Bladder Relaxant Preparations Review

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FDA-Approved Indications

Drug	Manufacturer	Indication(s)
darifenacin (Enablex®)	Novartis	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
oxybutynin (Ditropan®)	generic	Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria)
oxybutynin ER (Ditropan® XL)	generic	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency Treatment of pediatric patients aged six years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida)
oxybutynin transdermal (Oxytrol™)	Watson	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
solifenacin (VESIcare®)	GSK	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency
tolterodine (Detrol®)	Pfizer	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
tolterodine ER (Detrol® LA)	Pfizer	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
trospium (Sanctura®)	Esprit	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency
trospium ER (Sanctura® XR)	Esprit	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency

Overview

Overactive bladder (OAB) is a chronic and debilitating syndrome that is characterized by urinary urgency with or without urge incontinence, usually in combination with urinary frequency (eight or more voiding episodes per 24 hours) and nocturia (awakening more than one time per night to void).[1] The patient fear of urinary incontinence (driven by embarrassment and social stigma) can result in significant changes to a patient's quality of life (QoL). It has been recently estimated that 33 million Americans are affected by OAB.[2] The overall prevalence of OAB is equal in men (16 percent) and women (16.9 percent); however, more women suffer from OAB with incontinence.[3] The prevalence of OAB is over 30 percent in the elderly.

There are many potential causes for the symptoms of OAB including lower urinary tract conditions (e.g., urinary tract infection, obstruction), neurological conditions (e.g., stroke, Alzheimer's disease), systemic conditions (e.g., heart failure, vascular insufficiency), functional and behavioral conditions (e.g., impaired mobility), and use of various medications (e.g., diuretics, narcotics).[4,5,6]

In the resting state, the pressure within the bladder is lower than urethral resistance. In the normal individual, the bladder can hold between 350 and 500 mL, with the first urge to urinate occurring when the bladder contains around 200 mL. Urination occurs following a sequence of events that begins with a decrease in urethral resistance. Subsequently, the layered smooth muscle that surrounds the bladder (the detrusor muscle) contracts, causing the bladder to empty. This sequence of events begins when the bladder's sensory stretch receptors are activated by increased bladder filling.[7] The symptoms of OAB are usually associated with overactivity of the detrusor muscle as it contracts spastically, sometimes without a known cause. This results in sustained high bladder pressure and urgency or urge incontinence depending on the sphincter response.[8]

The management of OAB includes both pharmacological (antimuscarinic drugs) and non-pharmacological (e.g., bladder training, pelvic floor muscle exercises) interventions.[9,10]

Pharmacology

Although other neurotransmitter pathways are involved, acetylcholine is the major peripheral neurotransmitter responsible for bladder contraction. Acetylcholine causes this response through its interaction with muscarinic receptors on the detrusor muscle.[11] There are five known muscarinic receptor subtypes labeled M_1 through M_5. Subtypes M_2 and M_3 are associated primarily with bladder activity in a ratio of 80 to 20, respectively. Even though there are a greater number of M_2 receptors located in the detrusor muscle, it appears that M_3 receptors are primarily responsible for normal micturition contraction. In addition to their role in bladder contraction, the M_2 and M_3 muscarinic receptor subtypes are involved in contraction of gastrointestinal smooth muscle, saliva production, and iris sphincter function.

In general, antimuscarinic drugs depress both voluntary and involuntary bladder contractions. Antimuscarinic action on the lower urinary tract results in an increase in residual urine, reflecting an incomplete emptying of the bladder and a decrease in detrusor pressure.

Oxybutynin (Ditropan, Ditropan XL, Oxytrol) is a tertiary amine ester that is a potent, nonselective, competitive antimuscarinic receptor antagonist. Oxybutynin's effects on the detrusor muscle are mediated via M_3 receptors. Because it is a non-selective antimuscarinic, oxybutynin may produce side effects consistent with anticholinergic actions in the CNS, parotid gland, and GI tract. Oxybutynin also possesses minor local anesthetic properties.

