Agents for treatment of overactive bladder: a therapeutic class review

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Overactive bladder (OAB) is a medical syndrome defined by symptoms of urgency, with or without urge urinary incontinence (any involuntary loss of urine), usually with frequency and nocturia. Although anticholinergic agents have been the first-line treatment for OAB for many years, the efficacious pharmacologic management of this condition has been compromised by concerns regarding tolerability. Flavoxate was the first anticholinergic and antispasmodic agent approved by the Food and Drug Administration (FDA) to treat symptoms of OAB but is not routinely used today since newer agents are more effective. The more recent drugs, oxybutynin and tolterodine, have appeared to be equally efficacious in treating the symptoms of OAB in clinical trials; however, tolterodine has proven to be better tolerated with fewer adverse effects. In 2004, the FDA approved the three newest agents for the class: darifenacin, solifenacin, and trospium. Compared with oxybutynin and tolterodine, these agents have a more favorable side effect profile, which can enhance tolerability and patient compliance. Side effects are reduced in part because of the drugs' greater tissue selectivity for inhibiting the bladder muscle contraction over other anticholinergic receptors in the body. In recent clinical trials, darifenacin, solifenacin, and trospium have shown superiority to placebo and efficacy comparable to that of oxybutynin and tolterodine.

Symptoms of overactive bladder (OAB), also termed urge urinary incontinence, occur because the detrusor muscle is overactive and contracts inappropriately during the filling phase. The symptoms of OAB include urinary frequency, urgency, and urge incontinence. Anticholinergic/antispasmodic drugs are the first choice for OAB, as they have been proven to be the most effective agents in suppressing premature detrusor contractions, enhancing bladder storage, and relieving symptoms (1, 2). Anticholinergic and antispasmodic agents act by antagonizing cholinergic muscarinic receptors, through which different parasympathetic nerve impulses evoke detrusor contraction. In 1970, flavoxate was the first drug in this class to be approved by the Food and Drug Administration (FDA) to treat OAB. Then, in 1975, oxybutynin became the mainstay of treatment for OAB, as it was shown to be more efficacious than flavoxate. The next agent introduced in the class was tolterodine in 1996. Lastly, in 2004, three newer agents—darifenacin, solifenacin, and trospium—challenged older compounds by having a less frequent dosing schedule and a more favorable side effect profile.

Flavoxate is indicated for the symptomatic relief of cystitis, urethritis, prostatitis, and urethrocystitis/urethrotrigonitis. Darifenacin, oxybutynin, solifenacin, tolterodine, and trospium are indicated for the treatment of OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency (3–13). Additionally, oxybutynin is indicated in the treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with neurological conditions (i.e., spina bifida). These agents have also been used to treat voiding disorders in patients with spinal trauma or other neurological diseases, although they are not approved by the FDA for that indication.

Table 1 addresses dosing and administration guidelines for the class.

PHARMACOLOGY AND PHARMACOKINETICS

Of the five known muscarinic subtypes (M_1 through M_5), M_3 appears to be the most clinically relevant in the human bladder. M_2 muscarinic receptors are the predominant subtype (comprising about 80% of all muscarinic receptors); however, contraction of smooth muscle, including muscles in the urinary bladder, is mediated mainly by M_3 receptors. M_3 receptors are also involved in contraction of the gastrointestinal smooth muscle, saliva production, and iris sphincter function. Inhibition of the muscarinic receptors in the urinary bladder results in decreased urinary bladder contraction, increased residual urine volume, and decreased detrusor muscle pressure.

Oxybutynin, tolterodine, darifenacin, solifenacin, and trospium antagonize the effects of acetylcholine at muscarinic receptors on the detrusor muscle and are known as antimuscarinic agents. These agents potently and selectively bind to the M_3 receptor subtype more than other muscarinic receptor subtypes,

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Table 1. Dosing and administration of agents for overactive bladder

