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CLINICAL EFFICACY AND SAFETY OF TOLTERODINE IN THE TREATMENT OF OVERACTIVE BLADDER: A POOLED ANALYSIS

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ABSTRACT

Objectives. To examine the safety, efficacy, and tolerability of tolterodine in four randomized, double-blind, parallel, multicenter, 12-week studies of patients with overactive bladder.

Methods. Two of the four studies compared tolterodine (2 mg twice daily) to oxybutynin (5 mg three times daily) and placebo, one study compared tolterodine (2 mg twice daily) to oxybutynin (5 mg three times daily), and one study compared two dosages of tolterodine (1 and 2 mg twice daily) to placebo. Efficacy was determined from micturition diaries and patient perception of their bladder condition. Safety and tolerability were assessed from adverse events and laboratory measures.

Results. A total of 1,120 patients were randomized and treated at 134 centers. For the primary efficacy variable, the number of micturitions/24 hours, pooled results showed a significant decrease from baseline for the 1 mg tolterodine ($P < 0.001$), 2 mg tolterodine ($P < 0.001$), and 5 mg oxybutynin ($P < 0.01$) groups, compared to placebo. Both tolterodine doses and oxybutynin significantly decreased incontinence episodes/24 hours and significantly increased volume voided/micturition, compared to placebo. Tolterodine at a dose of 2 mg twice daily and 5 mg oxybutynin twice daily were significantly more effective in improving patient perception of bladder condition than placebo. Tolterodine at a dose of 2 mg and 5 mg oxybutynin were equivalent in their effectiveness. Tolterodine at doses of 1 mg and 2 mg were tolerated significantly better than oxybutynin when adverse events, dry mouth (both frequency and intensity), dose reductions, and patient withdrawals were considered.

Conclusions. Although oxybutynin is highly effective, its clinical utility is limited by systemic side effects that lead to frequent discontinuation of treatment or dose reductions. Patients receiving tolterodine should not experience these limitations and instead will get safe and long-term effective treatment for their condition.

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Symptoms of the overactive bladder are urgency, frequency, and urge incontinence caused by involuntary contractions of the detrusor muscle during bladder filling. As the detrusor contractions are mediated by cholinergic muscarinic receptor stimulation, antimuscarinic drugs have been used for the treatment of this condition.[1] The most commonly used antimuscarinic agent for treatment of overactive bladder is oxybutynin, which has been shown to be effective in controlled clinical studies.[2] However, the clinical usefulness of oxybutynin is limited by systemic side effects, particularly dry mouth,[3,4] which may be of sufficient severity to result in poor compliance or even discontinuation of treatment.[1,5]

Tolterodine is a new, potent, competitive muscarinic receptor antagonist developed for treatment of the overactive bladder. This compound was selected for development with the objective of achieving a separation of the antimuscarinic effects on the urinary bladder and salivary glands. Differences between tolterodine and oxybutynin have been demonstrated in a number of preclinical studies, including pharmacologic in vitro and in vivo studies.[6] It has been demonstrated that the two compounds are equipotent at bladder muscarinic receptors, as shown by radioligand binding and functional data.[6] However, radioligand binding data show that tolterodine has 8 times less potency than oxybutynin at the muscarinic receptors in the parotid gland.[6]

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TABLE I. *12-Week treatment duration phase III tolterodine studies*

Studies	Enrollment Objective (patients)	Treatment Duration (weeks)
Placebo-controlled		
94-OATA-009	250	12
Placebo- and active-controlled		
94-OATA-008	250	12
94-OATA-010	250	12
Active-controlled		
94-OATA-015	200	12

The tolterodine clinical development program was the largest such program ever undertaken with a medication for the treatment of overactive bladder. To date, a total of 29 studies (17 phase I, 4 phase II, and 8 phase III studies) have been conducted in 15 countries. More than 1,800 patients have been treated with tolterodine in clinical trials.

A total of eight phase III studies were undertaken to examine the safety, efficacy, and tolerability of tolerodine in patients with overactive bladder and symptoms of frequency and urge incontinence or urgency. The duration of treatment was 4 weeks in four of the studies and 12 weeks in the other four studies.

This article will detail the efficacy, safety, and tolerability results from the four studies that used a 12-week treatment duration.

