

A comparison of newer drug treatments for

URINARY INCONTINENCE

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The second part of this month's special feature looks at the newer drug treatments for urinary incontinence in detail, and presents clinical data in order to draw comparisons on the relative efficacy of each

Oxybutynin is often considered to be the "gold standard" drug in the treatment of patients with an unstable bladder. It is both clinically effective and cost-effective, but its use is often limited by adverse effects. However, it is still usual for this drug to be the first-line treatment for this condition.

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The newer drugs are often advertised as more effective and better tolerated than oxybutynin, but questions still remain over which of these newer agents should be the second-line drug of choice in patients unable to tolerate the adverse effects of oxybutynin.

PRINCIPLES OF TREATMENT

The principles of treatment take into

account the physiology of the bladder. The wall of the bladder comprises circular and longitudinal smooth muscle which is

called detrusor muscle. When the detrusor muscle relaxes, urine is stored, and when it contracts, micturition occurs. The bladder can normally hold between 300ml and 600ml of urine.

The bladder has somatic, parasympathetic and sympathetic innervation. The pudendal nerve is the somatic component and innervates the external urethral sphincter. Parasympathetic nerve fibres innervate the detrusor muscle, via cholinergic receptors, and originate from the second, third and fourth segments of the spinal cord. Parasympathetic stimulation of the detrusor muscle

Table 1: Prescribing information for the newer treatments for bladder instability

	Oxybutynin	Oxybutynin modified release	Propiverine	Tolterodine	Tolterodine prolonged-release	Tropium chloride
Licensed indications	Urinary incontinence, urgency and frequency in the unstable bladder due to neurogenic disorders or detrusor instability Nocturnal enuresis in children older than five years	Urinary incontinence, urgency and frequency in the unstable bladder due to neurogenic disorders or detrusor instability	Urinary incontinence, urgency and frequency in the unstable bladder due to neurogenic disorders or detrusor instability	Urinary frequency, urgency and incontinence	Urge incontinence and/or increased urinary frequency associated with urgency as may occur in patients with unstable bladder	Detrusor instability, detrusor hyper-reflexia with the symptoms of urinary frequency, urgency and urge incontinence
Dose	Adults: 5mg <i>bd</i> or <i>tds</i> to a maximum of 5mg <i>qds</i> Elderly: 2.5–5mg <i>bd</i> Children: 2.5–3mg <i>bd</i> , increasing to 5mg <i>bd</i> , if required	Adults: 5mg <i>od</i> increased by 5mg/week up to a maximum of 30mg/day	Adults: 15mg <i>bd</i> (range 15mg <i>od</i> –15mg <i>tds</i>). Maximum 15mg <i>qds</i> No reduction in elderly	Adults: 2mg <i>bd</i> reduced to 1mg <i>bd</i> if side effects troublesome Review after six months	Adults: 4mg once daily but 2mg <i>od</i> in impaired liver or renal function or if adverse effects are troublesome. Review need for treatment after six months	Adults: 20mg <i>bd</i> Renal failure: (creatinine clearance 10–30ml/min) 20mg <i>od</i> or 20mg on alternate days. Reassess every three to six months
Cost per patient per 28 days (MIMS November 2001)	£1.99–£2.99 (5mg <i>bd</i> –5mg <i>tds</i>)	£9.49–£56.94 (5mg <i>od</i> –30mg <i>od</i>)	£30.56 (15mg <i>bd</i>)	£29.03 (4mg <i>od</i>)	£25 (20mg <i>bd</i>)	
Side effects	Dry mouth, constipation, blurred vision, nausea, abdominal discomfort, facial flushing, headache	Dry mouth, nausea, constipation, blurred vision, dizziness, urinary retention, palpitations	Dry mouth, blurred vision, disturbance of GI function, decreased blood pressure, increased residual urine, and tiredness	Dry mouth, dyspepsia, constipation, abdominal pain, flatulence, vomiting, headache, dry skin, dry eyes, drowsiness, blurred vision, chest pain, urinary retention, confusion	Dry mouth, dyspepsia, constipation, nausea, abdominal pain, micturition disorders, tachycardia, diarrhoea, flatulence, dyspnoea, rash, asthenia, and chest pain	
Contraindications	Glaucoma, myasthenia gravis, bladder outflow obstruction, GI obstruction, severe ulcerative colitis, toxic megacolon	Glaucoma, myasthenia gravis, bladder outflow obstruction, GI obstruction, severe ulcerative colitis, toxic megacolon pregnancy, breastfeeding	Glaucoma, myasthenia gravis, bladder outflow obstruction, severe ulcerative colitis, toxic megacolon pregnancy, renal impairment, tachyarrhythmias, pregnancy, breastfeeding	Urinary retention, uncontrolled narrow angle glaucoma, myasthenia gravis, hypersensitivity to tolterodine, severe ulcerative colitis	Glaucoma, myasthenia gravis, bladder outflow obstruction, severe ulcerative colitis, toxic megacolon, dialysed renal insufficiency, children under 12 years	
Precautions	Elderly, autonomic neuropathy, hepatic or renal disease, hiatus hernia	Elderly, autonomic neuropathy, hepatic or renal disease, GI motility disorders	Autonomic neuropathy, hyperthyroidism, coronary artery disease, severe congestive heart failure, cardiac arrhythmias, tachycardias, prostatic hypertrophy, hiatus hernia, cerebral sclerosis may be aggravated	Autonomic neuropathy, significant bladder outflow obstruction, GI obstruction, hiatus hernia, neuropathy, liver impairment, renal impairment	Autonomic neuropathy, bladder outflow obstruction, GI obstruction, hiatus hernia, hyperthyroidism, coronary artery disease, congestive heart failure, liver impairment (no data available), renal impairment, pregnancy and breastfeeding	