The tertiary amine tolterodine (Detrol, Detrol LA) and its active metabolite, 5-hydroxymethyltolterodine, are also competitive muscarinic receptor antagonists. Tolterodine shows selectivity for the urinary bladder over salivary glands. Neither tolterodine nor its active metabolite exerts clinically significant effects on other neurotransmitter receptors or other pharmacologic targets such as calcium channels. Tolterodine and its active metabolite have a lipophilicity 30 and >350 times lower than oxybutynin, respectively, which limits their entry into the CNS and would therefore be expected to limit the drug's antimuscarinic activity in the CNS.[12,13]

Trospium (Sanctura, Sanctura XR) is an antispasmodic, competitive antimuscarinic agent that has high affinity to the M_1, M_2, and M_3 receptor subtypes with lower affinity for the M_4 and M_5 receptors.[14] When used at therapeutic doses, trospium has negligible affinity for nicotinic receptors. Trospium is a hydrophilic quaternary amine and does not cross the blood-brain barrier or conjunctiva like oxybutynin, a tertiary amine; this reduces the risk of CNS-related side effects such as sedation and dizziness.[15,16]

Darifenacin (Enablex) is a competitive muscarinic receptor antagonist. It is a selective antagonist at M_3 receptors.[17,18] In contrast to the non-selective agents, darifenacin has been reported to have selectivity for the bladder over the salivary gland *in vivo*. It is not clear if selective antagonism at the M_3 receptor improves patient tolerability or clinical efficacy versus currently available agents.

Solifenacin (VESIcare) is a competitive M_3-selective muscarinic receptor antagonist but has some effect on all muscarinic receptors.[19] Solifenacin has functional selectivity for the bladder compared to salivary muscarinic receptors; therefore, the antimuscarinic effects of solifenacin on the salivary gland are less pronounced. Due to its poor CNS penetration, CNS side effects are minimal.

Pharmacokinetics[20,21,22,23,24,25,26,27,28]

Drug	Time to Peak (hr)	Route of Metabolism	Half-life (hr)
darifenacin (Enablex)	6-8	CYP2D6[††], CYP3A4	13-19
oxybutynin (Ditropan)	<1	CYP3A4	2-3
oxybutynin ER (Ditropan XL)	12-13	CYP3A4	12-13
oxybutynin transdermal (Oxytrol)	10-48	CYP3A4[*]	7-8
solifenacin (VESIcare)	3-8	CYP3A4	45-68
tolterodine (Detrol)	1-2	CYP2D6, CYP3A4	2-4[†]
tolterodine ER (Detrol LA)	2-6	CYP2D6, CYP3A4	7-10[**]
trospium (Sanctura)	5-6	Ester hydrolysis	18-20
trospium ER (Sanctura XR)	5	Ester hydrolysis	36

[*] transdermal route reduces CYP3A4 metabolism in the liver and gut
[†] half-life of tolterodine tablets can be up to 9.6 hours in slow metabolizers
[**] half-life of tolterodine extended-release capsules can be up to 18 hours in slow metabolizers
[††] bioavailability of darifenacin is increased by 77 to 131 percent in poor metabolizers of CYP2D6

After oral administration, tolterodine (Detrol, Detrol LA) is metabolized in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically active metabolite. This metabolite, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. Like tolterodine, the 5-hydroxymethyl metabolite exhibits a high specificity for muscarinic receptors.

Administration of trospium (Sanctura) with a high fat meal reduces absorption, thus reducing bioavailability by 70 to 80 percent. Administration of trospium ER (Sanctura XR) immediately after a high-fat content meal reduced the oral bioavailability by 35 percent and the C_{max} by 60 percent. It is recommended that trospium and trospium ER be taken on an empty stomach.

Contraindications/Warnings[29,30,31,32,33,34,35,36]

All of the bladder relaxants are contraindicated in patients with uncontrolled narrow-angle glaucoma or gastric and/or urinary retention.

Drug Interactions

<u>oxybutynin (Ditropan, Ditropan XL, Oxytrol)</u> [37,38,39]

Concomitant use of oxybutynin with other anticholinergic agents or other agents that cause dry mouth, constipation, somnolence, or other anticholinergic-like effects may increase the frequency or severity of these effects. Anticholinergic agents may alter the absorption of some medications due to their effects on gastrointestinal motility.

tolterodine (Detrol, Detrol LA)[40,41]

Fluoxetine, a potent inhibitor of CYP2D activity, significantly inhibits the metabolism of tolterodine. The result is a 4.8-fold increase in tolterodine area-under the curve (AUC). There also was a 52 percent decrease in C_{max} and a 20 percent decrease in AUC of the 5-hydroxymethyl metabolite. The sums of unbound serum concentrations of tolterodine and its metabolite are only 25 percent higher during the interaction; no dose adjustment is required.