MATERIALS AND METHODS

Four randomized, double-blind, parallel, multicenter, 12-week treatment studies were conducted in nine countries. Two of the studies compared 2 mg tolterodine twice daily to 5 mg oxybutynin three times daily and placebo, one study compared 2 mg tolterodine twice daily to 5 mg oxybutynin three times daily, and one study compared two dosages of tolterodine (1 and 2 mg twice daily) to placebo (Table I). Patients completed a 2-week washout/run-in period before randomization to treatment. Patients were seen at entry (visit 1 at −1 or −2 weeks), at baseline (visit 2, day 1), and after 2, 4, 8, and 12 weeks of treatment (visits 3, 4, 5, and 6, respectively). In the studies comparing tolterodine and oxybutynin, dose reduction was permitted within the first 2 weeks of treatment in the case of intolerance to the study medication and only as an alternative to withdrawal.

In these studies, no upper age limit was set, no concomitant medications (except drugs with anticholinergic effects and drugs for urge incontinence) were excluded, and electrocardiograms (ECGs) were performed only at the end of treatment for patients in one study. This was due to the finding of an excellent safety profile for tolterodine in phase I and II studies.

Common inclusion criteria in the studies were 1) patients who understood and gave signed informed consent; 2) male and female patients ≥18 years of age; 3) evidence of detrusor overactivity (phasic detrusor contraction with an amplitude ≥ 10 cm H_2O); and 4) urinary frequency (an average of ≥8 micturitions/24 hours) and urge incontinence (an average of ≥1 incontinence episode/24 hours) or urinary frequency.

Common exclusion criteria in the studies were 1) clinically significant stress incontinence; 2) hepatic or renal disease; 3) recurrent urinary tract infections (UTIs); 4) interstitial cystitis; 5) uninvestigated hematuria or hematuria secondary to malignant disease; 6) indwelling catheter or intermittent catheterization; 7) treatment with any investigational drug in the 2 months prior to entry; 8) previous treatment with tolterodine; 9) electrostimulation therapy or bladder training within 14 days prior to entry or initiation during the study; 10) treatment with any anticholinergic drug or any drug for urinary urge incontinence within 14 days prior to the baseline visit or initiation during the study; 11) unstable dosage of any treatment with anticholinergic side effects or initiation of such treatment during the study; 12) previously demonstrated serious side effects on oxybutynin; 13) an average total voided volume >3,000 mL/24 h; and 14) clinically significant voiding difficulty with risk of urinary retention.

Efficacy of the different treatments was determined from micturition diaries collected by the patient for 7 days prior to each visit. Efficacy was measured by comparing the values after 12 weeks of treatment to baseline. Efficacy measures included the number of micturitions/24 hours (primary variable), number of incontinence episodes/24 hours, and mean urinary volume voided/micturition. Equivalence between 2 mg tolterodine twice daily and 5 mg oxybutynin three times daily was evaluated with measurements of mean number of micturitions/24 hours and mean number of incontinence episodes/24 hours. Efficacy was also evaluated through patients' perceptions of their bladder condition.

Safety was determined through spontaneously reported and observed adverse events, blood pressure measurements, routine clinical chemistry, and hematology measurements.

Appropriate parametric and nonparametric statistical methods were used for analysis, and significance was set at the 5% level. The efficacy variables were analyzed using analysis significance was set at the 5% level. The efficacy variables were analyzed using analysis of variance with the factors of treatment, visit, and patient within treatment and a treatment-by-visit interaction in the model. Equivalence (for the mean number of micturitions/24 hours and the mean number of incontinence episodes/24 hours) within the individual studies between 2 mg tolterodine twice daily and 5 mg oxybutynin three times daily was analyzed with 95% confidence intervals corresponding to a "double 1-sided α test." Mean relative changes in laboratory safety data were estimated using geometric means. Adverse events were summarized in frequency tables by treatment group, body system, preferred term, and intensity. The percentage of patients with at least one adverse event, the percentage with dry mouth, the percentage who reduced the dose, and the percentage of withdrawals were compared between groups using the chi-square test.

