REVIEW ARTICLE

Drug Safety 2004; 27 (13): 1043-1057
0114-5916/04/0013-1043/$31.00/0

Benefit-Risk Assessment of Tolterodine in the Treatment of Overactive Bladder in Adults

Alan D. Garely[1] and *Lara Burrows*[2]

1 Winthrop University Hospital, Department of Obstetrics and Gynecology, Division of Urogynecology and Pelvic Surgery, Mineola, New York, USA
2 University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Contents

Abstract

Overactive bladder is associated with symptoms of urgency, with or without urge incontinence, usually with daytime frequency and nocturia in the absence of local pathological factors. Muscarinic receptor antagonists (antimuscarinics) are the first-line pharmacotherapy. Tolterodine, a competitive, nonselective antimuscarinic specifically developed for the treatment of overactive bladder, demonstrated tissue selectivity for the bladder over the parotid gland in an animal model. As of March 5, 2003, the immediate-release (IR) formulation had been approved in 72 countries and the extended-release (ER) formulation had been approved in 28 countries, and tolterodine had been administered to 5 million patients. This review evaluates the benefit-risk profile of tolterodine in the treatment of adults with

overactive bladder, summarising clinical trial and postmarketing surveillance data.

Tolterodine has been found to significantly reduce micturition frequency, urgency perception and the number of episodes of urge incontinence and increase the volume voided per micturition. Dry mouth, an antimuscarinic class effect, is the most commonly reported adverse effect but is mostly mild to moderate in severity. Serious adverse effects are reported infrequently. Based on summary and review of postmarketing surveillance and clinical trial safety data received by the market authorisation holder and contained in the Periodic Safety Update Reports for tolterodine, several monitored serious events of the gastrointestinal tract (e.g. ileus or haemorrhage), nervous system (e.g. syncope, convulsions and memory disorders) and cardiovascular system (e.g. ventricular arrhythmia, atrial fibrillation, palpitations, bradycardia, transient ischaemic attacks and hypertension) were not considered related to tolterodine. QT or corrected QT (QTc) prolongation was not observed in any of the five cases of verified ventricular arrhythmia in patients administered tolterodine; there is insufficient evidence to indicate that tolterodine causes ventricular arrhythmia or extrasystoles or any specific type of cardiac rhythm abnormality. The safety profile of tolterodine is similar in patients aged ≥65 years and in younger adults. Clinically relevant drug interactions are limited to cytochrome P450 3A4 inhibitors, such as ketoconazole, and co-administration with such agents warrants a tolterodine dosage decrease.

In addition, tolterodine IR 2mg twice daily is similar in efficacy to oxybutynin IR 5mg three times daily, and tolterodine ER 4mg once daily is similar in efficacy to oxybutynin ER 10mg once daily. Dry mouth occurred less frequently with tolterodine than oxybutynin, and moderate to severe dry mouth occurred more than three times less frequently.

Based on the low frequency of adverse events, the absence of unexpected adverse events and the very low frequency of serious adverse events, we conclude that tolterodine is a well tolerated treatment for overactive bladder in adults, in whom it should be considered as first-line therapy.

Tolterodine, a competitive, nonselective, pure muscarinic receptor antagonist,[1] was specifically developed for the treatment of overactive bladder. It is indicated for symptoms of urinary frequency, urgency and urge incontinence diagnosed as overactive bladder or, in some countries, as unstable bladder. It significantly reduces micturition frequency and the number of episodes of urge incontinence, while it increases volume voided per micturition.[2]

Tolterodine is available in two formulations: immediate-release (IR), administered twice daily, and extended-release (ER)[1] capsules, administered once daily. These two formulations are bioequivalent in terms of pharmacological profile.[3] The ER formulation is associated with improved efficacy and tolerability compared with the IR formulation.[4]

Tolterodine was first approved in September 1997 in Sweden. As of March 5, 2003, the IR formulation was approved for sale in 72 countries and the ER formulation was approved for sale in 28 countries.[5] More than 5 million patients have been treated with tolterodine worldwide from launch to

1 In different parts of the world, tolterodine tartrate extended-release capsule brand names are Detrol® LA, Detrusitol® SR, Detrusitol® XL, Detrusitol® Neo, Detrusitol® Retard and UNIDET™. The use of trade names is for product identification purposes only and does not imply endorsement.

March 2003, the most recent date for which data are available.[5]

In comparison with oxybutynin, an anticholinergic used for the treatment of overactive bladder, the binding affinity of tolterodine was similar in the bladder but eight times lower in the parotid gland in an animal model.[1] In anaesthetised cats, tolterodine was more potent in inhibiting bladder contractions than salivation, whereas the reverse was true for oxybutynin.[1]

This review evaluates the benefit-risk profile of tolterodine in overactive bladder, summarising efficacy and safety data from several clinical trials, in addition to observations arising from postmarketing surveillance. Using the keyword 'tolterodine', Medline was searched from 1966 through August 2003 for English language, randomised controlled trials and long-term open-label extensions of randomised controlled trials reporting efficacy and/or safety data. Medline was also used to identify articles on postmarketing safety studies, drug interaction studies and studies that investigated the pharmacodynamic basis of observed adverse events. Alternative treatments were identified using the US National Library of Medicine MeSH® headings/subheadings 'urinary incontinence/drug therapy' OR 'urinary incontinence/therapy' AND 'overactive bladder'.

1. Benefit Evaluation: Clinical Efficacy

1.1 Epidemiology and Natural History of Overactive Bladder

Overactive bladder is associated with symptoms of urgency, with or without urge incontinence, usually with daytime frequency and nocturia in the absence of local pathological factors.[6] The recently published NOBLE (National Overactive BLadder Evaluation) survey, which included a sample of 5204 noninstitutionalised adults representative of the US population by sex, age and geographical region, determined that the overall prevalence of overactive bladder is similar between men (16%) and women (17%).[7] Identical results were found in a European population-based survey of 16 776 adults aged ≥40 years (men 16%; women 17%); frequency (85%) was reported most commonly, followed by urgency (54%) and urge incontinence (36%).[8]

The prevalence of overactive bladder symptoms increases with age. Overactive bladder with urge incontinence was more prevalent in women (range across increasing age groups 2–19%, with a marked increase in patients aged >44 years) than in men (range across increasing age groups 1–9%, with a marked increase in patients aged >64 years), whereas overactive bladder without urge incontinence was more common in men.[7] Although there is little information on the natural history of overactive bladder, urodynamic findings and symptoms of the syndrome suggest that the disorder is persistent, with little evidence of spontaneous resolution.[6]

1.2 Evidence of Benefit in Overactive Bladder

Overactive bladder, with or without urge incontinence, disrupts daily activities and sleep and can increase symptoms of depression.[7] The purpose and outcome of treatment is to decrease symptoms of urge incontinence, urgency and frequency, thereby increasing quality of life. When pelvic floor exercises, bladder retraining and lifestyle interventions are unsuccessful in controlling urinary incontinence, treatment alternatives include other physical therapy adjuncts, use of devices or external appliances, and pharmacotherapy with antimuscarinics.[9]

1.2.1 Clinical Efficacy Trials

Several urodynamic variables may be measured to assess bladder function, such as volume at normal desire to void and at first contraction, residual urinary volume, and maximal cystometric capacity. Tolterodine improves objective urodynamic variables in patients with overactive bladder, as demonstrated in a 4-week, double-blind, placebo-controlled trial.[10] Increase from baseline in mean values for volume at first contraction was 63% ($p \leq 0.001$) in patients randomised to tolterodine IR 2mg twice daily (n = 99) and 47% ($p \leq 0.001$) in those randomised to tolterodine IR 1mg twice daily (n = 99), compared with 29% in those randomised to placebo (n = 44).[10] Tolterodine 2mg, but not 1mg,

also significantly increased mean maximum cystometric capacity (16%; $p \leq 0.001$) and residual urine volume (64%; $p \leq 0.01$) and decreased detrusor pressure at maximal flow, compared with baseline. In addition, both tolterodine dosages significantly decreased mean values from baseline for maximal height of the detrusor contraction and number of waves of contractions and increased bladder compliance and urinary volumes (at first sensation, at normal desire to void and at strong desire to void) [$p < 0.05$]. Maximum urinary flow was not significantly affected. Compared with placebo, the change from baseline with tolterodine IR 2mg was significant for volume at first contraction ($p = 0.03$), cystometric capacity ($p = 0.034$) and residual urine volume ($p = 0.042$).