In the presence of ketoconazole, the mean C_{max} and AUC of tolterodine increases by 2- and 2.5-fold, respectively, in poor metabolizers. Based on these findings, other potent CYP3A4 inhibitors such as azole antifungals, macrolide antibiotics, cyclosporine, or vinblastine may also lead to increases of tolterodine plasma concentrations.

trospium (Sanctura, Sanctura XR) [42]

Trospium has not been associated with clinically relevant drug-drug interactions. It does have the potential to interact with other drugs that are eliminated by active tubular secretion (e.g., pancuronium, procainamide, morphine, metformin, vancomycin, tenofovir). Monitoring is recommended in patients receiving trospium and a drug eliminated in this manner.

darifenacin (Enablex)[43]

Darifenacin metabolism is primarily mediated by CYP2D6 and CYP3A4. Inducers of CYP3A4 or inhibitors of either enzyme may alter the pharmacokinetics of darifenacin. Coadministration with ketoconazole increases bioavailability of darifenacin by 389 and 1,150 percent for the 7.5 and 15 mg doses, respectively. Caution is recommended when darifenacin is used concomitantly with medications that have a narrow therapeutic index and that are primarily metabolized by CYP2D6 (such as tricyclic antidepressants). Administration of imipramine with darifenacin results in a 70 percent increase in bioavailability of the antidepressant.

solifenacin (VESIcare) [44]

Solifenacin is a substrate of CYP3A4. Inhibitors or inducers of CYP3A4 may alter the pharmacokinetics of solifenacin. Coadministration with ketoconazole, a potent CYP3A4 inhibitor, increases the bioavailability of solifenacin by 100 to 170 percent.

Adverse Effects

Drug	Constipation	Diarrhea	Dry mouth	Dyspepsia	Dizziness
darifenacin 15 mg (Enablex)[45]	21.3	0.9	35.3	8.4	1.3
oxybutynin 5-20 mg (Ditropan)[46]	12.6	5.0	71.4	7.0	15.6
oxybutynin ER 5-30 mg (Ditropan XL)[47]	13	9	61	7	6
oxybutynin transdermal 3.9 mg/day (Oxytrol)[48]	3.3	3.2	9.6	nr	nr
solifenacin 10 mg (VESIcare)[49]	13.4	nr	27.6	3.9	1.8
tolterodine ER 4 mg (Detrol LA)[50]	6	nr	23	3	2
tolterodine 4 mg (Detrol)[51]	7	4	35	4	5
trospium 40 mg (Sanctura)[52]	9.6	nr	20.1	1.2	nr
trospium ER 60 mg (Sanctura XR)[53]	8.5	nr	10.7	1.2	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from the package insert information and are not meant to be comparative. nr=not reported.

Erythema at the transdermal oxybutynin (Oxytrol) application site occurs in five to 40 percent of patients but is generally mild.[54] Itching occurs in 14 to 17 percent of patients treated with the oxybutynin transdermal patch.[55,56]

Special Populations

Pediatrics

Oxybutynin (immediate and extended-release tablets and syrup) are approved for use in pediatric patients with symptoms of detrusor activity associated with neurological condition. Significant data in this population are not available for other products in this class

Due to a paucity of data in the pediatric population, placebo-controlled trials have been included.

oxybutynin ER (Ditropan XL) versus tolterodine (Detrol) versus tolterodine ER (Detrol LA)

One hundred thirty-two children with a history of diurnal urinary incontinence were randomly assigned to oxybutynin ER, tolterodine IR, or tolterodine ER with dosage titration to effective, maximum recommended dosage or development of bothersome anticholinergic side effects.[57] An independent observer recorded the dose used, anticholinergic side effects, and efficacy of therapy (incidence of urinary frequency, urgency, posturing, and urinary incontinence). Oxybutynin ER and tolterodine ER were significantly more effective at reducing daytime urinary incontinence than tolterodine IR ($p<0.01$ and $p<0.05$, respectively). Oxybutynin ER was significantly more effective than tolterodine ER for complete resolution of diurnal incontinence ($p<0.05$).

tolterodine ER (Detrol LA) versus placebo

Two double-blind trials randomized 711 children ages five to 10 years with urge incontinence to receive tolterodine ER 2 mg or placebo daily for 12 weeks.[58] Compared to placebo, tolterodine ER did not have a significant effect on the number of incontinence episodes per week, voids per 24 hours, or the volume of urine per void. Authors felt that the dosage may have been low for some of the larger children and may have impacted the findings. Tolterodine ER was well tolerated with no serious adverse effects. Investigators had a financial relationship with the manufacturer.

