not have postbaseline efficacy data ( $n = 14$ ). Eleven patients (1% of those randomized: 4 taking tolterodine ER plus tamsulosin; 2, tolterodine ER; 3, tamsulosin, and 2, placebo) were

excluded from the ITT analysis based on the findings of a site audit based on the findings of a site audit performed due to irregularities in which some data, especially diary data from interim visits, could not be verified. A sensitivity analysis of the primary end point that included these 28 patients in the no-benefit category produced results consistent with the analysis that excluded them.

### Efficacy End Points

In the primary efficacy analysis, 172 (80%) of 215 patients receiving tolterodine ER plus tamsulosin reported treatment benefit by week 12 compared with 132 (62%) of 214 receiving placebo ( $P < .001$ ), 136 (65%) of 209 receiving tolterodine ER ( $P = .48$  vs placebo), or 146 (71%) of 207 receiving tamsulosin ( $P = .03$  vs placebo; TABLE 2). Neither group receiving monotherapy demonstrated significant differences vs placebo in percentages of patients reporting treatment benefit (Table 2). A post hoc analysis of patients with missing data for perception of treatment benefit at week 12 were assigned to the no-benefit group demonstrated results consistent with those from the analysis specified in the protocol (Table 2).

Treatment efficacy for overactive bladder symptoms was assessed using data from bladder diaries. Compared with placebo, significant reductions for all bladder diary variables (FIGURE 2) were demonstrated in the tolterodine ER plus tamsulosin group by week 12, as well as at earlier time points: week 1 for urgency episodes per 24 hours ( $P < .001$ ) and micturitions per 24 hours ( $P < .001$ ), and week 6 for urgency episodes per 24 hours ( $P = .006$ ), micturitions per 24 hours ( $P < .001$ ), and micturitions per night ( $P = .02$ ; Figure 2). Patients in the tolterodine ER group compared with those in the placebo group experienced significant reductions in only urgency urinary incontinence episodes per 24 hours at week 12 ( $P = .008$ ) and at week 6 ( $P = .001$ ; Figure 2). Although there were no significant differences between tamsulosin monotherapy and placebo for any diary variables at week 12, micturitions per 24 hours were significantly reduced at week 1 ( $P = .03$ ) and urgency

urinary incontinence episodes per 24 hours were significantly reduced at week 6 ( $P = .004$ ; Figure 2).

Similar trends were observed for the IPSS total and QOL item. By week 12, significant improvements on the IPSS total and QOL item were demonstrated in the tolterodine ER and tamsulosin group (both  $P$  values .003 vs placebo; FIGURE 3). In this group, significant improvements on the QOL item were observed as early as week 6 ( $P = .02$ ; Figure 3B). There were no significant differences between tolterodine ER and placebo on the total IPSS at any visit. There were significant

improvements vs placebo in the total IPSS among patients who received tamsulosin at week 12 ( $P = .007$ ; Figure 3A) and week 1 ( $P = .001$ ), but the effect was not observed at week 6. The tamsulosin group did not demonstrate a statistically significant improvement in the IPSS QOL item at either week 12 or week 6, although a transient improvement was observed at week 1 ( $P = .03$ ; Figure 3B).

### Safety and Tolerability

All 3 active interventions were well tolerated. The most frequent adverse event reported in patients receiving active treat-

**Table 1.** Demographics and Baseline Clinical Characteristics

Demographics	No. (%)			
	Placebo (n = 215)	Tolterodine ER (n = 210)	Tamsulosin (n = 209)	Tolterodine ER + Tamsulosin (n = 217)
Age, y				
Mean (SD)	62.8 (9.7)	61.8 (9.6)	61.7 (10.5)	61.0 (9.6)
Range	40-88	41-91	40-90	40-92
40-49	18 (8)	18 (9)	25 (12)	26 (12)
50-59	60 (28)	71 (34)	59 (28)	60 (28)
60-69	80 (37)	76 (36)	72 (34)	87 (40)
70-79	45 (21)	37 (18)	44 (21)	38 (18)
≥80	12 (6)	8 (4)	9 (4)	6 (3)
Race				
White	178 (83)	165 (79)	173 (83)	188 (87)
Black	20 (9)	27 (13)	19 (9)	9 (4)
Asian	1 (1)	3 (1)	2 (1)	2 (1)
Other	16 (7)	15 (7)	15 (7)	18 (8)
Common comorbidities*				
Hypertension	109 (49)	107 (49)	95 (44)	105 (47)
Arthritis	79 (36)	79 (36)	79 (37)	80 (36)
Hypercholesterolemia	74 (33)	59 (27)	57 (27)	45 (20)
Erectile dysfunction	59 (27)	57 (26)	49 (23)	53 (24)
Coronary artery disease	37 (17)	25 (12)	30 (14)	28 (12)
Diabetes, type 2	37 (17)	35 (16)	32 (15)	31 (14)
Depression	31 (14)	30 (14)	36 (17)	30 (13)
Diary variables, mean (SD)				
Urgency urinary incontinence episodes per 24 h†	0.98 (1.26)	0.84 (0.85)	0.71 (0.92)	1.40 (2.58)
Urgency episodes per 24 h	7.33 (3.82)	7.58 (3.49)	7.10 (3.83)	6.72 (3.95)
Micturitions per 24 h	11.86 (3.24)	11.79 (2.83)	12.10 (3.51)	11.92 (3.35)
Micturitions per night	2.02 (1.19)	1.97 (1.27)	1.74 (1.20)	2.07 (1.32)
Duration of symptoms, mean (SD), y	5 (6.68)	5 (4.86)	5 (5.06)	6 (7.27)
IPSS, mean (SD)				
IPSS total	20.00 (5.42)	19.53 (5.15)	20.04 (5.02)	20.10 (5.49)
IPSS QOL	4.58 (0.95)	4.57 (0.94)	4.57 (0.86)	4.55 (0.93)
Maximum urinary flow rate, mean (SD), mL/s	12.2 (6.6)	13.3 (7.8)	13.4 (7.6)	12.7 (6.8)
Postvoid residual volume, mean (SD), mL	47.1 (47.7)	50.5 (55.8)	56.5 (55.0)	58.8 (53.8)