results in contraction of the bladder, leading to micturition.

An unstable detrusor (or unstable bladder) is characterised by involuntary contractions during the filling phase, while the patient is attempting to inhibit micturition, leading to a desire to void, urgency or urge incontinence.

Various drugs are currently available for the treatment of patients with an overactive or unstable bladder. The majority are antimuscarinic drugs and produce inevitable unwanted effects which must be balanced against the perceived benefits. The usual adverse effects of antimuscarinic drugs are dry mouth, constipation, difficulty in visual accommodation and somnolence. Therefore, these drugs should be avoided in patients with obstructive uropathy, bowel obstruction, ulcerative colitis, narrow angle glaucoma or myasthenia gravis.

Oxybutynin has been the most frequently prescribed drug for urinary incontinence. It has antimuscarinic, antispasmodic and local anaesthetic properties, although not all of these properties are seen at therapeutic dose levels. Oxybutynin has a relatively short half-life of two to four hours and some patients find it useful to cover specific events such as a night out, rather than take the drug on a continual basis.

Other drugs which have been used include: propantheline (a cholinergic receptor antagonist), dicyclomine (which has a musculotropic and antimuscarinic effect on smooth muscles), flavoxate (a papaverine-like antispasmodic and phosphodiesterase inhibitor) and imipramine (a tricyclic antidepressant with anxiolytic and anticholinergic properties).

Newer treatments which have been introduced for the treatment of bladder instability include tolterodine, propiverine and trospium chloride. More recently, long-acting formulations of tolterodine and oxybutynin have been licensed which claim to have advantages over the standard-release formulations. These drugs are the ones which are discussed in more detail in this article. The prescribing data for each of these drugs are summarised in Table 1, p70.

Oxybutynin Oxybutynin is a tertiary amine with a high affinity for muscarinic receptors in the bladder and salivary glands. It has become the most established antimuscarinic agent and is generally the comparator against which newer treatments are measured.¹ Oxybutynin is an effective drug but dose-related side effects are commonly seen. Dry mouth occurs in 50-86 per cent of patients, with blurred vision, dry eyes, nausea, constipation and headache being other common side effects.

Oxybutynin can be taken as a once-daily controlled-release tablet containing 5mg or 10mg of oxybutynin hydrochloride in an osmotically active bilayer. Pharmacokinetic studies have shown that following the first dose of controlled-release oxybutynin, plasma concentrations rise for about six hours after which they are maintained for up to 24 hours. At steady state, controlled-release oxybutynin dosing maintains fairly constant plasma concentrations over the 24-hour dosing interval.²

The main clinical trials undertaken with controlled-release oxybutynin are presented in Table 2, pp 72-74.

Interactions Interactions can occur with other anticholinergic agents. Care with phenothiazines, amantadine, L-dopa and tricyclic antidepressants should also be taken.