Pregnancy[59,60,61,62,63,64,65,66]

Oxybutynin is Pregnancy Category B. The other drugs in this class are Pregnancy Category C.

Dosages

Drug	Usual Dose	Patients with Hepatic and/or Renal Dysfunction
darifenacin (Enablex)[67]	7.5 to 15 mg daily	7.5 mg daily (for moderate hepatic dysfunction only)
oxybutynin (Ditropan)[68]	5 mg two or three times daily	--
oxybutynin ER (Ditropan XL)[69]	5 to 10 mg daily	--
oxybutynin transdermal (Oxytrol)[70]	one patch applied twice weekly	--
solifenacin (VESIcare)[71]	5 to 10 mg daily	5 mg daily
tolterodine (Detrol)[72]	2 mg twice daily	1 mg twice daily
tolterodine ER (Detrol LA)[73]	4 mg daily	2 mg daily
trospium (Sanctura)[74]	20 mg twice daily	20 mg daily (for severe renal impairment only)
trospium ER (Sanctura XR)[75]	60 mg daily in the morning	Not recommended for severe renal impairment

For patients five to 12 years of age, oxybutynin immediate-release tablets or syrup are given at a dosage of 5 mg two or three times daily. For patients six to 15 years of age, oxybutynin extended-release tablets are given at a dosage of 5 mg once daily.

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed, www.ifpma.org/clinicaltrials, and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered,

the studies in this review have also been evaluated for validity and importance.

oxybutynin (Ditropan) versus oxybutynin transdermal (Oxytrol)

A total of 76 patients with detrusor instability who were currently responding to oxybutynin immediate-release were enrolled in a double-blind, double-dummy, dose titration study.[76] Those patients presenting with recurrence of incontinent symptoms after a two-week washout underwent confirmatory cystometrogram with subsequent randomization to transdermal or oral oxybutynin treatment. Patients applied two to four transdermal oxybutynin 1.3 mg/day transdermal patches twice weekly or oxybutynin 5 mg orally two or three times daily, plus the alternative placebo dosage form. The initial dose was based on prior dose requirements; subsequent dosages were titrated based on anticholinergic symptoms. More dose increases were tolerated in the transdermal group, with 68 percent of patients reaching the maximum dose compared with 32 percent of patients in the oral group. Daily incontinent episodes decreased in the transdermal group from 7.3 to 2.4 (66 percent reduction) and in the oral group from 7.4 to 2.6 (72 percent reduction; p=0.39). The visual analog scale reduction in urinary leakage improved from washout in both groups (p<0.001) with no difference between them (p=0.9). Average bladder volume at first detrusor contraction increased by 66 mL in the transdermal group (p=0.006) and 45 mL in the oral group (p=0.143; p=0.57). Dry mouth occurred in significantly fewer patients in the transdermal (38 percent) compared with those in the oral group (94 percent; p<0.001). Of the patients in the transdermal group, 67 percent noticed a reduction in dry mouth severity compared with previous oral treatment. Ten percent of patients in the transdermal group had moderate to severe skin erythema.

oxybutynin (Ditropan) versus tolterodine (Detrol)

In a randomized, double-blind trial, 378 patients 50 years or older with symptoms of OAB received two weeks of treatment with an initial dose of either tolterodine 2 mg or oxybutynin 2.5 or 5 mg twice daily for eight weeks.[77] Tolterodine and oxybutynin each caused a significant decrease in the mean number of voids per 24 hours, urge incontinence episodes per 24 hours, and mean voided volume after ten weeks of treatment (p=0.0001 for all endpoints). Both agents had comparable efficacy for improving urinary symptoms. Patients treated with tolterodine had significantly fewer adverse events (69 versus 81 percent, p=0.01), notably less dry mouth (37 versus 61 percent, p<0.0001), as well as a lower incidence of dose reduction (six versus 25 percent, p<0.0001) than those in the oxybutynin group.

oxybutynin (Ditropan) versus trospium (Sanctura)

