

TOLTERODINE ONCE-DAILY: SUPERIOR EFFICACY AND TOLERABILITY IN THE TREATMENT OF THE OVERACTIVE BLADDER

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ABSTRACT

Objectives. To evaluate the efficacy and tolerability of a new extended-release (ER), once-daily, capsule formulation of tolterodine, relative to placebo and the existing immediate-release (IR), twice-daily, tablet formulation, for treatment of the overactive bladder.

Methods. This was a double-blind, multicenter, randomized, placebo-controlled trial. One thousand five hundred twenty-nine patients (81% women) with urinary frequency (eight or more micturitions every 24 hours) and urge incontinence (five or more episodes per week) were randomized to oral therapy with tolterodine ER 4 mg once daily ($n = 507$), tolterodine IR 2 mg twice daily ($n = 514$), or placebo ($n = 508$) for 12 weeks. Efficacy was assessed at the end of the treatment period on the basis of the micturition diary variables. Tolerability and safety were assessed by evaluating the adverse events, electrocardiogram parameters, laboratory values, and treatment withdrawals.

Results. Tolterodine ER 4 mg once daily ($P = 0.0001$) and tolterodine IR 2 mg twice daily ($P = 0.0005$) both significantly reduced the mean number of urge incontinence episodes per week compared with placebo. The median reduction in these episodes as a percentage of the baseline values was 71% for tolterodine ER, 60% for tolterodine IR, and 33% for placebo. The ER formulation was 18% more effective than the IR formulation ($P < 0.05$). Treatment with both formulations of tolterodine was also associated with statistically significant improvements in all other micturition diary variables compared with placebo. For both formulations, the mean decreases in micturition frequency ($P < 0.0079$) and pad usage ($P < 0.0145$) were significant, and the mean volume voided per micturition increased ($P = 0.0001$). The rate of dry mouth (of any severity) was 23% for tolterodine ER, 30% for tolterodine IR, and 8% for placebo. The overall dry mouth rate for patients taking tolterodine ER was 23% lower than for tolterodine IR ($P < 0.02$), and the rate of severe dry mouth in the ER group was only 1.8%. The rates of withdrawal were comparable for the two active groups and the placebo group. No safety concerns were noted.

Conclusions. Tolterodine ER 4 mg once daily is effective and well tolerated in the treatment of overactive bladder with no safety concerns. Tolterodine ER demonstrated an improved efficacy for reducing urge incontinence episodes and a lower frequency of dry mouth compared with the existing IR twice-daily formulation. *UROLOGY* 57: 414–421, 2001. © 2001, Elsevier Science Inc.

Overactive bladder is a chronic, highly prevalent, and distressing medical condition characterized by urinary urgency and frequency, with or without urge incontinence.¹ Antimuscarinic

agents are the primary pharmacologic treatment for this condition.^{2,3} Previously, oxybutynin (eg, Ditropan) was the antimuscarinic drug of choice, although the usefulness of this agent has been lim-

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A complete list of the members of the Tolterodine Study Group is provided in the Appendix.

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ited by a lack of selectivity for the bladder, which gives rise to frequent, bothersome side effects (eg, dry mouth, constipation, and blurred vision).⁴ For these reasons, tolterodine was developed as the first antimuscarinic agent specifically targeted for the treatment of the overactive bladder. This agent has demonstrated a bladder-selective profile *in vivo*,⁵ leading to a more pronounced and longer lasting effect on the bladder than on salivation in humans.⁶ The currently available formulation of tolterodine requires twice-daily administration but given that overactive bladder is a chronic condition requiring long-term treatment, patient convenience and compliance could be improved with once-daily administration. Recently, an extended-release (ER) capsule formulation of tolterodine was developed that provides sustained release of the drug for 24 hours, producing a flatter serum concentration–time profile versus the immediate-release (IR) tablet formulation (data on file, Pharmacia Corporation). To date, however, the clinical efficacy and tolerability of this new formulation of tolterodine, relative to the existing IR tablet, have not been determined in patients with overactive bladder.

The primary aim of the present placebo-controlled, 12-week study was to evaluate the efficacy and tolerability of the new ER capsule formulation of tolterodine for once-daily treatment of the overactive bladder. A secondary aim was to determine whether the ER formulation provided additional improvements in efficacy and tolerability relative to the existing IR tablet formulation.

The findings for the tolterodine IR 2 mg and placebo treatment arms have been previously published⁷ and are reproduced with permission.