In two other double-blind, placebo-controlled trials, a dose-response relationship, assessed by linear regression analysis, was shown for volume at first contraction ($p = 0.01$[11] and $p = 0.05$[12]), maximum cystometric capacity ($p = 0.009$[11]), residual urine volume ($p = 0.0003$[12]) and volume at normal desire to void ($p = 0.001$[11] and $p = 0.05$[12]), for doses of tolterodine IR between 0.5mg and 4mg twice daily. One of these studies also showed a dose-response relationship for micturition diary parameters, including frequency ($p = 0.04$), leakage ($p = 0.002$) and the number of incontinence pads used ($p = 0.005$).[12] The dose-response effect on urodynamic variables was confirmed in a pooled analysis of four randomised, double-blind, placebo-controlled, phase II studies.[2]

Micturition diary parameters were improved significantly by treatment with tolterodine IR 2mg twice daily or 1mg twice daily and tolterodine ER 4mg once daily, as demonstrated in double-blind, controlled trials,[13-20] selected populations of adults aged ≥65 years (table I). Compared with baseline mean values, tolterodine IR and ER decreased micturition frequency and increased the volume of urine voided, improvements of approximately 20–30% being achieved in most studies. In the two largest trials, improvements from baseline for all micturition variables were significantly greater for tolterodine IR 2mg and for tolterodine ER 4mg compared with placebo.[4,15] Moreover, the number of incontinence episodes was approximately halved and incontinence pad usage was decreased by more than a third. Furthermore, in a secondary analysis of one of these two trials,[4] in which 772 patients with symptoms of urgency were assessed, the proportion of patients able to finish tasks before voiding in response to urgency increased from 5% at baseline to 33% among those treated with tolterodine ER 4mg once daily, compared with an increase from 6% to 18% among those treated with placebo ($p < 0.001$).[16]

Several studies compared tolterodine formulations or assessed demographic subpopulations. Tolterodine ER 4mg once daily was 18% more effective than tolterodine IR 2mg twice daily in reducing the number of incontinence episodes ($p \leq 0.05$).[4] There was no significant difference in the efficacy of tolterodine ER 4mg once daily between patients aged <65 years and those aged ≥65 years.[14] In the secondary analysis of patients with urgency described above, the improvement in urgency perception in men was similar between those receiving tolterodine ER (25%) and placebo (27%).[16] However, in women the improvement was significantly greater in patients receiving tolterodine ER compared with placebo (47% vs 27%, odds ratio 1.81 [95% CI 1.31, 2.49], $p < 0.001$).[16]

The efficacy of tolterodine IR 2mg twice daily,[21,22] and tolterodine ER 4mg once daily[23] was maintained during open-label follow-up of up to 12 months' duration. The efficacy of tolterodine was further confirmed by subjective assessments of improvement.[16,21-23] For example, four randomised, double-blind, placebo-controlled trials reported on patients' subjective assessments of improvement; in two of three trials of tolterodine IR and in the large trial of tolterodine ER, improvement was significantly greater with tolterodine than with placebo (table I).[14,15,17]

1.2.2 Quality of Life

Disruption of daily activities has been shown to improve with tolterodine treatment of overactive bladder. In a multinational, randomised, double-blind, placebo-controlled study, the health-related

Table I. Improvement in micturition diary variables in double-blind, placebo-controlled trials of tolterodine in the treatment of overactive bladder

Trial	Study duration (wk)	No. of subjects enrolled (age)	Active treatment	Percentage change from baseline in mean values[a]				Subjective assessment 'improved'
				frequency	incontinence episodes	incontinence pad usage	average volume of urine voided	
Van Kerrebroeck et al. 2001[4]	12	514	T IR 2mg bid	−30%§	−46%§	−36%‡	+21%§	NS
		507	T ER 4mg od	−32%§	−53%§	−36%†	+24%§	
		508	Placebo	−20%	−30%	−13%	+10%	
Malone-Lee et al. 2001[13]	4	73 (≥65y)	T IR 2mg bid	−0.7§[b]	−0.7‡[b]	NS	16‡[b]	NS
		61 (≥65y)	T IR 1mg bid	−0.7§[b]	−0.3[bc]		9[bc]	
		43 (≥65y)	Placebo	0[b]	0[b]		0[b]	
Zinner et al. 2002[14]	12	293 (<65y)	T ER 4mg od	−18%§	−56%§	NS	+25%§	60%§
		285 (<65y)	Placebo	−12%	−32%		+9%	52%
		214 (≥65y)	T ER 4mg od	−13%[c]	−50%§	NS	+23%§	54%§
		223 (≥65y)	Placebo	−8%	−27%		+12%	31%
Chancellor et al. 2000[15]	12	514	T IR 2mg bid	−15%‡	−46%*§	−36%‡	+21%§	61%§
		508	Placebo	−11%	−30%	−13%	+10%	43%
Millard et al. 1999[17][d]	12	129	T IR 2mg bid	−21%‡	−47%[c]	NS	+23%§	59%†
		123	T IR 1mg bid	−20%‡	−44%[c]		+18%‡	41%
		64	Placebo	−12%	−37%		+6%	38%
Drutz et al. 1999[18]	12	109	T IR 2mg bid	−17%**†	−46%**	NS	+22%*†	NS
		112	O IR 5mg tid	−17%**	−50%**		+34%*†	
		56	Placebo	−10%*	−29%*		+8%[e]	
Abrams et al. 1998[19]	12	118	T IR 2mg bid	−21%‡	−47%	NS	+27%§	50%
		118	O IR 5mg tid	−20%	−71%†		+31%§	49%
		57	Placebo	−11%	−19%		+7%	47%
Jacquetin and Wyndaele 2001[20]	4	103	T IR 2mg bid	−13%[c]	−41%‡	NS	+12%[c]	NS
		97	T IR 1mg bid	−13%[c]	−41%†		+13%[c]	
		51	Placebo	−10%	−17%		+5%	

a Calculated from the reported mean value at baseline and mean change from baseline, except for Malone-Lee et al.,[13] who reported the change from baseline as median values, and for Abrams et al. 1998[19] and Chancellor et al. 2000[15] who reported the percentage change.

b Because baseline values were reported as mean values and change from baseline reported as median values, a percentage change could not be calculated. Values reported are median change from baseline in mean number of micturitions/24 hours, mean number of incontinence episodes/24 hours and mean volume voided per micturition (mL).