Abbreviations: ER, extended release; IPSS, International Prostate Symptom Score; ITT, intent to treat; QOL, quality of life.

\*All randomized patients.

†Among ITT patients with urgency urinary incontinence episodes of at least 1 in 24 hours at baseline (placebo, 48; tolterodine ER, 53; tamsulosin, 50; tolterodine ER plus tamsulosin, 52).

**Table 2.** Patients Reporting Treatment Benefit at Week 12

	Placebo (n = 215)	Tolterodine ER (n = 210)	Tamsulosin (n = 209)	Tolterodine ER + Tamsulosin (n = 217)
<b>Protocol-Specified Intention-to-Treat Analysis*</b>				
Missing, No.	1	1	2	2
Patient report, No. (%)				
Benefit	132 (61.7)	136 (65.1)	146 (70.5)	172 (80.0)
No benefit	82 (38.3)	73 (34.9)	61 (29.5)	43 (20.0)
Pairwise comparison, <i>P</i> value (95% CI for difference), %†				
Placebo		.48 (−6 to 13)	.06 (−1 to 19)	<.001 (9 to 28)
Tolterodine ER			.25 (−4 to 15)	.001 (6 to 25)
Tamsulosin				.03 (1 to 19)
<b>Post Hoc Intention-to-Treat Analysis‡</b>				
	(n = 222)	(n = 217)	(n = 215)	(n = 225)
Patient report, No. (%)				
Benefit	132 (59.5)	136 (62.7)	146 (67.9)	172 (76.4)
No benefit	90 (40.5)	81 (37.3)	69 (32.1)	53 (23.6)
Pairwise comparison, <i>P</i> value (95% CI for difference), %†				
Placebo		.49 (−6 to 13)	.07 (−1 to 18)	<.001 (8 to 26)
Tolterodine ER			.27 (−4 to 15)	.002 (5 to 23)
Tamsulosin				.06 (0 to 18)

Abbreviations: CI, 95% 2-sided exact confidence interval; ER, extended release.

\*Values reflect intention-to-treat analysis in which missing data for patient perception of treatment benefit were handled by imputation using the last observation carried forward.

†Between-group analyses compared percentages of patients who answered "yes" to the question: "Have you had any benefit from your treatment?"

‡Values reflect intention-to-treat analysis in which missing data for patient perception of treatment benefit were handled by imputation assuming no change from baseline values.

ment was dry mouth. Two patients taking tamsulosin and 5 patients taking tolterodine ER plus tamsulosin stopped treatment because of dry mouth. The incidences of adverse events reported for 2% or more of any treatment group are reported in TABLE 3.

All treatment groups demonstrated slight changes in maximum urinary flow rate compared with baseline (placebo, −0.53; tolterodine ER, −0.60; tamsulosin, −0.22; and tolterodine ER plus tamsulosin, 0.07). Neither the changes from baseline nor comparisons between any 2 groups were statistically significant (all *P* values >.3). Patients treated with tolterodine ER and those treated with tolterodine ER plus tamsulosin demonstrated 5 to 6 mL increases in postvoid residual volume from baseline (placebo, −3.61; tolterodine ER, 5.27; tamsulosin, 0.11; tolterodine ER plus tamsulosin, 6.42). These increases were not statistically or clinically significant, and there were no significant differences in the change in postvoid residual volume between any 2 groups.

Nine patients reported increased voiding difficulties, including urinary retention (n=6), decreased urinary flow (n=2), or both (n=1). Two patients taking placebo; 1, tolterodine ER; and 1, tolterodine ER plus tamsulosin discontinued treatment because of urinary retention, decreased urinary flow, or both. Of these 4 patients, 2 required urinary bladder catheterization (TABLE 4). The first patient, 75 years old, required catheterization after taking tolterodine ER plus tamsulosin for 4 days. He discontinued that day. The other, 78 years old, reported decreased urinary flow after 5 days of tolterodine ER treatment. He recovered the same day, but on day 11, he reported urinary retention, underwent catheterization, and dropped out of the study.