MATERIAL AND METHODS

This multinational, randomized, double-blind, placebo-controlled study was conducted in 167 centers in Australasia ($n = 4$), Europe ($n = 89$), and North America ($n = 74$). The study was conducted in accordance with the Good Clinical Practice Guidelines and the Declaration of Helsinki. The ethics committees approved the study protocol, and all patients gave written informed consent before the start of the study.

PATIENTS

Male and female patients, 18 years of age or older, with urinary frequency (eight or more micturitions every 24 hours), urge incontinence (five or more incontinence episodes per week), and symptoms of an overactive bladder for 6 months or longer were eligible for inclusion. Micturition diaries completed before randomization were used to quantify the baseline urinary frequency and urge incontinence episodes. Patients were recruited solely on the basis of these symptoms, irrespective of whether they had received prior treatment and irrespective of their response to prior antimuscarinic therapy.

The exclusion criteria were demonstrable stress incontinence, total daily urine volume greater than 3 L, any contra-

indications to antimuscarinic treatment, significant hepatic or renal disease (biochemical markers twice the upper limit of the normal reference range), symptomatic or recurrent urinary tract infections, interstitial cystitis, hematuria or bladder outlet obstruction, current electrostimulation or bladder training therapy, and indwelling catheter or intermittent self-catheterization. Pregnant or nursing women and women of childbearing potential not using reliable contraceptive methods were also excluded from enrollment. Other treatments for an overactive bladder such as anticholinergic drugs or drugs that inhibit cytochrome P450 3A4 isoenzymes were not allowed. An exception was made for those receiving estrogen treatment who had started therapy more than 2 months before randomization. Treatment with an investigational drug in the 2 months before study entry was also prohibited by the protocol.

STUDY DESIGN

At an initial screening visit, a complete medical and drug history was taken, along with a full laboratory screen and a midstream specimen of urine for culture/urinalysis. Eligible patients were enrolled into a 1 to 2-week washout/run-in period, during which the number of incontinence episodes and frequency of micturition were recorded for 7 consecutive days using micturition diaries. The volume voided (in milliliters) for every micturition and the use of incontinence pads were recorded for at least 2 complete days.

Eligible patients were subsequently randomized (1:1:1), using the procedure of random permuted blocks, to oral therapy with tolterodine ER capsules 4 mg once daily, tolterodine IR tablets 2 mg twice daily, or placebo for 12 weeks. A double-dummy drug packaging technique was used to maintain blinding. No dosage adjustment was allowed during the study. A follow-up visit 1 week after the end of treatment was performed to record any adverse events and changes in concomitant medication. Compliance was assessed by counting the returned unused study medication.

CLINICAL ASSESSMENTS

The primary efficacy variable was the change in the number of incontinence episodes per week from baseline to week 12. Treatment efficacy was assessed by comparing the changes in the micturition diary variables from baseline to week 12. The following variables were calculated from the patient micturition diaries: number of incontinence episodes per week, number of micturitions every 24 hours, volume voided per micturition, and number of pads used every 24 hours.

TOLERABILITY AND SAFETY

The adverse events reported during the 12-week treatment period and 1 week of follow-up were categorized, and the likelihood of a causal relationship to the study medication was documented. Dry mouth was further subcategorized in terms of intensity (mild, does not interfere with patient's usual function; moderate, interferes to some extent with patient's usual function; and severe, interferes significantly with patient's usual function).

Laboratory assessments for clinical chemistry and hematologic variables were assessed at the end of the treatment period. A subset ($n = 154$) of elderly patients (65 years old or older) also underwent electrocardiography at baseline and study end to monitor cardiac safety. Patients could be withdrawn from the study if it was thought medically necessary or at the patient's request.

STATISTICAL ANALYSIS

An analysis of efficacy was performed for all randomized patients on an intent-to-treat basis using the last observation