Drug name	Initial dose	Maximum dose	Adjust for renal or hepatic dysfunction	Geriatric dosing	Adjustment for CYP3A4 interactions
Darifenacin (Enablex)	7.5 mg daily	15 mg daily	7.5 mg daily for moderate hepatic impairment	N/A	7.5 mg daily
Flavoxate (Urispas)	100–200 mg 3–4 times daily	200 mg 4 times daily	No	N/A	N/A
Oxybutynin IR (Ditropan)	5 mg 2–3 times daily	5 mg 4 times daily	No	Initial dose: 2.5 mg 2–3 times daily	N/A
Oxybutynin ER (Ditropan XL)	5–10 mg daily	30 mg daily	No	N/A	N/A
Oxybutynin patch (Oxytrol)	1 patch (36 mg) twice weekly		No	N/A	N/A
Solifenacin (Vesicare)	5 mg daily	10 mg daily	Maximum 5 mg daily for severe renal and moderate hepatic impairment	N/A	5 mg daily
Tolterodine IR (Detrol)	1 mg twice daily	2 mg twice daily	Maximum 1 mg twice daily for severe renal impairment Avoid use in severe hepatic impairment	N/A	1 mg twice daily
Tolterodine ER (Detrol LA)	2 mg daily	4 mg daily	Maximum 2 mg daily for severe renal impairment Avoid use in severe hepatic impairment	N/A	2 mg daily
Trospium (Sanctura)	20 mg daily	20 mg twice daily	Maximum 20 mg daily for severe renal impairment Avoid use in severe hepatic impairment	20 mg daily	N/A

IR indicates immediate-release formulation; ER, extended-release formulation; severe renal impairment, creatinine clearance <30 mL/minute; moderate hepatic impairment, Child-Pugh class B; severe hepatic impairment, Child-Pugh class C; N/A, not applicable.

with the exception of tolterodine, which has demonstrated no specificity for any subtype. Oxybutynin is a racemic mixture of *R*- and *S*-isomers, and its antimuscarinic actions are predominantly a result of the *R*-isomer. All of the antimuscarinic agents exhibit functional selectivity for urinary bladder over secretory glands (e.g., salivary) and have little or no affinity for nicotinic receptors compared with muscarinic receptors. The newer agents (i.e., darifenacin, solifenacin, and trospium) have demonstrated greater tissue selectivity for inhibition of detrusor contraction over salivation, offering an advantage over other agents by reducing adverse effects and improving compliance.

Oxybutynin also exerts a direct spasmolytic (papaverine-like) action on smooth muscles to allow an increased urinary bladder capacity. Flavoxate is a spasmolytic agent with no antimuscarinic activity. Flavoxate and oxybutynin have little or no effect on the smooth muscle of blood vessels, unlike papaverine. In animals in vitro, flavoxate's and oxybutynin's spasmolytic effects have been demonstrated in the small intestine, gallbladder, uterus, seminal vesicle, and colon in addition to the detrusor muscle. Flavoxate and oxybutynin have also shown moderate antihistaminic, some local anesthetic, some mild analgesic, and low mydriatic and antisialagogue activity in animals.

Trospium, a quaternary ammonium antimuscarinic, is hydrophilic and theoretically should not cross the blood-brain barrier like lipophilic anticholinergic agents (e.g., oxybutynin, tolterodine); therefore, adverse central nervous system (CNS) effects (e.g., dizziness) should be minimal.

The pharmacokinetics for each agent are listed in *Table 2*.

CLINICAL TRIALS

Flavoxate

The efficacy and safety of flavoxate in the treatment of OAB have not been evaluated in recent clinical trials.

Oxybutynin IR vs ER

Two randomized, double-blind clinical studies have been conducted to compare the efficacy and safety of oxybutynin extended release (ER) and oxybutynin immediate release (IR) (5). When decreases in the number of episodes of urge incontinence were compared, one study indicated that the formulations were comparable; although comparable efficacy was not demonstrated according to predetermined criteria in the second study, there was no substantial difference between the formulations. The efficacy of oxybutynin ER tablets was maintained after 12 weeks of therapy in one study (10).