c Not statistically significant versus placebo.

d Additional efficacy measures included achievement of normalised voiding frequency, defined as <8/24 hours (tolterodine 2mg 43% of patients, tolterodine 1mg 26%, and placebo 24%; $p \leq 0.05$ for tolterodine 2mg vs 1mg and placebo, chi-square test) and cured incontinence, defined as complete dryness (tolterodine 2mg 19% of patients, tolterodine 1mg 10%, and placebo 11%; not statistically significant between groups).

e Not statistically significant versus baseline.

bid = twice daily; **ER** = extended-release; **IR** = immediate-release; **NS** = not stated; **O** = oxybutynin; **od** = once daily; **T** = tolterodine; **tid** = three times daily; **y** = years; * $p \leq 0.05$, ** $p \leq 0.001$ vs baseline; † $p \leq 0.05$, ‡ $p \leq 0.01$, § = $p \leq 0.001$ vs placebo.

quality of life (HR-QOL) of 1529 adults (mean age 60 years) with overactive bladder was assessed using the King's Health Questionnaire, a disease-specific instrument with a ten-symptom severity checklist and 32 items across several HR-QOL domains. Compared with placebo, treatment with tolterodine IR 2mg twice daily or tolterodine ER 4mg once daily for 12 weeks significantly improved symptom severity and all HR-QOL domains selected *a priori* as primary endpoints (e.g. incontinence impact and role limitations) or secondary endpoints (e.g. physical limitations, sleep and energy, and severity [coping] measures); the domains of social limitations, personal relationships, emotions and general health perception were not significantly improved.[24] During 12 months of open-label extension, symptom severity and all HR-QOL domains, except general health perception, were significantly improved relative to untreated baseline.[25]

1.3 Comparison with Alternative Treatments

There are no studies comparing the efficacy of tolterodine with that of pelvic floor exercises, bladder retraining or other physical therapy adjuncts for the treatment of overactive bladder. However, the addition of bladder retraining to a regimen of tolterodine IR 2mg twice daily significantly augmented the efficacy of tolterodine. The median percentage reduction in the voiding frequency was 25% for tolterodine and 33% for tolterodine plus retraining, and the median percentage increase in volume voided was 20% and 31%, respectively ($p < 0.001$ vs baseline for each, and between tolterodine and tolterodine plus retraining).[26] The decrease in the number of episodes of urgency and incontinence and the subjective assessment of improvement were highly significant for each group ($p < 0.001$) but did not differ between the groups.

Antimuscarinics dominate the pharmacotherapy for overactive bladder. The comparative efficacy of tolterodine and oxybutynin is dependent on the formulation and the dosage, with no difference in efficacy between tolterodine IR 2mg twice daily and oxybutynin IR 5mg three times daily in double-blind, placebo-controlled comparisons (table I).[18,19] Equivalence was confirmed in a pooled analysis of four randomised, double-blind, multicentre studies.[27]

Several trials that lacked placebo control have compared other formulations and dosages of tolterodine and oxybutynin. In patients aged ≥50 years, tolterodine IR 2mg twice daily was found to be equivalent in efficacy to oxybutynin IR 2.5–5mg twice daily.[28] In another study, equivalence, predefined as a between-group difference of ±1.5 for the 95% CI, was not established for tolterodine IR 2mg twice daily and oxybutynin IR 5mg twice daily; tolterodine achieved larger decreases from baseline in the mean number of micturitions (2.6 vs 1.8) and mean number of incontinence episodes (2.2 vs 1.4).[29] In yet another trial, differences between these dosages of tolterodine and oxybutynin were not achieved for micturition diary variables, but tolterodine was associated with a significantly greater objective reduction in urinary leakage (e.g. change in urinary pad weight; $p < 0.05$) and approached significance for the subjective improvement in symptom severity (e.g. visual analogue scale; $p = 0.053$).[30] Comparison of the ER formulation of oxybutynin (10mg once daily) with the IR formulation of tolterodine (2mg twice daily), using analysis of covariance, indicated greater decreases from baseline in the mean number of urge incontinence episodes, total incontinence episodes and micturition frequency for oxybutynin ER ($p = 0.02$–0.03).[31] However, both drugs were highly effective in decreasing all three micturition variables ($p < 0.001$), and 95% and 96% of participants, respectively, had fewer incontinence episodes.[31] When the ER formulations of tolterodine (4mg once daily) and oxybutynin (10mg once daily) were compared in 790 women with severe urge incontinence (21–60 episodes/week) in the recently reported OPERA (Overactive bladder: Performance of Extended Release Agent) trial, the weekly mean micturition frequency decreased more in the oxybutynin recipients compared with the tolterodine recipients (28 vs 25; $p < 0.003$), but improvement in the primary efficacy outcome, the weekly mean number of urge incontinence episodes, was identical between treat-

ments (decreased from 37 to 11 episodes).[32] In another comparison of the ER formulations of tolterodine (2 and 4mg once daily) and oxybutynin (5 and 10mg once daily) in 1289 patients with overactive bladder, 70% of those treated with tolterodine ER 4mg reported improvement in their bladder problems as measured on a 6-point Likert scale, compared with 60% in both the tolterodine ER 2mg group and the oxybutynin ER 10mg group and with 59% in the oxybutynin ER 5mg group ($p < 0.01$).[33]

Other antimuscarinics approved for the treatment of overactive bladder include propiverine, trospium chloride, emepronium bromide and flavoxate. Although randomised, double-blind trials comparing propiverine or trospium chloride with tolterodine IR 2mg twice daily have been reported, full details of these trials have not been published. In a trial of 155 patients with overactive bladder, propiverine 15mg twice daily was reported to be comparable to tolterodine in efficacy, tolerability and improvement in quality of life.[34] Trospium-chloride 20mg twice daily was reported to be at least as effective as tolterodine IR 2mg twice daily in reducing micturition frequency in a study of 232 patients with urge syndrome.[35] No comparative data with tolterodine were found for other antimuscarinics. However, clinical trials have failed to show that flavoxate offers any advantage compared with placebo for patients with symptoms of overactive bladder.[36,37]

Comprehensive literature review indicates that currently available alternatives to antimuscarinics for urinary incontinence, such as α-adrenoceptor agonists and estrogen, are of limited use.[38,39] There is only weak evidence to suggest that adrenergics offer any advantage over placebo for the treatment of stress urinary incontinence (e.g. phenylpropanolamine, midodrine).[38] Systemic estrogen replacement therapy can improve or cure urge incontinence, but combined therapy with progesterone reduces the likelihood of response, and the risk of endometrial and breast cancer limits the usefulness of estrogen replacement therapy in this setting.[39] Although locally administered estrogen products are effective in reducing the signs and symptoms of vaginal atrophy, data on efficacy in the treatment of urinary symptoms are conflicting.[40]

Potential future therapies for overactive bladder include new antimuscarinics, such as solifenacin and darifenacin, and locally administered capsaicin, botulinum toxin or other agents.[41] Injection of botulinum toxin into the detrusor muscle[42] and intravesical instillation of resiniferatoxin and capsaicin[43] have shown efficacy and good tolerability in patients with overactive bladder resistant to antimuscarinics, such as patients with spinal cord injury. The longer term direction for future research includes several drug classes that have shown activity on bladder function (i.e. potassium channel agonists, tachykinin antagonists, neurokinin antagonists and β-adrenoceptor agonists), as well as pharmacogenomics, gene therapy and tissue engineering.[41]