TABLE I. Demographic and baseline disease characteristics

Characteristic	Treatment Group		
	Tolterodine ER 4 mg qd (n = 507)	Tolterodine IR 2 mg bid (n = 514)	Placebo (n = 508)
Men/women (n)	90/417	106/408	98/410
Age (yr)	60 (20–89)	60 (22–92)	61 (22–93)
Previous drug therapy for overactive bladder* (n)	270 (53)	276 (54)	263 (52)
Percentage with poor efficacy	43	38.4	40.7
No. of incontinence episodes/wk	22.1 (0–168.0)	23.2 (0–168.0)	23.3 (0–168.0)
≥5 incontinence episodes/wk* (n)	492 (97)	498 (97)	494 (97)
No. of micturitions/24 hr	10.9 (2.3–51.3)	11.1 (2.0–48.6)	11.3 (2.0–37.4)
≥8 micturitions/24 hr* (n)	458 (90)	469 (91)	467 (92)
Volume voided per micturition (mL)	141 (36–338)	137 (38–283)	136 (21–374)
No. of pads used/24 hr	1.4 (0–18)	1.4 (0–25)	1.5 (0–22)

KEY: ER = extended release; IR = immediate release; qd = once daily; bid = twice daily.
Data presented as the mean, with the range in parentheses, unless otherwise indicated.

* Numbers in parentheses are percentages for these items.

carried forward to estimate the values for patients that dropped out of the study early. Between-group comparisons were made using analysis of variance, which included treatment, country, and treatment-by-country as factors. Test statistics and 95% confidence intervals for the difference between the active treatment groups and placebo group were subsequently performed using the least square means from the analysis of variance. Between-group differences for the categorical variables were analyzed using the chi-square test. The percentage change in the number of incontinence episodes per week was also analyzed using a stratified Wilcoxon rank-sum test, accounting for country differences. This analysis was performed to reduce the effect of outliers and to give equal weight to all the patients who had 100% improvement. In this analysis, a patient going from 40 to 20 episodes would have the same weight as a patient going from 8 to 4 (as opposed to the first patient having a fivefold larger effect in the raw difference). All other variables were analyzed descriptively.

RESULTS

A total of 1529 patients with overactive bladder were randomized into the study. The study population was representative of an expected population of patients with overactive bladder. Thus, most patients (81%) were women and approximately 50% of patients in each treatment group had received previous treatment for overactive bladder, 41% of whom had experienced poor results. The treatment groups were also well matched with regard to demographic and baseline disease characteristics (Table I).

All randomized patients were included in the intent-to-treat population. Overall, a total of 187 patients (12%) were prematurely withdrawn from the study. The main reason for withdrawal in all treatment groups was adverse events. Acceptable levels of compliance were seen in approximately 95% of all patients.

MICTURITION DIARY VARIABLES

The efficacy data after 12 weeks of treatment are presented in Table II. Both tolterodine ER ($P = 0.0001$) and tolterodine IR ($P = 0.0005$) demonstrated highly statistically significant reductions in the number of incontinence episodes (primary efficacy variable) compared with placebo. Given the positively skewed nature of the data, the median reductions of the percentage change from baseline (Fig. 1) (placebo 33%, tolterodine IR 60%, and tolterodine ER 71%) were calculated. These data revealed that the ER formulation was 18% more effective than the IR formulation ($P < 0.05$). These improvements in incontinence rates were accompanied by a reduction in pad usage to one pad daily or a 36% reduction from baseline in both groups, significantly different from placebo ($P < 0.02$ for each group). Taken together, the mean total micturition (voluntary and incontinence episodes) frequency for patients in the ER group decreased by 25% from baseline, representing a 59% improvement over placebo ($P = 0.0001$) (Fig. 2).

Treatment with both formulations of tolterodine produced statistically significant improvements in all other micturition diary variables compared with placebo (Table II).

TOLERABILITY AND SAFETY

The most common adverse events in all treatment groups were dry mouth, constipation, and headache. Other less common symptoms, including gastrointestinal upset, visual disturbances, and cognitive impairment, are also listed (Table III). Aside from dry mouth, all the other side effects were seen with a similar frequency in the treatment and placebo groups. No nervous system or cardiovascular system safety concerns were noted.

TABLE II. Effect of 12 weeks' treatment with a new extended-release formulation of tolterodine compared with the immediate-release formulation and placebo on micturition diary variables in patients with overactive bladder