Propiverine Propiverine hydrochloride is a bladder spasmolytic agent that has both anticholinergic and calcium antagonistic properties. The manufacturers claim that this dual action results in stronger inhibition of detrusor contractions than is observed with agents showing either anticholinergic effects or calcium antagonism alone.³

Table 2 presents the clinical trial data for propiverine.

Interactions Interactions include an increased effect with tricyclic antidepressants, tranquillisers, anticholinergics, amantadine, neuroleptics and beta-sympathomimetics.

Tolterodine Tolterodine is a potent, competitive, specific muscarinic receptor antagonist that has been specifically developed for the treatment of patients with an overactive bladder. Both tolterodine and its major active 5-hydroxymethyl metabolite exhibit selectivity for muscarinic receptor types found in the bladder over those found in salivary glands. This selectivity should lead to tolterodine causing fewer adverse effects than non-selective antimuscarinic agents.⁴

Table 2 presents data on some of the more recent clinical trials undertaken with tolterodine.

A prolonged-release formulation of tolterodine was recently introduced. This drug is released over a 24-hour period, producing flatter serum concentration-time profiles than the immediate release formulation. In this way, the peak concentrations which may be associated with adverse effects are lower, and the antimuscarinic effects of the drug are maintained for a full 24-hour period.

Table 2 presents data on the one major clinical study of this formulation to date, comparing it with immediate release tolterodine in over 1,500 patients with an overactive bladder.

Interactions Interactions include an increased effect with other anticholinergic agents and a decreased effect with muscarinic cholinergic receptor agonists.

Tolterodine may antagonise the gastrointestinal effects of metoclopramide and domperidone.

Trospium chloride Trospium chloride is an anticholinergic drug which binds specifically to muscarinic receptors. Trospium chloride appears to have higher specificity for muscarinic receptors in the bladder, but its actions *in vivo* may be partly explained by a local effect since 80 per cent of the drug is excreted unchanged in the urine and therefore high concentrations are seen in the bladder.⁵

Due to its hydrophilic nature, and in contrast to tertiary amines such as oxybutynin and tolterodine, central anticholinergic effects of trospium chloride cannot be detected since the drug hardly passes through the blood-brain barrier.

Table 2 presents clinical trial data for trospium chloride.

Interactions Interactions include an increased effect with other anticholinergic agents and beta-agonists.

Trospium chloride may antagonise the gastrointestinal effects of metoclopramide and domperidone.

Cholestyramine and cholestipol may reduce the absorption of trospium chloride.