2. Risk Evaluation

The risk evaluation of tolterodine is based on a review of the published medical literature and the relevant Periodic Safety Update Reports (PSURs). The PSUR, a regulatory document, summarizes medically confirmed postmarketing and serious clinical trial safety data received by the market authorisation holder, in this case Pfizer. The tolterodine PSURs included in this document are the Bridging Summary Report for January 1, 1997 through March 5, 2002,[44] which provides 5 years of collected safety data, and the subsequent reports for the 6-month periods of March 6, 2002 through September 5, 2002 and September 6, 2002 through March 5, 2003.[45]

2.1 Adverse Effects

2.1.1 Antimuscarinic Effects

In clinical trials and postmarketing surveillance, the most commonly reported adverse reaction to tolterodine was dry mouth. In phase III clinical trials, dry mouth occurred in 35% of 986 patients receiving tolterodine IR 2mg twice daily for 12 weeks, compared with 10% of 683 patients receiving placebo, and in 24% of 505 patients receiving tolterodine ER 4mg once daily for 12 weeks, com-

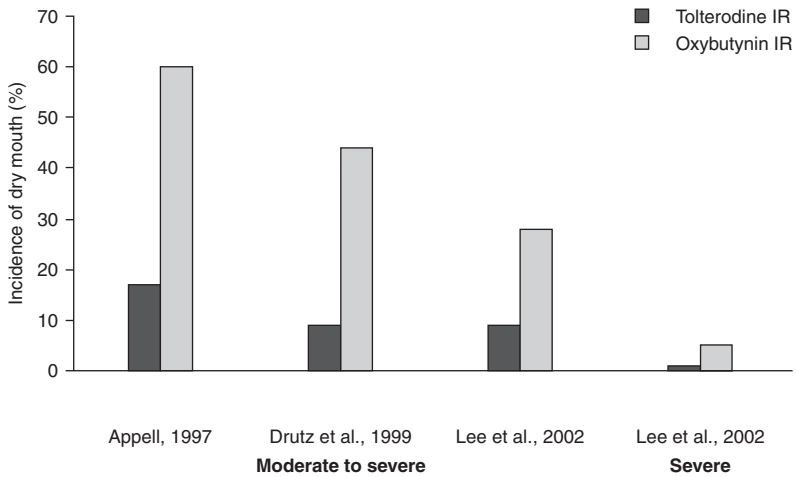

Fig. 1. Incidence of moderate to severe dry mouth and severe dry mouth with tolterodine IR 2mg twice daily compared with oxybutynin IR 5mg twice or three times daily for the treatment of patients with overactive bladder, as reported in randomised, double-blind trials by Appell,[27] Drutz et al.[18] and Lee et al.[29]

pared with 8% of 507 patients receiving placebo.[46,47] Most cases of dry mouth were mild to moderate in intensity. Severe dry mouth was reported during treatment with tolterodine IR or tolterodine ER by only 1–5% of patients in several large, placebo-controlled studies: 0% (0 of 98, 1mg twice daily),[10] 1% (1 of 99, 2mg twice daily),[10] 1% (1 of 129, 2mg twice daily),[17] 2% (12 of 512, 2mg twice daily),[15] 2% (2 of 97, 1mg twice daily),[20] 2% (9 of 505, 4mg once daily),[4] 3% (2 of 123, 1mg twice daily)[17] and 5% (5 of 103, 2mg twice daily).[20] In addition, it was reported by only 2–3% during open-label follow-up of up to 12 months' duration: 2% (19 of 1077, 4mg once daily),[23] 2% (17 of 854, 3mg twice daily)[22] and 3% (21 of 714, 2mg twice daily).[21]

Available data indicate that dry mouth is less common with tolterodine than with oxybutynin. In large randomised, double-blind studies of patients with overactive bladder and a pooled analysis of four such studies, tolterodine IR 2mg twice daily caused significantly less dry mouth than oxybutynin IR 5mg twice or three times daily ($p < 0.001$).[18,19,27,29] Compared with tolterodine IR 2mg twice daily, oxybutynin IR 5mg twice or three times daily was associated with a three to five times increase in moderate to severe dry mouth[18,27,29] and a five times increase in severe dry mouth (figure 1).[29] Indeed, in a randomised, double-blind, placebo-controlled comparison, dry mouth caused 15 of 20 withdrawals among 118 oxybutynin recipients (e.g. 13% of patients withdrew because of dry mouth), compared with one of ten from among 118 tolterodine recipients (1%) and two of seven from among 57 placebo recipients (4%).[19] Tolterodine IR 2mg twice daily was associated with a similar incidence of moderate to severe dry mouth as oxybutynin ER 10mg once daily.[31] However, comparison of the ER formulations of the two medications showed that tolterodine ER 4mg caused significantly less dry mouth than oxybutynin ER 10 mg[32] and that the dry mouth was of lesser severity ($p = 0.03$).[33]

The difference in the reported incidence of dry mouth between tolterodine and oxybutynin in patients with overactive bladder is supported by the results of a small pharmacology study that assessed saliva output. In this double-blind, randomised, placebo-controlled crossover study of 36 healthy adult volunteers (mean age 27 years), saliva output was compared after administration of single doses of tolterodine IR 2mg, oxybutynin IR 5mg and oxybutynin XL 10mg.[48] The area under the curve over the 12-hour measurement period showed higher saliva

output with tolterodine IR compared with oxybutynin IR ($p < 0.01$). There was no significant difference in saliva output between tolterodine IR and oxybutynin ER.

The manufacturer's Tolterodine Core Data Sheet states that other antimuscarinic events include dry eyes and abnormal vision (including abnormal accommodation), reported by 1–10% of patients treated with tolterodine in clinical trials.[5] In a randomised, double-blind, placebo-controlled comparison, abnormal accommodation was reported by 2% of 57 patients administered placebo, 3% of 118 patients treated with tolterodine IR 2mg twice daily, and 7% of 118 patients treated with oxybutynin IR 5mg three times daily.[19] The pharmacological basis for potential differences in accommodation was explored in a double-blind, randomised, crossover study of 16 healthy volunteers.[49] Tolterodine IR 5mg (a supratherapeutic dose) and oxybutynin IR 5mg each increased accommodation, producing an approximately 20% maximum change in near-point vision, but tolterodine 5mg produced twice the increase in bladder capacity as did oxybutynin 5mg (93% vs 45% increase).[49]

2.1.2 Gastrointestinal Events

Older patients, who constitute a large proportion of the population with overactive bladder, are particularly susceptible to gastrointestinal adverse effects, such as constipation. Impaired general health and decreased mobility and physical activity contribute to the risk of constipation in older adults. Constipation is a particularly noteworthy adverse effect in older adults with overactive bladder because it is associated with lower urinary tract symptoms.[50] Alleviation of chronic constipation in a group of elderly patients with lower urinary tract symptoms significantly improved urinary tract symptoms (e.g. urgency, frequency, burning, urinary stream abnormalities, residual urine and bacteriurial events).[50]

