REVIEW ARTICLE

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Pharmacotherapy for Overactive Bladder

An Evidence-Based Approach to Selecting an Antimuscarinic Agent

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Abstract

Multiple drugs are now available for the treatment of overactive bladder. Currently, the pharmacological approach is to deal with the problem at the neuromuscular junction by attempting to stop the activity of the neurotransmitter with antimuscarinic medications. This article reviews the positive and negative aspects of the agents that are currently available for use in the US. In randomised clinical trials, extended-release formulations of these agents appear as effective as the immediate-release formulations, but are associated with fewer adverse effects. Attempts to use entities that are muscarinic M_3 selective antimuscarinic agents have not significantly improved the efficacy, but have reduced the major adverse effect of excessively dry mouth. Dose escalation or titration is addressed to enhance efficacy further. None of these drugs appear to cause significant cardiac or CNS adverse events. This supports the continued use of these agents for overactive bladder symptomatology, as they appear to be effective in reducing symptoms and remain generally well tolerated.

Overactive bladder (OAB) refers to symptoms of urgency, with or without urge incontinence, usually accompanied by urinary frequency and nocturia.[1] Approximately 17% of adult Americans are affected

by OAB and the incidence increases with age, suggesting that the healthcare burden of OAB will continue to increase as the global population ages.[2] For the individual, OAB can negatively affect physical, psychosocial and occupational performance. It is associated with increased risks of falls and fractures, urinary tract and skin infections, and sleep disorders and depression.[3]

Pharmacological treatment of OAB aims to reduce the symptoms of urgency and the frequencies of micturition and incontinent events. Because many patients will require lifelong treatment, to ensure good compliance the ideal intervention should be effective, easy to administer and have an acceptable safety profile.

Antimuscarinic agents are the mainstay of pharmacological treatment for OAB. These agents suppress involuntary bladder contractions by blocking muscarinic M_3 receptor activity in the bladder. Muscarinic receptors are also found in salivary glands, the gastrointestinal tract and other tissues, which may account for some of the adverse effects seen with these agents. As a class, the adverse-effect profile of antimuscarinic agents is similar to that of typical anticholinergic agents, such as atropine, and includes dry mouth, constipation, headache, dizziness and blurred vision. Most of these effects are mild to moderate in severity and only infrequently require discontinuation of treatment.

The two most commonly used antimuscarinic agents in the US are oxybutynin and tolterodine, which are now available in extended-release formulations that allow for once-daily administration. A transdermal patch that delivers oxybutynin is also available. Recently, three new antimuscarinic agents have been approved: darifenacin, solifenacin and trospium chloride. This article reviews the clinical effects of the available antimuscarinic agents for the treatment of OAB, based on data from key randomised, controlled clinical trials.

1. Oxybutynin and Tolterodine

The two standard antimuscarinic agents used in the US, as noted, are oxybutynin and tolterodine. Immediate-release oxybutynin has been available since the 1970s, but its long-term use is often limited by its poor adverse effect profile and the need for multiple daily doses. Immediate-release tolterodine has been shown to be as effective as immediate-release oxybutynin but is associated with fewer adverse effects.[4-6] Extended-release formulations of oxybutynin and tolterodine allow for more convenient, once-daily administration and provide more consistent pharmacokinetics, which may help to reduce the incidence of adverse events compared with immediate-release formulations.

In randomised clinical trials, extended-release oxybutynin (oxybutynin ER) was found to be as effective as the immediate-release formulation, but was associated with fewer adverse effects (table I).[7-10] Specifically, oxybutynin ER was associated with a lower frequency of dry mouth than the immediate-release formulation. Compared with immediate-release tolterodine, the extended-release formulation of tolterodine (tolterodine ER) was found to be as effective but caused fewer adverse events.[11] The transdermal oxybutynin patch is also associated with low rates of anticholinergic adverse effects, perhaps because of a reduced breakdown of oxybutynin into its metabolites (especially desethyloxybutynin, which is associated with reduced salivary activity), as it bypasses the gastrointestinal tract cytochrome P450 activity. However, some patients (up to 17%) may experience application site reactions, including erythema and pruritus.[12] Transdermal systems are unlikely to be developed for the other medications for OAB because of low lipophilicity, even though the patch includes an agent (triacetin) to carry the drugs through the skin barrier; hydrophilic drugs such as tolterodine and trospium chloride will not pass, and the success with trans-

