

Update on tolterodine extended-release for treatment of overactive bladder

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Abstract: Overactive bladder is a prevalent condition which negatively impacts quality of life and puts a significant economical burden on society. First-line therapy often includes pharmacotherapy with antimuscarinic medications, and numerous research studies have demonstrated that tolterodine extended-release (ER) is an efficacious and tolerable formulation of this class of medication. This review provides an update on the clinical use of tolterodine ER, detailing the current literature on its efficacy, tolerability, adverse effects, and comparability with other commonly prescribed medications for the treatment of overactive bladder.

Keywords: antimuscarinics, efficacy, quality of life, overactive bladder, tolterodine, urgency, urge urinary incontinence

Background

Overactive bladder (OAB) is a symptom syndrome defined by the International Continence Society as urgency with or without urge incontinence, usually with increased frequency and nocturia.¹ This chronic prevalent condition affects both men and women, with slightly more prevalence in women (12.8% versus 10.8%, respectively, based in a population-based survey of patients in five countries).² This condition has been shown to have a great economic impact on society as a whole, in addition to having a profound negative impact on health-related quality of life (HRQoL) of affected individuals.^{3,4} Treatment options for OAB include behavioral and lifestyle interventions and pharmacotherapy, with antimuscarinic medications often being first-line treatment.⁵ Tolterodine was one of the first in this class of medications designed specifically for the treatment of OAB, and in 2001 once-daily tolterodine extended-release (ER) became available as an efficacious and more tolerable formulation compared with the twice-daily immediate-release (IR) form of the medication.^{6,7} This article provides an update on the clinical use of tolterodine ER for the treatment of OAB.

Pharmacology

Tolterodine ER is a nonselective competitive muscarinic receptor antagonist. After oral administration, tolterodine is metabolized in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a pharmacologically active metabolite. The 5-hydroxymethyl metabolite, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. Compared with the IR formulation, once-daily tolterodine ER releases the drug in a steady but constant manner, lowering peak and trough drug levels.

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Clinical efficacy

Tolterodine extended-release versus immediate-release

Tolterodine ER became available in 2001 as a once-daily formulation to improve the tolerability and compliance of patients with OAB using the tolterodine IR twice-daily regimen. Theoretically, once-daily medication regimens are more convenient for patients, and a meta-analysis of 50 randomized, controlled clinical trials of antimuscarinic medications for the treatment of OAB demonstrated that the ER formulations of this class of medications were more tolerable and effective than the IR formulations. The authors of this meta-analysis concluded that the ER formulations are preferable to the IR forms of this medication.⁸ One large multicenter, double-blind, placebo-controlled trial conducted in 2001 by van Kerrebroeck et al (Table 1) looked specifically at the efficacy and safety of tolterodine ER compared with the IR formulation of tolterodine and found similar results.⁷ A total of 1529 patients (both men and women) with OAB and urinary urge incontinence symptoms were randomized to either 4 mg once-daily dosing of tolterodine ER, 2 mg twice-daily dosing of tolterodine IR, or placebo for 12 weeks. Both tolterodine ER and IR were significantly more effective in the reduction of incontinence episodes ($P = 0.0001$ and $P = 0.005$, respectively) when compared with placebo. Furthermore, when tolterodine ER was compared with tolterodine IR, the ER formulation was 18% more effective in reducing incontinence episodes ($P < 0.05$), with less occurrence of the dry mouth side effect (23% versus 30% in the IR group, $P < 0.02$).⁷

Urinary urgency and urinary urge incontinence

Urinary urgency is one of the hallmark symptoms of OAB, and several pivotal studies have shown improvement in

urgency in patients treated with tolterodine ER; in one such study when compared with placebo, 44% of patients treated with tolterodine ER had significant improvement in urgency symptoms ($P < 0.001$). In addition, the percentage of patients unable to hold their urine in response to urgency was significantly reduced by 58% in the patients treated with tolterodine ER versus only 32% in the placebo group ($P < 0.001$).⁹ In another randomized, double-blind, placebo-controlled trial, the efficacy of tolterodine ER in 854 patients with mixed incontinence and predominant urge incontinence was compared with placebo after eight weeks of treatment,¹⁰ and 4 mg once-daily dosing of tolterodine ER was found to be successful in reducing urinary urge incontinence episodes ($P < 0.0001$), urge episodes, and urinary frequency (both $P < 0.0001$). In addition, the median voided volume increased significantly when compared with placebo ($P < 0.0001$).¹⁰