RESULTS

A total of 1,120 patients were randomized and treated in the four studies at a total of 134 study centers. Of these 1,120 patients, 121 were randomized to 1 mg tolterodine, 474 to 2 mg tolterodine, 349 to oxybutynin, and 176 to placebo. Of these patients, 181 withdrew before completion of treatment: 7 (6%) taking 1 mg tolterodine, 63 (13%) taking 2 mg tolterodine, 94 (27%) taking 5 mg oxybutynin, and 17 (10%) taking placebo. Significantly more patients treated with oxybutynin withdrew prior to study completion when compared to patients treated with 1 mg tolterodine, 2 mg tolterodine, or placebo ($P < 0.001$ for all compari-

sons). The primary reason for early termination in the 2 mg tolterodine, 5 mg oxybutynin, and placebo groups was the occurrence of adverse events.

The treatment groups were well balanced. Analysis of baseline demographics, disease characterization, micturition charts, and urodynamic variables for each of the studies revealed no significant differences between the treatment groups. The mean age of patients participating in these studies was 59.0 years and 75% of the patients were women.

For the primary efficacy variable, the number of micturitions/24 hours, pooled results showed a significant decrease from baseline for the 1 mg tolterodine ($P < 0.001$), 2 mg tolterodine ($P < 0.001$), and 5 mg oxybutynin ($P < 0.01$) groups, compared to the placebo group (Fig. 1). Each active treatment reduced the mean daily micturition frequency by approximately 20% from the baseline mean. After 12 weeks of treatment, equivalence was observed between the groups receiving 2 mg tolterodine twice daily and 5 mg oxybutynin three times daily with regard to decreases in the number of micturitions/24 hours in all three studies where oxybutynin was compared to tolterodine (Fig. 2).

For the variable number of incontinence episodes/24 hours, pooled results showed a significant decrease from baseline for both tolterodine doses and oxybutynin compared to placebo ($P < 0.05$ for all comparisons; see Fig. 1). Each active treatment reduced mean daily incontinence episodes by 40% to 60% from the baseline mean. After 12 weeks of treatment, equivalence was observed between the 2 mg tolterodine twice daily and 5 mg oxybutynin three times daily groups with regard to decreases in the number of incontinence episodes/24 hours in all three studies where oxybutynin was compared to tolterodine (Fig. 3).

For the efficacy variable, change in volume voided/micturition, pooled results showed a significant increase from baseline for both tolterodine doses and oxybutynin compared to placebo ($P < 0.001$ for all comparisons). Each active treatment increased the mean volume voided/micturition by 18% to 28% when compared to baseline levels.

Analysis of patients' perceptions of their bladder condition revealed that 39% of patients who received placebo, 41% of those treated with 1 mg tolterodine, 52% of those treated with 2 mg tolterodine, and 50% of those treated with 5 mg oxybutynin perceived improvement in their condition after 12 weeks of treatment compared to baseline. The percentage of patients reporting improvement was significantly higher in the 2 mg tolterodine group ($P = 0.003$) and the 5 mg oxybutynin group ($P = 0.017$) than in the placebo group. Approximately 10% of patients in each group perceived that their condition worsened after 12 weeks of treatment compared to baseline.

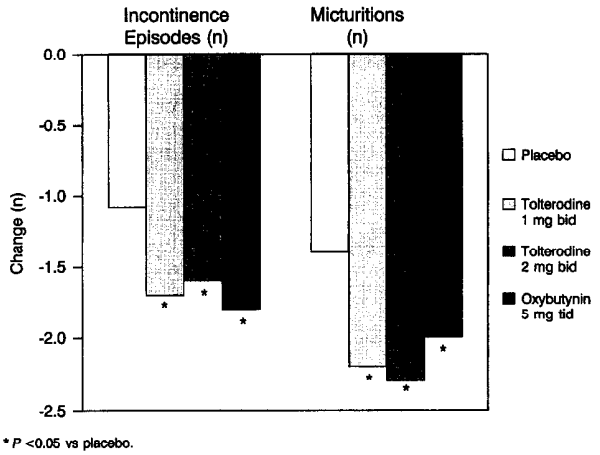

FIGURE 1. *Change from baseline in number of micturitions and incontinence episodes after 12 weeks of treatment.*