Micturition Variable	Treatment Group			P Value (95% CI)	
	Tolterodine ER 4 mg qd (n = 507)	Tolterodine IR 2 mg bid (n = 514)	Placebo (n = 507)	Tolterodine ER vs. Placebo	Tolterodine IR vs. Placebo
No. of incontinence episodes/wk	-11.8 ± 17.8	-10.6 ± 16.9	-6.9 ± 15.4	0.0001 (-7.2 to -2.5)*	0.0005 (-6.0 to -1.3)*
No. of voluntary micturitions/24 hr	-1.8 ± 3.4	-1.7 ± 3.3	-1.2 ± 2.9	0.0047 (-1.0 to -0.2)	0.0079 (-0.9 to -0.1)
No. of total micturitions/24 hr [†]	-3.5 ± 4.9	-3.3 ± 4.4	-2.2 ± 4.0	0.0001 (-1.8 to -0.7)	0.0002 (-1.6 to -0.5)
Volume voided per micturition (mL)	+34 ± 51	+29 ± 47	+14 ± 41 [‡]	0.0001 (14 to 26)	0.0001 (10 to 21)
No. of pads used/24 hr	-0.5 ± 1.4	-0.5 ± 1.8	-0.2 ± 1.4	0.0145 (-0.4 to 0)	0.0035 (-0.5 to -0.1)

KEY: CI = confidence interval; other abbreviations as in Table I.

Data presented as the mean change from baseline ± standard deviation.

* 97.5% CI (according to Bonferroni).

[†] Total equals voluntary and involuntary (incontinence) micturitions.

[‡] Data missing for 1 patient.

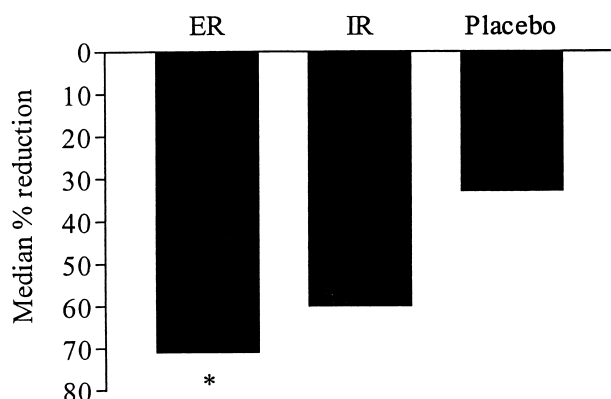


FIGURE 1. Median percentage reduction in incontinence episodes after 12 weeks of treatment with the new extended-release (ER) formulation of tolterodine, existing immediate-release (IR) formulation of tolterodine, and placebo (*ER versus IR, $P < 0.05$).

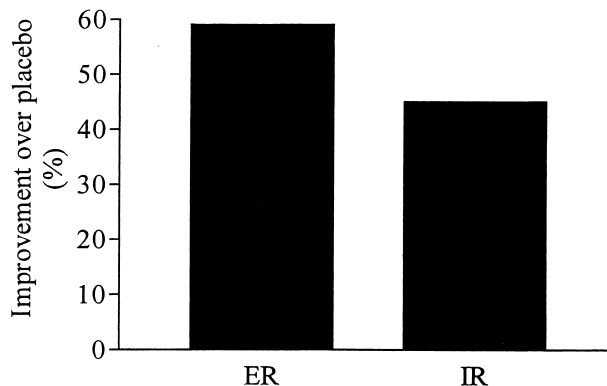


FIGURE 2. Percentage improvement over placebo in mean total micturitions (voluntary and incontinence episodes) for tolterodine extended-release (ER) and immediate-release (IR) formulations.

Most instances of dry mouth were categorized as mild or moderate in intensity; only 1.8% of those treated with the new ER formulation of tolterodine experienced severe dry mouth (Fig. 3). The total rate of dry mouth was 23%, 30%, and 8% for tolterodine ER, tolterodine IR, and placebo, respectively. Patients taking the new formulation (ER) had 23% less dry mouth than those taking the existing IR formulation ($P < 0.02$).

A total of 88 patients were prematurely withdrawn from the study due to adverse events: 27 (5%), 28 (5%), and 33 (6%) in the tolterodine ER, tolterodine IR, and placebo groups, respectively. Of the 27 patients who withdrew from the toltero-

dine ER arm, 7 (1.4%) may have withdrawn primarily because of dry mouth, but not necessarily.

A total of 37 patients reported serious adverse events during the study (tolterodine ER, $n = 7$; tolterodine IR, $n = 12$; and placebo, $n = 18$), which led to the premature withdrawal of 14 patients (tolterodine ER, $n = 1$; tolterodine IR, $n = 5$; and placebo, $n = 8$). No causal relationship was thought to account for any serious adverse event. Two deaths occurred during the study, one each in the tolterodine ER and placebo group. Neither was considered to be drug related. No clinically relevant changes in the laboratory safety or electrocardiogram parameters were noted between baseline and study end.