In a randomized, double-blind, multicenter trial, 95 patients with spinal cord injuries and detrusor hyperreflexia were evaluated.[78] Treatment consisted of a two-week administration period of either oxybutynin 5 mg three times daily or trospium 20 mg twice daily with an additional placebo at midday. Maximum bladder capacity was increased 97 mL in the trospium group and 163 mL in the oxybutynin group. The increase in maximum bladder capacity was significant in both groups compared with baseline (p<0.001) but did not differ significantly between groups (p=0.057). With both drugs, there was a significant decrease in maximum voiding detrusor pressure and a significant increase in compliance and residual urine compared to placebo; there were no statistically significant differences between the treatment groups. The percentage of patients who reported severe dryness of the mouth was lower in the trospium cohort (four percent) than in the oxybutynin group (23 percent). Withdrawal from treatment was less frequent in those receiving trospium (six percent) than in those receiving oxybutynin (16 percent).

A total of 358 patients with urge syndrome or urge incontinence were randomized to 52 weeks of treatment with either trospium 20 mg or oxybutynin 5 mg, each given twice daily.[79,80] Analysis of the patient micturition diary indicated a reduction of incontinence frequency and a reduction of the number of urgencies in both treatment groups. Mean maximum cystometric bladder capacity increased during treatment with trospium chloride by 92 mL after 26 weeks and 115 mL after 52 weeks (p=0.001). Micturition frequency was reduced 31 percent with trospium and 34 percent with oxybutynin (p=NS). Adverse events occurred in 65 percent of the patients treated with trospium and 77 percent of those treated with oxybutynin (p<0.01). Dry mouth was reported by 33 percent of trospium-treated patients and 50 percent of oxybutynin-treated patients (p<0.01). Very good tolerability was reported for 63 percent of patients in the trospium group compared with 42 percent of patients in the oxybutynin group (p=0.004). The evaluation of vital parameters, laboratory results, and ECGs did not show any relevant changes attributable to the action of the anticholinergics.

oxybutynin ER (Ditropan XL) versus tolterodine ER (Detrol LA)

The OPERA (OAB: Performance of Extended Release Agents) trial was a multicenter, randomized, double-blind, active-control study. In the study, oxybutynin ER 10 mg per day or tolterodine ER 4 mg per day were given for 12 weeks to women with 21 to 60 episodes of urge urinary incontinence per week and an average of 10 or more voids per 24 hours.[81] Episodes of urge urinary incontinence, total incontinence, and micturition were recorded in 24-hour urinary diaries at baseline and for 12 weeks. Improvements in weekly urge urinary incontinence episodes were similar for women who received the ER formulations of oxybutynin (n=391) or tolterodine (n=399). Oxybutynin ER was significantly more effective than tolterodine ER in reducing micturition frequency (p=0.003). No episodes of urinary incontinence were reported by 23 percent of women taking oxybutynin ER compared with 16.8 percent of women taking tolterodine ER (p=0.03). Dry mouth, usually mild, was more common with oxybutynin ER (p=0.02). Adverse events were generally mild and occurred at low rates, with both groups having similar discontinuation of treatment due to adverse events.

oxybutynin transdermal (Oxytrol) versus tolterodine ER (Detrol LA)

A multicenter trial compared the effects of transdermal oxybutynin with those of tolterodine ER in patients with moderate to severe OAB who had responded well to prior pharmacologic treatment.[82] After withdrawal of their previous therapy, 361 adult patients were randomized to receive 12 weeks of double-blind, double-dummy treatment with oxybutynin 3.9 mg/day transdermal patch twice weekly, tolterodine ER 4 mg daily, or placebo. Both active treatments were significantly more effective than placebo in decreasing the number of daily incontinence episodes, increasing average void volume, and improving QoL. Micturition frequency decreased by a mean of 1.9 episodes per day in the oxybutynin group (p=NS compared to placebo) compared with a decrease of 2.2 episodes per day in the tolterodine ER group (p<0.05 compared to placebo). The most common adverse event for transdermal oxybutynin was localized pruritis occurring in 14 percent of patients and resulting in discontinuation in nearly ten percent of patients. Anticholinergic adverse effects were more common in the tolterodine ER group compared with the oxybutynin group; adverse effects included dry mouth (7.3 and 4.1 percent, respectively) and constipation (5.7 and 3.3 percent, respectively). Dry mouth was significantly more common in the tolterodine ER group than in the placebo group, but the smaller increase of dry mouth in the oxybutynin group was not significantly elevated above placebo. Of those who received tolterodine ER, 1.6 percent discontinued therapy because of fatigue or dizziness. The manufacturer of oxybutynin transdermal patches, which also employed one of the study authors, funded the study.