The safety and efficacy of once-daily controlled and IR oxybutynin was evaluated in a multicenter, randomized, double-blind study by Anderson et al (14). One hundred five patients with urge incontinence or mixed incontinence with a clinically significant urge component received dose titration of oxybutynin ER 5, 10, 15, 20, 25, or 30 mg daily or oxybutynin IR 5 mg one to four times daily. The number of weekly urge incontinence episodes decreased from 27.4 to 4.8 with oxybutynin ER and from 23.4 to 3.1 with oxybutynin IR. Total weekly incontinence episodes decreased from 29.3 to 6 and from 26.3 to 3.8, respectively. Continence was achieved in 41% of oxybutynin ER patients and 40% of oxybutynin IR patients. A lower

Table 2. Pharmacokinetics of agents for overactive bladder*

Parameter	Darifenacin	Flavoxate	Oxybutynin	Solifenacin	Tolterodine	Trospium
Oral bioavailability	15%–25%	N/A	6%	90%	77%	9.6%
Affected by food	No	No	Yes (increased serum concentrations ~25%)	No	No	Yes (70%–80% reduced absorption with high-fat meal)
Time to peak concentration (hours)	7	2	1 (IR) 3–6 (ER) 24–48 (patch)	3–8	1–2 (IR) 2–6 (ER)	4–6
Half-life (hours)	13–19	N/A	1.1–2.3 (IR) 12–16 (ER)	40–68	1.9–3.7 (EM) 9.6 (PM)	20
Excretion: feces	40%	N/A	N/A	23%	17%	85%
Excretion: renal	60%	57%	<0.1%	3%–6%	77%	6%
Metabolism	Liver by CYP3A4 and 2D6 to inactive metabolites	Mechanism unknown to active metabolite	Liver by CYP3A4 to active metabolite (desethyloxybutynin)	Liver by CYP3A4 to active metabolite (4R-hydroxysolifenacin)	Liver by CYP2D6 to active metabolite (5-hydroxyethyltolterodine)	Liver, not CYP to inactive metabolites

*From references 3 and 4.

IR indicates immediate release; ER, extended release; EM, extensive metabolizers; PM, poor metabolizers; CYP, cytochrome P-450 isoenzyme.

incidence of dry mouth was reported for oxybutynin ER (68%) than for oxybutynin IR (87%) (14).

Tolterodine IR vs ER

Single daily doses of tolterodine ER appear to be slightly more effective in relieving certain urinary symptoms (e.g., urge incontinence) than two daily doses of tolterodine IR. In a 12-week comparative, randomized, double-blind, placebo-controlled study in patients with OAB by Van Kerrebroeck et al (15), 1529 patients were randomized to treatment with tolterodine ER 4 mg once daily, tolterodine IR 2 mg twice daily, or placebo. Median decreases in the number of micturitions per 24 hours were 1.8, 1.7, and 1.2, respectively; median increases in the volume of urine voided per micturition were 34, 29, and 14 mL, respectively; and median decreases in the number of incontinence episodes per week were 11.8, 10.6, and 6.9, respectively. The overall rate of dry mouth for patients taking tolterodine ER was 23% lower than for tolterodine IR (15).

Oxybutynin IR vs tolterodine IR

In one multicenter, randomized, double-blind, placebo-controlled study of 12 weeks' duration by Abrams et al, the efficacy of oxybutynin 5 mg three times daily and tolterodine 2 mg twice daily appeared to be similar in reducing the symptoms of OAB (16). Two hundred ninety-three patients with a >6-month history of urinary symptoms were randomized to receive either oxybutynin (n = 118), tolterodine (n = 118), or placebo (n = 57). Tolterodine and oxybutynin were equivalent in decreasing urinary frequency: the number of micturitions per 24 hours decreased by 19.5%, 21%, and 10.5% of patients taking oxybutynin, tolterodine, and placebo, respectively. The mean number of episodes of incontinence decreased by 71%, 47%, and 19%, respectively. Compared with placebo, however, only tolterodine produced a significantly greater decrease in urinary frequency, and only oxybutynin produced a significantly greater decrease in incontinence episodes. In addition, increases in the volume of urine voided per micturition were similar in patients receiving oxybutynin (31%) and tolterodine (27%) compared with patients receiving placebo (7%).