TABLE III. Summary of adverse events*

Adverse Event	Treatment Group		
	Tolterodine ER 4 mg qd (n = 505)	Tolterodine IR 2 mg bid (n = 512)	Placebo (n = 507)
Parasympathetic			
Dry mouth	118 (23)	156 (30)	39 (8)
Xerophthalmia	17 (3)	12 (2)	10 (2)
Abnormal vision	6 (1)	4 (1)	2 (0.5)
Dry skin	2 (0.5)	6 (1)	1 (0.5)
Gastrointestinal			
Constipation	30 (6)	35 (7)	22 (4)
Dyspepsia	15 (3)	16 (3)	7 (1)
Abdominal pain	19 (4)	13 (3)	8 (2)
Diarrhea	10 (2)	16 (3)	11 (2)
Flatulence	10 (2)	14 (3)	9 (2)
Nausea	7 (1)	10 (2)	10 (2)
Nervous system			
Headache	32 (6)	19 (4)	23 (5)
Somnolence	14 (3)	13 (3)	9 (2)
Dizziness	11 (2)	9 (2)	5 (1)
Fatigue	11 (2)	6 (1)	4 (1)
Insomnia	7 (1)	2 (0.5)	9 (2)
Urinary			
Urinary tract infection	16 (3)	13 (3)	20 (4)
Dysuria	5 (1)	8 (2)	1 (0.5)
General			
Peripheral edema	7 (1)	7 (1)	4 (1)

KEY: Abbreviations as in Table I.

Numbers in parentheses are percentages.

* Reported by $\geq 5\%$ of patients in any treatment group or relevant to antimuscarinic therapy during 12 weeks' treatment.

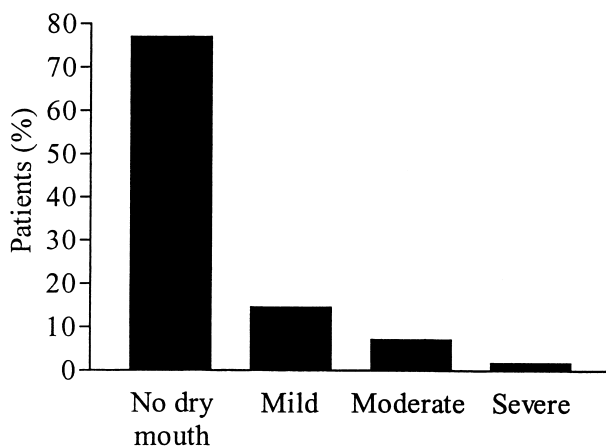


FIGURE 3. Incidence and maximum intensity of dry mouth during 12 weeks of treatment with a new extended-release formulation of tolterodine 4 mg for once-daily treatment of overactive bladder.

COMMENT

Overactive bladder is a chronic condition that requires long-term treatment to maintain symptom relief. Numerous large, multinational, multi-

center studies have confirmed the efficacy of tolterodine IR in treating the symptoms of overactive bladder.⁸⁻¹² However, a once-daily administration may be viewed as potentially more convenient by patients, and this could lead to increased compliance.¹³ This study was the first large, multinational, multicenter, placebo-controlled investigation of the new ER formulation of tolterodine for once-daily treatment of the overactive bladder and is the largest placebo-controlled study ever conducted in patients with overactive bladder.

Treatment with the ER formulation of tolterodine for 12 weeks resulted in significant improvement compared with placebo for all voiding diary variables. Similar findings were observed for the IR formulation of tolterodine,⁷ given at the same total daily dose (ie, 4 mg/day), consistent with earlier observations.^{8-10,12}

With regard to the effect on incontinence (primary efficacy variable) in patients taking tolterodine ER, a mean reduction from baseline of 11.8 episodes per week occurred (Table II). However, to understand how this affected the individual patient, and given the skewed nature of the distribution of this variable, the median percentage reduction from baseline was computed. This yielded a 71% decrease in incontinence episodes (Fig. 1), which is impressive, given that this was studied in a natural population of patients, of whom approximately 50% were treatment naive and for whom prior therapy had failed in nearly one quarter. What this means is that one half of all the patients in this group had a greater than 71% reduction in incontinence. This decrease in incontinence was accompanied by a significant reduction in the use of incontinence pads. These findings may have a positive economic impact on patients and health service providers.