tolterodine (Detrol) versus tolterodine ER (Detrol LA)

In a placebo-controlled safety and efficacy evaluation, 1,529 patients with urinary incontinence were randomized in a double-blind fashion to tolterodine ER 4 mg once daily, tolterodine 2 mg twice daily, or placebo.[83] Both active dosage forms significantly decreased the number of urge incontinence episodes per week (by 71 and 60 percent, respectively) compared to placebo (33 percent). Micturition frequency decreased and volume increased in both tolterodine groups. The incidence of dry mouth was 23 percent in the tolterodine ER group, 30 percent in the tolterodine group, and eight percent in the placebo group. Of the 1,377 patients completing the study, 1,077 chose to continue with 12 months of open-label treatment with tolterodine ER 4 mg once daily.[84] During the 12-month treatment period, efficacy of tolterodine ER was maintained, and there was no increase in the frequency of adverse events relative to the short-term treatment.

tolterodine (Detrol) versus trospium (Sanctura)

Trospium was compared with tolterodine in a double-blind, placebo-controlled study enrolling 234 patients with urgency or urge incontinence.[85] Patients were randomly assigned therapy with either 20 mg trospium, 2 mg tolterodine, or placebo, each given twice daily for three weeks. In the 180-patient population, micturition frequency was reduced by 3.4 episodes per 24 hours in the trospium group, 2.6 episodes in the tolterodine group, and 1.9 episodes in the placebo group. Adverse events occurred with similar frequency in the trospium and tolterodine groups.

trospium ER (Sanctura XR) versus placebo

A multicenter, double-blind, placebo-controlled study enrolled 601 patients with OAB symptoms into a 12-week study.[86] Patients were randomly assigned to therapy with either trospium ER 60 mg or placebo given once daily. Primary endpoints included change in daily urinary frequency and urgency urinary incontinence episodes. Secondary end points were urgency severity, volume voided per void and the number of urgency voids per day. Safety was assessed by clinical examination, adverse event monitoring, clinical laboratory values and resting electrocardiograms. Patients (n=298) in the trospium ER group showed a statistically significant ($p<0.01$) improvement over the placebo (n=303) group in all primary and secondary outcomes at week one through week 12.The most common adverse events were dry mouth (trospium 8.7 versus placebo 3 percent) and constipation (trospium 9.4 percent versus placebo 1.3 percent). Central nervous system adverse events were rare (headache with trospium one percent versus placebo 2.6 percent). No clinically meaningful changes in laboratory, physical examination or electrocardiogram parameters were noted.

darifenacin (Enablex) versus placebo

A multicenter, double-blind, parallel-group study enrolled 561 patients (ages 19 to 88 years; 85 percent female) with OAB symptoms for at least six months into a 12-week study.[87] After washout and a two-week placebo run-in, patients were randomized to darifenacin 3.75, 7.5, or 15 mg tablets or placebo, each given once daily. Darifenacin 7.5 and 15 mg had a rapid onset of effect with significant improvement compared with placebo for most parameters at the first evaluation at week two. At the conclusion of the study, the number of incontinence episodes per week was reduced from baseline by 67.7 percent with darifenacin 7.5 mg and 72.8 percent with darifenacin 15 mg compared with 55.9 percent with placebo ($p=0.010$ and 0.017, respectively, versus placebo). The darifenacin 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. Darifenacin 7.5 and 15 mg, respectively, were significantly superior to placebo for

improvements in micturition frequency (both p<0.001), bladder capacity (p<0.040, p<0.001), frequency of urgency (p<0.001, p=0.005), severity of urgency (p<0.001, p=0.002), and number of incontinence episodes leading to a change in clothing or pads (p<0.001, p=0.002). There was no significant reduction in nocturnal awakenings due to OAB. The most common adverse events were mild-to-moderate dry mouth and constipation. No patients withdrew from the study as a result of dry mouth, and discontinuation related to constipation was rare (<1 percent). There were no reports of blurred vision, and the safety profile was comparable to placebo.

solifenacin (VESIcare) versus tolterodine (Detrol)