## COMMENT

This study is, to our knowledge, the first large-scale, randomized, double-blind, placebo-controlled study to investigate the efficacy of an antimuscarinic agent, an  $\alpha$ -receptor antagonist, and treatment with both active drugs in men both

ered by lower urinary tract symptoms, including use of a diary to document overactive bladder symptoms. A significantly greater proportion of patients in the tolterodine ER plus tamsulosin group reported treatment benefit than the 3 other groups. The proportion of patients reporting treatment benefit in the tolterodine ER and tamsulosin monotherapy groups were not significantly different from placebo.

The symptoms of urgency urinary incontinence, urgency, and 24-hour and nocturnal micturition frequency were also significantly improved by week 12 in the group receiving tolterodine ER plus tamsulosin vs placebo but not in the tamsulosin group. In the tolterodine ER group, only urgency urinary incontinence episodes per 24 hours were significantly reduced at week 12. The IPSS total and QOL item scores were significantly improved by week 12 among patients receiving tolterodine ER plus tamsulosin. In the tamsulosin group, total IPSS was significantly improved by week 12, but the QOL item was not significantly improved compared with placebo. Tolterodine ER monotherapy was not associated with significant improvements on the IPSS total or QOL item score. Changes in postvoid residual volume, maximum urinary flow rate, or incidence of acute urinary retention did not differ significantly among the 4 treatment groups.

The question about the patient's perception of treatment benefit was selected as the primary end point because it is based on the assumption that the patient provides a global response that weighs the risks (eg, adverse events) and benefits (eg, symptom relief, life impact) of treatment.<sup>21</sup> Patient-reported outcomes are particularly important for evaluating the therapeutic benefit of pharmacotherapies that do not cure chronic conditions.<sup>27</sup>

However, determining how much change in a patient-reported outcome measure is clinically meaningful can be a challenge. The concept of a minimally important difference—the smallest change in a patient-reported outcome measure that would be considered

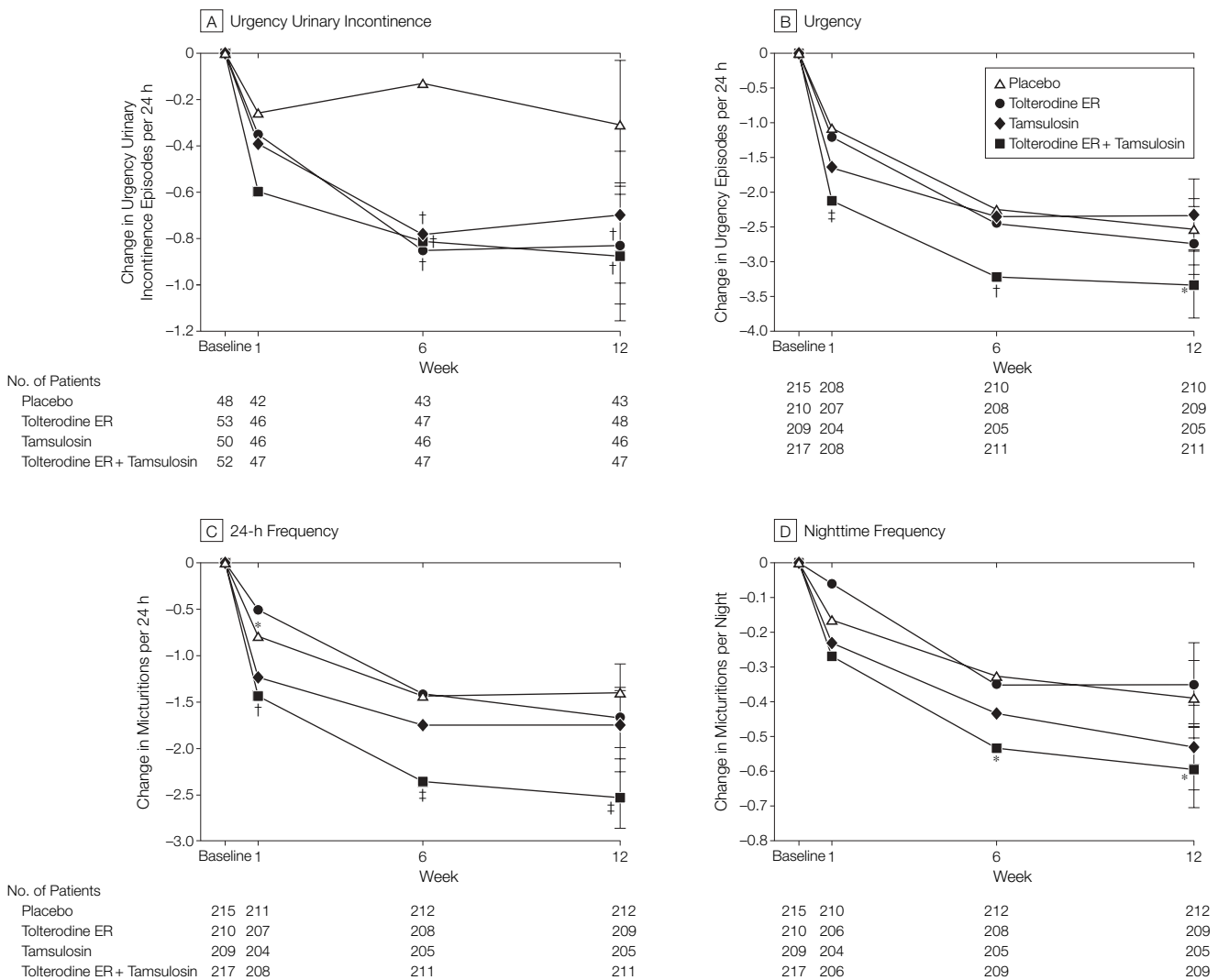
meaningful to a patient—was developed to quantify these changes.<sup>28</sup> Although the minimally important difference for how patients perceive treatment benefit has not been determined, this question was used to anchor (ie, serve as an external criterion with which to compare changes in a health-related QOL domain<sup>29</sup>) studies determining the minimally important difference of 2 validated overactive bladder–specific health-related QOL, the Overactive Bladder