Dry mouth was the most commonly reported adverse event but occurred with significantly greater frequency and severity in the oxybutynin group than in the tolterodine group. Treatment withdrawals and dose reductions also occurred significantly more often in the oxybutynin group than in the tolterodine group. The authors acknowledged that the 5-mg dose of oxybutynin used in this study was higher than the typical starting dose used in clinical practice. Nonetheless, the 32% of patients who did elect to reduce their oxybutynin dose did not experience an overall reduction in adverse events or a change in the severity of dry mouth (16). Three additional reports noted similar findings for tolterodine and oxybutynin (17–19).

Darifenacin

In more than 1400 patients with symptoms of urinary frequency, urgency, and/or urge or mixed incontinence that had persisted for at least 6 months, the safety and efficacy of darifenacin was established in four 12-week randomized, double-blind, placebo-controlled studies. In these studies, darifenacin 7.5 to 15 mg daily was more effective than placebo in reducing the number of urge incontinence episodes per week, reducing the number of micturitions per 24 hours, and increasing the volume of urine voided per micturition.

One multicenter, double-blind, placebo-controlled study enrolled 561 patients with symptoms of OAB (20). Patients were randomized (1:4:2:3) to once-daily darifenacin 3.75, 7.5, or 15 mg or placebo for 12 weeks. Reduction in the number

of urge incontinence episodes was observed within the first 2 weeks of therapy, and this effect was sustained throughout the 12-week treatment period. At 12 weeks the number of incontinence episodes per week was reduced from baseline by 67.7% with darifenacin 7.5 mg and 72.8% with darifenacin 15 mg compared with 55.9% with placebo. The 3.75-mg group was included for proof of concept of dose flexibility; therefore, formal sample sizing and statistical analysis were not performed for this group.

The most common adverse events were mild to moderate dry mouth (18.8% with darifenacin 7.5 mg, 31.3% with darifenacin 15 mg, and 8.5% with placebo) and constipation (14.4%, 13.9%, and 6.7%, respectively). However, no patients withdrew from the study as a result of dry mouth, and discontinuation related to constipation was rare (0.6% placebo vs 0.9% darifenacin). In addition, there was a low need for laxative use, with no difference between the darifenacin groups and the placebo group. There were no reports of blurred vision, and the CNS and cardiac safety profile was comparable to that of placebo (20).

In a flexible-dose study by Steers et al, 395 patients were randomized to receive darifenacin 7.5 mg once daily (with the option to increase dosage to 15 mg once daily) or placebo for 12 weeks (21). In this study, urge incontinence episodes were decreased from baseline by 8.2 and 6 occurrences per week, urinary frequency was decreased from baseline by 1.9 and 1 micturition per 24 hours, and urine volume voided per micturition was increased by 18.8 and 6.6 mL per micturition in patients receiving darifenacin or placebo, respectively. Among patients who required dosage escalation to 15 mg daily, the clinical outcome achieved at 12 weeks was comparable to that achieved in patients who initially responded to the 7.5-mg daily dosage. The most common treatment-related adverse events were mild to moderate dry mouth and constipation, which led to discontinuation in <3% of patients in the darifenacin group and <1% of patients in the placebo group. The number of CNS and cardiovascular adverse events was comparable to that with placebo (21).

Darifenacin vs oxybutynin IR

A 2-week multicenter, randomized, double-blind, placebo-controlled crossover study evaluated the efficacy of darifenacin (15 mg once daily) compared with oxybutynin IR (5 mg three times daily) in reducing the frequency of urinary incontinence and the frequency and severity of urgency in 76 patients with OAB (22). Darifenacin and oxybutynin were associated with significantly fewer incontinence episodes per week (10.93 darifenacin, 9.45 oxybutynin, and 14.64 placebo) and fewer and less severe urgency episodes at week 2 than placebo (7.95, 8.12, and 8.71, respectively); however, the effects of darifenacin and oxybutynin on OAB symptoms were comparable. Among the 61 patients evaluated for tolerability, oxybutynin was associated with a higher rate of dry mouth (36%) than either darifenacin (13%) or placebo (5%). Blurred vision and dizziness were reported only during oxybutynin therapy (22).