A consequence of overactive bladder is compensatory increased voiding to avoid incontinence. It appears that the tolterodine-treated patients were able to decrease this coping behavior, as the drug caused a reduction in micturition frequency and an increase in bladder capacity (volume voided), presumably by inhibiting urgency.

Before the introduction of tolterodine, oxybutynin was regarded as the reference standard for the treatment of overactive bladder. Comparative studies in such patients have shown that tolterodine (2 mg twice daily) is therapeutically equivalent to oxybutynin (5 mg three times daily) but has superior tolerability, particularly in the frequency of bothersome dry mouth. In these studies, proportionally more patients in the oxybutynin-treated group reduced their dose or withdrew because of side effects.⁸⁻¹⁰ These and other studies used the

current IR tablet formulation of tolterodine (ie, Detrol, Detrusitol).

Although ER formulations provide increased patient convenience and compliance by way of the once-daily dosing, it has until now remained unclear whether such formulations confer significantly better efficacy and/or improved tolerability. A recent study comparing conventional versus ER oxybutynin (Ditropan XL) demonstrated similar efficacy and tolerability profiles for the two formulations.¹⁴ In the current study, tolterodine ER was 18% ($P < 0.05$) more effective in reducing the incontinence episodes than the IR formulation. Similar differences were not noted in the pad reduction data because, with treatment (both formulations), the mean number of pads used was one daily. It is possible that this represents prophylactic use before patient confidence increased with the duration of therapy. The improvement in incontinence with the ER formulation was accompanied by a 23% ($P < 0.02$) lower frequency of dry mouth compared with the IR formulation. It is not clear why the tolterodine ER formulation should result in such improvements, but the reason may be related to the attainment of a more steady-state blood level rather than the fluctuation seen with twice-daily IR therapy. In the latter case, troughs in the plasma concentrations may lead to diminished efficacy and peaks to increased side effects. These marginal improvements in the efficacy and side-effect profile when taken singly may not be clinically significant but, when considered in combination, probably do result in higher levels of patient satisfaction, compliance, and improved quality of life.

The major limitations of traditional antimuscarinic agents for overactive bladder are related to their tolerability problems, such as their propensity to cause dry mouth, dry eyes, blurred vision, constipation and other gastrointestinal side effects, and cognitive dysfunction. Dry mouth is the most problematic adverse event and occurs in up to 80% of oxybutynin recipients.^{8,10} Several approaches have been investigated as a means of overcoming the tolerability problems of oxybutynin,¹⁵ including the use of ER oral formulation technology, although these have not led to major improvements.^{14,16,17} In contrast, the current study demonstrated the incidence of dry mouth to be 30% in the tolterodine IR group and 23% in the ER group, a statistically significant difference ($P < 0.02$). The dry mouth rates for Ditropan XL (68%)¹⁸ and tolterodine ER (23%), strictly speaking, should not be compared, because they were derived from different studies using different study populations. The Ditropan XL studies were carried out in a responder population who were known to be tolerant to antimuscarinic medication, and the

current tolterodine ER study was done in a mixed (treatment naive and experienced) population.

Another characteristic side effect of the antimuscarinic class of drugs is constipation. This was not a significant problem in the present study, as it was reported to a similar extent among the groups: 6%, 7%, and 4% for the tolterodine ER, tolterodine IR, and placebo groups, respectively (Table III). This is in contrast to the published reports on IR oxybutynin and Ditropan XL, in which 31% and 30% of these patients experienced constipation.¹⁸ Again, caution should be exercised when making comparisons, given that the study populations were different; however, any differences between these medications may be because tolterodine was specifically developed for the treatment of overactive bladder and oxybutynin was initially developed for gastrointestinal hypermotility disorders.^{19,20} Constipation can be troublesome for all patients but is particularly worrying and perhaps dangerous for patients with Parkinson's disease who, in many cases, have decreased gastrointestinal motility.²¹

Perhaps a serious cause of concern with antimuscarinic agents is cognitive impairment.²² Avoiding this is crucial, especially in the elderly, and it has been suggested that such patients should not take oxybutynin.²³ In the current study, the incidence of somnolence and dizziness with tolterodine was comparable with that of placebo (Table III), an observation consistent with the results of a recent study²⁴ that showed that tolterodine did not affect quantitative electroencephalographic parameters, whereas oxybutynin did.