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Table I. Comparisons of extended- and immediate-release formulations of the same antimuscarinic agent in patients with overactive bladder

Study (year)	Patients	Treatment	Efficacy	Most common adverse events	Withdrawal rate
Oxybutynin ER vs oxybutynin					
Barkin et al.[8] (2004)	125 with urinary incontinence (≥7 episodes/wk) and frequency (≥8 micturitions/d)	Oxybutynin ER vs oxybutynin. Starting dose 15 mg/d; titration possible	Equally effective in reducing incontinence episodes (p = 0.404), voiding frequency (p = 0.286), and the frequency (p = 0.116), and severity (p = 0.255) of urgency	Dry mouth (68% vs 72%), dry throat (31% vs 37%). Moderate to severe dry mouth occurred in 38% and 45% of patients, respectively	Total: 20% vs 37%; p = 0.047. Due to adverse events: 17% vs 20%
Birns et al.[9] (2000)	130 with detrusor instability or detrusor hyper-reflexia with stable symptoms on oxybutynin	Oxybutynin ER vs oxybutynin for 4wk at a fixed dose (10 mg/d)[a]	Equally effective in achieving daytime continence (53% vs 58%; p = 0.62)	Overall: 55% vs 67%. Dry mouth (23% vs 17%), dizziness (1.6% vs 9.1%), vision abnormality (6.5% vs 4.5%), cough (3.2% vs 4.5%), headache (0% vs 4.5%)	After randomisation: 2 patients vs 3 patients
Versi et al.[10] (2000)	226 with urge incontinence (≥7 episodes/wk) responsive to anticholinergic therapy	Oxybutynin ER vs oxybutynin. Starting dose 5 mg/d; titration possible (max. 20 mg/d)	Equally effective in reducing urge (p = 0.36) and total incontinence episodes/wk (p = 0.41) and achieving continence (p = 0.85)	Dry mouth (48% vs 59%; p = 0.09). First reports of moderate to severe dry mouth and cumulative incidence of any grade dry mouth were lower in the oxybutynin ER group (p = 0.007 and p = 0.003 vs oxybutynin, respectively)	Total: 7 patients vs 9 patients. Due to adverse events: 3 patients vs 7 patients
Anderson et al.[7] (1999)	105 with urge incontinence or mixed incontinence with a clinically significant urge component; prior response to oxybutynin	Oxybutynin ER vs oxybutynin. Starting dose 5 mg/d; titration possible (max. 30 mg/d)	Equally effective in reducing urge episodes (p = 0.6) and total incontinence episodes/wk (p = 0.6). Equally effective in achieving continence (p = 0.9)	Anticholinergic events (87% vs 94%). Dry mouth (68% vs 87%; p = 0.04); moderate or severe dry mouth (25% vs 46%; p = 0.03)	Total: 7 patients vs 6 patients
Tolterodine ER vs tolterodine					
van Kerrebroeck et al.[11] (2001)	1529 with urge incontinence (≥5 episodes/wk) and urinary frequency (≥8 micturitions/d)	Tolterodine ER vs tolterodine vs placebo; fixed doses (4 mg/d) for 12wk	Median reduction in incontinence episodes/wk: 71% vs 60% (p < 0.05) vs 33%	Dry mouth (23% vs 30% [p < 0.02] vs 8%); constipation (6% vs 7% vs 4%); headache 6% vs 4% vs 5%). Severe dry mouth with ER: 1.8%	Total: 5% vs 5% vs 6%. Due to serious adverse events: 1, 5 and 8 patients

a All patients received immediate-release oxybutynin for 2wk prior to randomisation.

ER = extended release; **max.** = maximum.