— TRIAL SUMMARY

Table 2: The main clinical trials undertaken with drugs for bladder instability

Trial	Design	Number of patients	Method	Results	Conclusion
Sustained-release oxybutynin (OXY MR)					
Appell R.A. <i>et al</i> ⁸	(OBJECT study) Prospective, double-blind, randomised, parallel group study to compare OXY MR and tolterodine (TOL)	378 patients with an overactive bladder	Patients received OXY MR 10mg <i>od</i> or TOL 2mg <i>bd</i> for 12 weeks	OXY MR was significantly more effective than TOL in reducing weekly urge incontinence, total incontinence and micturition frequency episodes. Both drugs significantly improved symptoms of overactive bladder from baseline. Dry mouth was reported by 28.1 per cent of OXY MR patients and 33.2 per cent of TOL patients. Rates of other adverse events were similar between groups. Withdrawal rate due to adverse events was 7.6 per cent in the OXY MR group and 7.8 per cent in the TOL group	OXY MR was more effective than TOL and showed a similar rate of adverse events
Versi E. <i>et al</i> ⁷	A double-blind, randomised, parallel group study to compare OXY MR with immediate release oxybutynin (OXY)	226 patients responsive to anticholinergic therapy with > 7 episodes of urge incontinence per week	After a two-week placebo run-in, patients were randomised to receive OXY or OXY MR at an initial dose of 5mg <i>od</i> , increased weekly by 5mg per day to a max of 20mg per day	Reduction in urge incontinence episodes was 83 per cent in OXY MR group and 76 per cent in the OXY group (non-significant difference). Dry mouth increased with dose in both groups and was reported as 47.7 per cent in the OXY MR group and 59.1 per cent in the OXY group. First report of moderate to severe dry mouth was significantly lower in the OXY MR group compared with the OXY group	At the same daily dose, OXY MR and OXY demonstrated similar efficacy and rates of dry-mouth
Anderson R. U. <i>et al</i> ⁹	A double-blind, randomised, parallel group study to compare OXY MR with OXY	105 patients with urinary incontinence episodes	After one week washout, patients were randomised to OXY MR or OXY. Both groups started with 5mg daily and dose was increased as required	Similar decreases in weekly urge incontinence episodes and total incontinence episodes were seen in both groups. Continence was achieved in 41 per cent of OXY MR patients and 40 per cent of OXY patients. Dry mouth was reported in 68 per cent of OXY MR patients and 87 per cent of the MR patients with moderate or severe dry mouth reported in 25 and 46 per cent respectively	OXY MR and OXY showed similar efficacy. A lower incidence of dry mouth was seen in patients taking OXY MR
Propiverine (PRO)					
Madersbacher H. <i>et al</i> ¹⁰	Prospective, randomised, double-blind, double-dummy, parallel group study to compare PRO with OXY	366 patients with urgency and urge incontinence	After a one-week washout, patients were randomised to receive propiverine (PRO) 15mg <i>tds</i> , oxybutynin (OXY) 5mg <i>bd</i> or placebo (PL) for four weeks	PRO and OXY both significantly increased bladder capacity compared with placebo, but there was no significant difference between the two drugs. Improvement in clinical symptoms was seen in 83.3 per cent of PRO patients, 79.3 per cent of OXY patients and 68.3 per cent of PL patients. Adverse events were reported in 65 per cent of PRO patients and 73 per cent of OXY patients. Dry mouth was seen in 25.6 per cent of PRO patients and 39.1 per cent of OXY patients ($P=0.022$) (placebo adjusted rate)	PRO is as effective as OXY in the treatment of urgency and urge incontinence. Incidence and severity of dry mouth was less with PRO than OXY
Stohrer M. <i>et al</i> ¹⁰	Double-blind, placebo-controlled trial to compare PRO with placebo (PL)	113 patients with detrusor hyperreflexia following spinal cord injury	Patients were randomised to receive PRO 15mg <i>tds</i> or PL for two weeks	PRO significantly increased max. bladder capacity compared with placebo. Symptoms were improved in 63 per cent of PRO patients compared with 23 per cent of PL patients. Dry mouth was reported in 37 per cent of PRO patients and 8 per cent of PL patients	PRO improves urodynamic measurements and symptoms, compared with PL, in the treatment of detrusor hyper-reflexia
Thuroff J.W. ¹¹	Post-marketing surveillance conducted over 12 weeks	4,390 patients	Dry mouth occurred in 34 per cent of patients after four weeks and 26 per cent after 12 weeks. Accommodation disorders occurred in 11.4 per cent of patients at four weeks and 6.3 per cent at 12 weeks and were mainly mild. There was no increase in incidence of dry mouth or accommodation disorders in elderly patients. 2.9 per cent of patients discontinued treatment due to adverse events		

Table 2: *The main clinical trials undertaken with drugs for bladder instability (Continued)*