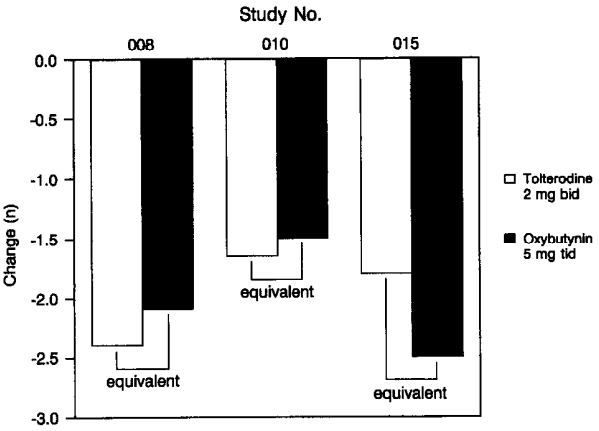

FIGURE 2. *Change from baseline in number of micturitions after 12 weeks of treatment in studies 008, 010, and 015.*

Comparisons between the tolterodine and oxybutynin treatment groups revealed that 1 mg and 2 mg tolterodine twice daily were tolerated significantly better than oxybutynin when adverse events, dry mouth, study withdrawal, and dose reductions were considered.

Adverse events were reported by 78%, 74%, 75%, and 93% of patients treated with placebo, 1 mg tolterodine twice daily, 2 mg tolterodine twice daily, and oxybutynin, respectively. The number of adverse events per patient was higher in the oxybutynin group (2.9 per patient) than in the placebo, 1 mg tolterodine twice daily, or 2 mg tolterodine twice daily groups (2.0, 1.9, and 1.8 per patient, respectively). The most frequently reported adverse events were autonomic nervous system disorders (21% in the placebo group, 29% in the 1 mg tolterodine group, 43% in the 2 mg tolterodine group, and 81% in the oxybutynin group); gastrointestinal disorders (27% in the placebo group, 22% in the 1 mg tolterodine group,

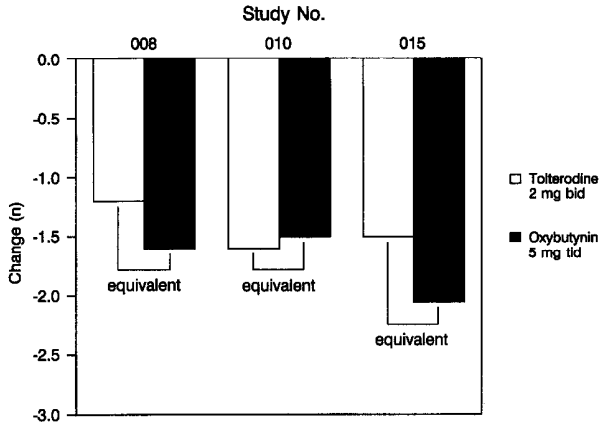

FIGURE 3. *Change from baseline in number of incontinence episodes after 12 weeks of treatment in studies 008, 010, and 015.*

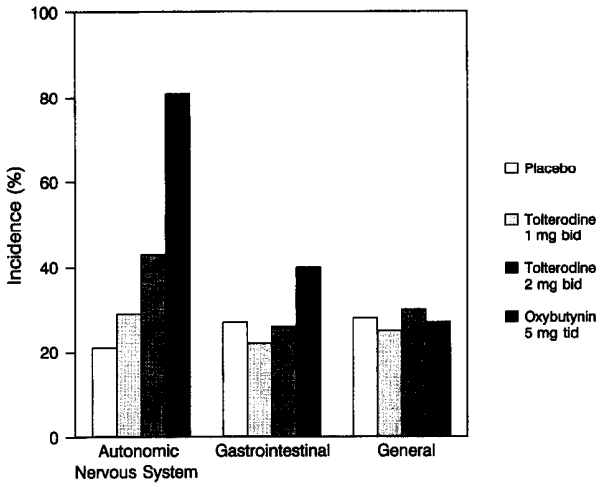

FIGURE 4. *Percentage of patients reporting autonomic nervous system, gastrointestinal, or general body system adverse events.*