Night-time voiding symptoms

Night-time dosing of tolterodine ER has been shown to decrease nocturnal OAB micturitions significantly and still maintain clinical efficacy throughout the day. In a study of 850 patients randomized to 12 weeks of treatment with either placebo or 4 mg tolterodine ER administered four hours or sooner before bedtime, there were significant reductions in OAB nocturnal micturitions in the tolterodine ER group ($P = 0.0086$). Tolterodine ER also significantly reduced both 24 hours and daytime intervals. Serious side effects were reported in 1.2% of patients in this study, and all of these effects were considered to be unrelated to treatment.¹¹ Another study also determined that tolterodine ER maintained clinical efficacy over 24 hours and should be effective for OAB symptoms, without regard to whether symptoms occur during the day or at night.¹²

Table 1 Summary of tolterodine extended-release efficacy studies

Authors	Study population	Study design	Efficacy
van Kerrebroeck et al ⁷	A total of 1529 men and women with urinary frequency and urge incontinence	Randomized, double-blind placebo-controlled trial comparing tolterodine ER with IR and placebo	Tolterodine ER and IR formulations significantly reduced incontinence episodes compared with placebo. Tolterodine ER was more effective at reducing incontinence episodes than IR
Rackley et al ¹¹	850 patients with OAB and nocturia	Randomized, placebo-controlled trial, double-blind study of 4 mg tolterodine ER and placebo	Significantly reduced OAB-related and severe OAB nocturnal micturitions compared with placebo. Total number of nocturnal micturitions was reduced compared with placebo but this was not statistically significant
Dmochowski et al ¹²	Patients with OAB and UUI	Post hoc analysis of a 12-week, placebo-controlled trial of tolterodine ER 4 mg and placebo effect on specific day-time and night-time intervals over 24 hours	Tolterodine ER maintained clinical efficacy over a 24-hour period, and significantly and consistently increased voided volume and reduced UUI episodes and voiding frequency

Abbreviations: OAB, overactive bladder; UUI, urinary urge incontinence; ER, extended-release; IR, immediate release.

Urodynamic parameters

A total of 111 women with a urodynamic diagnosis of detrusor overactivity were prospectively divided into two groups, one with involuntary detrusor contractions during the cystometric filling phase (Group 1) and the other after provocative maneuvers (Group 2). Both groups were prescribed 4 mg once-daily tolterodine ER. After 12 weeks, there was a significant difference ($P = 0.0008$) between the groups in terms of the efficacy of tolterodine ER, with a better response rate in Group 1. The authors concluded that the efficacy of tolterodine ER may be related to the different urodynamic findings for detrusor overactivity.¹³

HRQoL parameters

The long-term effects of tolterodine ER on HRQoL in patients diagnosed with OAB and incontinence were assessed in a randomized, double-blind, safety and efficacy trial comparing tolterodine ER with placebo in a 12-month open-label continuation trial. HRQoL information was obtained from the King's Health Questionnaire (KHQ) and the Short Form-36 that were administered at baseline, at the end of the 12-week trial, and three and 12 months following open-label treatment with tolterodine ER. One thousand and seventy-seven patients were included in the intent-to-treat (ITT) population. KHQ translations were available for 838 patients (mean age 61.1 years, 80.9% women) in the ITT population. HRQoL, as measured by the KHQ, significantly improved from baseline to months 3 and 12 for impact on incontinence, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep and energy, severity (coping) measures, and symptom severity.¹⁴ Other studies have evaluated the effect of 4 mg tolterodine ER on OAB symptoms and sexual and emotional health in women. In an early study, 413 sexually active women were randomized to placebo or tolterodine ER, and at 12 weeks, the tolterodine ER group had a significant reduction in urinary urge incontinence episodes and total urinary incontinence episodes ($P = 0.0029$ and $P = 0.0006$, respectively).¹⁵ This group also had significant improvement in sexual health measures.¹⁵ A secondary analysis of this study was performed in 161 patients who continued tolterodine ER for 24 weeks, and improvements in OAB symptoms and HRQoL parameters were maintained.¹⁶