Taken together, these findings suggest that the ER formulation of tolterodine has a superior profile to other agents currently prescribed. A better appraisal of these issues by prospective comparative studies of the clinical efficacy and tolerability of the ER formulation of tolterodine and other agents currently used for the treatment of overactive bladder is necessary.

CONCLUSIONS

At a dosage of 4 mg once daily, the ER formulation of tolterodine produces significant improvements in the symptoms of overactive bladder compared with placebo. The ER formulation was more effective in reducing the incontinence episodes and was better tolerated than the IR formulation, with a lower frequency of dry mouth at all severity levels. The advent of this new, once-daily formulation of tolterodine, combining highly effective relief of symptoms with minimal side effects and maximal patient convenience, is a significant improvement over currently available therapies.

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APPENDIX

A complete list of the members of the Tolterodine Study Group in alphabetical order follows.

In Australia: Barton Clarke, Brisbane; Frank Gardiner, Herston; Richard Millard, Little Bay, NSW; Kate Moore, Kogarah, NSW.

In Austria: Herrmann Enzelsberger, Steyr; Peter Gebhartl, Vöcklabruck; Helmut Heidler, Linz; Helmut Madersbacher, Innsbruck; Günther Primus, Graz; Gerhard Struhal, Wien; Karl Tamussino, Graz.

In Belgium: Jean de Leval, Liège; Karel Everaert, Gent; Dirk Maes, Gent; Johan Mattelaer, Kortrijk; Claude Schulman, Bruxelles; Kristiaan Vekemans, Hasselt; Jean-Jacques Wyn-daele, Edegem.

In Canada: Jerzy Gajewski, Halifax; Sender Herschorn, Toronto; Benjamin Okafo, Miramachi; Gary Peers, Calgary; Sydney Radomski, Toronto; Gary Steinhoff, Victoria; Luc Valiquette, Montréal; Paul J. Whelan, Hamilton; Kin Yuen, Winnipeg; Joseph Zadra, Barrie.

In France: Gerard Amarenco, Aulnay s/Bois; Michel Boulogne, Saint Pol sur Mer; Francois Deruelle, Avignon; Bernard Jaquetin, Clermont-Ferrand; Christian Jouffroy, Metz; Albert Leriche, Saint-Genis Laval; Annik Mombet, Paris; Christian Saussine, Strasbourg; Jean-Marc Soler, Cerbère.

In Germany: Schanss Alloussi, Homburg/Saar; H.-M. Blümlein, Forchheim; Florian Deindl, München; Thomas Dimpfl, München; Wolfgang Dorschner, Leipzig; Martina Horn, Hannover; Jens Kemper, Berlin-Steglitz; Martin Kennerknecht, Garmisch-Partenkirchen; Reinhard Laszig, Kiel; Kurt Niklas, Saarlouis; Harald Pauthner, Bad Homburg; Helga Walter-Vitek, Mannheim; Peter Weitz, Frankfurt; Sibylle Wilke, Berlin.

In Ireland: Paul Byrne, Dublin; Tom Creagh, Dublin; Paul Hughes, Cork; Declan Keane, Dublin; David Quinlan, Dublin.

In Italy: Pierfranco Bolis, Varese; Aldo Vittorio Bono, Varese; Paolo Di Benedetto, Trieste; Giancarlo Minini, Brescia; Francesco Pagano, Padova; Arcangelo Pagliarulo, Bari; Al-bergo Zanollo, Magenta.

In New Zealand: Ted Arnold, Christchurch; Colin McRae, Auckland; Don Wilson, Otago.

In Norway: Morten Anderson, Moelv; Tom Engebretsen, Sarpsborg; Hans Ejner Ipsen, Ålesund; Hjalmar Schiøtz, Tønsberg; Sigmund Vaage, Stavanger.

In Russia: S. Buyanova, Moscow; Dmitri Pushkar, Moscow; Gabriel Ter-Avanesov, Moscow; Svetlana Tolstova, Moscow.

In The Netherlands: B.L.H. Bemelmans, Nijmegen; J.L. Bruins, Winterswijk; C.P. Buiks, Ewijk; W.A. de Backer, Rijswijk; K.P.J. Delaere, Heerlen; A.W.H.M. Lutkie, Made; P.P.A.F. Martens, Landgraaf; E.J. Messelink, Amsterdam; P.E.V.A. Van Kerrebroeck, Maastricht; H.J.E.J. Vrijhof, Eindhoven; A.F.G.V.M. Ypma, Deventer; A.G.M. Zeegers, Zwijndrecht.

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