A comparison of newer drug treatments for urinary incontinence

By CARL BOOTH, MPhil, MRPharmS, and DEBBIE PASCOE, BPharm, MRPharmS

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.

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

<table>
<thead>
<tr>
<th>Licensed indications</th>
<th>Oxybutynin</th>
<th>Oxybutynin modified release</th>
<th>Propiverine</th>
<th>Tolterodine</th>
<th>Tolterodine prolonged-release</th>
<th>Tropisium chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>Urinary incontinence, urgency and frequency in the unstable bladder due to neurogenic disorders or detrusor instability. Nocturnal enuresis in children older than five years.</td>
<td>Urinary incontinence, urgency and frequency in the unstable bladder due to neurogenic disorders or detrusor instability.</td>
<td>Urinary incontinence, urgency and frequency in the unstable bladder due to neurogenic disorders or detrusor instability.</td>
<td>Urinary frequency, urgency and incontinence.</td>
<td>Urinary frequency and/or increased urinary frequency associated with urgency as may occur in patients with unstable bladder.</td>
<td>Detrusor instability, detrusor hyper-reflexia with the symptoms of urinary frequency, urgency and urge incontinence.</td>
</tr>
<tr>
<td>Adults: 5mg bd or tid to a maximum of 5mg qds</td>
<td>Adults: 5mg od increased by 5mg/week up to a maximum of 30mg/day</td>
<td>Adults: 15mg bd (range 15mg od–15mg tid), Maximum 15mg qds</td>
<td>No reduction in elderly</td>
<td>Adults: 2mg bd reduced to 1mg bd if side effects troublesome</td>
<td>Review after six months</td>
<td>Adults: 4mg once daily but 2mg od in impaired liver or renal function or if adverse effects are troublesome. Review need for treatment after six months. Reassess every three to six months.</td>
</tr>
<tr>
<td>Elderly: 2.5–5mg bd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adults: 20mg bd</td>
</tr>
<tr>
<td>Children: 2.5–3mg bd, increasing to 5mg bd, if required</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Renal failure: (creatinine clearance 10–30ml/min) 20mg od or 20mg on alternate days. Reassess every three to six months.</td>
</tr>
</tbody>
</table>

- **Side effects**
  - Dry mouth, constipation, blurred vision, nausea, abdominal discomfort, facial flushing, headache
  - 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

- **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
  - Glaucoma, myasthenia gravis, bladder outflow obstruction, severe ulcerative colitis, toxic megacolon pregnancy, breastfeeding

- **Precautions**
  - Elderly, autonomic neuropathy, hepatic or renal disease, hiatus hernia
  - 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, 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

<table>
<thead>
<tr>
<th><strong>Cost per patient per 28 days (MIMS November 2001)</strong></th>
<th>£1.99–£2.99 (5mg bd–5mg tid)</th>
<th>£9.49–£56.94 (5mg od–30mg od)</th>
<th>£30.56 (15mg bd)</th>
<th>£30.56 (2mg bd)</th>
<th>£29.03 (4mg od)</th>
<th>£25 (20mg bd)</th>
<th>£1.99–£2.99 (5mg bd–5mg tid)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glaucoma, myasthenia gravis, bladder outflow obstruction, GI obstruction, severe ulcerative colitis, toxic megacolon pregnancy, breastfeeding</strong></td>
<td>Dry mouth, constipation, blurred vision, nausea, abdominal discomfort, facial flushing, headache</td>
<td>Glaucoma, myasthenia gravis, bladder outflow obstruction, GI obstruction, severe ulcerative colitis, toxic megacolon pregnancy, breastfeeding</td>
<td>Glaucoma, myasthenia gravis, bladder outflow obstruction, severe ulcerative colitis, toxic megacolon pregnancy, breastfeeding</td>
<td>Glaucoma, myasthenia gravis, bladder outflow obstruction, severe ulcerative colitis, toxic megacolon pregnancy, breastfeeding</td>
<td>Glaucoma, myasthenia gravis, bladder outflow obstruction, severe ulcerative colitis, toxic megacolon pregnancy, breastfeeding</td>
<td>Glaucoma, myasthenia gravis, bladder outflow obstruction, severe ulcerative colitis, toxic megacolon, dialysed renal insufficiency, children under 12 years</td>
<td></td>
</tr>
</tbody>
</table>
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 muscolotropic 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.

**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. 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.

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 phe- nothiazines, amantadine, L-dopa and tricyclic antidepressants should also be taken.

**Propiverine** Propiverine hydrochloride is a bladder spasmylytic 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.

Table 2 presents the clinical trial data for propiverine.