Comparison with other antimuscarinics

In a Cochrane systematic review of 61 placebo-controlled trials of various anticholinergic medications, the reviewers found significant improvement in symptoms in people taking

anticholinergics, including a decrease in leakage episodes during 24 hours (-0.54 weighted mean difference [WMD]; 95% confidence interval [CI]: -0.67 to -0.41) and a decrease in number of voids in 24 hours (-0.69 WMD; 95% CI: -0.84 to -0.54), as well as improved HRQoL scores.¹⁷ The active medication groups experienced more dry mouth (relative risk [RR] 3.0; 95% CI: 2.70–3.34) but treatment withdrawal rates were similar between the active medication and placebo groups (RR 1.11; 95% CI: 0.91–1.36). Sensitivity analysis demonstrated a low likelihood that the findings were affected by type of medication, age or gender of participants, or their diagnosis.¹⁷ In a previous Cochrane systematic review of 49 trials including 11,332 patients published in 2005 comparing different anticholinergic medications, the authors found that oxybutynin and tolterodine were similarly efficacious, but there were insufficient data to draw any conclusions regarding the other anticholinergic medications. The ER formulations of both oxybutynin and tolterodine were favored over the IR agents, due to a decrease in side effects, including dry mouth.¹⁸ Another systematic review which included 56 randomized, controlled trials and 17,692 patients concluded that most anticholinergic medications, including IR and ER tolterodine, were well tolerated compared with placebo, and with the exception of IR oxybutynin.¹⁹ A summary of both tolterodine formulations (IR and ER) with specific comparison against commonly prescribed anticholinergic medications is provided here.

Oxybutynin

There are two randomized, actively controlled trials comparing ER tolterodine and ER oxybutynin. ACET (Antimuscarinic Clinical Effectiveness Trial) involved two parallel studies with identical protocols that compared two doses of ER tolterodine (2 mg and 4 mg) in 669 subjects, and two doses of ER oxybutynin (5 mg and 10 mg) in 620 subjects.²⁰ After eight weeks, subjects in the 4 mg tolterodine group experienced greater improvement in bladder symptoms than subjects in the 2 mg tolterodine group or the oxybutynin groups. Although participants in both groups experienced some dose-dependent increases in side effects, fewer participants withdrew from the 4 mg tolterodine group compared with both oxybutynin groups (12% versus 19% and 21%, $P = 0.01$ and $P = 0.002$).²⁰

The OPERA (Overactive Bladder Performance of Extended Release Agents) trial involved 790 women with OAB from 71 centers who were randomized to either 4 mg of ER tolterodine or 10 mg of ER oxybutynin for 12 weeks.²¹ Although more women in the oxybutynin group experienced episodes of no incontinence (23% versus 17%, $P = 0.03$) and

decreased micturition frequency, there were no differences in the average weekly urge incontinence episodes. The differences in efficacy between oxybutynin and tolterodine were seen more often in women who had previously taken anticholinergic medications than in anticholinergic-naïve women.²² More women who took oxybutynin experienced dry mouth (30% versus 22%, $P = 0.02$), but the discontinuation rates were similar between the groups. Despite the higher lipid solubility of tolterodine, rates of adverse central nervous system events were also low and similar between the groups (8% for tolterodine and 9% for oxybutynin).²³ ER tolterodine has also been compared with transdermal oxybutynin, with comparable efficacy results.²⁴ More patients experienced local skin irritation in the transdermal oxybutynin group.