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dermal oxybutynin relates to the drug's non-hydrophilic nature.[13-15]

Two randomised studies have compared the efficacy and safety of oxybutynin ER with tolterodine and tolterodine ER. A third recent study compared the efficacy and safety of transdermal oxybutynin with tolterodine ER. The OBJECT (Overactive Bladder: Judging Effective Control and Treatment) study compared oxybutynin ER with immediate-release tolterodine.[16] In this study, 378 patients who had 7–50 episodes of urge incontinence per week and ten or more voids per day at baseline were randomised to receive daily oxybutynin ER 10mg or twice-daily tolterodine 2mg. The data on all 378 patients were included in the safety analyses, but the efficacy analyses were based on the responses of the 332 patients who completed the 12-week study. At baseline, the mean numbers of urge incontinence episodes per week were 25.6 and 24.1 for patients in the oxybutynin ER and tolterodine groups, respectively. After 12 weeks of treatment, patients receiving oxybutynin ER had significantly fewer weekly urge incontinence episodes (6.1 vs 7.8; p = 0.03), total incontinence episodes (7.1 vs 9.3; p = 0.02), and micturition episodes (67.1 vs 71.5; p = 0.02), compared with those receiving tolterodine. The most common adverse event was dry mouth, which occurred in 28.1% of patients receiving oxybutynin ER and 33.2% of patients receiving tolterodine (p = 0.32). Other events, including those related to the CNS, occurred at low rates and with similar frequency in both treatment groups. The rate of discontinuation due to adverse events was approximately 8% in both treatment groups. This trial demonstrates that oxybutynin ER provides greater efficacy than immediate-release tolterodine, without an accompanying increase in adverse events or treatment withdrawals.

The second study, OPERA (Overactive Bladder: Performance of Extended Release Agents), directly compared the efficacy and safety of oxybutynin ER with that of tolterodine ER.[17] A total of 790 women with 21–60 urge urinary incontinence episodes per week and ≥10 voids per day were randomised to daily oxybutynin ER 10mg or daily tolterodine ER 4mg. The mean numbers of urge incontinence episodes per week declined from 37.2 and 36.9 at baseline to 10.8 and 11.2 at endpoint for patients in the oxybutynin ER and tolterodine ER groups, respectively. During the 12-week treatment period, patients receiving oxybutynin ER consistently had numerically superior results compared with tolterodine ER for all efficacy parameters; the differences were statistically significant at about half the assessment points. At week 12, the reductions in weekly urge incontinence episodes and total incontinence episodes were similar with both agents, but patients receiving oxybutynin ER had a significantly greater reduction in weekly micturition frequency (table II). In addition, significantly more patients receiving oxybutynin ER reported no urinary incontinence by the final week of treatment, compared with those

Table II. Efficacy outcomes after 12 weeks of treatment with oxybutynin extended release (ER) and tolterodine ER in patients with overactive bladder[17]

Outcome	Oxybutynin ER (n = 391)		Tolterodine ER (n = 399)		p-Value[a]
	baseline	week 12	baseline	week 12	
Mean urge urinary incontinence episodes per week	37.2	10.8	36.9	11.2	0.28
Mean total incontinence episodes per week	43.4	12.3	42.4	13.8	0.08
Mean micturition episodes per week	94.8	66.4	96.3	71.1	0.003
Percentage of patients with no urinary incontinence (total dryness)		23.0		16.8	0.03

a p-Values refer to the difference between treatment groups at week 12.

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receiving tolterodine ER (23.0% vs 16.8%; p = 0.03). Dry mouth was reported more frequently in the oxybutynin ER group (29.7% vs 22.3% in the tolterodine ER group; p = 0.02). However, most of these events were mild (22.3% vs 17.3% for oxybutynin ER and tolterodine ER, respectively) and few patients discontinued treatment (seven patients in the oxybutynin ER group and four in the tolterodine ER group). Other adverse events, including CNS-related events (e.g. dizziness, somnolence, depression, confusion) were infrequent and occurred at similar rates in both treatment groups (figure 1). Withdrawal rates due to adverse events were also similar in both treatment groups (5.1% vs 4.8% for oxybutynin ER and tolterodine ER, respectively), suggesting that the improved efficacy of oxybutynin ER was gained without compromising tolerability.