A multicenter, double-blind trial enrolled 1,281 patients in a tolterodine- and placebo-controlled trial conducted to evaluate the safety and efficacy of solifenacin.[88] Adult patients with symptomatic OAB for at least three months were eligible. After a single-blind, two-week placebo run-in period, patients were randomized to 12 weeks of treatment with either solifenacin 5 or 10 mg once daily, tolterodine 2 mg twice daily, or placebo. In the 1,033 patients evaluated for efficacy, the change from baseline in the mean number of urgency episodes per 24 hours was lower with solifenacin 5 mg (-2.85; p<0.001) and 10 mg (-3.07; p<0.001), but not with tolterodine (-2.05; p=0.051). There was not a statistically significant decrease in episodes of incontinence with tolterodine (-1.14; p=0.112) but a significant decrease in patients treated with solifenacin 5 mg (-1.42; p=0.008) and 10 mg (-1.45; p=0.004). Compared with placebo, the mean number of voids per 24 hours was significantly lower in patients receiving tolterodine (-1.88; p=0.015), solifenacin 5 mg (-2.19; p<0.001), and 10 mg (-2.61; p <0.001). The mean volume per void was significantly higher with all three active treatments (p<0.001). The most common adverse effect, dry mouth which was mostly mild, was reported in 18.6 percent of patients receiving tolterodine, 14 percent receiving solifenacin 5 mg, and 21.3 percent receiving solifenacin 10 mg.

solifenacin (VESIcare) versus tolterodine ER (Detrol LA)

The STAR trial (Solifenacin and Tolterodine extended-release as an Active comparator in a Randomized trial) was a prospective, double-blind, double-dummy, two-arm, parallel-group, 12-week study to compare the efficacy and safety of solifenacin 5 or 10 mg and tolterodine ER 4 mg once daily in patients with OAB.[89] After the first four weeks of therapy, patients could request a dose increase, but the blinding was maintained since a dose increase was only allowed for the solifenacin-treated group. More of the solifenacin-treated patients showed reduced urgency episodes, incontinence, urge incontinence, pad usage, and increased volume voided per micturition. Also, the majority of side effects were mild with a low discontinuation rate for both groups.

Summary

Oral oxybutynin (Ditropan, Ditropan XL) and tolterodine (Detrol, Detrol LA) are effective for the treatment of OAB. Both are available as either immediate-release or extended-release dosage forms. Oxybutynin immediate-release and extended-release tablets are indicated for children as young as five and six years of age, respectively. One trial directly comparing the ER dosage forms of oxybutynin and tolterodine has been completed. In the pediatric study, once daily oxybutynin ER was more effective than once daily tolterodine ER for resolving diurnal incontinence. In general, due to its specificity, tolterodine ER has a lower incidence of anticholinergic side effects than oxybutynin ER.

Trospium (Sanctura, Sanctura XR) is effective for the treatment of OAB. It is available as either immediate-release or extended-release dosage form. In a study comparing it to oxybutynin IR in

patients with spinal cord injury, the two drugs were equally effective. Trospium has a lower incidence of some potentially bothersome adverse effects (blurred vision, dizziness, somnolence) than oxybutynin and, perhaps, some of the other agents in this class, likely due to its quaternary structure.[90]

The transdermal form of oxybutynin (Oxytrol) is equally effective to immediate-release oxybutynin and immediate- and extended-release tolterodine. The transdermal medication appears to cause fewer anticholinergic adverse effects, likely by avoiding first-pass metabolism to N-desethyloxybutynin, an active metabolite partly responsible for such effects. The transdermal patches are associated with a relatively high rate of cutaneous reactions, often resulting in discontinuation of the agent. At present, there are no data supporting the relative efficacy and tolerance of transdermal oxybutynin and the ER dosage form of oxybutynin or trospium.

Darifenacin (Enablex) and solifenacin (VESIcare) are relatively selective for the M_3 subtype of muscarinic receptors. The incidence of anticholinergic adverse events is lower than or equal to the other agents in this class.

A key factor to consider in differentiating these agents is their extensive metabolism via the CYP450 system and the formation of pharmacologically active metabolites, thus increasing the likelihood of metabolic drug interactions.[91] In addition, oxybutynin crosses the blood–brain barrier, inducing distinct CNS effects and thereby affecting patients' daily routines; in contrast, tolterodine and trospium lack distinct CNS effects, suggesting that they both act primarily in the periphery.[92]

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