**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.

Due to its hydrophilic nature, and in contrast to tertiary amines such as oxybutynin and trospium, 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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Number of patients</th>
<th>Method</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sustained-release oxybutynin (OXY MR)</strong></td>
<td>Appell R.A. <em>et al</em> (OBJECT study)</td>
<td>378 patients with an overactive bladder</td>
<td>Patients received OXY MR 10mg od or TOL 2mg bd for 12 weeks</td>
<td>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.</td>
<td>OXY MR was more effective than TOL and showed a similar rate of adverse events.</td>
</tr>
<tr>
<td></td>
<td>Venzi E. <em>et al</em></td>
<td>226 patients responsive to anticholinergic therapy with &gt; 7 episodes of urge incontinence per week</td>
<td>After a two-week placebo run-in, patients were randomised to receive OXY or OXY MR at an initial dose of 5mg od, increased weekly by 5mg per day to a max of 20mg per day</td>
<td>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.</td>
<td>At the same daily dose, OXY MR and OXY demonstrated similar efficacy and rates of dry-mouth.</td>
</tr>
<tr>
<td></td>
<td>Anderson R.U. <em>et al</em></td>
<td>105 patients with urinary incontinence episodes</td>
<td>After one week washout, patients were randomised to OXY MR or OXY. Both groups started with 5mg daily and dose was increased as required</td>
<td>Similar decreases in weekly urge incontinence episodes and total incontinence episodes were seen in both groups. Conti nence 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.</td>
<td>OXY MR and OXY showed similar efficacy. A lower incidence of dry mouth was seen in patients taking OXY MR.</td>
</tr>
<tr>
<td><strong>Propiverine (PRO)</strong></td>
<td>Madersbacher H. <em>et al</em></td>
<td>366 patients with urgency and urge incontinence</td>
<td>After a one-week washout, patients were randomised to receive propiverine (PRO) 15mg tds, oxybutynin (OXY) 5mg bd or placebo (PL) for four weeks</td>
<td>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 reported in 25.6 per cent of PRO patients and 39.1 per cent of OXY patients (P=0.022) (placebo adjusted rate).</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Stohrer M. <em>et al</em></td>
<td>113 patients with detrusor hyper-reflexia following spinal cord injury</td>
<td>Patients were randomised to receive PRO 15mg tds or PL for two weeks</td>
<td>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.</td>
<td>PRO improves urodynamic measurements and symptoms, compared with PL, in the treatment of detrusor hyper-reflexia.</td>
</tr>
<tr>
<td></td>
<td>Thuroff J.W.</td>
<td>4,390 patients</td>
<td>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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 2: The main clinical trials undertaken with drugs for bladder instability (Continued)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Number of patients</th>
<th>Method</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tolterodine (TOL)</strong></td>
<td>Double-blind, randomised, placebo-controlled, parallel group, multicentre study comparing TOL with placebo (PL)</td>
<td>1,022 patients with urge incontinence and urinary frequency</td>
<td>Patients received TOL 2mg bd, or PL for 12 weeks</td>
<td>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.</td>
<td>TOL 2mg bd is an effective treatment for the symptoms of overactive bladder</td>
</tr>
<tr>
<td>Drutz H.P. et al (^*)</td>
<td>Double-blind, randomised, placebo-controlled, parallel group, multicentre study comparing TOL with OXY</td>
<td>277 patients with detrusor overactivity, and urinary frequency and urge incontinence</td>
<td>After a two-week washout, patients received TOL 2mg bd, OXY 5mg tds, or PL for 12 weeks</td>
<td>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. 31 per cent of OXY patients and 13 per cent of TOL patients withdrew due to adverse events.</td>
<td>TOL and OXY demonstrated equivalent effectiveness. TOL, however, was associated with fewer adverse events</td>
</tr>
<tr>
<td>Appell R.A. (^*)</td>
<td>Pooled analysis of four randomised, double-blind, parallel, multicentre, 12-week studies</td>
<td>1,120 patients in total with overactive bladder</td>
<td>Two studies compared TOL 2mg bd with OXY 5mg tds and PL, one study compared TOL 2mg bd with OXY 5mg tds, and one study compared two dosages of TOL (1mg bd and 2mg bd) with PL</td>
<td>TOL 1mg bd and 2mg bd, and OXY 5mg tds, 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.</td>
<td>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</td>
</tr>
<tr>
<td>Abrams P et al (^*)</td>
<td>A randomised, double-blind, placebo-controlled, parallel group, multinational study</td>
<td>293 patients with an overactive bladder</td>
<td>Patients received TOL 2mg bd, OXY 5mg tds, or PL. Doses could be reduced to 1mg or 2.5mg, respectively, to avoid withdrawal</td>