In a third study, the efficacy and safety of transdermal oxybutynin were compared with those of tolterodine ER and placebo in 361 patients who were currently responding to treatment for urge or mixed urinary incontinence.[12] After a 2-week washout period, baseline symptoms were recorded for 1–2 weeks. The patients were randomised to 12 weeks of double-blind, double-dummy treatment with transdermal oxybutynin administered twice-weekly to give a daily delivered dosage of 3.9mg, tolterodine ER 4 mg/day or placebo. At baseline, the mean numbers of incontinence episodes per day were 4.7, 5.0 and 5.0 for the oxybutynin, tolterodine and placebo groups, respectively. At endpoint, patients receiving transdermal oxybutynin and tolterodine ER experienced a decrease in incontinence episodes compared with placebo (−2.9, −3.2 and −2.1 for oxybutynin, tolterodine and placebo, respectively; oxybutynin vs placebo, p = 0.0137; tolterodine vs placebo, p = 0.0011). The treatment groups also experienced declines in micturition frequency compared with placebo, from 12.4 to 10.4 for oxybutynin, from 12.1 to 9.9 for tolterodine, and from 12.3 to 10.9 for placebo (oxybutynin vs placebo, p = 0.1010; tolterodine vs placebo, p = 0.0025). Mean void volumes also increased in the treatment groups compared with the placebo group, from 165 to 198mL for the oxybutynin group, 165 to 193mL for the tolterodine group, and from 165 to 171mL for the placebo group (oxybutynin vs placebo, p = 0.0010; tolterodine vs placebo, p = 0.0017). The most common treatment-related adverse events in the oxybutynin group were application site reactions, including erythema (8.3% vs 1.7% with placebo) and pruritus (14.9% vs 4.3% with placebo). Patients in both treatment groups experienced anticholinergic adverse events, particularly dry mouth (7.3% tolterodine vs 1.7% placebo, p = 0.0379 and 4.1% oxybutynin vs 1.7% placebo, p = 0.2678). The low level of anticholinergic adverse events in this study is probably due to the inclusion requirement of currently successful treatment of OAB. This requirement would exclude patients who had previously experienced intolerable cholinergic adverse effects.

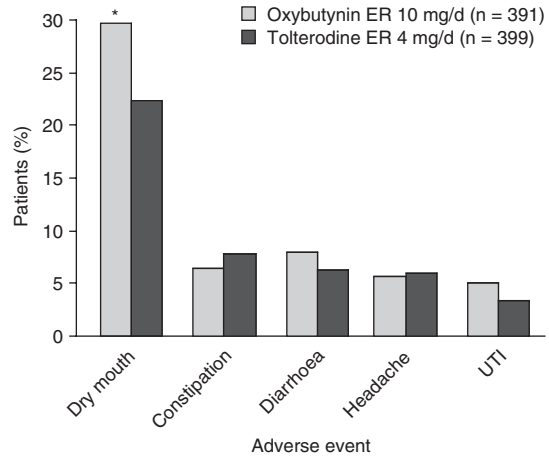

Fig. 1. Incidence of adverse events reported in at least 5% of patients.[18] **ER** = extended release; **UTI** = urinary tract infection; * p = 0.02 vs tolterodine.

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2. Darifenacin, Solifenacin and Trospium Chloride

The efficacy of an antimuscarinic agent depends primarily on its ability to block the activity of M_3 receptors in the bladder, which are responsible for regulating involuntary bladder contractions. The M_1 and M_2 receptors play important roles in other tissues, including cardiac tissue and the CNS. The adverse effects of the less selective antimuscarinic agents, such as oxybutynin and tolterodine, are thought to arise from interactions with these muscarinic receptors. M_3-selective antimuscarinic agents, such as darifenacin and solifenacin, are expected to reduce the symptoms of OAB while avoiding some of the adverse effects commonly seen with less selective antimuscarinic agents.