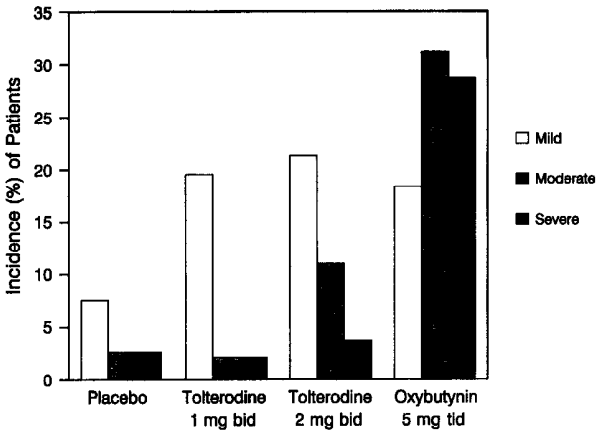

FIGURE 5. *Percentage of patients reporting dry mouth, by severity.*

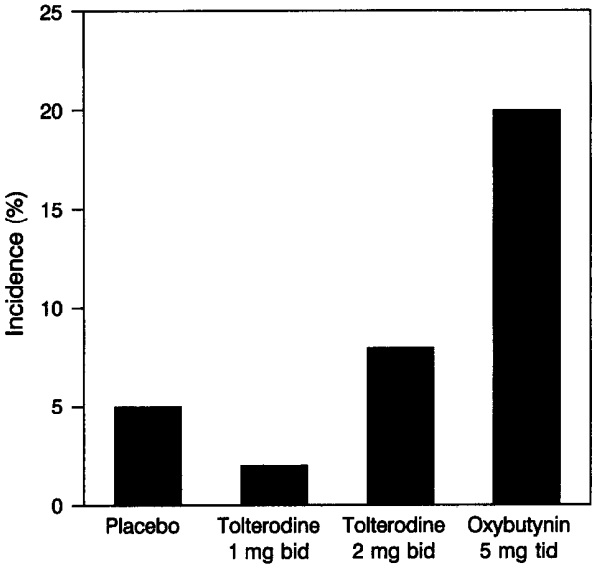

FIGURE 6. *Percentage of patients withdrawing due to adverse events.*

26% in the 2 mg tolterodine group, and 40% in the oxybutynin group); and general body disorders (28% in the placebo group, 25% in the 1 mg tolterodine group, 30% in the 2 mg tolterodine group, and 27% in the oxybutynin group; Fig. 4).

Dry mouth was the most frequently reported adverse event in each treatment group (reported by 16% of the placebo group, 24% of the 1 mg tolterodine group, 40% of the 2 mg tolterodine group, and 78% of the oxybutynin group). The percentage of patients reporting dry mouth was significantly higher in the oxybutynin group than in the tolterodine or placebo groups ($P < 0.001$ for all comparisons). In addition, the percentage of patients reporting moderate or severe dry mouth was significantly higher in the oxybutynin group (60%) compared to the 1 mg tolterodine (4%), 2 mg tolterodine (17%), and placebo (6%) groups ($P < 0.001$ for all comparisons; Fig. 5).

Other commonly reported adverse events included headache, dyspepsia, dizziness, and UTI. Headache was reported by 10% of patients treated with 2 mg tolterodine and 7% of those treated with oxybutynin, whereas dyspepsia was reported by significantly more patients treated with oxybutynin (11%) than with 2 mg tolterodine (6%, $P = 0.006$). The proportion of patients reporting other events was generally consistent between treatments.

A total of 34 patients were withdrawn from the studies because of adverse events: 5% in the placebo group, 2% in the 1 mg tolterodine group, 8% in the 2 mg tolterodine group, and 20% in the oxybutynin group (Fig. 6). The proportion of patients who withdrew because of adverse events was significantly higher in the oxybutynin group than in either of the tolterodine groups or the placebo group ($P < 0.001$ for all comparisons).