Solifenacin

The safety and efficacy of solifenacin have been established in four 12-week randomized, double-blind, placebo-controlled studies in more than 3000 patients with symptoms of urinary frequency and urgency and/or urge/mixed incontinence that had persisted for at least 3 months. In these studies, solifenacin 5 to 10 mg daily was more effective than placebo in reducing the number of micturitions and urge incontinence episodes per 24 hours and increasing the volume of urine voided per micturition (12).

The study by Cardozo et al found that solifenacin 10 mg daily may also be effective in decreasing the frequency of nocturia (23). This multicenter, multinational, randomized, double-blind, placebo-controlled trial enrolled 1091 patients for 12 weeks. Compared with changes obtained with placebo (–1.59), micturitions per 24 hours were significantly decreased with solifenacin 5 mg (–2.37) and 10 mg (–2.81). A significant decrease was observed in the number of incontinence episodes and episodes of urge incontinence. Of patients reporting incontinence at baseline, 50% achieved continence after treatment with solifenacin. Episodes of urgency were significantly reduced with solifenacin 5 mg (–51%) and 10 mg (–52%). Mean volume voided per micturition was significantly increased with both solifenacin doses. Episodes of nocturia were significantly decreased in patients treated with solifenacin 10 mg (–38.5%) vs placebo (–16.4%). Treatment with solifenacin was well tolerated; dry mouth, mostly mild, was reported in 7.7% of patients receiving solifenacin 5 mg and 23% receiving 10 mg vs 2.3% with placebo (23).

Solifenacin vs tolterodine

In a multicenter, placebo- and tolterodine-controlled double-blind dose-finding trial, solifenacin 5 mg and 10 mg doses were found to be the most clinically effective and best tolerated in the treatment of OAB (24). Two hundred twenty-five patients were randomized to receive either solifenacin 2.5, 5, 10, or 20 mg once daily, tolterodine IR 2 mg twice daily, or placebo for 4 weeks. The number of voids per 24 hours showed a significant improvement for patients receiving solifenacin 5, 10, or 20 mg daily ($P < 0.05$). However, the change caused by solifenacin 2.5 mg daily was not significantly different than that of placebo. Tolterodine 2 mg twice a day caused a change that was between that caused by solifenacin 2.5 and 5 mg once daily but was not statistically different from that of placebo. Furthermore, the mean volume voided with solifenacin 5, 10, or 20 mg was significantly larger than with either tolterodine or placebo. Efficacy for all parameters with solifenacin was dose-related. There were also fewer episodes of urgency or incontinence with solifenacin than with either tolterodine or placebo. The most prominent adverse effect was dry mouth, which was most frequent with solifenacin 20 mg (38%) followed by tolterodine 2 mg (24%) and solifenacin 5 and 10 mg (14%). Constipation occurred in 19% and dyspepsia in 16% of patients receiving solifenacin 20 mg. All adverse effects were mild to moderate and led to a low rate of discontinuation of therapy (24).

Solifenacin 5 and 10 mg once daily improved symptoms of OAB and was well tolerated in an international multicenter, randomized, double-blind, tolterodine- and placebo-controlled phase 3 clinical trial (25). Patients participated in a 2-week, single-blind, placebo run-in period, followed by treatment with solifenacin 5 mg (n = 279) or 10 mg (n = 269) once a day, tolterodine 2 mg twice a day (n = 263), or placebo (n = 267) for 12 weeks. After the 12-week treatment phase, there was a similar decrease in urgency episodes per 24 hours in patients receiving placebo and tolterodine (33% and 38%, respectively), and there were significant decreases from baseline in urgency episodes per 24 hours in patients receiving solifenacin 5 or 10 mg (–52% and –55%, respectively) and in the number of urge incontinence episodes in patients receiving solifenacin 5 and 10 mg (–1.41 and –1.36, respectively). There was also an increase from baseline in mean volume per void for the placebo group (7.4 mL), which was significantly different with tolterodine (24.2 mL), solifenacin 5 mg (32.9 mL), and solifenacin 10 mg (39.2 mL). The percentage of patients discontinuing therapy because of an adverse effect was 3.7% in the placebo group, 1.9% in the tolterodine group, and 3.2% and 2.6% in the solifenacin 5 and 10 mg groups, respectively. The most common adverse reactions were dry mouth, constipation, and blurred vision. Solifenacin treatment resulted in withdrawal rates similar to those for placebo (25).