2.1 Darifenacin

Darifenacin is an M_3-selective antimuscarinic agent that can be given once daily at doses of 7.5mg or 15mg. In placebo-controlled studies, darifenacin effectively reduced the number of weekly incontinence episodes, micturition frequency, and the frequency and severity of urgency.[18-20] A pooled analysis of data from more than 1000 patients who participated in three phase III studies of darifenacin revealed that darifenacin 7.5 and 15mg once daily reduced the median number of incontinence episodes per week by 8.8 and 10.6 episodes, respectively (both $p < 0.01$ vs placebo) in 12 weeks.[21] At both dosages, the number of weekly incontinence episodes resulting in a change of clothing or pads was reduced by 78% (both $p < 0.001$ vs placebo) and daily micturition frequency was reduced by 17% (both $p < 0.001$ vs placebo). The most commonly reported adverse effects were dry mouth (darifenacin 7.5mg 20%; darifenacin 15mg 35%; placebo 8%) and constipation (darifenacin 7.5mg 15%; darifenacin 15mg 21%; and placebo 6%). The rates of cardiac and CNS events associated with darifenacin were similar to those associated with placebo. Treatment discontinuation due to adverse events was generally infrequent (darifenacin 7.5mg 1.5%; darifenacin 15mg 5.1%; placebo 2.6%). Trials comparing darifenacin with active controls, such as oxybutynin or tolterodine, have not been reported.

2.2 Solefinacin

Solifenacin, like darifenacin, is selective for M_3 receptors. It can be given once daily at doses of 5mg or 10mg. In two phase III studies, the most commonly reported adverse effects associated with solifenacin were dry mouth (5mg 8–14%; 10mg 21–23%; placebo 2–5%), constipation (5mg 4–7%; 10mg 8–9%; placebo ~2%), and blurred vision (5mg ~4%; 10mg ~6%; placebo ~3%).[22,23] The rates of withdrawal due to adverse events in these studies were generally low at both doses of solifenacin (5mg 2–3%; 10 mg 3–4%) and were similar to that in the placebo group (3–4%). In a pooled analysis of data from more than 3000 patients with OAB treated with solifenacin, immediate-release tolterodine or placebo, the treatment effect of solifenacin (treatment – placebo) was −1.12 and −1.48 daily episodes of incontinence at dosages of 5 mg/day and 10 mg/day, respectively (both $p < 0.001$ vs placebo).[24] The treatment effect of tolterodine was a significant reduction in daily incontinence episodes at −0.64 (tolterodine vs placebo $p = 0.031$). The percentage of patients treated with solifenacin who had at least a 50% reduction in urgency episodes from baseline was 62–66% (compared with a baseline level of approximately six episodes), and 55% in patients taking tolterodine 2mg twice daily. Although solifenacin appeared to be at least as effective as immediate-release tolterodine, with a comparable safety profile, trials that included a tolterodine arm were not sufficiently powered for direct comparisons between the two active agents.[23] No trials have been reported that compare solifenacin with

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oxybutynin ER. However, a recent comparative study of solifenacin and tolterodine ER has been completed.[25] The aim of this prospective, double-blind, double-dummy, two-arm, parallel-group, 12-week study was to compare the efficacy and safety of once-daily solifenacin 5 or 10mg and once-daily tolterodine ER 4mg in patients with OAB. After 4 weeks of treatment, patients had the option to request a dose increase, but were dummied throughout because approved product labeling only allowed for an increase for those individuals receiving solifenacin, as there is only the single approved tolterodine ER dosage of 4 mg/day. Solifenacin, with the flexible dose regimen, was found to be superior to tolterodine ER with regard to decreasing urgency episodes, incontinence, urge incontinence and pad usage, while increasing the volume voided per micturition. More of the patients who received solifenacin became continent and reported improvements in assessments of perception of bladder condition. Discontinuations were comparable and very low in both groups, as most of the adverse effects were mild to moderate in nature. There are issues with this type of trial. For example, is it correct to compare a single dose of one drug (tolterodine ER 4 mg/day) with two doses of another drug (in this case, solifenacin 5 mg/day increasing to 10 mg/day)? In addition, if performed in this manner, should the efficacy and adverse effects be broken down for each drug at each dose? In this study there was 'pooling' of the two dosages of solifenacin with respect to efficacy and tolerability results. A more useful and fair data comparison would have required two sets of studies comparing tolterodine ER 4 mg/day with each of the two solifenacin dosages to truly give strength to the statistical analysis.