<td>After 12 weeks, TOL and OXY caused similar reductions in the mean frequency of micturition, and the mean number of incontinence 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.</td>
<td>TOL is as effective as OXY in the treatment of patients with bladder instability. It is better tolerated than OXY</td>
</tr>
<tr>
<td><strong>Modified-release tolterodine (TOL MR)</strong></td>
<td>Double-blind, multicentre, randomised, placebo controlled trial comparing TOL MR, TOL and PL</td>
<td>1,529 patients with urinary frequency and urge incontinence</td>
<td>Following a one to two week washout period, patients were randomised to receive either TOL MR 4mg od, TOL 2mg bd, or PL for 12 weeks</td>
<td>TOL MR 4mg od, and TOL 2mg bd 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&lt;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&lt;0.02)).</td>
<td>TOL MR 4mg od 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.</td>
</tr>
<tr>
<td>Trial</td>
<td>Design</td>
<td>Number of patients</td>
<td>Method</td>
<td>Results</td>
<td>Conclusion</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Trospium chloride (TCl)</td>
<td>(Phase III, placebo-controlled, double-blind, multi-centre trial with two parallel treatments to compare TCl and PL)</td>
<td>208 with confirmed detrusor instability</td>
<td>Patients received TCl 20mg bd or PL for 21–24 days after a washout period of seven days</td>
<td>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) 68 per cent of TCl patients experienced adverse events compared to 62 per cent of PL patients. The most frequently reported event was dry mouth (TCl 43 patients, PL 18 patients) followed by GI disorders, headache and dizziness. 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. 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. 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.</td>
<td>TCI showed a statistically and clinically significant effect on bladder capacity and volume at first unstable contraction accompanied by a favourable safety profile</td>
</tr>
<tr>
<td>Madersbacher H., et al</td>
<td>Randomised, double-blind, multicentre trial treatments to compare TCl and OXY</td>
<td>95 patients with spinal cord injuries and detrusor hyperreflexia</td>
<td>Following a seven-day washout, patients received TCl 20mg bd + PL at midday or OXY 5mg tds for two weeks</td>
<td>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. 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. 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.</td>
<td>TCI and OXY demonstrated equal effects on detrusor hyperactivity. TCI, however, was better tolerated than OXY</td>
</tr>
<tr>
<td>Osca Garcia J.M., et al</td>
<td>Randomised, double-blind trial to compare TCl with OXY</td>
<td>67 patients with detrusor hyperreflexia</td>
<td>Patients received TCl 20mg bd or OXY 5mg tds</td>
<td>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. 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. 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.</td>
<td>TCI showed similar efficacy to OXY but tolerability was better</td>
</tr>
<tr>
<td>Junemann K. P. and Al-Shukri S. (Abstract)</td>
<td>Double-blind, placebo-controlled, multicentre trial to compare TCl and TOL</td>
<td>232 patients with urge-syndrome</td>
<td>Patients received TCl 20mg bd, TOL 2mg bd or PL for three weeks</td>
<td>TCI significantly reduced the 24-hour micturition frequency compared with PL. TOL caused a reduction that was not significant compared with PL. Both TCI and TOL significantly increased mean volume per voiding compared with PL. Incontinence episodes were significantly reduced in the TCI group compared with TOL and PL. Dry mouth was reported in 28 per cent TCI patients, 29 per cent of TOL patients and 8 per cent of PL patients. Other adverse events were reported at a rate &lt;4 per cent.</td>
<td>TCI is as effective as TOL in reducing symptoms of urge syndrome and is more effective at reducing incontinence episodes. Tolerability was similar between TCI and TOL</td>
</tr>
<tr>
<td>Hofner K., et al (Abstract)</td>
<td>52-week double-blind, controlled, multicentre study to assess long-term tolerability of TCI and OXY</td>
<td>358 patients with urge-syndrome or urge-incontinence</td>
<td>Patients received TCl 20mg bd or OXY 5mg bd for 52 weeks</td>
<td>Statistically fewer patients in the TCI group experienced adverse reactions compared to the OXY group. 33 per cent of TCI patients experienced dry mouth compared with 50 per cent of OXY patients (P&lt;0.01), and GI effects were reported by 39 per cent of TCI patients compared with 51 per cent of OXY patients (P=0.02). Good tolerability was reported by 63 per cent of TCI patients and 42 per cent of OXY patients (P=0.004). Efficacy between the two groups was comparable.</td>
<td>In long-term treatment TCI and OXY had a similar efficacy but TCI showed a lower incidence of adverse events.</td>
</tr>
</tbody>
</table>

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

**REFERENCES**