Gastroesophageal reflux was reported by <1% of patients treated with tolterodine in clinical trials, and dyspepsia, constipation, abdominal pain and flatulence were reported by 1–10%.[5] The incidence of gastrointestinal adverse events was similar between the IR and ER formulations.[4] In a multicentre, randomised, double-blind study of patients with overactive bladder, the incidence of abdominal pain in 103 patients treated with tolterodine IR 2mg twice daily was similar compared with 51 patients administered placebo (4% each), and the incidence of constipation was half that in those administered placebo (2% vs 4%).[20] During open-label administration for up to 12 months, abdominal pain was reported by 6% (42 of 714[21] and 50 of 854[22]) and constipation by 7% (57 of 854[22]) of patients treated with tolterodine IR 2mg twice daily; constipation was reported by 3% and dyspepsia by 2% of 1075 patients treated with tolterodine ER 4mg once daily.[23] However, in a UK postmarketing prescription-event monitoring study, constipation, dyspepsia and abdominal pain were each reported by <2% of the 14 526 patients who received tolterodine during the 6 months following its launch.[51]

The incidence of gastrointestinal events tends to be lower in patients treated with tolterodine compared with those treated with oxybutynin. In a randomised, double-blind, placebo-controlled trial, dyspepsia was reported by 3 of 57 (5%) patients administered placebo, 11 of 118 (9%) patients treated with tolterodine IR 2mg twice daily, and 27 of 118 (23%) patients treated with oxybutynin IR 5mg three times daily.[19] In a pooled analysis of four such studies, dyspepsia was reported by 6% of 474 patients treated with tolterodine IR 2mg twice daily and by 11% of 349 treated with oxybutynin IR 5mg three times daily ($p = 0.006$).[27]

Gastrointestinal events monitored during postmarketing include decreased motility (which could be related to antimuscarinic activity) and haemorrhage, both of which have been reported infrequently and, based on PSUR summary and review, lack a clear association with tolterodine.[5,44]

2.1.3 Nervous System Events

Nervous system adverse events, reported in the Core Data Sheet, are experienced by 1–10% of patients treated with tolterodine in clinical trials and include headache, dizziness/vertigo, somnolence and fatigue.[5] In placebo-controlled studies, the incidence of headache did not exceed 6% and was similar to that in placebo recipients, in patients

treated with tolterodine IR 2mg twice daily (3% [3 of 103],[20] 3% [3 of 99],[10] 4% [19 of 512],[4] 4% [19 of 512]),[15] or tolterodine ER 4mg once daily (6% [32 of 505]).[4] In a multicentre, double-blind comparison, somnolence, dizziness and fatigue were each reported by ≤3% patients randomised to tolterodine IR 2mg twice daily (n = 514), tolterodine ER 4mg once daily (n = 507) or placebo (n = 508).[4] During open-label administration for up to 12 months, headache was reported by 6% (42 of 714)[21] to 7% (57 of 854)[22] of patients treated with tolterodine IR 2mg twice daily and by 2.4% (26 of 1075) of those treated with tolterodine ER 4mg once daily.[23] However, in a UK postmarketing surveillance study, headache, dizziness, fatigue (e.g. malaise, lassitude) and somnolence (e.g. drowsiness, sedation) were each reported by <2% of patients who received tolterodine during the 6 months following its launch.[51]

In direct comparisons, the incidence of nervous system events reported with tolterodine was generally similar to that reported for oxybutynin.[18,27,29,31] The pharmacological basis for nervous system events was examined in a randomised, single-blind, parallel-group comparison of oxybutynin IR 5mg three times daily, tolterodine IR 2mg twice daily, trospium chloride 15mg three times daily and placebo, each in 16 healthy volunteers.[52] Global subjective tolerability was reported to be 'comparable' between all the groups, with 50% of oxybutynin recipients, 56% of trospium chloride recipients, 63% of tolterodine recipients and 81% of placebo recipients reporting very good tolerability.[52] However, statistically significant changes in the quantitative-topographical EEG compared with baseline values were seen in subjects administered oxybutynin, but not tolterodine or trospium chloride ($p < 0.05$),[52] and adverse events related to the CNS occurred in half as many patients who received tolterodine (n = 4) as in patients who received oxybutynin (n = 8) or trospium chloride (n = 8).

Nervous system events reported in <1% of patients receiving tolterodine in clinical trials include confusion and hallucinations.[5] Hallucinations, predominantly visual and mostly occurring in elderly women, were an unexpected event that first surfaced in the UK postmarketing surveillance study, with nine 'probably-related' or 'possibly-related' events among the 14 526 patients (0.06%).[51] Other nervous system events monitored postmarketing include syncope, convulsions and memory disorders (amnesia, memory loss and memory impairment). Based on PSUR summary and review by the market authorisation holder, there is insufficient evidence to conclude that these events were associated with tolterodine.[5,44,45]

2.1.4 Urinary Events

Dysuria occurs in 1–10% of patients receiving tolterodine, and urinary retention occurs in <1% of patients, according to the Core Data Sheet.[5] This is confirmed by the results of the UK postmarketing surveillance study, which reported an incidence of 2% for micturition disorder and 0.5% for retention, but noted that these symptoms are characteristic of the underlying condition, overactive bladder.[51]

2.1.5 Other Events

Oedema associated with tolterodine is almost always mild and peripheral.[44] In a multicentre, double-blind comparison, peripheral oedema was reported by 1% of patients randomised to either tolterodine IR 2mg twice daily (n = 514), tolterodine ER 4mg once daily (n = 507) or placebo (n = 508).[4]

Tachycardia is a well known class effect for antimuscarinic drugs.[44] However, in the UK postmarketing surveillance study, a probable or possible relationship to tolterodine was assigned to only 17 cases of tachycardia or palpitations (0.1%) and to only 21 cases of chest pain (0.1%).[51] Other cardiovascular events monitored during postmarketing include ventricular arrhythmia, atrial fibrillation, cardiac failure, palpitations, bradycardia, collapse, transient ischaemic attacks and hypertension, which are reported infrequently and generally in older patients; based on PSUR summary and review, there is insufficient evidence for a causal relationship to tolterodine.[5,44,45] QT or corrected QT (QTc) prolongation was not observed in any of the five cases of verified ventricular arrhythmia reported during 6 years of postmarketing surveillance.[5,44] Thus, there is insufficient evidence indicating that tolterodine

causes ventricular arrhythmia or extrasystoles, or any specific type of cardiac rhythm abnormality.

Dermatological (e.g. flushed skin) and sensitivity (e.g. allergic) reactions are reported in <1% of patients treated with tolterodine.[5] Anaphylactic reaction was added to the Core Data Sheet in 1999 based on the identification of four cases, despite suspicion of other medications in two of these and an underlying predisposition in the other two cases.[44]

Other events listed in the tolterodine Core Data Sheet include bronchitis and weight gain, associated with the IR formulation only, and sinusitis, associated with the ER formulation only; these events are reported in 1–10% of patients.[5] Other events monitored postmarketing, for which there is insufficient evidence of an association with tolterodine, include hepatic dysfunction, renal dysfunction and depression.[44]

2.2 Safety in Special Populations

2.2.1 Older Patients

Because hepatic and renal function decrease with age, drug accumulation can be a potential source of safety problems, particularly with drugs that have a prolonged half-life. The tolterodine steady-state half-life in healthy volunteers, who are not poor metabolisers (see section 2.3), is approximately 3 hours for the IR formulation and approximately 6 hours for the ER formulation.[3] The pharmacokinetic properties of tolterodine in the healthy elderly population are similar to those observed in younger volunteers.[53]