Trospium

In two 12-week randomized, placebo-controlled clinical studies in adults with OAB, trospium 20 mg twice daily was more effective than placebo in reducing the number of micturitions per 24 hours, reducing the number of urge incontinence episodes per week, and increasing the volume of urine voided per micturition (13).

In the first clinical study by Zinner et al, 523 adult patients with OAB received trospium 20 mg twice daily or placebo (26). The results of this study found decreases from baseline in urinary frequency by a mean of 2.4 or 1.3 micturitions per 24 hours, decreases in urge incontinence episodes from baseline by a mean of 15.4 or 13.9 occurrences per week, and increases in urine volume voided per micturition by a mean of 32.1 or 7.7 mL per micturition in the trospium and placebo groups, respectively. Dry mouth occurred in 21.8% in the trospium group compared with 6.5% in the placebo group, and constipation occurred in 9.5% vs 3.8%, respectively. Adverse events leading to discontinuation occurred in 8.8% for trospium vs 5.7% for placebo (26).

In the second, nearly identical study of 658 patients with OAB, urinary frequency decreased from baseline by a mean of 2.7 or 1.8 micturitions per 24 hours, urge incontinence episodes decreased from baseline by a mean of 16.1 or 12.1 occurrences per week, and urine volume voided per micturition increased by a mean of 35.6 or 9.4 mL per micturition, respectively (13).

Trospium vs oxybutynin or tolterodine

Trospium 20 mg twice daily was compared with oxybutynin 5 mg twice daily in a prospective randomized, placebo-controlled, multicenter clinical trial over 52 weeks (27). Three hundred fifty-eight patients were enrolled. At 26 and 52 weeks of treatment, trial physicians assessed tolerability as very good for 49% and 63% of trospium-treated patients and 36% and 42% of oxybutynin-treated patients, respectively. Appraisal by the patients gave almost identical results. Ninety-one patients (25.4%) terminated the study prematurely: 67 patients (25.0%) from the trospium group and 24 (26.7%) from the oxybutynin group. Dry mouth was noted by 33% of patients treated with trospium and 50% of those treated with oxybutynin as the most frequent adverse event.

Efficacy was measured by urodynamic evaluations in 276 patients. Increases in maximum cystometric bladder capacity from baseline and volume at the first sensation to void were not significantly different between the trospium and oxybutynin groups. The increase in volume at the first unstable contraction was significantly more pronounced with trospium than with oxybutynin (46 and 36.7 mL, respectively). The frequency of incontinence episodes and episodes of urgency decreased similarly between groups. The frequency of micturitions in 24 hours at 2, 26, and 52 weeks was 1.2, 2.9, and 3.5, respectively, for trospium-treated patients and 1.5, 3.4, and 4.2, respectively, for oxybutynin-treated patients; the differences were not statistically significant (27).

Trospium appears to be as effective as oxybutynin or tolterodine in decreasing urinary frequency, and limited information indicates that the drug may be more effective than IR preparations of tolterodine in decreasing urgency incontinence compared with placebo (28, 29). However, some clinicians state that trospium appears to offer no advantage over oxybutynin ER or tolterodine ER for the treatment of OAB (30).

CONTRAINDICATIONS AND PRECAUTIONS

Darifenacin, oxybutynin, solifenacin, tolterodine, and trospium are contraindicated in patients at risk of or with known urinary or gastric retention or uncontrolled angle-closure glaucoma. Tolterodine and trospium are also contraindicated in myasthenia gravis (3). Flavoxate is contraindicated in patients with pyloric or duodenal obstruction, obstructive intestinal lesions or ileus, achalasia, gastrointestinal hemorrhage, or obstructive uropathies of the lower urinary tract. In patients with known hypersensitivity to the specific product or any of its components, use is contraindicated. Because of the risk of urinary retention, darifenacin, oxybutynin, solifenacin, tolterodine, and trospium should be used with caution in patients with clinically important bladder outflow obstruction.