Dose reduction was permitted in the tolterodine/

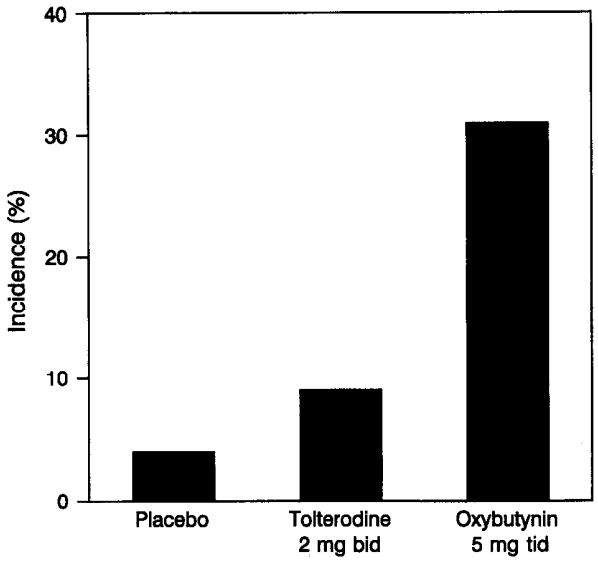

FIGURE 7. *Percentage of patients having dose reductions.*

oxybutynin comparative studies within the first 2 weeks of treatment in case of intolerance to the study medication and only as an alternative to study withdrawal. Dose reduction was reported for 4%, 9%, and 32% of patients receiving placebo, 2 mg tolterodine, and oxybutynin, respectively (Fig. 7). The proportion of patients who had a reduction in the dose of the study drug was significantly higher in the oxybutynin group than in the 2 mg tolterodine ($P < 0.001$) or placebo ($P < 0.001$) groups.

Tolterodine was shown in the 12-week studies to be as safe as oxybutynin and placebo. Serious adverse events were reported by 3% of patients in the placebo group, 4% in each tolterodine group, and 4% in the oxybutynin group. Serious adverse events possibly indicating cardiac dysfunction were reported by 1.7% of patients in the placebo group, 0.8% in the 2 mg tolterodine group, and 0.3% in the oxybutynin group. No serious cardiac adverse events were reported in the group receiving 1 mg tolterodine twice daily.

Overall, cardiovascular adverse events were reported most commonly in the 1 mg tolterodine group (12.4%), with lower percentages in the placebo (8.0%), 5 mg oxybutynin three times daily (6.3%), and 2 mg tolterodine (4.2%) groups. The cardiovascular adverse event that accounted for the difference between the 1 mg tolterodine group and the other treatment groups was palpitations, reported by 6.6% of patients receiving 1 mg tolterodine twice daily, 2.4% of those receiving placebo, 0.4% of those receiving 2 mg tolterodine twice daily, and 2.3% of those receiving oxybutynin. The lack of a dose-response relationship for this event suggests that these findings represent a random fluctuation of the incidence of palpitations in this patient population.

Evaluations of blood pressure, clinical chemistry, and hematologic values indicated no clinically significant differences between the treatment groups.

COMMENT

Individually and collectively, these four phase III studies with 12-week treatment durations document the vastly greater tolerability of tolterodine compared to oxybutynin at equivalent doses. Patients treated with tolterodine experienced significantly fewer occurrences of dry mouth (in terms of both frequency and severity), overall adverse events, study withdrawals, and dose reductions when compared to patients treated with oxybutynin. Patients treated with tolterodine were more compliant in taking their medication than were patients treated with oxybutynin.

The general safety of antimuscarinic medications for the treatment of overactive bladder was shown in these studies. The percentage of patients experiencing serious adverse events was comparable between the active treatment groups and placebo. Urinary retention and micturition disorders were reported only rarely, with a lower percentage of patients in the tolterodine groups reporting these events when compared with the placebo and oxybutynin groups. Also, no differences were noted between the groups with regard to blood pressure, clinical chemistry, and hematologic values.

No cardiovascular safety concerns (as measured from adverse events) were noted in either of the tolterodine treatment groups compared to placebo. Information on cardiac safety, determined from ECGs, was available from only one of the four studies. Electrocardiograms were not performed after 12 weeks of treatment in all the studies due to the fact that ECGs were extensively studied in phase I (five studies) and phase II (four studies). These showed that tolterodine had no effect on cardiac conduction in any patient groups, including the elderly. Electrocardiographic data after 12 weeks of treatment in the one study confirmed the results from the phase I and II studies. In addition, it was shown that tolterodine has no effect on cardiac conduction in patients taking concomitant diuretics (unpublished data).

The efficacy parameters used in the studies were selected based on their relevance to patients with overactive bladder. The change in the number of micturitions/day was selected as the primary efficacy variable. The change in the number of incontinence episodes/day, while also of relevance to the patient, was selected only as a secondary efficacy variable because not all patients with overactive

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