questionnaire<sup>30</sup> and the King’s Health questionnaire.<sup>31</sup> In these studies, patients reporting treatment benefit also experienced improvements in most health-related QOL domains.

Previous clinical studies have demonstrated that the reduction in urgency urinary incontinence episodes is a robust end point with regard to response to antimuscarinic therapy.<sup>8,25,32</sup> Not surprisingly, patients receiving tolterodine ER alone demonstrated significant re-

ductions in episodes of urgency urinary incontinence compared with placebo. For the other bladder diary variables, only patients receiving both active drugs demonstrated significant reductions compared with placebo. Significant improvements on the total IPSS were observed by week 12 among patients receiving tamsulosin and among those receiving tolterodine ER plus tamsulosin. However, data from the tamsulosin group suggest that a significant

**Figure 2.** Outcomes Measures Among Treatment Groups



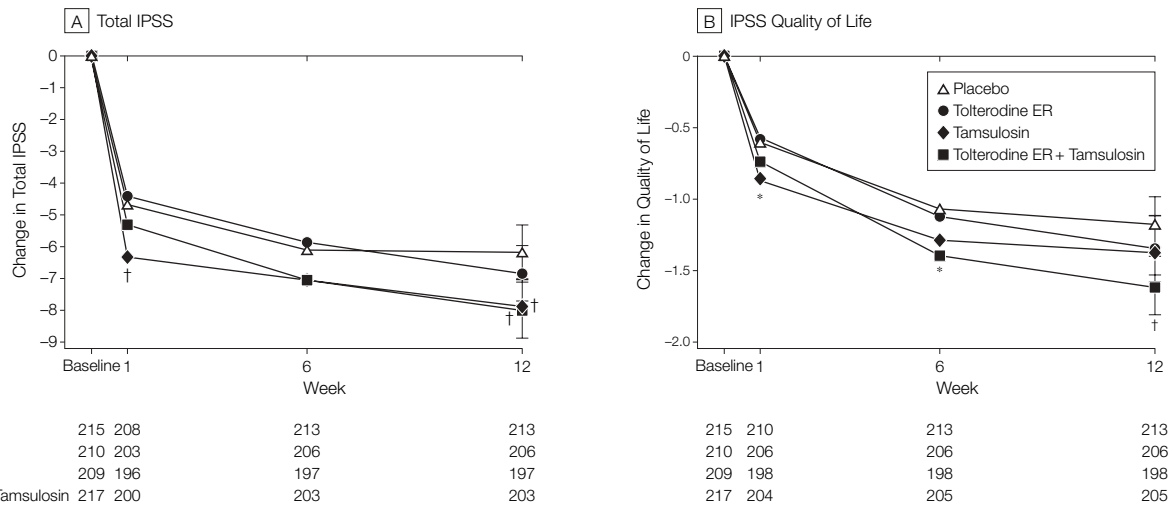
Panel B represents patients who at baseline reported experiencing at least 1 urgency urinary incontinence episode within 24 hours. Values are adjusted means (ie, least-squares means). ER indicates extended release.

\* $P < .05$ .

† $P < .01$ .

# $P < .001$  vs placebo.

**Figure 3.** Changes From Baseline in International Prostate Symptom Score and Quality of Life Scores



Values are adjusted means (ie, least-squares means). ER indicates extended release; IPSS, International Prostate Symptom Score.

\* $P < .05$ .

† $P < .01$  vs placebo.