The safety profile of tolterodine for the treatment of overactive bladder does not appear to be affected by patient age. In randomised, double-blind studies, no clinically important changes in clinical chemistry, haematological parameters or ECG recordings (heart rate or cardiac conduction) were found in older patients treated with tolterodine.[14,28]

Placebo-controlled trials have assessed tolterodine IR 1mg and 2mg twice daily for 4 weeks (n = 177) in patients ≥65 years[13] and tolterodine ER 4mg once daily for 12 weeks in patients aged ≥65 years (n = 437) compared with younger adults (n = 578).[14] Dry mouth, the most commonly occurring adverse event associated with tolterodine, occurred in a similar incidence in older patients (24% [52 of 214]) compared with younger patients (23% [66 of 291])[14] and was the only event that occurred significantly more frequently with tolterodine than with placebo in older patients ($p = 0.013$[13] and $p < 0.001$ for tolterodine vs placebo[14]). Most instances of dry mouth were mild to moderate in intensity; only 2% (4 of 214)[14] to 3% (2 of 73)[13] of tolterodine recipients, compared with 1% (3 of 223) to 2% (1 of 43)[13] of placebo recipients, discontinued therapy because of dry mouth.[13,14] With the exception of headache, which occurred more frequently in younger patients than older patients (8% [24 of 291] vs 4% [8 of 214]; $p = 0.04$), all other adverse events occurred at a similar frequency in younger and older patients with placebo or with tolterodine treatment.[14]

As is the case with younger patients, the incidence of dry mouth in older patients is lower with tolterodine treatment than with oxybutynin treatment. Patients aged 50–90 years (mean 65 years) with symptoms of overactive bladder were randomised under double-blind conditions to tolterodine IR 2mg twice daily for 10 weeks (n = 190) or to oxybutynin IR 2.5mg three times daily for 2 weeks, increasing to 5mg for the remaining 8 weeks (n = 188).[28] A higher proportion of patients receiving oxybutynin than patients receiving tolterodine had dry mouth overall (61% vs 37%; $p < 0.0001$, chi-square test), severe dry mouth (15% vs 4%; not statistically significant), and dry mouth resulting in withdrawal from the study (7% vs 3%; not statistically significant).[28]

2.2.2 Hepatic and Renal Impairment

When volunteers with liver cirrhosis were compared with healthy volunteers, tolterodine IR achieved an increased serum concentration and a prolonged elimination half-life.[54] The urine is the major route of excretion of tolterodine, mainly as metabolites.[55] Consequently, in patients with hepatic or renal impairment, the maximum recommended dosage of tolterodine is 1mg twice daily (IR formulation) or 2mg once daily (ER formulation).

2.2.3 Pregnancy and Lactation

Tolterodine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (US FDA pregnancy category C), and use during lactation should be avoided because no data are available on excretion of the drug into human breast milk.[5] The UK postmarketing surveillance study reported that six women took tolterodine during the first trimester, at a median daily dose of 4mg (range 1–4mg). The outcomes of these pregnancies were five live births with no congenital abnormalities and one spontaneous abortion.[51]

2.3 Drug Interactions

Tolterodine is eliminated mainly by metabolism, with two oxidative metabolic pathways identified: (i) hydroxylation by cytochrome P450 (CYP) 2D6 to the 5-hydroxymethyl (5-HM) metabolite, which is pharmacologically active and equipotent to the parent drug *in vitro*; and (ii) N-dealkylation by CYP3A4.[56] The small percentage of the population that lacks the CYP2D6 enzyme, known as poor metabolisers, has relatively high serum concentrations of tolterodine and metabolises the drug through CYP3A4-mediated N-dealkylation.[57] However, CYP2D6 polymorphism has little influence on the pharmacodynamics of tolterodine, probably because of an additive pharmacodynamic effect between the parent drug and 5-HM.[58]

Probe drug studies have shown that tolterodine is unlikely to alter the metabolism of drugs that are substrates for the isoenzymes CYP2D6, CYP3A4, CYP2C19 or CYP1A2.[56] For example, in a randomised, double-blind, crossover study in healthy men, tolterodine did not alter the anticoagulant activity or pharmacokinetics of racemic warfarin.[59] R-(+)-warfarin is metabolised by CYP2C and CYP1A2, but hydroxylation by CYP3A4 may also be a major pathway; S-(−)-warfarin is almost entirely oxidised by CYP2C9.[59] Continued postmarketing monitoring provides insufficient evidence that tolterodine interacts with warfarin or other coumarin derivatives or increases the international normalised ratio or bleeding.[44] Similarly, tolterodine did not cause any clinically relevant effect on the pharmacokinetics or pharmacodynamics of a combination oral contraceptive containing ethinylestradiol and levonorgestrel.[60] Both the estrogen and progestogen components of combination oral contraceptives are metabolised by CYP3A4-mediated N-dealkylation.[61]

A series of studies was conducted to assess the potential for the metabolism of tolterodine to be altered by other drugs. Neither racemic warfarin[59] nor a combination estrogen/progestogen contraceptive[60] produced any clinically relevant alterations of the pharmacokinetics of tolterodine. Fluoxetine, a potent CYP2D6 inhibitor, significantly inhibited the hydroxylation of tolterodine, increasing serum tolterodine concentrations while decreasing 5-HM concentrations. However, similar to the situation in CYP2D6 poor metabolisers, this interaction is unlikely to be clinically relevant.[62] As previously mentioned, poor metabolisers of CYP2D6 metabolise tolterodine through CYP3A4-mediated N-dealkylation. This introduces the potential for drug interaction between tolterodine and potent inhibitors of CYP3A4 (i.e. macrolide antimicrobials, azole antifungals, ciclosporin and vinblastine).[54] For example, ketoconazole increased the plasma concentrations of tolterodine when coadministered to poor metabolisers.[57] Consequently, the recommended dosage of tolterodine in patients being treated concomitantly with a CYP3A4 inhibitor is 1mg twice daily (IR formulation) or 2mg once daily (ER formulation).

A recent report suggested a potential pharmacodynamic interaction between tolterodine and acetylcholinesterase inhibitors used in the treatment of Alzheimer's disease and dementia.[63] Within 1–2 weeks of addition of tolterodine therapy, delirium developed in two men whose symptoms had been stabilised with donepezil for 2 months and 2 years, respectively, and a woman whose symptoms had been stabilised with rivastigmine for 3 years; all were 82 years of age. Delirium improved or baseline status was regained within 24–48 hours of tolterodine discontinuation. A review of postmarketing surveillance data revealed no discernible pattern to implicate tolterodine.[45]

3. Benefit-Risk Evaluation

Antimuscarinics are the first-line pharmacotherapy for the treatment of overactive bladder. Tolterodine improves objective urodynamic variables and micturition diary parameters and decreases urgency perception in patients with overactive bladder, alleviating the disruption of daily activities. The comparative efficacy of tolterodine and oxybutynin in the treatment of overactive bladder depends on the formulation and the dosage. Tolterodine IR 2mg twice daily is similar in efficacy to oxybutynin IR 5mg given three times daily. As for the once-daily, long-acting formulations, tolterodine ER 4mg and oxybutynin ER 10mg were comparable in efficacy in controlling the number of urge incontinence episodes. The absence of comparative data precludes comparison of tolterodine with other currently marketed antimuscarinics.