The entire issue of dose escalation (or even the titration of drug dosages) in a patient and then comparison of data among different agents warrants further investigation on its own. The only study looking at this in depth relates to oxybutynin ER in a review by MacDiarmid.[26] He found that, if left up to the patient, between 48% and 65% would increase their dose to >10mg of oxybutynin to achieve continence, which is higher than the doses used in both the OBJECT[16] and OPERA[17] studies. MacDiarmid demonstrated that few physicians appear to dose adjust for maximal benefit in OAB.

2.3 Trospium Chloride

Trospium chloride is a nonselective antimuscarinic agent that does not cross the blood-brain barrier because of its low lipid solubility, and is therefore expected to avoid CNS-related adverse effects.[13] In two trials with 3-week durations performed in patients with detrusor overactivity, twice-daily trospium chloride 20mg significantly improved urodynamic factors, such as bladder capacity (median treatment effect 52.0mL vs placebo; $p < 0.0001$) and urinary volume voided (median treatment effect 48.0mL vs placebo; $p = 0.0001$). In addition, patients receiving trospium chloride perceived that they had greater clinical improvements than those receiving placebo, and more often rated the treatment effect as 'cure' or 'marked improvement' (47.9% vs 19.7%; $p < 0.0001$).[27] In two larger, 12-week studies, trospium chloride significantly reduced the frequency of urge incontinence episodes and micturition, as well as urge frequency and severity, compared with placebo.[28,29] The most common adverse effects of trospium chloride were dry mouth (20–22% vs 5–7% with placebo) and constipation (10–11% with trospium chloride vs 4–6% with placebo). The rates of withdrawal due to adverse events in these studies were 7–9% in patients taking trospium chloride, compared with 5–6% in patients taking placebo. In a 12-month study comparing trospium chloride 20mg twice daily with immediate-release oxybutynin 5mg twice daily in 358 patients with detrusor instability, trospium chloride was as effective as oxybutynin and had a better adverse effect profile; the relative risk of

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experiencing any adverse event was 0.60 (p-values not reported) in favour of trospium chloride.[30] The overall rate of treatment discontinuation was similar in both treatment groups (25.0% for trospium chloride vs 26.7% for oxybutynin). The rates of discontinuation due to adverse events were approximately 6% and 10% in patients taking trospium chloride and oxybutynin, respectively. Trials comparing trospium chloride with oxybutynin ER or tolterodine ER have not been reported.

3. Cardiac and CNS-Related Adverse Events

Important issues in antimuscarinic treatment are the potential risks of cardiac and CNS-related adverse events, particularly in the elderly. These events may arise from nonselective muscarinic receptor blockade: the M_3 receptor subtype is the target of treatment for OAB, but the M_1 and M_2 receptors play pivotal roles in other tissues, such as the heart and the CNS. Therefore, it has been suggested that M_3-selective antimuscarinic agents may cause fewer cardiac and CNS-related adverse events than oxybutynin or tolterodine.[13] Indeed, the frequency of cardiac and CNS-related events in trials of darifenacin is similar to that of placebo.[18-21,23] However, solifenacin appears to lengthen the corrected QT interval in a dose-dependent manner (studied at 10 and 30 mg/day).[15] In another double-blind study of solifenacin, using the recommended doses of 5 mg/day and 10 mg/day, no effect was observed on electrocardiograms.[23] Dizziness in response to solifenacin treatment occurs at the same rate as it does with placebo treatment.[15] Trospium chloride, a quaternary amine unlikely to cross the blood-brain barrier, appears to be free of CNS adverse effects, as well as cardiovascular effects.[14,27,28,30,31]