**Table 3.** Incidence of All-Cause Adverse Events (Safety Population)

Adverse Event	Placebo (n = 220)	Tolterodine ER (n = 216)	Tamsulosin (n = 215)	Tolterodine ER + Tamsulosin (n = 225)
Constipation	5 (2)	9 (4)	2 (1)	8 (4)
Diarrhea	3 (1)	7 (3)	6 (3)	5 (2)
Dizziness	2 (1)	3 (1)	12 (6)	6 (3)
Dry mouth	5 (2)	16 (7)	15 (7)	47 (21)
Dyspepsia	5 (2)	2 (1)	1 (1)	3 (1)
Ejaculation failure	0 (0)	0 (0)	4 (2)	7 (3)
Fatigue	6 (3)	2 (1)	3 (1)	2 (1)
Headache	7 (3)	2 (1)	9 (4)	14 (6)
Nasal congestion	2 (1)	0 (0)	3 (1)	10 (4)
Somnolence	2 (1)	2 (1)	5 (2)	4 (2)

Abbreviation: ER, extended release.

**Table 4.** Urinary Retention Summary

	Placebo (n = 220)	Tolterodine ER (n = 216)	Tamsulosin (n = 215)	Tolterodine ER + Tamsulosin (n = 225)
No. of reported adverse events	4	4	0	2
Urinary retention	3	2	0	2
Urinary flow decreased	1	2	0	0
No. of discontinuation due to adverse event	2	1	0	1
Catheterization required	0	1	0	1

Abbreviation: ER, extended release.

change on the total IPSS does not necessarily correspond to a significant improvement on the IPSS QOL item in this population. The IPSS does not include an item for urgency urinary inconti-

nence nor does it measure urgency or daytime or nocturnal micturition frequency in a quantitative manner. In addition, only 3 of the 7 IPSS questions relate to overactive bladder symptoms. This

may explain why tolterodine ER monotherapy did not significantly improve total IPSS, although it significantly reduced urgency urinary incontinence.

Dry mouth was the adverse event most frequently reported by patients receiving active treatment. The 7% incidence of dry mouth experienced by the tolterodine ER group is less than what has been reported in previous trials of patients receiving tolterodine ER for overactive bladder (23%,<sup>25</sup> 34%<sup>32</sup>). However, some evidence suggests that nighttime dosing may reduce the incidence of dry mouth and other adverse events.<sup>33</sup> The reason for the difference between the incidence of dry mouth in the monotherapy groups (7%) and the combination group (21%) requires further investigation.

There has been concern that the inhibitory effect of antimuscarinic agents on detrusor muscle contraction could theoretically aggravate the voiding difficulties or cause urinary retention and possible bladder outlet obstruction. To address this concern, maximum urinary flow rate, postvoid residual volume, discontinuation from trial with symptoms suggestive of urinary retention, and incidence of acute urinary retention were evaluated. There were no significant changes in maximum uri-

nary flow rate or postvoid residual volume for any treatment group.

Tamsulosin monotherapy significantly increased maximum urinary flow rate in previous studies, and differences in the results between those and the current study may be attributed to differences in baseline values. Baseline maximum urinary flow rate was 9 to 10 mL/s in phase 3 tamsulosin studies<sup>34</sup>; these values suggest bladder outlet obstruction.<sup>35</sup> Maximum urinary flow rate increased approximately 2 mL/s with tamsulosin treatment.<sup>34</sup>

In the current study, mean maximum urinary flow rate at baseline was 12.9 mL/s. Improvements in maximum urinary flow rate may be less likely in patients with greater flow rates at baseline, reflecting unilateral regression to the mean artifact and part of the placebo effect complex.<sup>36</sup> The incidence of acute urinary retention was low among patients receiving active treatment (tolterodine ER plus tamsulosin, 0.5%; tolterodine ER, 0.5%). The low incidence of acute urinary retention is consistent with rates reported for men enrolled in previous 3- to 6-month studies of tolterodine ER monotherapy<sup>7-9</sup> or in addition to  $\alpha$ -receptor antagonists.<sup>10,18</sup> In these studies, the incidence of acute urinary retention with active treatment was comparable with placebo.

Results from previous small-scale, non-placebo-controlled studies support the use of tolterodine plus  $\alpha$ -receptor antagonist therapy in men with lower urinary tract symptoms, presumably including overactive bladder symptoms. Lee et al<sup>10</sup> reported that 32 (73%) of 44 men with urodynamically confirmed detrusor overactivity and bladder outlet obstruction who did not respond to treatment with doxazosin experienced symptomatic improvements (>3-point reduction on the total IPSS) after 3 months of treatment with doxazosin and tolterodine. In another study, Athanasopoulos et al<sup>18</sup> administered tamsulosin to 50 men with urodynamically confirmed bladder outlet obstruction and detrusor overactivity. After a week, these men were randomized to tamsulosin plus tolterodine or tamsulosin alone for 3 months. Significant improvements in

urodynamics and a QOL measure were observed in patients receiving both tamsulosin and tolterodine, but not among those receiving tamsulosin alone. The current study extends the understanding of the efficacy and safety of treatment with tolterodine alone or with an  $\alpha$ -receptor because of its large-scale, 4-group, placebo-controlled design and inclusion of patients based on overactive bladder and BPH research entry criteria rather than urodynamic criteria.