Dry mouth is a class effect of antimuscarinics. An often overlooked complication of dry mouth is the potential to contribute to the development of dental caries and gingivitis.[64,65] Dry mouth is the most commonly reported adverse drug reaction associated with tolterodine, but the condition is mostly mild to moderate in intensity. In comparisons with oxybutynin, dry mouth occurred less frequently ($p < 0.001$) and moderate to severe dry mouth occurred more than three times less frequently ($p < 0.001$).

Serious adverse events are reported infrequently in patients treated with tolterodine. There is insufficient evidence that several monitored serious events from the gastrointestinal tract (e.g. ileus and haemorrhage), nervous system (e.g. syncope, convulsions and memory disorders) and cardiovascular system (atrial fibrillation, palpitations, bradycardia, transient ischaemic attacks and hypertension) are treatment related. Furthermore, in the 6 years of safety data included in this review, there is insufficient evidence indicating that tolterodine causes ventricular arrhythmia or extrasystoles, or any specific type of cardiac rhythm abnormality.

The safety profile of tolterodine in adults aged ≥65 years is similar to that in younger adults. Clinically relevant drug interactions are limited to CYP3A4 inhibitors, such as ketoconazole, which warrant a decrease in tolterodine dosage. There were no safety issues specific to any tolterodine formulation, there were no new events unique to the ER formulation, and the frequency and nature of observed events were consistent for both formulations.

Based on the low frequency of adverse events, the absence of unexpected adverse events and the very low frequency of serious adverse events reported since the launch of tolterodine in September 1997, we conclude that tolterodine is a well tolerated therapy for the treatment of overactive bladder. This benefit-risk analysis supports the continued use of tolterodine for the indication of overactive bladder in adult patients, in whom it should be considered a first-line therapy.

Acknowledgements

Dr Garely is a consultant, speaker and investigator for Pfizer Inc. This work was supported by Pfizer Inc.

References

1. Nilvebrant L, Andersson KE, Gillberg PG, et al. Tolterodine: a new bladder-selective antimuscarinic agent. Eur J Pharmacol 1997; 327: 195-207
2. Larsson G, Hallen B, Nilvebrant L. Tolterodine in the treatment of overactive bladder: analysis of the pooled phase II efficacy and safety data. Urology 1999; 53 (5): 990-8
3. Olsson B, Szamosi J. Multiple dose pharmacokinetics of a new once daily extended release tolterodine formulation versus immediate release tolterodine. Clin Pharmacokinet 2001; 40 (3): 227-35
4. Van Kerrebroeck P, Kreder K, Jonas U, et al. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. Urology 2001; 57 (3): 414-21
5. Periodic Safety Update Report (PSUR) for Detrusitol/Detrol tablets and Detrusitol/Detrol prolonged-release capsules (tolterodine). Period covered: 2002 Sep 06 through 2003 Mar 5. North Peapack (NJ): Pharmacia Corporation, 2003
6. Garnett S, Abrams P. The natural history of the overactive bladder and detrusor overactivity: a review of the evidence regarding the long-term outcome of the overactive bladder. J Urol 2003; 169 (3): 843-8
7. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. World J Urol 2003; 20 (6): 327-36
8. Milsom I, Abrams P, Cardozo L, et al. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 2001; 87 (9): 760-6
9. Scientific Committee of the First International Consultation on Incontinence. Assessment and treatment of urinary incontinence. Lancet 2000; 355 (9221): 2153-8
10. Jonas U, Hofner K, Madersbacher H, et al. Efficacy and safety of two doses of tolterodine versus placebo in patients with

detrusor overactivity and symptoms of frequency, urge incontinence, and urgency: urodynamic evaluation. The International Study Group. World J Urol 1997; 15 (2): 144-51
11. Van Kerrebroeck PE, Amarenco G, Thuroff JW, et al. Dose-ranging study of tolterodine in patients with detrusor hyperreflexia. Neurourol Urodyn 1998; 17 (5): 499-512
12. Rentzhog L, Stanton SL, Cardozo L, et al. Efficacy and safety of tolterodine in patients with detrusor instability: a dose-ranging study. Br J Urol 1998; 81 (1): 42-8
13. Malone-Lee JG, Walsh JB, Maugourd MF. Tolterodine: a safe and effective treatment for older patients with overactive bladder. J Am Geriatr Soc 2001; 49 (6): 700-5
14. Zinner NR, Mattiasson A, Stanton SL. Efficacy, safety, and tolerability of extended-release once-daily tolterodine treatment for overactive bladder in older versus younger patients. J Am Geriatr Soc 2002; 50 (5): 799-807
15. Chancellor MB, Freedman S, Mitcheson HD, et al. Tolterodine, an effective and well tolerated treatment for urge incontinence and other overactive bladder symptoms. Clin Drug Invest 2000; 19 (2): 83-91
16. Freeman R, Hill S, Millard R, et al. Reduced perception of urgency in treatment of overactive bladder with extended-release tolterodine. Obstet Gynecol 2003; 102 (3): 605-11
17. Millard R, Tuttle J, Moore K, et al. Clinical efficacy and safety of tolterodine compared to placebo in detrusor overactivity. J Urol 1999; 161 (5): 1551-5
18. Drutz HP, Appell RA, Gleason D, et al. Clinical efficacy and safety of tolterodine compared to oxybutynin and placebo in patients with overactive bladder. Int Urogynecol J Pelvic Floor Dysfunct 1999; 10 (5): 283-9
19. Abrams P, Freeman R, Anderstrom C, et al. Tolterodine, a new antimuscarinic agent: as effective but better tolerated than oxybutynin in patients with an overactive bladder. Br J Urol 1998; 81 (6): 801-10
20. Jacquetin B, Wyndaele J. Tolterodine reduces the number of urge incontinence episodes in patients with an overactive bladder. Eur J Obstet Gynecol Reprod Biol 2001; 98 (1): 97-102
21. Abrams P, Malone-Lee J, Jacquetin B, et al. Twelve-month treatment of overactive bladder: efficacy and tolerability of tolterodine. Drugs Aging 2001; 18 (7): 551-60
22. Appell RA, Abrams P, Drutz HP, et al. Treatment of overactive bladder: long-term tolerability and efficacy of tolterodine. World J Urol 2001; 19 (2): 141-7
23. Kreder K, Mayne C, Jonas U. Long-term safety, tolerability and efficacy of extended-release tolterodine in the treatment of overactive bladder. Eur Urol 2002; 41 (6): 588-95
24. Kelleher CJ, Reese PR, Pleil AM, et al. Health-related quality of life of patients receiving extended-release tolterodine for overactive bladder. Am J Manag Care 2002; 8 (19 Suppl.): S608-15
25. Kelleher CJ, Kreder KJ, Pleil AM, et al. Long-term health-related quality of life of patients receiving extended-release tolterodine for overactive bladder. Am J Manag Care 2002; 8 (19 Suppl.): S616-30
26. Mattiasson A, Blaakaer J, Hoye K, et al. Simplified bladder training augments the effectiveness of tolterodine in patients with an overactive bladder. BJU Int 2003; 91 (1): 54-60
27. Appell RA. Clinical efficacy and safety of tolterodine in the treatment of overactive bladder: a pooled analysis. Urology 1997; 50 (6A Suppl.): 90-6
28. Malone-Lee J, Shaffu B, Anand C, et al. Tolterodine: superior tolerability than and comparable efficacy to oxybutynin in individuals 50 years old or older with overactive bladder: a randomized controlled trial. J Urol 2001; 165 (5): 1452-6
29. Lee JG, Hong JY, Choo MS, et al. Tolterodine: as effective but better tolerated than oxybutynin in Asian patients with symptoms of overactive bladder. Int J Urol 2002; 9 (5): 247-52
30. Leung HY, Yip SK, Cheon C, et al. A randomized controlled trial of tolterodine and oxybutynin on tolerability and clinical efficacy for treating Chinese women with an overactive bladder. BJU Int 2002; 90 (4): 375-80
31. Appell RA, Sand P, Dmochowski R, et al. Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT Study. Mayo Clin Proc 2001; 76 (4): 358-63
32. Diokno AC, Appell RA, Sand PK, et al. Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. Mayo Clin Proc 2003; 78 (6): 687-95
33. Sussman D, Garely A. Treatment of overactive bladder with once-daily extended-release tolterodine or oxybutynin: the antimuscarinic clinical effectiveness trial (ACET). Curr Med Res Opin 2002; 18 (4): 177-84
34. Junemann KP, Halaska M, Rittstein T, et al. Propiverine vs tolterodine: efficacy and tolerability in patients with detrusor overactivity [abstract]. International Continence Society; 2003 Oct 5-9; Florence
35. Junemann KP, Al-Shukr S. Efficacy and tolerability of trospium chloride and tolterodine in 234 patients with urge syndrome: a double-blind, placebo-controlled, multicentre clinical trial [abstract]. International Continence Society; 2000 Aug 27-Sep 3; Tampere
36. Chapple CR, Parkhouse H, Gardener C, et al. Double-blind, placebo-controlled, cross-over study of flavoxate in the treatment of idiopathic detrusor instability. Br J Urol 1990; 66 (5): 491-4
37. Briggs RS, Castleden CM, Asher MJ. The effect of flavoxate on uninhibited detrusor contractions and urinary incontinence in the elderly. J Urol 1980; 123 (5): 665-6
38. Alhasso A, Glazener CM, Pickard R, et al. Adrenergic drugs for urinary incontinence in adults. Cochrane Database Syst Rev 2003; (2): CD001842
39. Moehrer B, Hextall A, Jackson S. Oestrogens for urinary incontinence in women. Cochrane Database Syst Rev 2003; (2): CD001405
40. Crandall C. Vaginal estrogen preparations: a review of safety and efficacy for vaginal atrophy. J Womens Health (Larchmt) 2002; 11 (10): 857-77
41. Yoshimura N, Chancellor MB. Current and future pharmacological treatment for overactive bladder. J Urol 2002; 168 (5): 1897-913
42. Schurch B, Stohrer M, Kramer G, et al. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. J Urol 2000; 164 (3 Pt 1): 692-7
43. Giannantoni A, Di Stasi SM, Stephen RL, et al. Intravesical capsaicin versus resiniferatoxin in patients with detrusor hyperreflexia: a prospective randomized study. J Urol 2002; 167 (4): 1710-4
44. PSUR Bridging Summary Report for Detrusitol/Detrol. Peapack (NJ): Pharmacia Corporation, 2002
45. Periodic Safety Update Report (PSUR) for Detrusitol/Detrol tablets and Detrusitol/Detrol prolonged-release capsules