Solifenacin

In STAR (solifenacin versus tolterodine randomized trial), 5 mg or 10 mg of solifenacin was compared with 4 mg of ER tolterodine in 1177 men and women.²⁵ In this trial, the participants could choose to increase the dose of solifenacin up to 10 mg after four weeks of usage. After 12 weeks, solifenacin was found to be similar to tolterodine in terms of decreasing the frequency of daily voids. Participants in the solifenacin group had significantly greater improvements in episodes of urgency, urge incontinence, and overall incontinence compared with baseline than subjects in the tolterodine group. More subjects in the solifenacin group experienced at least a 50% reduction in incontinence episodes or experienced total continence with decreased incontinence pad usage than subjects in the tolterodine group. Although more patients experienced side effects in the solifenacin group, these differences were not statistically significant, and the overall discontinuation rates in both groups were low (3.5% in the solifenacin group and 3% in the tolterodine group).

Propiverine

Tolterodine 2 mg twice daily was compared with propiverine 15 mg twice daily in a randomized, multicenter study in patients with detrusor overactivity over the course of 28 days.²⁶ Both agents were comparable in terms of patient improvement in HRQoL, efficacy, and tolerability.

Fesoterodine

In randomized, placebo- and active-controlled study designed to address the efficacy, tolerability, and safety of fesoterodine, a prodrug which is metabolized to the

same active metabolite as tolterodine (5-hydroxymethyl tolterodine), participants taking 4 mg or 8 mg fesoterodine or 4 mg tolterodine experienced a decrease in micturition episodes, urgency episodes, and urge incontinence episodes, and improve HRQoL compared with the placebo group.²⁷ Although this study was not designed to compare fesoterodine with tolterodine, the authors published a post hoc analysis reporting that subjects in the 8 mg fesoterodine group had significantly greater improvement in urge incontinence episodes, mean voided volume, and number of continent days per week than subjects in the tolterodine group.²⁸ The rates of medication discontinuation was similar between the groups (2% placebo, 3% tolterodine, 5% fesoterodine). However, more subjects in the 8 mg fesoterodine group experienced side effects, including dry mouth (34% fesoterodine, 17% tolterodine, 7% placebo). In another randomized, placebo-controlled trial designed to compare the efficacy and tolerability of 8 mg fesoterodine with that of 4 mg ER tolterodine, more patients taking fesoterodine reported no episodes of urge incontinence than subjects taking tolterodine (64% versus 57%; $P = 0.015$).²⁹ Participants taking fesoterodine also reported greater improvements in urge incontinence, mean voided volume, and decreased micturition episodes, along with greater improvements in most HRQoL assessments. Discontinuation rates were similar between groups.

Trospium chloride

Although the efficacy of tolterodine has not been compared with trospium chloride, there was a study that addressed electroencephalographic (EEG) changes in patients after taking ER tolterodine compared with trospium chloride and oxybutynin.³⁰ Despite being a tertiary amine and being able to cross the blood-brain barrier, tolterodine was found to cause minimal EEG changes and was comparable with trospium, which is a quaternary amine that does not enter the central nervous system to a significant extent. Oxybutynin, also a tertiary amine, caused more EEG changes than tolterodine and trospium.

Adverse effects

Both IR and ER tolterodine have been extensively studied and found to be tolerable, having similar side effect profiles, with the IR formulation resulting in more adverse events. In a randomized, placebo-controlled trial comparing the efficacy and tolerability of ER tolterodine and IR tolterodine, the ER agent was more effective at reducing incontinence episodes than IR tolterodine, with decreased reporting of dry mouth

(23% versus 30%) and similar rates of withdrawal, even when compared with placebo.⁷

In another study addressing adherence and switch rates for the IR and ER formulations of tolterodine and oxybutynin, the authors found that the ER formulations resulted in higher adherence rates compared with the IR formulation (35% for ER tolterodine, 24% for IR tolterodine, 36% for ER oxybutynin, 15% for IR oxybutynin; $P < 0.001$).³¹ The overall switch rate was 13%, with fewer patients switching from ER tolterodine than from the other agents (10% for ER tolterodine, 14% for IR tolterodine, 17% for ER oxybutynin, 19% for IR oxybutynin; $P = 0.020$), with an overall median time to discontinuation of 31 days.