All efficacy results should be interpreted in light of the limitation that the study was only powered to differentiate the effects of treatment between the tolterodine ER plus tamsulosin and the placebo groups. However, the inclusion of the monotherapy groups was important to provide insight into the response to monotherapy of men who meet standard research criteria for inclusion in both overactive bladder and BPH trials and to identify potential clinical factors that may predict a patient's response to monotherapy. The large placebo response observed in this study for all efficacy end points also deserves mention. The placebo group cannot be viewed as a nontreatment group in this study, principally, because patients were required to complete bladder diaries. Bladder diaries provide insights into behavioral modifications that may improve symptoms by enhancing patients' awareness of their bladder habits.<sup>37</sup> Men are generally not required to complete bladder diaries in BPH trials; thus, the patients enrolled in the current study were susceptible to the training effect of the bladder diary. Finally, the short duration of this trial necessitates the investigation of tolterodine ER plus tamsulosin therapy for a longer period.

Urinary function is affected by detrusor contractility and urethral resistance, including that imparted by smooth muscle of the prostate and bladder neck. Improved urinary function in men who met the standard research criteria for both overactive bladder and BPH required normalization of detrusor contractility in addition to reduction in the smooth muscle tone of the prostate and bladder neck. Neither tolterodine ER nor tamsulosin alone was suffi-

cient to achieve significant treatment benefit, suggesting that attenuation of lower urinary tract symptoms in this population requires a treatment strategy that targets both the bladder and the prostate.

Closer examination of this study population's characteristics may offer insight into which men will respond to monotherapy and which men may require antimuscarinic plus  $\alpha$ -receptor therapy. For example, the mean IPSS total and QOL item for men enrolled in this study were 19.9 and 4.6, respectively, compared with 16.9<sup>13</sup> and 3.0 according to C.G.R. (September 1, 2006) in the Medical Therapy of Prostatic Symptoms study.<sup>13</sup> The higher baseline IPSS scores appear to be largely driven by the storage subscale (baseline IPSS storage subscale, 10.1 compared with the Medical Therapy of Prostatic Symptoms study, 7.6, according to C.G.R. (September 1, 2006), which reflects the entry requirement for significant urgency and frequency.

Retrospective evaluation of the baseline characteristics (IPSS and diary variables) of men who have failed treatment with  $\alpha$ -receptor antagonists<sup>7,10,13</sup> or antimuscarinic agents<sup>8,9</sup> in previous clinical trials and open-label studies may be informative. For instance, patients who did not respond to  $\alpha$ -receptor antagonists may have had more severe symptoms at baseline, including the symptoms that characterize overactive bladder. These patients may represent the best candidates for antimuscarinic plus  $\alpha$ -receptor antagonist treatment. Carefully designed epidemiological studies may help determine the size of this subgroup in the general population and the best methods to identify them.

## CONCLUSIONS

The results of this study demonstrate that some men bothered by lower urinary tract symptoms, including bladder diary–documented overactive bladder symptoms, might not respond to monotherapy with either  $\alpha$ -receptor antagonists or antimuscarinic agents. Treatment with tolterodine ER plus tamsulosin resulted in statistically and clinically significant treatment benefit. Similarly low incidences of acute urinary retention were observed in all treat-

ment groups, and there were no significant differences in maximum urinary flow rate or postvoid residual volume between any 2 groups.

**Author Contributions:** Dr Kaplan had full access to all of 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:* Kaplan, Roehrborn, Rovner, Carlsson, Bavendam, Guan.

*Acquisition of data:* Rovner, Bavendam, Guan.

*Analysis and interpretation of data:* Kaplan, Roehrborn, Rovner, Carlsson, Bavendam, Guan.

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

*Critical revision of the manuscript for important intellectual content:* Kaplan, Roehrborn, Rovner, Bavendam, Guan.

*Statistical analysis:* Roehrborn, Carlsson.

*Obtained funding:* Bavendam.

*Administrative, technical, or material support:* Kaplan, Bavendam, Guan.

*Study supervision:* Kaplan, Roehrborn, Guan.

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**Role of the Sponsor:** Mr Carlsson and Drs Bavendam and Guan were involved in all elements of this study, including, but not limited to, study design and monitoring. In addition, the database containing the findings at all 95 investigator sites was maintained by Pfizer Inc, and statistical analyses were performed at Pfizer Inc by Mr Carlsson. All authors, including those employed by Pfizer Inc, reviewed and edited the manuscript.

**Independent Statistical Analysis:** All study data were transferred from Pfizer Inc to the Department of Obstetrics and Gynecology at the University of Texas Southwestern Medical Center for independent reanalysis by Donald D. McIntyre, PhD. The independent statistical analysis involved the primary and secondary outcomes, participant demographics, and safety as described in this article. There were no discrepancies between the results of the reanalysis and those presented in the article. Compensation for Dr McIntyre was provided through an unrestricted grant from Weill Medical College. Pfizer did not provide funds to support the independent statistical analysis.