(tolterodine). Period covered: 2002 Mar 6 through 2002 Sep 2. North Peapack (NJ): Pharmacia Corporation, 2002

46. Detrol® (tolterodine tartrate tablets): full prescribing information. Kalamazoo (MI): Pharmacia and Upjohn Company, 2003
47. Detrol® LA (tolterodine tartrate extended release capsules): full prescribing information. Kalamazoo (MI): Pharmacia and Upjohn Company, 2003
48. Chancellor MB, Appell RA, Sathyan G, et al. A comparison of the effects on saliva output of oxybutynin chloride and tolterodine tartrate. Clin Ther 2001; 23 (5): 753-60
49. Chapple CR, Nilvebrant L. Tolterodine: selectivity for the urinary bladder over the eye (as measured by visual accommodation) in healthy volunteers. Drugs R D 2002; 3 (2): 75-81
50. Charach G, Greenstein A, Rabinovich P, et al. Alleviating constipation in the elderly improves lower urinary tract symptoms. Gerontology 2001; 47 (2): 72-6
51. Layton D, Pearce GL, Shakir SA. Safety profile of tolterodine as used in general practice in England: results of prescription-event monitoring. Drug Saf 2001; 24 (9): 703-13
52. Todorova A, Vonderheid-Guth B, Dimpfel W. Effects of tolterodine, trospium chloride, and oxybutynin on the central nervous system. J Clin Pharmacol 2001; 41 (6): 636-44
53. Clemett D, Jarvis B. Tolterodine: a review of its use in the treatment of overactive bladder. Drugs Aging 2001; 18 (4): 277-304
54. Abrams P. Evidence for the efficacy and safety of tolterodine in the treatment of overactive bladder. Expert Opin Pharmacother 2001; 2 (10): 1685-701
55. Brynne N, Stahl MM, Hallen B, et al. Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity. Int J Clin Pharmacol Ther 1997; 35 (7): 287-95
56. Brynne N, Bottiger Y, Hallen B, et al. Tolterodine does not affect the human in vivo metabolism of the probe drugs caffeine, debrisoquine and omeprazole. Br J Clin Pharmacol 1999; 47 (2): 145-50
57. Brynne N, Forslund C, Hallen B, et al. Ketoconazole inhibits the metabolism of tolterodine in subjects with deficient CYP2D6 activity. Br J Clin Pharmacol 1999; 48 (4): 564-72
58. Brynne N, Dalen P, Alvan G, et al. Influence of CYP2D6 polymorphism on the pharmacokinetics and pharmacodynamic of tolterodine. Clin Pharmacol Ther 1998; 63 (5): 529-39
59. Rahimy M, Hallen B, Narang P. Effect of tolterodine on the anticoagulant actions and pharmacokinetics of single-dose warfarin in healthy volunteers. Arzneimittel Forschung 2002; 52 (12): 890-5
60. Olsson B, Landgren BM. The effect of tolterodine on the pharmacokinetics and pharmacodynamics of a combination oral contraceptive containing ethinyl estradiol and levonorgestrel. Clin Ther 2001; 23 (11): 1876-88
61. Spina E, Pisani F, Perucca E. Clinically significant pharmacokinetic drug interactions with carbamazepine: an update. Clin Pharmacokinet 1996; 31 (3): 198-214
62. Brynne N, Svanstrom C, Aberg-Wistedt A, et al. Fluoxetine inhibits the metabolism of tolterodine-pharmacokinetic implications and proposed clinical relevance. Br J Clin Pharmacol 1999; 48 (4): 553-63
63. Edwards KR, O'Connor JT. Risk of delirium with concomitant use of tolterodine and acetylcholinesterase inhibitors. J Am Geriatr Soc 2002; 50 (6): 1165-6
64. Ciancio SG. Medications as a risk factor for caries and periodontal disease. N Y State Dent J 1997; 63 (8): 32-6
65. Lenander-Lumikari M, Loimaranta V. Saliva and dental caries. Adv Dent Res 2000; 14: 40-7

Correspondence and offprints: Dr *Alan D. Garely*, 120 Mineola Boulevard, Suite 100, Mineola, NY 11501, USA.
E-mail: agarely@winthrop.org