Discontinuation rates for all antimuscarinic medications used in the treatment of OAB are high. Specifically, a large database review of 29,369 women with 49,419 episodes of anticholinergic medication therapy found the adjusted cumulative incidence of medication discontinuation for IR tolterodine was 61% (95% CI: 59.4–64.3) and for ER tolterodine was 54% (95% CI: 52.3–57.7) at six months.³² The median time to discontinuation of any medication was 4.8 months. In a study addressing medication adherence in the US Military Health System National Capital Region, in which patients do not pay for medication, the most commonly dispensed anticholinergic was ER tolterodine (60%), followed by IR oxybutynin (26%).³³ Patients taking ER tolterodine were found to have a higher rate of not refilling the prescription than subjects taking IR oxybutynin (89% versus 68%; $P < 0.01$).

Xerostomia

Xerostomia, or dry mouth, is the most commonly reported side effect in patients taking anticholinergic medications. In the original placebo-controlled study addressing the efficacy and safety of tolterodine, the incidences of dry mouth were 30% for the IR agent, 23% for the ER formulation, and 8% for placebo.⁷ Although tolterodine does not selectively bind muscarinic receptor subtypes found in the urinary tract, it has been shown to have functional selectivity for these receptor subtypes over receptors in the salivary gland.^{34,35} In a clinical study comparing ER tolterodine with oxybutynin, fewer subjects taking tolterodine had dry mouth (22% versus 30%; $P = 0.02$).²⁰

Blurry vision and xerophthalmia

Tolterodine can affect smooth muscle in the iris, and has been found to cause blurry vision in 1% of subjects.⁷ It can also inhibit lacrimation, and was found to result in xerophthalmia in 2%–3% of cases.

Gastrointestinal effects

Like other anticholinergic agents, tolterodine does decrease gastrointestinal motility. However, it has not been consistently found to result in significant gastrointestinal side effects. In the original efficacy and safety study, subjects taking tolterodine had similar constipation rates when compared with participants taking placebo.⁷ However, in a randomized, placebo-controlled trial specifically addressing the gastrointestinal effects of ER tolterodine 4 mg, tolterodine was not found to cause significant changes in gastrointestinal transit time, but patients taking the medication did have fewer bowel movements (1.0 ± 0.1 versus 1.34 ± 0.1 ; $P = 0.02$), without any changes in ease of defecation or stool consistency.³⁶

Central nervous system effects

Although tolterodine does cross the blood–brain barrier, it has not been found to cause significant EEG changes.³⁰ However, there have been reports in the literature of impaired cognitive function in the elderly and in patients with Alzheimer's disease taking this medication.^{37,38}

Cardiac effects

In one study, patients taking ER tolterodine were found to have increased heart rates compared with subjects taking darifenacin or placebo, with more patients experiencing increased heart rates.³⁹ In another trial, IR tolterodine 2 mg or 4 mg twice daily was not found to have a significant effect on QT interval.⁴⁰ In healthy female volunteers, high doses of ER tolterodine at 8 mg, but not at 4 mg, have also been found to reduce resting heart rate variability, which is an important predictor for cardiac mortality.⁴¹

Cost-effectiveness

A cost-utility analysis was performed as part of a systematic review and meta-analysis of the efficacy and safety of antimuscarinics, consisting of solifenacin, tolterodine IR and ER formulations, darifenacin, fesoterodine, and oxybutynin. The analysis included costs directly associated with treatment for OAB, ie, antimuscarinic therapy, consultations with general practitioners, and outpatient contacts. The study was conducted in the UK and costs were reported at 2007 and 2008 prices. Tolterodine ER was determined to be less cost-effective when compared with solifenacin for the treatment of OAB.⁴²

Conclusion

OAB is a prevalent and often life-altering condition. The purpose of any form of treatment is to reduce symptoms of urinary urgency and frequency and urge incontinence

episodes, and to improve the overall HRQoL effectively in patients with this symptom syndrome. Antimuscarinic pharmacotherapy, such as tolterodine ER, is often used as first-line treatment. Several research studies have demonstrated tolterodine ER to be an effective, tolerable, and safe therapeutic option for patients with OAB.

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