In preliminary studies conducted in healthy volunteers, the less selective antimuscarinic agent oxybutynin (15mg of the immediate-release form) has been shown to cross the blood-brain barrier and alter electroencephalogram results.[14,31] Another study found that oxybutynin was associated with cognitive impairment.[32] However, the clinical implications of these findings are unclear, given that studies of oxybutynin generally report low incidences of CNS events. In the OBJECT and OPERA trials, the incidence of CNS adverse events, including dizziness, somnolence, insomnia and depression, was between 1% and 4% for both oxybutynin ER and tolterodine ER.[16,17] Other CNS effects occurred in <1% of patients in these trials. At this time, there is insufficient evidence to suggest an increased risk of CNS or cardiac events with less selective antimuscarinic agents, such as oxybutynin and tolterodine. However, further study on the relative cardiac and CNS safety of antimuscarinic agents is warranted.

4. Conclusion

Randomised, controlled clinical trials suggest that current antimuscarinic agents effectively reduce symptoms related to OAB and are generally well tolerated, supporting the continued use of these agents in the pharmacological treatment of patients with OAB.[33] Only a few of the reported trials reviewed in this article directly compared the currently available antimuscarinic agents, making it difficult to draw conclusions about their relative efficacy and safety. More trials that directly compare these agents would be needed to fully explore the possible differences in activity among these agents.

The OPERA study is the only published study that has directly compared oxybutynin ER and tolterodine ER.[17] Oxybutynin ER at a fixed dose of 10mg daily was superior to tolterodine ER at a dose of 4mg daily in reducing micturition frequency and in the percentage of patients reporting no urinary incontinence episodes at study endpoint. In other measures of efficacy, the two drugs were statistically indistinguishable. In terms of safety, tolterodine

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was associated with fewer adverse events, particularly dry mouth. However, the tolerability of the two agents was comparable and both treatment groups had similar rates of treatment withdrawals due to adverse events. This suggests that the increased efficacy of oxybutynin ER was accompanied by an increased risk of adverse events, but it did not compromise the overall tolerability of the agent. Because the difference in adverse events was mostly attributed to an increase in mild to moderate dry mouth, it could be inferred that the clinical benefits of treatment with oxybutynin ER may have outweighed the burden of mild anticholinergic adverse effects. Given that flexibility within a wide range of approved doses (5–30mg) is possible with oxybutynin ER, this agent may offer a good chance of achieving a balance between efficacy and tolerability in patients with OAB.

The currently available antimuscarinic agents represent a considerable advance in the treatment of OAB, compared with older formulations. Extended-release formulations of oxybutynin and tolterodine are as effective as immediate-release formulations, but are easier to administer and better tolerated. Agents such as darifenacin, solifenacin and trospium chloride, which were designed to reduce some of the unwanted anticholinergic effects, appear to be effective and well tolerated, although there are fewer data available on these agents compared with oxybutynin ER and tolterodine ER.

The improvements in tolerability seen with currently available antimuscarinic agents may lead to increased treatment compliance and persistence rates, resulting in better long-term efficacy of treatment for patients with OAB. Because few studies have been reported that directly compare the efficacy and safety of the currently available agents, the choice of antimuscarinic agent should be based on its potential to provide maximum efficacy with an acceptable safety profile and long-term tolerability.

In the US, there is currently a choice of six branded products (oxybutynin patch and extended-release oral agent; tolterodine immediate and extended-release oral agents; trospium chloride immediate-release oral agent; darifenacin and solifenacin extended-release oral agents) and one generic product (immediate-release oxybutynin) for the treatment of OAB. Attempts to compare these formulations either in theoretical head-to-head studies, phase III studies versus placebo, or the numerous 'promotional science' studies sponsored and conducted by the pharmaceutical companies who make the agents have yielded no clear 'winner'. Future studies into the pathophysiology of OAB may yet yield a truly selective antimuscarinic for the lower urinary tract alone, or establish the need for agents that work in some other way to reduce the symptoms of this disorder that lead to such an impaired quality of life. This is the hope of the physicians that treat and the patients that live with OAB.

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