The antimuscarinic agents oxybutynin, tolterodine, trospium, solifenacin, and darifenacin may decrease gastrointestinal motility. Caution should be used in patients with severe constipation, intestinal atony, ulcerative colitis, or myasthenia gravis. Since diarrhea may be a symptom of partial intestinal obstruction, especially in patients with ileostomies or colostomies, the possibility of intestinal obstruction should be excluded before these agents are administered to patients with diarrhea. Because of the risk of gastric retention, darifenacin, oxybutynin, tolterodine, and trospium should be used with caution in pa-

Table 3. Incidence of adverse events associated with anticholinergic agents

Adverse event	Darifenacin	Flavoxate*	Oxybutynin†	Solifenacin	Tolterodine	Trospium
Dry mouth	20.2%–35.3%	*	29%–61%	10.9%–27.6%	23%	20.1%
Constipation	14.8%–21.3%	*	7%–13%	5.4%–13.4%	6%	9.6%
Upper abdominal pain	2.4%–3.9%	No report	<5	1.2%–1.9%	4%	1.5%
Dyspepsia	2.7%–8.4%	*	5%–7%	1.4%–3.9%	3%	1.2%
Nausea	1.5%–2.7%	*	2%–9%	1.7%–3.3%	*	>0.5%
Diarrhea	0.9%–2.1%	*	7%–9%	No report	*	No report
Urinary retention	No report	*	<5%	1.4%	No report	1.2%
Urinary tract infection	4.5%–4.7%	No report	5%	2.8%–4.8%	1%	1.2%
Vertigo	1.3%–2.1%	*	4%–6%	1.9%	2%	No report
Blurred vision	>1%	*	1%–8%	3.8%–4.8%	1%	>0.5%
Drowsiness	0.9%–2.1%	*	2%–12%	1.0%–2.1%	3%	1.9%
Headache	No report	*	6%–10%	No report	6%	4.2%
Dry eyes	1.5%–2.1%	*	3%–6%	0.3%–1.6%	3%	No report

*Incidence not defined.

†Oxybutynin transdermal system adverse events also include local reactions (i.e., pruritus, erythema, vesicles, rash, or macules at the application site; see reference 14).

tients with obstructive gastrointestinal disorders (e.g., pyloric stenosis). Fecal impaction, colonic obstruction, and intestinal obstruction have been reported rarely with solifenacin 10 mg daily. Severe constipation has been reported with darifenacin. Chronic constipation persisting for up to 9 months and requiring hospitalization was reported in at least one patient receiving darifenacin.

Oxybutynin also should be used with caution in patients with gastroesophageal reflux and/or in patients receiving oxybutynin concomitantly with drugs that can cause or exacerbate esophagitis (e.g., bisphosphonates). As with other nondeformable material, oxybutynin ER tablets should be used with caution in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic) since obstruction may occur. Tolterodine, solifenacin, darifenacin, and trospium should be used only if the potential benefits outweigh the risks in patients being treated for angle-closure glaucoma and then only when careful monitoring is available. Flavoxate, oxybutynin, and tolterodine should be administered with caution to patients performing hazardous tasks requiring mental alertness or physical coordination because of possible drowsiness, dizziness, and blurred vision. Alcohol or other sedative drugs may enhance these effects.

Solifenacin and tolterodine have been observed to cause prolongation of the QT interval. Caution should be used if a patient has a history of QT prolongation or is receiving class 1A or III antiarrhythmic agents that prolong the QT interval. In a study on the effects of solifenacin on QT interval, a dosage of 30 mg daily (three times the maximum recommended dosage) had a greater effect in prolonging the QT interval than a dosage of 10 mg daily. Prolongation of the QT_c interval has been observed following administration of therapeutic (2 mg twice daily) and supratherapeutic (4 mg twice daily) dosages of tolterodine in healthy adults. Administration of oxybutynin during hot weather can cause heat exhaustion (i.e., fever and heat stroke secondary to suppression of sweating). The possibility that these agents, especially oxybutynin, may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension, myasthenia gravis, or prostatic hypertrophy should be considered when prescribing (3–13).

ADVERSE EVENTS

A comparison of adverse events associated with anticholinergic agents is outlined in *Table 3* (4, 6–13).