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dence base for treatment approach and goals of therapy is limited.<sup>2</sup> We also concur with the point of Mr Cormican and Dr Seidman about the potential value of referring older adults with functional limitations to an occupational therapist for evaluation and treatment.

Kenneth Boockvar, MD, MS  
 kenneth.boockvar@mssm.edu  
 James J. Peters VA Medical Center  
 Bronx, NY  
 Diane Meier, MD  
 Mount Sinai School of Medicine  
 New York, NY

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## CORRECTION

**Omission of Text in Financial Disclosures:** In the Original Contribution entitled "Tolterodine and Tamsulosin for Treatment of Men With Lower Urinary Tract Symptoms and Overactive Bladder: A Randomized Controlled Trial" published in the November 15, 2006, issue of *JAMA* (2006;295:2319-2328), text in 2 sentences of the financial disclosure was inadvertently omitted. The sentence that read "Dr Roehrborn is also a consultant for GlaxoSmithKline, Sanofi Aventis, and Lilly ICOS, a consultant for Allergan and Esprit, a speaker for Astellas and Esprit, and a study investigator for Allergan and Q-Med" should have read "Dr Roehrborn is also a consultant for GlaxoSmithKline, Sanofi Aventis, and Lilly ICOS, and is a study investigator for Lilly ICOS. Dr Rovner is a paid consultant, speaker, meeting participant, and study investigator for Pfizer; a consultant for Allergan and Esprit; a speaker for Astellas and Esprit; and a study investigator for Allergan and Q-Med."

Without books, history is silent, literature dumb, science crippled, thought and speculation at a standstill. They are engines of change, windows on the world, lighthouses erected in the sea of time.  
 —Barbara Tuchman (1912-1989)

blood pressure regulation and provides the basis for targeting research to the stimulation of endogenous nitric oxide synthesis as a novel blood pressure-lowering principle.

Dirk Taubert, MD, PhD  
 dirk.taubert@medizin.uni-koeln.de  
 Department of Pharmacology  
 Norma Jung, MD  
 Department of Internal Medicine  
 Renate Roesen, PhD  
 Department of Pharmacology  
 University Hospital of Cologne  
 Cologne, Germany

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## CORRECTIONS

**Incorrect Data:** In the Original Contribution entitled "Tolterodine and Tamsulosin for Treatment of Men With Lower Urinary Tract Symptoms and Overactive Bladder: A Randomized Controlled Trial" published in the November 15, 2006, issue of *JAMA* (2006;296[19]:2319-2328), a *P* value was incorrectly reported. On page 2323 in the "Efficacy End Points" subsection, the section of the first sentence that read "or 146 (71%) of 207 receiving tamsulosin (*P*=.03 vs placebo)" should have read "(*P*=.064 vs placebo)."

**Incorrect Title:** In the Perspectives on Care at the Close of Life: Coda entitled "Lateral Sclerosis: 'Prepare for the Worst and Hope for the Best'" published in the September 12, 2007, issue of *JAMA* (2007;298[10]:1208-1208), the title should have read "Amyotrophic Lateral Sclerosis: 'Prepare for the Worst and Hope for the Best.'"

**Incorrect Data:** In the Original Contribution entitled "Neurologic Adverse Events Associated With Smallpox Vaccination in the United States, 2002-2004" published in the December 7, 2005, issue of *JAMA* (2005;294[21]:2744-2750) the abstract misstated the subgroups of civilian and military vaccinees. The 665 000 persons vaccinated against smallpox were compiled from the experience of the Departments of Defense (n=625 400) and Health and Human Services (n=39 400). The erroneously reported subtotal values (Department of Defense n=590 400 and Department of Health and Human Services n=64 600) appeared only in the abstract, were not used in the analyses, and did not influence the information reported in the body of the article. On page 2748, at the top of the second column, the reporting rate of Bell palsy among primary vaccinees was also misstated. The correct rate is 1.4/100 000, not 0.9/100 000. The overall rate described was correctly stated (1.7/100 000 vaccinations). The number of seizures reported in Table 3 was also misstated, although they are correctly stated elsewhere in the article. Overall 8 seizures were reported, of which 7 (85%) were among primary vaccinees. Five of these occurred in the interval of 2-30 days, and thus 29 adverse events occurred in that interval in Table 3. The error in reported seizure cases was carried over to the total number of serious neurologic events reported elsewhere in the article. The correct value is 38 (not 39), with 26 (not 27) among primary vaccinees, and a proportion among primary vaccinees of 68% (not 69%). On page 2748, in the first sentence of the first paragraph in column 2, the word "median" is missing. That sentence should read, "Eight patients had reported seizures a median of 9 days after vaccination." We consider none of these errors to affect the discussion points or the conclusions of this article, nor to affect the validity of the conclusions reached in our study.

blood pressure regulation and provides the basis for targeting research to the stimulation of endogenous nitric oxide synthesis as a novel blood pressure-lowering principle.