Trial	Design	Number of patients	Method	Results	Conclusion
Tolterodine (TOL)					
Chancellor M. <i>et al</i> ¹²	Double-blind, randomised, placebo-controlled, parallel group, multicentre study comparing TOL with placebo (PL)	1,022 patients with urge incontinence and urinary frequency	Patients received TOL 2mg <i>bd</i> , or PL for 12 weeks	TOL reduced urge incontinence episodes by 46 per cent from baseline. This was significant compared with PL ($P=0.0005$). Significant decreases from baseline were seen with micturition frequency (-15 per cent) and pad usage (-36 per cent) compared with PL. In TOL patients, there was a significant increase in volume per micturition (+21 per cent). Forty per cent of TOL patients reported "much benefit" from treatment compared with 22 per cent of PL patients Dry mouth was reported by 30 per cent of TOL patients compared with 8 per cent of PL patients.	TOL 2mg <i>bd</i> is an effective treatment for the symptoms of overactive bladder
Drutz H.P. <i>et al</i> ¹³	Double-blind, randomised, placebo-controlled, parallel group, multicentre study comparing TOL with OXY	277 patients with detrusor overactivity, and urinary frequency and urge incontinence	After a two-week washout, patients received TOL 2mg <i>bd</i> , OXY 5mg <i>tds</i> or PL for 12 weeks	TOL and OXY both significantly increased volume voided per micturition and decreased micturitions and incontinence events per 24 hours compared with PL. Only TOL was significantly better than PL at reducing micturition frequency. TOL was significantly better tolerated than OXY. Dry mouth was reported by 30 per cent of TOL patients compared with 69 per cent of OXY patients. Headache was reported by 10 per cent of OXY patients and 15 per cent of TOL patients with 31 per cent of OXY patients and 13 per cent of TOL patients withdrew due to adverse events	TOL and OXY demonstrated equivalent effectiveness. TOL, however, was associated with fewer adverse events
Appell R.A. ¹⁴	Pooled analysis of four randomised, double-blind, parallel, multicentre, 12-week studies	1,120 patients in total with overactive bladder	Two studies compared TOL 2mg <i>bd</i> with OXY 5mg <i>tds</i> and PL, one study compared TOL 2mg <i>bd</i> with OXY 5mg <i>tds</i> , and one study compared two dosages of TOL (1mg <i>bd</i> and 2mg <i>bd</i>) with PL	TOL 1mg <i>bd</i> and 2mg <i>bd</i> , and OXY 5mg <i>tds</i> , reduced the number of micturitions per 24h, incontinence episodes per 24h and significantly increased volume voided per micturition compared with placebo. TOL 2mg and OXY 5mg were equivalent in their effectiveness. TOL was significantly better tolerated in terms of dry mouth, dose reductions and withdrawals	OXY is an effective drug but its usefulness is limited by the number of adverse effects. TOL is as effective but causes significantly fewer adverse effects
Abrams P. <i>et al</i> ¹⁵	A randomised, double-blind, placebo-controlled, parallel group, multinational study	293 patients with an overactive bladder	Patients received TOL 2mg <i>bd</i> , OXY 5mg <i>tds</i> or PL. Doses could be reduced to 1mg or 2.5mg, respectively, to avoid withdrawal	After 12 weeks, TOL and OXY caused similar reductions in the mean frequency of micturition, and the mean number of incontinent episodes among those with urge incontinence at baseline. Dry mouth was the most common adverse event and was more common in OXY treated patients. There were more withdrawals and dose reductions in the OXY group	TOL is as effective as OXY in the treatment of patients with bladder instability. It is better tolerated than OXY
Modified-release tolterodine (TOL MR)					
van Kerrebroek P. <i>et al</i> ¹⁶	Double-blind, multicentre, randomised, placebo controlled trial comparing TOL MR, TOL and PL	1,529 patients with urinary frequency and urge incontinence	Following a one to two week washout period, patients were randomised to receive either TOL MR 4mg <i>od</i> , TOL 2mg <i>bd</i> , or PL for 12 weeks	TOL MR 4mg <i>od</i> , and TOL 2mg <i>bd</i> both significantly reduced the mean number of urge incontinence episodes per week, compared with PL. TOL MR was 18 per cent more effective than standard TOL ($P<0.05$). The rate of dry mouth was 23 per cent for TOL XL, 30 per cent for TOL, and 8 per cent for PL. This was a significant difference between the two formulations of TOL ($P<0.02$)	TOL MR 4mg <i>od</i> is an effective treatment in patients with an overactive bladder. It appears to be more effective than the standard formulation, and causes a lower incidence of dry mouth

Table 2: The main clinical trials undertaken with drugs for bladder instability (Continued)