Anaphylactoid reactions (e.g., angioedema) have been reported in at least one patient receiving solifenacin and in patients receiving tolterodine during postmarketing surveillance studies.

DRUG INTERACTIONS

Darifenacin, oxybutynin, and solifenacin are metabolized by the CYP3A4 isoenzyme. Pharmacokinetic interactions by CYP3A4 inhibitors are possible; therefore, caution should be exercised when using these drugs concomitantly with CYP3A4 inhibitors. The manufacturers of darifenacin and solifenacin recommend dosage adjustments for patients receiving a potent CYP3A4 inhibitor concomitantly with these agents. Darifenacin is also metabolized by CYP2D6; however, no dosage adjustment is required in patients receiving concomitant CYP2D6 inhibitors. Tolterodine is metabolized by CYP2D6 and inhibits it at high concentrations. In individuals who are devoid of the CYP2D6 isoenzyme or who are receiving other CYP2D6 inhibitors, the primary metabolic pathway of tolterodine involves the CYP3A4 isoenzyme. Therefore, concomitant use of tolterodine with other potent CYP3A4 inhibitors also may result in increased plasma tolterodine concentrations, and dosage adjustments are recommended.

Table 4. Acquisition cost of agents for overactive bladder

Drug	Usual daily dose	Cost per dose (inpatient)
Darifenacin (Enablex)		
7.5 mg	7.5–15 mg daily	$3.09
15 mg		$3.09
Flavoxate (Urispas)	100–200 mg	
100 mg	3–4 times daily	$1.42
Oxybutynin (Ditropan)		
5 mg		$0.08
Syrup 5 mg/5 mL	5 mg 2–3 times daily	$1.22
Patch		$10.54
Oxybutynin ER (Ditropan XL)		
5 mg XL		$2.52
10 mg XL	5–10 mg daily	$2.52
15 mg XL		$2.55
Solifenacin (Vesicare)		
5 mg	5–10 mg daily	$2.87
10 mg		$2.87
Tolterodine (Detrol)		
1 mg	1–2 mg twice daily	$1.61
2 mg		$1.65
Tolterodine ER (Detrol LA)		
2 mg LA	2–4 mg daily	$2.79
4 mg LA		$2.87
Trospium (Sanctura)		
20 mg	20–40 mg daily	$1.68

Flavoxate and trospium are not metabolized via CYP isoenzymes (5). Concomitant administration of these agents with other anticholinergic drugs may increase the frequency and/or severity of adverse anticholinergic effects (e.g., dry mouth, constipation, and somnolence). By inhibiting the motility of the gastrointestinal tract, this class of anticholinergic agents may alter gastrointestinal absorption of some concomitantly administered drugs; this may be of concern for drugs with a narrow therapeutic index.

Oral oxybutynin preparations should be used with caution in patients concurrently receiving drugs that can cause or exacerbate esophagitis (e.g., bisphosphonates) (9, 10). Specific drug interaction studies with the oxybutynin transdermal system have not been conducted to date (11). Active tubular secretion is a major route of elimination of trospium, implying possible competition for renal secretion with other drugs that are eliminated by the same route (e.g., digoxin, metformin, morphine, pancuronium, procainamide, tenofovir, vancomycin).

PHARMACOECONOMICS

Table 4 compares the daily cost of agents for the treatment of OAB based on acquisition costs at Baylor University Medical Center.

CONCLUSIONS

Darifenacin, oxybutynin, solifenacin, tolterodine, and trospium suppress premature detrusor contractions and allow enhanced bladder storage and relief of symptoms of OAB. Oxybutynin and flavoxate also have antispasmodic effects and more side effects than the other agents. Flavoxate is not commonly used in clinical practice, and its effectiveness has not been validated as have the other agents through recent clinical trials. Tolterodine and oxybutynin appear to be equally effective in relieving the symptoms of OAB. Yet, tolterodine is much better tolerated than oxybutynin in comparative studies. The three newest agents in the class, darifenacin, solifenacin, and trospium, have the lowest incidence of adverse events and exhibit efficacy rates comparable to those of tolterodine and oxybutynin.

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