Dirk Taubert, MD, PhD  
 dirk.taubert@medizin.uni-koeln.de  
 Department of Pharmacology  
 Norma Jung, MD  
 Department of Internal Medicine  
 Renate Roesen, PhD  
 Department of Pharmacology  
 University Hospital of Cologne  
 Cologne, Germany

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## CORRECTIONS

**Incorrect Data:** In the Original Contribution entitled "Tolterodine and Tamsulosin for Treatment of Men With Lower Urinary Tract Symptoms and Overactive Bladder: A Randomized Controlled Trial" published in the November 15, 2006, issue of *JAMA* (2006;296[19]:2319-2328), a *P* value was incorrectly reported. On page 2323 in the "Efficacy End Points" subsection, the section of the first sentence that read "or 146 (71%) of 207 receiving tamsulosin (*P*=.03 vs placebo)" should have read "(*P*=.064 vs placebo)."

**Incorrect Title:** In the Perspectives on Care at the Close of Life: Coda entitled "Lateral Sclerosis: 'Prepare for the Worst and Hope for the Best'" published in the September 12, 2007, issue of *JAMA* (2007;298[10]:1208-1208), the title should have read "Amyotrophic Lateral Sclerosis: 'Prepare for the Worst and Hope for the Best.'"

**Incorrect Data:** In the Original Contribution entitled "Neurologic Adverse Events Associated With Smallpox Vaccination in the United States, 2002-2004" published in the December 7, 2005, issue of *JAMA* (2005;294[21]:2744-2750) the abstract misstated the subgroups of civilian and military vaccinees. The 665 000 persons vaccinated against smallpox were compiled from the experience of the Departments of Defense (n=625 400) and Health and Human Services (n=39 400). The erroneously reported subtotal values (Department of Defense n=590 400 and Department of Health and Human Services n=64 600) appeared only in the abstract, were not used in the analyses, and did not influence the information reported in the body of the article. On page 2748, at the top of the second column, the reporting rate of Bell palsy among primary vaccinees was also misstated. The correct rate is 1.4/100 000, not 0.9/100 000. The overall rate described was correctly stated (1.7/100 000 vaccinations). The number of seizures reported in Table 3 was also misstated, although they are correctly stated elsewhere in the article. Overall 8 seizures were reported, of which 7 (85%) were among primary vaccinees. Five of these occurred in the interval of 2-30 days, and thus 29 adverse events occurred in that interval in Table 3. The error in reported seizure cases was carried over to the total number of serious neurologic events reported elsewhere in the article. The correct value is 38 (not 39), with 26 (not 27) among primary vaccinees, and a proportion among primary vaccinees of 68% (not 69%). On page 2748, in the first sentence of the first paragraph in column 2, the word "median" is missing. That sentence should read, "Eight patients had reported seizures a median of 9 days after vaccination." We consider none of these errors to affect the discussion points or the conclusions of this article, nor to affect the validity of the conclusions reached in our study.

dence base for treatment approach and goals of therapy is limited.<sup>2</sup> We also concur with the point of Mr Cormican and Dr Seidman about the potential value of referring older adults with functional limitations to an occupational therapist for evaluation and treatment.

Kenneth Boockvar, MD, MS  
 kenneth.boockvar@mssm.edu  
 James J. Peters VA Medical Center  
 Bronx, NY  
 Diane Meier, MD  
 Mount Sinai School of Medicine  
 New York, NY

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1. Berenstein EG, Ortiz Z. Megestrol acetate for the treatment of anorexia-cachexia syndrome. *Cochrane Database Syst Rev.* 2005;(2):CD004310.
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## CORRECTION

**Omission of Text in Financial Disclosures:** In the Original Contribution entitled "Tolterodine and Tamsulosin for Treatment of Men With Lower Urinary Tract Symptoms and Overactive Bladder: A Randomized Controlled Trial" published in the November 15, 2006, issue of *JAMA* (2006;296:2319-2328), text in 2 sentences of the financial disclosure was inadvertently omitted. The sentence that read "Dr Roehrborn is also a consultant for GlaxoSmithKline, Sanofi Aventis, and Lilly ICOS, a consultant for Allergan and Esprit, a speaker for Astellas and Esprit, and a study investigator for Allergan and Q-Med" should have read "Dr Roehrborn is also a consultant for GlaxoSmithKline, Sanofi Aventis, and Lilly ICOS, and is a study investigator for Lilly ICOS. Dr Rovner is a paid consultant, speaker, meeting participant, and study investigator for Pfizer; a consultant for Allergan and Esprit; a speaker for Astellas and Esprit; and a study investigator for Allergan and Q-Med."

Without books, history is silent, literature dumb, science crippled, thought and speculation at a standstill. They are engines of change, windows on the world, lighthouses erected in the sea of time.  
 —Barbara Tuchman (1912-1989)