Trial	Design	Number of patients	Method	Results	Conclusion
Trospium chloride (TCl)					
Cardozo L. <i>et al</i> ¹⁷	(Phase III, placebo-controlled, double-blind, multi-centre trial with two parallel treatments to compare TCl and PL	208 with confirmed detrusor instability	Patients received TCl 20mg <i>bd</i> or PL for 21–24 days after a washout period of seven days	TCl produced significant improvement in maximum bladder capacity and urinary volume at first unstable contraction. Patient assessment of efficacy showed significantly greater improvement in the TCl group compared to the PL group. (This resulted in early termination of the study)	TCl showed a statistically and clinically significant effect on bladder capacity and volume at first unstable contraction accompanied by a favourable safety profile
Madersbacher H. <i>et al</i> ¹⁸	Randomised, double-blind, multicentre trial treatments to compare TCl and OXY	95 patients with spinal cord injuries and detrusor hyperreflexia	Following a seven-day washout, patients received TCl 20mg <i>bd</i> + PL at mid-day or OXY 5mg <i>tds</i> for two weeks	Both drugs showed a significant increase in maximum bladder capacity, a significant decrease in maximum voiding detrusor pressure and a significant increase in compliance and residual urine. There was no significant difference between the treatment groups.	TCl and OXY demonstrated equal effects on detrusor hyperactivity. TCl, however, was better tolerated than OXY
Osca Garcia J.M. <i>et al</i> ¹⁹	Randomised, double-blind trial to compare TCl with OXY	67 patients with detrusor hyperreflexia	Patients received TCl 20mg <i>bd</i> or OXY 5mg <i>tds</i>	4 per cent of patients receiving TCl reported dry mouth compared with 23 per cent of OXY patients. Withdrawal from treatment was 6 per cent in the TCl group compared with 16 per cent in the OXY group	TCl showed similar efficacy to OXY but tolerability was better
Junemann K.P. and Al-Shukri S. (Abstract) ²⁰	Double-blind, placebo-controlled, multicentre trial to compare TCl and TOL	232 patients with urge-syndrome	Patients received TCl 20mg <i>bd</i> , TOL 2mg <i>bd</i> or PL for three weeks	Both drugs were reported as showing significant improvement in maximum bladder capacity, maximum detrusor pressure and subjective symptoms. Dry mouth was reported in twice as many OXY patients as TCl patients	TCl is as effective as TOL in reducing symptoms of urge syndrome and is more effective at reducing incontinence episodes. Tolerability was similar between TCl and TOL
Hofner K. <i>et al</i> (Abstract) ²¹	52-week double-blind, controlled, multicentre study to assess long-term tolerability of TCl and OXY	358 patients with urge-syndrome or urge-incontinence	Patients received TCl 20mg <i>bd</i> or OXY 5mg <i>bd</i> for 52 weeks	Dry mouth was reported in 28 per cent TCl patients, 29 per cent of TOL patients and 8 per cent of PL patients. Other adverse events were reported at a rate <4 per cent	In long-term treatment TCl and OXY had a similar efficacy but TCl showed a lower incidence of adverse events

The following points summarise the data presented in Table 2.

- The extended-release preparation of oxybutynin has shown similar efficacy to, and better tolerability than, immediate-release oxybutynin. The OBJECT study⁶ suggests it may be more effective than tolterodine. The incidence of adverse events seen with extended-release oxybutynin and tolterodine is similar and both cause fewer adverse effects than immediate-release oxybutynin
- Recent studies of tolterodine show it to be more effective than placebo and as effective as oxybutynin but with fewer adverse effects. Extended-release tolterodine appears to be more effective, and cause fewer adverse effects than the immediate-release formulation of tolterodine
- Studies with propiverine show it to be more effective than placebo and as effective as immediate-release oxybutynin. The incidence and severity of dry mouth is lower with propiverine than with oxybutynin
- Trial evidence for trospium chloride shows it to be similar in efficacy to oxybutynin and tolterodine. It is better tolerated than standard-release oxybutynin and has a similar tolerability to tolterodine

CONCLUSION

Oxybutynin is an established and effective first-line drug for the treatment of patients with an unstable bladder, and is the most cost-effective. However, its use is often limited by its adverse effects. In patients who cannot tolerate the adverse effects, a second-line agent may be considered. None of the second-line agents described in this article has been shown directly to have better efficacy than oxybutynin.

There appear to be advantages with the long-acting formulations of oxybutynin and tolterodine. These possibly include improved compliance with treatment, and reduced risk of adverse effects due to a flatter time-concentration profile. At the lower end of the dose range, modified-release oxybutynin is more cost-effective than prolonged-release tolterodine, but becomes more expensive where higher doses are required.

The place of immediate-release tolterodine in treatment is now unclear considering the efficacy and cost advantages of the long-acting alternative.

Propiverine and trospium chloride have both been shown to be as effective as oxybutynin but cause fewer adverse effects. They

can be considered as alternatives for second line treatment, but comparative trials against the long-acting formulations of oxybutynin and tolterodine would be helpful in deciding their place in treatment.

There are no clear cut differences in efficacy between the second-line drugs described in this article, and therefore tolerability and cost should be the main considerations when making formulary decisions or prescribing for individual patients.

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